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Preparation of novel steroidal conjugates as potential diagnostic and therapeutic agents with an emphasis on quinoid and halogenated moieties

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PREPARATION OF NOVEL STEROIDAL CONJUGATES AS POTENTIAL DIAGNOSTIC AND THERAPEUTIC AGENTS WITH AN EMPHASIS ON QUINOID AND HALOGENATED MOIETIES

Nuha Obaid Juma Alsoom

This thesis is submitted in partial fulfilment of the requirements for the degree of Master of Science in Chemistry

Under the Supervision of Professor Thies Thiemann

May 2016

Declaration of Original Work

I, Nuha Obaid Juma Alsoom the undersigned, a graduate student at the United Arab Emirates University (UAEU), and the author of this thesis entitled "*Preparation of Novel Steroidal Conjugates as Potential Diagnostic and Therapeutic Agents with an Emphasis on Quinoid and Halogenated Moieties*", hereby, solemnly declare that this thesis is my own original research work that has been done and prepared by me under the supervision of Professor Thies Thiemann, in the College of Science at UAEU. This work has not previously been presented or published, or formed the basis for the award of any academic degree, diploma or a similar title at this or any other university. Any materials borrowed from other sources, (whether published or unpublished) and relied upon or included in my thesis have been properly cited and acknowledged in accordance with appropriate academic conventions. I further declare that there is no potential conflict of interest with respect to the research, data collection, authorship, presentation and, or publication of this thesis.

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Abstract

Steroids bonded to pharmaceutically active molecules are interesting candidates as therapeutic agents. In this work, a number of potentially bioactive residues, which include the quinoid moiety, have been synthesized as a simple steroid quinone hybrid, where the steroid component will be estradiol derived or the steroid cholesterol derived. For this purpose, two novel reactions have been explored namely, the modification of the APPEL reaction to connect residues by using $PPh_3/BrCCl_3$ for amidation and esterification of carboxylic acids. Another one is the hydrogenation reaction of alkenes by using NaBH4, AcOH, Pd/C and toluene or benzene in the presence of benzyl groups with hydrogen production *in situ.* The halogenation of residues that can be linked to steroids has also been attempted. The main aim of the proposal work is the development of a strategy that can be adopted for the radio-halogenation of the residues that function as potential radio-diagnostic agents when linked to the steroid.

Keywords: Synthesis organic compounds, steroidal conjugates, therapeutic agent, quinoid, halogenated moieties, radiolabelling, APPEL reaction.

Title and Abstract (in Arabic)

تحضير ستيرويدات مترافقة جديدة واستخدامها كعوامل تشخيصية وعلاجية محتملة مع التركيز على الكينودات ذات الهالوجينات المتنوعة

الملخص

الستيرويدات المرتبطة مع الجزيئات النشطة صيدلانيا وجدت اهتمام خاصا من قبل الباحثيين كعوامل علاجية. في هذا الدراسة، استخدمت بعض المركبات الكيمائية ذات النشاط البيولوجي، والتي تشمل كينويد، تم تخليقها اصطناعيا كستيرويدات بسيطة التركيب، حيث مكون الستيرويد سيكون استراديول مشتقة أو اشتقاق الكوليسترول الستيرويدي. لهذا الغرض، تم استخدام إثنين من التفاعلات الكيميائية الجديدة وهي تعديل للتفاعل بإستخدام $PPh_3/BrCCl_3$ وإضافة الأميد وأسترة الأحماض الكربوكسيلية، و الآخرهو تفاعل هدرجة الألكينات بإستخدام $Pd/C, NaBH_4, AcOH,$ والتولوين أو البنزين في وجود مجموعات البنزايل مع إنتاج الهيدروجين في الموضع نفسه. إضافة إلى ذلك، قد أجريت محاولات لربط المشتقات المهلجنة بالستيرويدات. والهدف الرئيس من هذا الدراسة هو وضع إستراتيجية يمكن اعتمادها في الهلجنة المشعة من المخلفات التي تعمل كعوامل للأشعة التشخيصية عندما ترتبط الستيرويدات مع بعضها.

مفاهيم البحث الرئيسية: المركبات العضوية المخلقة، الستيرويدات، كينويدات، العوامل العلاجية، الترميز الاشعاعي، تفاعل أبيل.

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Greetings of love and appreciation, a lot of thanks and gratitude to my dear mother to the standing next to me and continuous supporting otherwise I would not complete in this way in the face of all the troubles. I do not have enough words that give her thankful and gratitude, but I can pray to my god always to have a good health and wellness.

I would like to express my great special gratitude to my husband, my beloved children Hoor, Nawal, Yousef and Khalid for cheering me up. Special thanks to husband's family members for the encourage during the course of the study. Another special thanks to who help me in the building my scientific life and to who help me for putting the pieces together to reach to the end of this way crowned with success.

Dedication

To professor Thies Thiemann, my beloved mother and family

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List of Abbreviations

Bn	Benzyl protective group
CAN	Cerium Ammonium Nitrate
DMF	DiMethylFormamide
DMSO	Dimethylsulfoxide
[^{18}F]FES	16α-[^{18}F]Fluoroestradiol
hr.	hour
IR	Infrared
MP	Melting Point
NBS	N-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
PET	Positron Emission Tomography
RT	Room Temperature
SPECT	Single Photon Emission Computed Tomography
UV-VIS	Ultra-Violet Visible

Chapter 1: Introduction

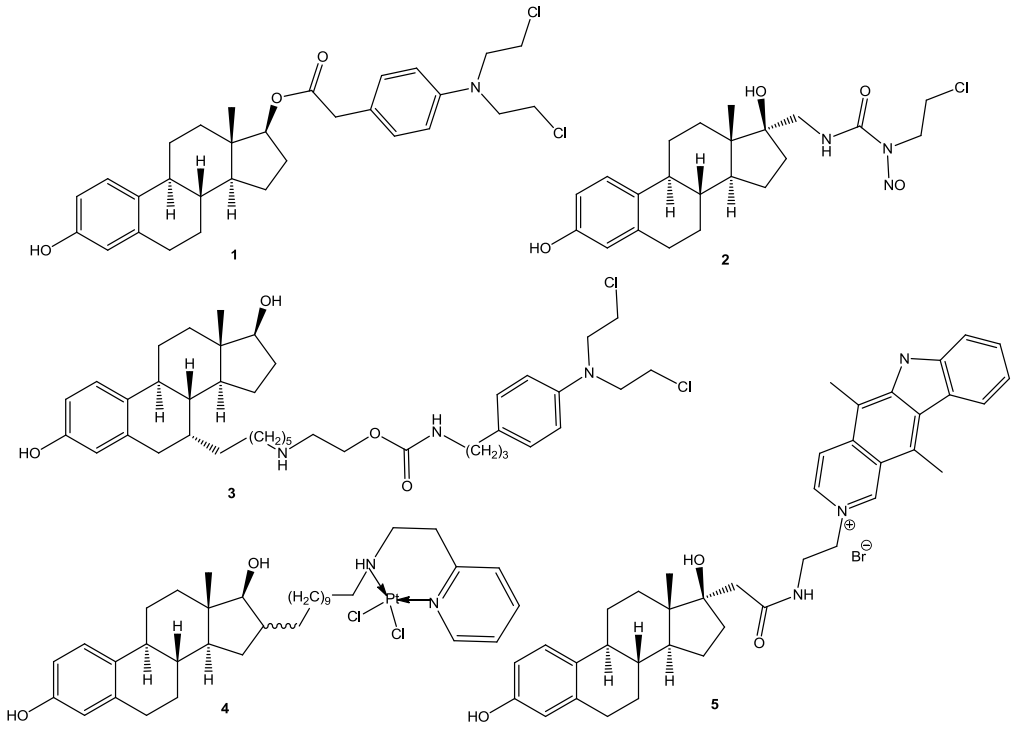
1.1 Steroids-Bioactive Linkage

Hybrids of biomolecules and bioactive residues or residues with diagnostic markers have become of great interest in diagnosis and therapy. In the steroidal field, steroids have been linked to cancer-active residues (Bansal and Acharya 2014), and they have been either radiolabeled within their steroidal framework or have been connected to a moiety that itself has been radiolabeled. It is hoped that the derivatised steroid interacts with the receptor of the natural, non-derivatised steroid. At that time, the bioactive residue would "perform its work" or the radiolabel would send its signal to help localize the molecule within the tissue.

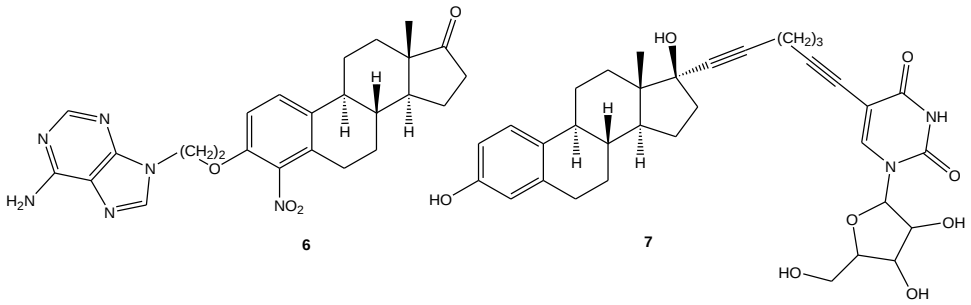
There exist diseases where certain natural receptors are overexpressed. One such receptor is the estrogen receptor ERα. Over the years, a number of estradiol derived steroids connected to bioactive molecules have been published. These include conjugates with mustards, eg. **1** and **3** (Vollmer et al. 1973; Mitra et al. 2002), nitrosourea **2**(Lam et al. 1979), and platinum complexes such as **4** (Georgiades et al. 1987; Perron et al. 2004) and estradiol has been connected to ellipticinium **5** (Delbarre et al. 1985) (Scheme 1). Also, estradiol has been connected to nucleosides and nucleotides such as **6** and **7**(Ali et al. 2006; Iyer et al. 1983) (Scheme 2).

In all of these cases, the estradiol component is used as a drug delivery system, ultimately not only bringing the bioactive component to the right tissue but oftentimes into the nucleus of ERα- overexpressed cells. It is believed that in 60-70% of all breast

cancer the cancer cells exhibit an overexpression of ERα, the natural receptor for estradiol.



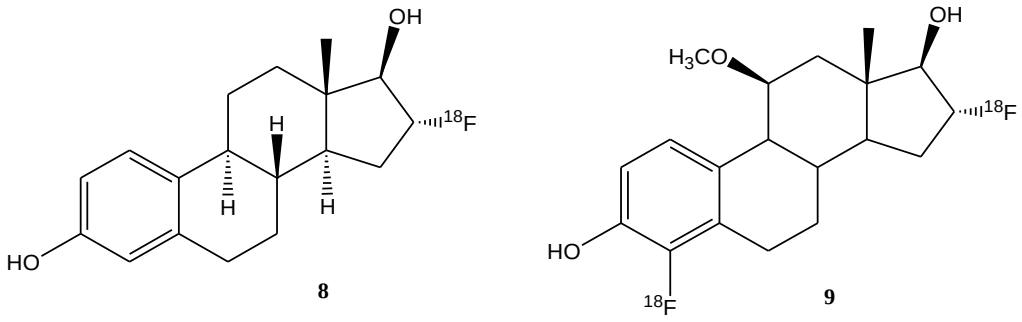
Scheme 1: Estradiol derivatives connected to cancer-active residues



Scheme 2: Estradiol and estrone linked to adenine and uridine

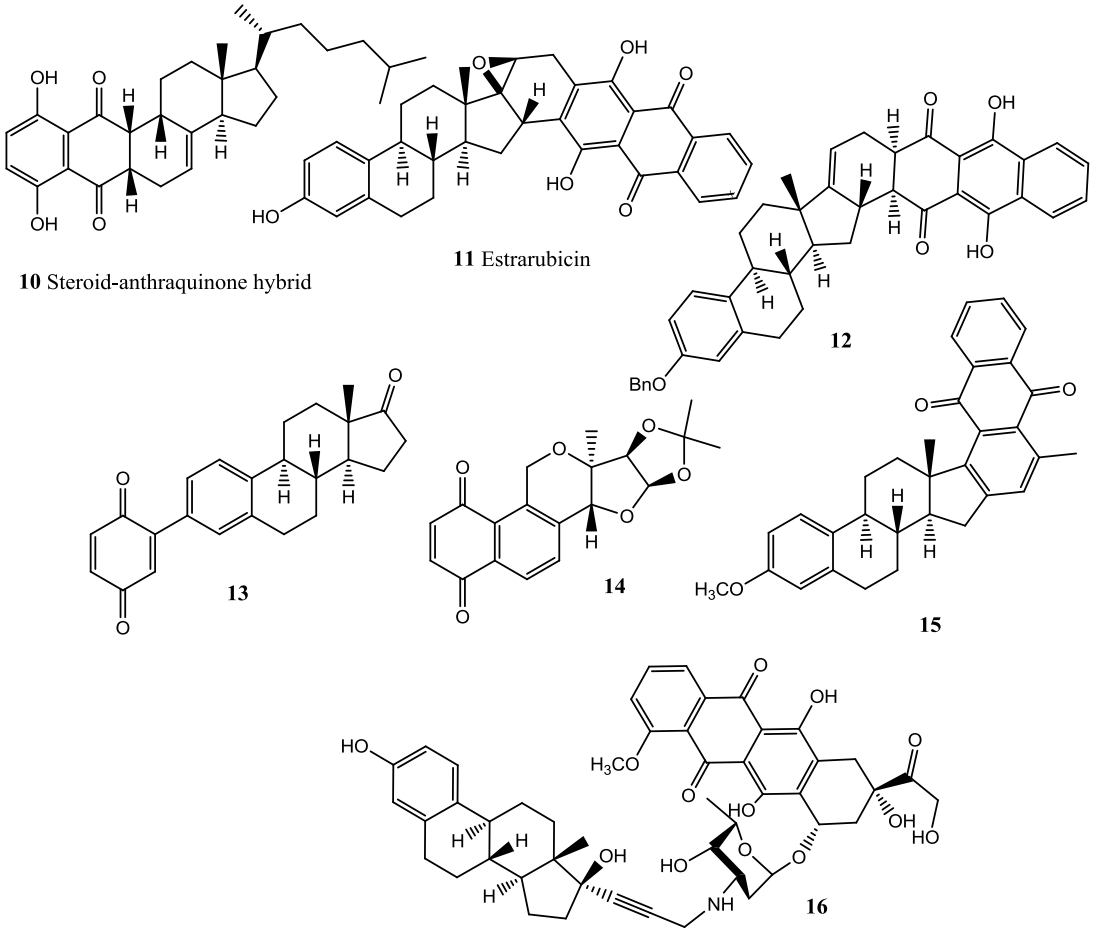
Analogous is the reasoning behind using radiolabelled estradiol derivatives as diagnostics and therapeutics (Al Jasem et al., 2016; Oliveira et al, 2012; Oliveira et al., 2013, Cunha, 2013). Here, the steroid is equipped with a radiolabel that emits gamma radiation of a certain energy that can be detected. Typical radiotracers used are ^{123}I for Single Photon Emission Computed Tomography (SPECT), ^{18}F for Positron Emission Tomography (PET) and ^{99m}Tc (SPECT). All of these have been studied, when attached to an estradiol derivative. ^{18}F-derived steroids used for diagnostic purposes have been studied in clinical trials, already (Mintun et al. 1988, McGuire et al. 1991, Deshdashti et al. 1995).

The most important derivatives to date are 16α-[^{18}F]fluoroestradiol[^{18}F]FES and 11βmethoxy-4,16α-[^{18}F]difluoroestradiol (4F-M[^{18}F]FES) (**Scheme 3**). Radiolabelled steroids can also be used in therapy. In principle, here not only emitted gamma radiation is used, but also emitted Auger electrons. One possible radionuclide for Auger therapy (Kassis 2003) is [^{77}Br] bromine and [^{125}I] iodine (Bodei et al. 2003). Thiemann group has already worked in collaboration with the Instituto Tecnológico e Nuclear, Instituto Superior Técnico, Universidade de Lisboa in Sacavem, Portugal with ^{99m}Tc and ^{123}I-labelled estradiol derivatives (Melo e Silva 2001, Neto 2012A, Neto 2012B).



Scheme 3: [^{18}F]FES as PET diagnostic agents

1.1.1 Steroids-Quinones Linkage



Scheme 4: Steroid derived quinone and mimic quinone hybrids (Delbarre, 1985)

Quinones are distributed widely in living organisms. Some of the more familiar ones are plastoquinone and phylloquinone, both quinones needed in photosynthesis, and ubiquinone, also known as coenzyme Q10, which participates in the aerobic cellular respiration. The entire above are substituted *p*-benzoquinones. Anthracyclines can be viewed as having a quinoid group. A number of members of this family such as daunorubicin and doxorubicin are used in cancer chemotherapy. Also menadione (2-methylnaphtho-1,4-quinone), which is sold as a nutritional supplement as a vitamin K mimic, has been viewed as a potential drug for prostate cancer treatment (Jamison 2001). Overall, in 1991, quinones constituted the second largest group of cytotoxins used in chemical cancer therapy, after specifically alkylating agents such as mustards (O'Brien 1991), with about 1500 quinones already tested in 1974 (Driscoll et al. 1974).

Quinones have a number of actions in the body. In strongly dividing cells, their most influential action is the interaction with DNA material, which may lead either to DNA damage or to change DNA resulting in cell mutations (O'Brien 1991). In non-dividing cells or in cells at rest the main action of the quinones is a possible alkylation of proteins through their thiol or amino groups (O'Brien 1991). Most important, though, is the reduction of the quinones to the respective semi-quinone radicals by reductase. The semi-quinoneradicals in turn reduce oxygen to superoxide radicals and reform as quinones. The superoxide radicals, which are usually scavenged in the body by the enzyme superoxide dismutase, are very toxic and lead among others the oxidation of cysteine residues to cysteine in proteins and the oxidation of glutathione (GSH) to glutathione disulphide (GSSG) as stated by O'Brien, 1991.

It has been found that the protein NAD(P)H: quinone oxidoreductase 1 (QR1) is overexpressed in many human solid tumours such as adrenal, thyroid, breast, ovarian, colon, and non-small-cell lung cancer (Siegel and Ross 2000). This enzyme poses a possible target for quinone drugs. Recently, the crystal structure of the protein complex to different synthetic quinones has been published (Falg et al., 2001). Among other details, it had been shown that the protein is relatively flexible to ligand differently substituted quinones, which may bind to QR1 in different orientations.

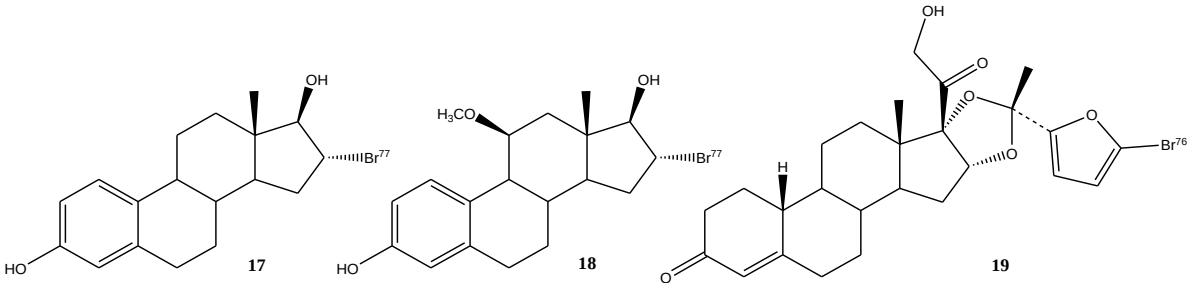
With the known cancer activity of anthracyclines, anthracyline-steroid hybrids (Dao *et al.*, 2012) such as **16** (**Scheme 4**) (Hartman *et al.*, 1990) were synthesized and their biological activity was investigated. These studies were extended to dihydroxy-arenoquinone containing steroids such as **10**,**11**and **12** (de Riccardis *et al.*, 1997; de Riccardis *et al.*, 1998), then to quinoid containing steroid **13** (Fujiwara *et al.*, 2011), and steroidal mimic **14** (Kaliappan & Ravikumar, 2005). Thiemann group had communicated the annealed steroidal anthraquinone **15** previously (Morais et al., 2005). In this thesis, a pathway is to be found for a facile synthesis of steroid quinone hybrids, where the steroid component will be estradiol derived foreasy accessibility of the steroid cholesterol derived.

1.2 Brominated Steroids: SPECT Imaging Agents

76-Bromine, 77-bromine, 78-bromine isotopes are Auger-electron emitters. The Auger electron emitters often decay with sufficient positron emission, so that they can also be used as agents for positron emission tomography (PET). This can be used to complement diagnosis with therapy (DeSombre et al. 1988; DeSombre et al. 1992; Kassis

et al. 1982). The life-time of 76-bromine is sufficiently long that it will allow for a target-tissue selective biodistribution, but sufficiently short that much of it will have decayed in the cell before metabolism and excretion of the compound.

The synthesis of a number of estradiols labeled with SPECT radionuclide bromine-77 have been reported (McElvany et al. 1982, Senderoff et al. 1982, Katzenellenbogen et al. 1981, Katzenellenbogen et al. 1982). Some of these have been evaluated both in animals and in humans. Their use in imaging has been limited to date, however. Especially, 16α-[^{77}Br] estradiol has been reported to have potential as SPECT imaging agent. A bromine-76 analogue has not yet been prepared.



Scheme 5: [^{76}Br]-Bromo-labelled steroids as Auger emitters

More recently, 16α, 17α-[(R)-1'-α-(5-[^{76}Br]bromofurylmethylidene)dioxyl]-21-hydroxy-19-norpregn-4-ene-3,20-dione (**19**) has been synthesized and its biodistribution been studied in immature Sprague-Dawley rats. It showed progesterin receptor (PR) mediated uptake. The biodistribution was found to be favorable, but its metabolism was too rapid (Zhou et al. 2008). While radio-brominated steroidal estrogens and progestins have been prepared, the study of these compounds is still limited by their poor accessibility. Thus, knowledge of radiobrominated steroids is much less advanced than

that of radioiodinated or radiofluorinated steroids. In this work, the bromination of a prosthetic group that will be linked to the steroidal system is to be studied. This is to show a future pathway to a radiobrominated compound, where the prosthetic group is linked to the steroid.

Chapter 2: Methodology

2.1 Introduction

Initially, modification of two synthetic reactions was needed. The first reaction was an Appel-type linkage of an acid to a second moiety via an ester or amide function. Here, the reaction was carried out with the new reagent triphenyl-phosphine-bromo-trichlorocarbon (PPh_3-$BrCCl_3$). A number of amides and esters were synthesized in order to optimize this type of reaction for the target products. The second reaction was the hydrogenation of a double bond using sodium borohydride ($NaBH_4$), acetic acid (AcOH) and palladium on carbon (Pd/C), this reaction was also used to *O*-debenzylate*O*-benzylarenes, albeit under forced conditions. In order to understand how to control alkene-hydrogenation over reductive *O*-debenzylation, a number of *O*-benzylcinnamates, *O*- and *N*-benzyl-cinnamamides were tested under different reaction conditions. The products from the reactions above were characterized by ^{1}H NMR (400 MHz) spectroscopy, ^{13}C NMR (100.5 MHz) spectroscopy, IR and melting point.

Next, a number of 1,4-dimethoxy-phenyl-propionates and 1,4-dimethoxy-phenyl-propionamides, obtained from the reactions above, were treated with cerium ammonium nitrate (CAN) in order to acquire the corresponding quinones. Also, a variety of 3-hydroxy-4-methoxyphenylpropionates and 3-hydroxy-4-methoxypropionamides were subjected to oxidation with CAN and transformed to methoxyquinonylpropinates and methoxyquinonylpropionamides. The products from the reactions above were characterized by ^{1}H NMR (400 MHz) spectroscopy, ^{13}C NMR (100.5 MHz) spectroscopy, IR and UV-VIS spectroscopy, and melting point.

Cholesterol was esterified with 1,4-dimethoxyphenylpropionic acid, with 2,5-dimethoxybenzoic acid and with 3-hydroxy-4-methoxyphenylpropionic acid under the modified Appel conditions, developed by us. 3-*O*-Methylestradiol was reacted with 1,4-dimethoxypropionic acid under these conditions, also. These steroidal esters were reacted with CAN to give the corresponding quinone-steroid hybrids. The steroid-quinone hybrids were characterized by ^{1}H NMR (400 MHz) spectroscopy, ^{13}C NMR (100.5 MHz) spectroscopy, IR and UV-VIS spectroscopy, and melting point.

Finally, 3-hydroxy-4-methoxyphenylpropionamides prepared were brominated with N-bromosuccinimide (NBS) in DMF to investigate the ease of monobromination for the purpose of linking the 3-hydroxy-4-methoxyphenylpropionyl function to a steroidal alcohol or amine as a prosthetic group and attaching a bromo-label selectively to a prosthetic group. A sample, cinnamaldehyde oxime, was sent out to the Department of Inorganic Chemistry, University of Hamburg, for X-ray structural analysis. The cinnamaldehyde was to be used to test the reduction of oximes adjacent to double bonds to amines. These reactions were abandoned as not promising.

2.2 Experimental Part

The adopted experimental procedure followed the course of APPEL reaction and Alkenes hydrogenation (Al Soom & Thiemann, 2016).

2.2.1 Chemical and Solvents

- CH_3CN (190 far UV, super purity, (Romil Chemicals) and CH_2Cl_2 (Aldrich) were used as solvents for the UV-VIS spectroscopic measurements as received.

- $NaBH_4$ (Fisher Scientific), ammonium cerium nitrate (CAN, Fisher Scientific), ethyl bromo-acetate (Ventron), bromo-tri-chloromethane ($BrCCl_3$, Aldrich), tetra-chloro-carbon (CCl_4, Riedel-de-Haën), 2,5-dimethoxy-benzaldehyde (**25d**), 3-hydroxy-4-methoxy-benzaldehyde (**24a**) (Aldrich), tri-phenyl-phosphine (PPh_3, Aldrich), Pd/C (Aldrich, 5 wt%, 205680) were acquired commercially, and were used as received.

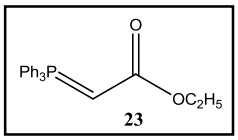
2.2.2 Instrumentation

- **Melting points** were measured on Stuart SMP 10 melting point apparatus, and were uncorrected.
- **Infrared spectra** were measured with a Thermo/Nicolet Nexus 470 FT-IR ESP Spectrometer.
- **^{1}H and ^{13}C NMR spectra** were recorded with a Varian 400 NMR (^{1}H at 395.7 MHz, ^{13}C at 100.5 MHz) and a Varian 200 MHz NMR spectrometer (^{1}H at 200.0 MHz, ^{13}C at 50.3 MHz). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted).
- **Mass spectra** were measured with a JMS-01-SG-2 spectrometer.
- **CHN-analysis** was performed on a LECO TruSpec Micro instrument.
- **Column chromatography** was carried out on silica gel (60 A, 230 – 400 mesh, Sigma-Aldrich).
- **UV-VIS absorption spectra** were recorded using a Cary-50 spectrophotometer.

***Safety notice*:** Regarding caution for hydrogenations using $NaBH_4$, Pd/C, AcOH in toluene or benzene. In the presence of dry palladium on carbon, hydrogen enflames upon contact with air. Therefore, it is advisable to purge the reaction flasks with an inert gas before use in the described hydrogenation. Also, where filtrating the reaction mixture directly, especially when using a paper filter, it must be noted that the filter cake upon drying can enflame due to the fact that unreacted sodium borohydride slowly hydrolyses with air moisture, thereby releasing hydrogen. Therefore, after diligent washing with chloroform, the filter and filter cake should be immersed fully in water for sometimes.

2.2.3 Preparation

Ethoxycarbonylmethylidenetriphenylphosphorane (**23**)

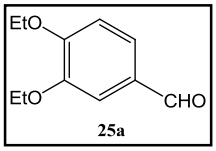


23

To a solution of triphenyl-phosphine (**20**, PPh_3, 12.3 g, 46.8 mmol) in $CHCl_3$ (25 mL) was added ethyl bromoacetate (**21**, 7.77 g, 46.8 mmol, careful: lachrymator!). The solution heated up during the addition. The reaction mixture was stirred at RT for 14 hr. Then, it was poured into ether (300 mL). The precipitate formed was allowed to settle for 3 hr. This is mainly **ethoxycarbonylmethyltriphenylphosphonium bromide** (**22**). The ethereal supernatant was decanted thereafter and aq. Na_2CO_3 (10 g Na_2CO_3 in 100 mL H_2O) was added, followed by CH_2Cl_2 (35 mL). The reaction mixture was stirred at RT for 45 min. Thereafter, the mixture was extracted with CH_2Cl_2 (3 X 35 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to leave an oily residue from, which ethoxycarbonylmethylidenetriphenylphosphorane (**23**) crystallized upon seeding

to give compound **23** as a colourless solid (14.1 g, 87%). ν_{max} (KBr/cm^{-1}) 3055, 2975, 2900, 1605, 1483, 1437, 1371, 1330, 1121, 1062, 892, 755, 695, 545, 507.

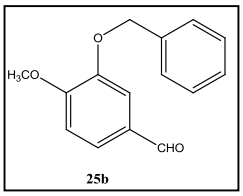
3,4-Diethoxybenzaldehyde (**25a**)



25a

To finely ground KOH (560 mg, 10 mmol) in DMSO (15 mL) is added 3,4-dihydroxybenzaldehyde (protocathecuic acid, compound **24a**, 700 mg, 5.07 mmol). The mixture was stirred at RT for 15 min. Then, ethyl iodide (6.0 g, 38.5 mmol) was added dropwise. The reaction mixture was stirred at RT for 36 hr. Then, water (35 mL) was added, and the mixture was extracted with $CHCl_3$ (3 X 35 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel ($CHCl_3$-hexane 2:1) to give compound **25a** (640 mg, 76%) slowly solidifying, colorless oil; δ_H (400 MHz, $CDCl_3$) 1.48 (6H, t, ^3J = 6.8 Hz, 2 CH_3), 4.16 (2H, q, ^3J = 6.8 Hz, OCH_2), 4.17 (2H, q, ^3J = 6.8 Hz, OCH_2), 6.95 (1H, d, ^3J = 8.0 Hz), 7.39 (1H, s), 7.40 (1H, d, ^3J = 8.0 Hz), 9.82 (1H, s, CHO); δ_C (100.5 MHz, $CDCl_3$) 14.5 (CH_3), 14.6 (CH_3), 64.5 (OCH_2), 64.6 (OCH_2), 110.6 (CH), 111.5 (CH), 126.6 (CH), 129.7 (C_{quat}), 149.0 (C_{quat}), 154.2 (C_{quat}), 191.0 (CHO).

3-Benzyloxy-4-methoxybenzaldehyde (**25b**).

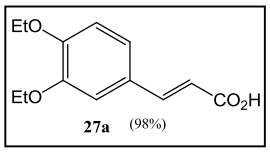


25b

A suspension of finely ground KOH (1.12 g, 20 mmol) in DMSO (20 mL) was stirred at RT for 15 min., and thereafter 3-hydroxy-4-methoxybenzaldehyde (**24b,** 2.00 g, 13.1 mmol) was added, and the resulting mixture was stirred for 35 min. Then, benzyl chloride (3.30 g, 26.4 mmol) was added drop-wise, and the mixture was stirred for 14 hr at RT. Then, it was given into water (40 mL) and extracted with $CHCl_3$ (3 X 35 mL). The organic phase was dried over

anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane/CH_2Cl_2 1:3) to give compound **25b** (3.1 g, 97.5%) as a pale yellow solid, MP. 61 ^oC (Lit. 63-65 ^oC [Schrittwieser et al. 2011]); ν_{max} (neat/cm^{-1}) 1684, 1585, 1434, 1267, 1133, 1017; δ_H (400 MHz, $CDCl_3$) 3.95 (3H, s, OCH_3), 5.18 (2H, s, OCH_2), 6.98 (1H, d, ^3J = 8.0 Hz), 7.31 – 7.44 (7H, m), 9.80 (1H, s, CHO); δ_C (67.8 MHz, $CDCl_3$) 56.2 (OCH_3), 70.8 (OCH_2), 110.7 (CH), 111.2 (C_{quat}), 126.9 (CH), 127.5 (2C, CH), 128.0 (C_{quat}), 128.1 (CH), 128.7 (2C, CH), 129.9 (C_{quat}), 136.2 (CH), 148.6 (C_{quat}), 155.0 (C_{quat}), 190.0 (CHO).

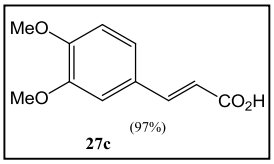
(*E*)-3,4-Diethoxycinnamic acid (**27a**).



27a (98%)

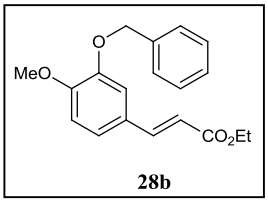
A mixture of 3,4-diethoxybenzaldehyde (**25a**, 970 mg, 5.0 mmol) and ethoxycarbonylmethylidenetriphenylphosphorane (2.09 g, 6.0 mmol) in aq. NaOH (2.0 g NaOH in 20 mL H_2O) was stirred at 70 ^oC for 2 hr and at 90 ^oC for 12 hr. The cooled solution was acidified with half-conc. aq. HCl. The formed suspension was let to stand for 3hr. Thereafter, the precipitate was filtered off and the filter cake was washed diligently with water (3 X 25 mL). The solid was air-dried to give compound **27a** (1.16 g, 4.91 mmol, 98%) as a colorless solid; MP. 154 – 156^oC; ν_{max} (KBr/cm^{-1}) 3500 – 2850 (bs, OH), 1696, 1629, 1596, 1517, 1430, 1398, 1330, 1040, 978, 802, 594, 529; δ_H (400 MHz, $CDCl_3$) 1.46 (6H, t, ^3J = 6.8 Hz, 2 CH_3), 4.12 (2H, q, ^3J = 6.8 Hz, OCH_2), 4.13 (2H, q, ^3J = 6.8 Hz, OCH_2), 6.28 (1H, d, ^3J = 16.0 Hz), 6.85 (1H, d, ^3J = 8.0 Hz), 7.07 (1H, s), 7.08 (1H, d, ^3J = 8.0 Hz), 7.70 (1H, d, ^3J = 16.0 Hz); δ_C (100.5 MHz, $CDCl_3$) 14.6 (CH_3), 14.7 (CH_3), 64.5 (OCH_2), 64.6 (OCH_2), 111.9 (CH), 112.6 (CH), 114.6 (CH), 123.1 (CH), 126.9 (C_{quat}), 147.1 (CH), 148.8 (C_{quat}), 151.3 (C_{quat}), 172.4 (C_{quat}, CO).

(*E*)-3,4-Dimethoxycinnamic acid (**27c**).



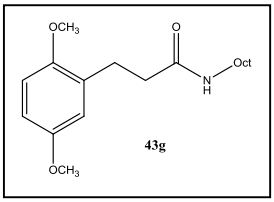
Prepared analogous to **27a**: (97%) as a colorless solid; [Lit. 181-183 °C Aldrich Catalogue]; ν_{max} (KBr/cm^{-1}) 3300 – 2500 (bs, OH), 1677, 1624, 1596, 1517, 1463, 1426, 1340, 1250, 1140, 1025, 975, 840, 579, 536; δ_H (400 MHz, DMSO-d^6) 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 6.41 (1H, d, ^3J = 16.0 Hz), 7.50 (1H, d, ^3J = 16.0 Hz), 12.19 (1H, bs, OH); δ_C (100.5 MHz, DMSO-d^6) 56.0, 56.1, 110.7, 112.0, 117.2, 123.1, 127.5, 144.6, 149.4, 151.2, 168.3.

Ethyl (E)-3-benzyloxy-4-methoxycinnamate (**28b**).



A mixture of 3-benzyloxy-4-methoxybenzaldehyde (**25b**, 2.42g, 10 mmol) and ethoxycarbonylmethylidenetriphenyl phosphorane (**23**, 5.57 g, 16 mmol) in CHCl3 (10 mL) was stirred for 2 hr at 80 ^{o}C. Direct column chromatography on silica gel (CH_2Cl_2) gave compound **28b** (3.10 g, 99%) as a colorless solid, MP. 91 ^{o}C; ν_{max} (KBr/cm^{-1}) 2932, 1705, 1635, 1512, 1265, 1177, 1136, 1011, 751, 699, 607, 541; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, ^3J = 7.2 Hz, CH_3), 3.90 (3H, s, OCH_3), 4.23 (2H, q, ^3J = 7.2 Hz, OCH_2), 5.15 (2H, s, OCH_2), 6.22 (1H, d, ^3J = 16.0 Hz), 6.87 (1H, d, ^3J = 8.8 Hz), 7.07 (1H, d, ^4J = 2.0 Hz), 7.10 (1H, dd, ^3J = 8.8 Hz, ^4J = 2.0 Hz), 7.28 – 7.47 (5H, m), 7.56 (1H, d, ^3J = 16.0 Hz); δ_C (67.8 MHz, $CDCl_3$) 14.4 (CH_3), 56.0 (OCH_3), 60.4 (OCH_2), 71.0 (OCH_2), 111.4 (CH), 112.4 (CH), 115.9 (CH), 122.9 (CH), 127.3 (2C, CH), 127.6 (CH), 128.6 (2C, CH), 136.6 (C_{quat}), 144.5 (CH), 148.2 (C_{quat}), 156.7 (C_{quat}), 167.3 (C_{quat}, CO).

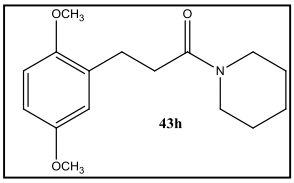
***N*-Octyl 3-(1,4-dimethoxyphen-2-yl) propionamide (43g)**



43g

As a colorless solid, MP. 63 - 64 ^{o}C; ν_{max} (KBr/cm^{-1}) 3325 (NH), 2999, 2959, 2923, 2852, 1641, 1533, 1504, 1469, 1220, 1047, 852, 807, 696; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, ^3J = 6.8 Hz, CH_3), 1.20 – 1.29 (10H, m), 1.37 – 1.44 (2H, m), 2.45 (2H, t, ^3J = 7.2 Hz), 2.90 (2H, t, ^3J = 7.2 Hz), 3.18 (2H, bq, ^3J = 6.4 Hz, NCH_2), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 6.69 (1H, dd, ^3J = 8.8 Hz, ^4J = 3.2 Hz), 6.73 (1H, d, ^4J = 3.2 Hz), 6.76 (1H, d, ^3J = 8.8 Hz); δ_C (67.8 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 26.9 (CH_2), 29.2 (CH_2), 29.2(5) (CH_2), 29.6 (CH_2), 31.8 (CH_2), 36.9 (CH_2), 39.6 (CH_2), 55.6 (OCH_3), 55.8 (OCH_3), 111.3 (CH), 111.7 (CH), 116.2 (CH), 130.2 (C_{quat}), 151.4 (C_{quat}), 153.5 (C_{quat}), 172.4 (Cquat, CO).

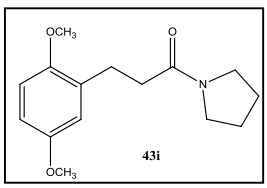
N-Piperidinyl 3-(1,4-dimethoxyphen-2-yl) propionamide (43h)



43h

As a colorless oil; ν_{max} (KBr/cm^{-1}) 2997, 2938, 2856, 2834, 1635, 1500, 1443, 1223, 1049, 1028, 752; δ_H (400 MHz, $CDCl_3$) 1.59 (1H, m), 1.49 (4H, bs), 2.57 (2H, m), 2.89 (2H, m), 3.35 (2H, bs), 3.54 (2H, bs), 3.74 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 6.69 (1H, dd, ^3J = 8.8 Hz, ^4J = 2.8 Hz), 6.75 (1H, d, ^4J = 2.8 Hz), 6.76 (1H, d, ^3J = 8.8 Hz); δ_C (67.8 MHz, $CDCl_3$) 24.5 (CH_2), 25.6 (bs, CH_2), 26.4 (bs, CH_2), 27.1 (CH_2), 33.7 (CH_2), 42.7 (bs, CH_2), 46.6 (bs, CH_2), 55.7 (OCH_3), 55.8 (OCH_3), 111.1 (CH), 111.4 (CH), 116.3 (CH), 130.8, 151.7 (C_{quat}), 153.5 (C_{quat}), 171.0 (Cquat, CO).

N-Pyrrolidinyl 3-(1,4-dimethoxyphen-2-yl) propionamide (43i)

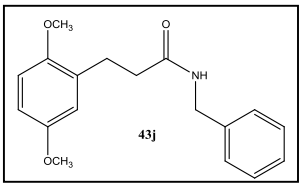


43i

As a colorless oil; (KBr/cm^{-1}) ν_{max} 2950, 2874, 2834, 1635 ($CONR_2$), 1501, 1442, 1224, 1047, 733; δ_H (400 MHz, $CDCl_3$) 1.79 – 1.89 (4H, m), 2.51 (2H, t, ^3J = 8.4 Hz), 2.92 (2H, t, ^3J = 8.4 Hz), 3.31 (2H, dd, ^3J = 6.8 Hz, ^3J = 6.8

Hz, ^3J = 6.8 Hz), 3.45 (2H, dd, ^3J = 6.8 Hz, ^3J = 6.8 Hz), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 6.69 (1H, dd, ^3J = 8.8 Hz, ^4J = 3.2 Hz), 6.75 (1H, d, ^3J = 8.8 Hz), 6.76 (1H, d, ^4J = 3.2 Hz); δ_C (100.5 MHz, $CDCl_3$) 24.4 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 35.1 (CH_2), 45.6 (CH_2), 46.5 (CH_2), 55.7 (OCH_3), 55.9 (OCH_3), 111.2 (CH), 111.5 (CH), 116.3 (CH), 131.0 (C_{quat}), 151.7 (C_{quat}), 153.5 (C_{quat}), 171.3 (C_{quat}, CO).

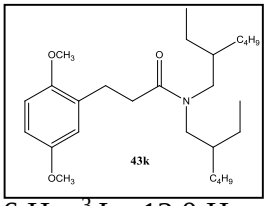
***N*-Benzyl 3-(1,4-dimethoxyphen-2-yl) propionamide (43j)**



43j

As a colorless solid;(KBr/cm^{-1}) ν_{max} 3600 - 3150, 3412, 3284, 2943, 2910, 2833, 1642, 1534, 1453, 1417, 1222, 1944, 807, 744, 698; δ_H (400 MHz, $CDCl_3$) 2.45 (2H, t, ^3J = 7.6 Hz), 2.88 (2H, t, ^3J = 7.6 Hz), 3.64 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 4.33 (2H, d, ^3J = 5.6 Hz), 5.78 (1H, bs, NH), 6.63 – 6.69 (3H, m), 7.08 – 7.11 (2H, m), 7.18 – 7.25 (3H, m); δ_C (100.5 MHz, $CDCl_3$) 24.6 (CH_2), 36.8 (CH_2), 43.6 (N<u>C</u>H_2), 55.7 (OCH_3), 55.8 (OCH_3), 111.3 (CH), 111.8 (CH), 116.2 (CH), 127.4 (CH), 127.7 (2C, CH), 128.6 (2C, CH), 130.0 (C_{quat}), 138.3 (C_{quat}), 151.4 (Cquat), 153.5 (Cquat), 172.3 (Cquat, CO).

N, N-Bis(2-ethylhexyl) 3-(1,4-dimethoxyphen-2-yl) propionamide (43k)



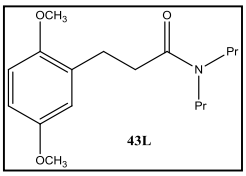
43k

As a colorless oil; ν_{max} (neat/cm^{-1}) 2958, 2930, 2872, 1643, 1501, 1464, 1224, 1052, 754; δ_H (400 MHz, $CDCl_3$) 0.83 – 0.89 (16H, m), 1.19 – 1.29 (20H, m), 1.50 – 1.65 (2H, m), 2.57 – 2.88 (2H, m), 2.90 (2H, d, ^3J = 9.0 Hz), 3.11 (2H, d, ^3J = 7.6 Hz), 3.24 (2H, ddd, ^2J = 7.6 Hz, ^3J = 12.0 Hz, ^4J = 2.0 Hz), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 6.69 (1H, dd, ^3J = 9.2 Hz, ^4J = 2.8 Hz), 6.75 (1H, d, ^3J = 9.2 Hz), 6.76 (1H, d, ^4J = 2.8 Hz); δ_C (67.8 MHz, $CDCl_3$, DEPT) 10.6 (CH_3), 10.9 (CH_3), 14.0(5) (CH_3), 14.1 (CH_3), 23.0 (CH_2), 23.1 (CH_2), 23.7(5) (CH_2),

23.8 (CH_2), 27.5 (CH_2), 28.7 (CH_2), 28.7 (5) (CH_2), 30.4 (CH_2), 30.5 (CH_2), 33.7 (CH_2), 36.9 (CH), 38.4 (CH), 48.7 (NCH_2), 51.4 (NCH_2), 55.6 (OCH_3), 55.7 (OCH_3), 110.9 (CH), 111.5 (CH), 116.4 (CH), 130.8 (C_{quat}), 151.7 (C_{quat}), 153.4 (C_{quat}), 173.3 (C_{quat}, CO).

***N*, *N*-Di(*n*-propyl) 3-(1,4-dimethoxyphen-2-yl) propionamide** (**43L**)

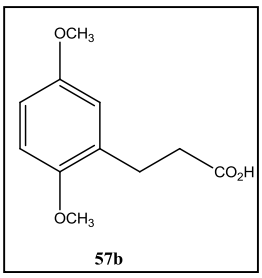
As a colorless oil; ν_{max} neat/cm^{-1}) 2965, 1638, 1502, 1466, 1224, 1051, 802; δ_H (400 MHz, $CDCl_3$) 0.86 (6H, t, ^3J = 7.2 Hz, 2 CH_3), 1.48 – 1.54 (4H, m), 2.55 (2H, t, ^3J = 8.0 Hz), 2.91 (2H, t, ^3J = 8.0 Hz), 3.14 (2H, t, ^3J = 7.6 Hz), 3.25 (2H, t, ^3J = 7.6 Hz), 3.74 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 6.69 (1H, dd, ^3J = 6.8 Hz, ^4J = 2.8 Hz), 6.75 (1H, d, ^3J = 6.8 Hz), 6.77 (1H, d, ^4J = 2.8 Hz); δ_C (67.8 MHz, $CDCl_3$) 11.2 (CH_3), 11.4 (CH_3), 21.0 (CH_2), 21.2 (CH_2), 27.4 (CH_2), 33.4 (CH_2), 47.6 (NCH_2), 49.6 (NCH_2), 55.6(5) (OCH_3), 55.7 (OCH_3), 111.0 (CH), 111.5 (CH), 116.4 (CH), 130.8 (Cquat), 151.7 (Cquat), 153.4 (Cquat), 172.4 (Cquat, CO).



43L

3-(2,5-Dimethoxyphenyl) propionic acid (**57b**).

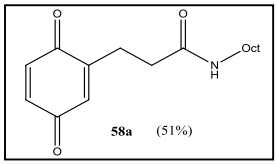
Ethyl 3-(2,5-dimethoxyphenyl) propionate (**27b**, 3.2 g, 13.4 mmol) in a mixture of aq. NaOH (10 w%, 30 mL) and methanol (8 mL) was heated at reflux for 12h. Then, half. conc. aq. HCl is added to the cooled solution. Thereafter, the mixture is extracted with chloroform (3 X 15 mL). The organic phase is dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue is filtered over a small column of silica gel (ether-$CHCl_3$, 1:1, v/v) to give compound **27b** (2.56 g, 89%) as colorless needles, MP. 66 – 67 ^oC [Lit. MP. 66 – 67 ^oC]; ν_{max} (KBr/cm^{-1}) 3500 – 2050 (bs, OH), 2955, 2835, 1699, 1504, 1449, 1430, 1307, 1281, 1182, 1127, 927, 916, 865, 795, 717, 499; δ_H (400 MHz, $CDCl_3$) 2.65 (2H, t, ^3J = 7.6 Hz), 2.91 (2H,



57b

t, ^3J = 7.6 Hz), 6.71 (1H, dd, ^3J = 8.4 Hz, ^4J = 3.2 Hz), 6.75 (1H, d, ^4J = 3.2 Hz), 6.76 (1H, d, ^3J = 8.4 Hz), δ_C (67.8 MHz, $CDCl_3$) 26.0 (CH_2), 33.9 (CH_2), 55.6 (OCH_3), 55.7 (OCH_3), 111.0, 111.6, 116.3, 129.6, 151.7 (C_{quat}), 153.3 (C_{quat}), 179.7 (C_{quat}, CO).

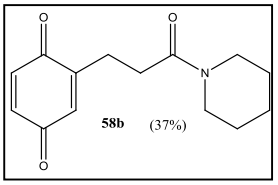
***N*-Octylcarboxamidoethyl-*p*-benzoquinone** (**58a**).



58a (51%)

To compound **43g** (442 mg, 1.32 mmol) in acetonitrile (15 mL) was added dropwise and at RT and within 15 min. a solution of CAN (2.23 g, 8.14 mmol) in H_2O (15 mL). The resulting mixture was stirred for an additional 5 min. at RT. Thereafter, water was added and the mixture was extracted with CH_2Cl_2 (3 X 15 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to chromatographic separation on silica gel (CH_2Cl_2/Et_2O 8:2) to give compound **58a** (206 mg, 51%) as a yellow solid, MP. 111-113^{o}C ν_{max} (KBr/cm^{-1}) 3331 (vs, NH), 3052, 2954, 2924, 2851, 1655 (CO), 1537, 1427, 1311, 1131, 921, 837, 427; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, ^3J = 6.8 Hz, CH_3), 1.19 – 1.22 (10H, m), 1.37 – 1.42 (2H, m), 2.34 (2H, t, ^3J = 7.6 Hz), 2.71 (2H, dt, ^3J = 7.6 Hz, ^4J = 1.6 Hz), 3.16 (2H, dt, ^3J = 7.2 Hz, J = 7.2 Hz), 5.53 (1H, bs, NH), 6.55 – 6.56 (1H, m), 6.65 (1H, dd, ^3J = 10.0 Hz, ^4J= 2.4 Hz), 6.70 (1H, d, ^3J = 10.0 Hz); δ_C (67.8 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 25.3 (CH_2), 26.9 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.6 (CH_2), 31.8 (CH_2), 34.3 (CH_2), 39.7 (CH_2), 133.1 (CH), 136.4 (CH), 136.7 (CH), 147.8 (Cquat), 170.7 (Cquat, CONH), 187.4 (Cquat, CO), 187.5 (Cquat, CO).

N-Piperidinylcarboxamidoethyl-*p*-benzoquinone (**58b**).

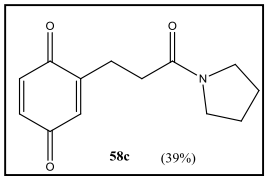


58b (37%)

To compound **43h** (450 mg, 1.64 mmol) in acetonitrile (15 mL) was added dropwise and at RT and within 15 min. a solution of

CAN (2.74 g, 10 mmol) in H_2O (15 mL). The resulting mixture was stirred for an additional 5 min. at rt. Thereafter, water was added and the mixture was extracted with CH_2Cl_2 (3 X 15 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to chromatographic separation on silica gel ($CHCl_3$/ Et_2O/ hexane 1:1:1) to give compound **58b** (169 mg, 37 [5] %) as a yellow-orange solid, MP. 105-106 ^oC; ν_{max} (KBr/cm^{-1}) 3049, 3017, 2918, 2848, 1656, 1598, 1455, 1429, 1299, 1216, 1012, 915, 855, 834, 428; δ_H (400 MHz, $CDCl_3$)1.51 (4H, bm), 1.58 – 1.64 (2H, m), 2.53 (2H, t, ^3J = 6.8 Hz), 2.73 (2H, t, ^3J = 6.8 Hz, ^4J = 1.2 Hz), 3.38 (1H, bs), 3.49 (1H, bs), 6.58 (1H, m), 6.67 (1H, d, ^3J = 10 Hz, ^4J = 1.2 Hz), 6.72 (1H, d, ^3J = 10 Hz); δ_C (67.8 MHz, $CDCl_3$) 24.4 (2C, CH_2), 25.2 (CH_2), 25.5 (bs, CH_2), 26.4 (bs, CH_2), 31.3 (CH_2), 42.8 (bs, CH_2), 46.2 (bs, CH_2), 133.1 (CH), 136.3 (CH), 136.8 (CH), 148.5 (C_{quat}), 169.1 (C_{quat}, CON), 187.5 (C_{quat}, CO), 187.6 (Cquat, CO).

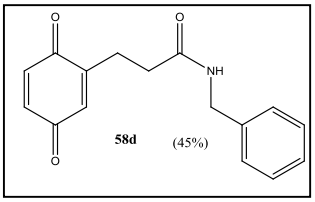
N-Pyrrolidinylcarboxamidoethyl-*p*-benzoquinone (**58c**).



58c (39%)

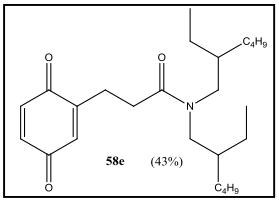
Reacted according to the preparation of compound **58a**: light brown solid; (KBr/cm^{-1}) ν_{max} 3054, 2953, 2874, 1660, 1442, 1328, 1295, 1035, 989, 916, 753, 427; δ_H (400 MHz, $CDCl_3$) 1.81 – 1.86 (2H, m), 1.90 – 1.96 (2H, m), 2.49 (2H, d, ^3J = 7.2 Hz), 2.77 (2H, t, ^3J = 7.2 Hz), 3.38 (2H, t, ^3J = 6.4 Hz), 3.44 (2H, t, ^3J = 7.2 Hz), 6.58 (1H, m), 6.67 (1H, d, ^3J = 10 Hz, ^4J = 1.2 Hz), 6.72 (1H, d, ^3J = 10 Hz); δ_C (100.5 MHz, $CDCl_3$) 24.3 (CH_2), 24,6 (CH_2), 26.1 (CH_2), 32.6 (CH_2), 45.8 (CH_2), 46.5 (CH_2), 133.1 (CH), 136.3 (CH), 136.8 (CH), 148.5 (C_{quat}), 169.5 (C_{quat}, CON), 187.5 (C_{quat}, CO), 187.6 (C_{quat}, CO).

***N*-Benzyl carboxamidoethyl-*p*-benzoquinone** (**58d**).



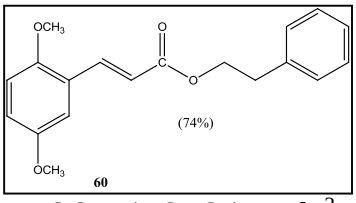
Reacted analogous to the preparation of compound **58a**: light brown solid; (KBr/cm^{-1}) ν_{max} 3299, 2927, 1670, 1660, 1530, 1295, 1219, 1073, 930, 754, 697, 578; δ_C (100.5 MHz, $CDCl_3$) 25.3 (CH_2), 34.2 (CH_2), 43.7 (NCH_2), 127.6 (CH), 127.8 (2C, CH), 128.8 (2C, CH), 132.2 (CH), 136.4 (CH), 136.7 (CH), 137.9 (C_{quat}), 147.7 (C_{quat}), 170.7 (C_{quat}, CONH), 187.3 (C_{quat}, CO), 187.4 (Cquat, CO).

N, N-Bis(2-ethylhexyl)carboxamidoethyl-*p*-benzoquinone (**58e**).



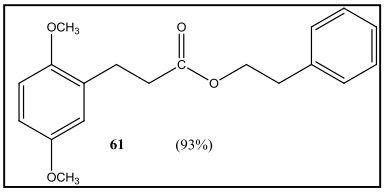
To compound **43k** (417 mg, 0.96 mmol) in CH_3CN (11 mL) was added dropwise a solution of CAN (1.63 g, 5.94 mmol) in H_2O (11 mL). The resulting solution was stirred for 15 min. at RT. Then, water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3X25 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography on silica gel (CH_2Cl_2-ether 10:1) gave compound **58e** (165 mg, 43%) as a yellow oil; ν_{max} (neat/cm^{-1}) 2931, 1658, 1463, 1380, 1291, 1220, 1129, 1080, 903; δ_H (400 MHz, $CDCl_3$) 0.81 – 0.87 (16H, m), 1.13 – 1.24 (20H, m), 1.58 (2H, m), 2.55 (2H, t, ^3J = 7.2 Hz), 2.76 (2H, dt, ^3J = 7.2 Hz, ^4J = 2.4 Hz), 3.11 (2H, d, ^2J = 7.6 Hz), 3.23 (2H, ddd, ^2J = 7.6 Hz, ^3J = 12.0 Hz, ^4J = 2.0 Hz), 6.59 (1H, m), 6.68 (1H, dd, ^3J = 10.0 Hz, ^4J = 2.4 Hz), 6.73 (1H, d, ^3J = 10.0 Hz); δ_C (67.8 MHz, $CDCl_3$) 10.6 (CH_3), 10.9 (CH_3), 14.0 (CH_3), 14.1 (CH_3), 23.0 (CH_2), 23.1 (CH_2), 23.7(5) (CH_2), 23.8 (CH_2), 25.5 (CH_2), 28.6 (CH_2), 28.7 (CH_2), 30.4 (CH_2), 30.5 (CH_2), 31.4 (CH_2), 36.9 (CH), 38.3 (CH), 48.8 ($N\underline{C}H_2$), 51.3 ($N\underline{C}H_2$), 133.2 (CH), 136.3 (CH), 136.7 (CH), 148.4 (C_{quat}), 171.3 (C_{quat}, $\underline{C}ON$), 187.5 (C_{quat}, CO), 187.6 (C_{quat}, CO).

2-Phenylethyl 1,4-dimethoxy-2-cinnamate (**60**)



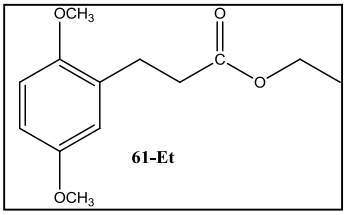
As a yellow oil; ν_{max} (neat/cm^{-1}) 1720, 1496, 1454, 1221, 1164, 1046; δ_H (400 MHz, $CDCl_3$) 3.01 (2H, t, ^3J = 6.8 Hz), 3.78 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.41 (2H, t, ^3J = 6.8 Hz), 6.46 (1H, d, ^3J = 16.0 Hz), 6.84 (1H, d, ^3J = 9.2 Hz), 6.90 (1H, dd, ^3J = 9.2 Hz, ^4J = 3.2 Hz), 7.03 (1H, d, ^4J = 3.2 Hz), 7.21 – 7.33 (5H, m), 7.96 (1H, d, ^3J = 16.0 Hz); δ_C (67.8 MHz, $CDCl_3$) 33.2 (CH_2), 55.8 (OCH_3), 56.1 (OCH_3), 64.9 (OCH_2), 112.4 (CH), 113.2 (CH), 117.1 (CH), 118.6 (CH), 123.9 (C_{quat}), 126.5 (CH), 128.5 (2C, CH), 129.0 (2C, CH), 137.9 (Cquat), 140.0 (CH), 152.8 (Cquat), 153.4 (Cquat), 167.3 (Cquat, CO).

2-Phenylethyl 1,4-dimethoxy-2-phenylpropionate (**61**)



As a colorless oil; ν_{max} (neat/cm^{-1}) 1731, 1501, 1224, 1157, 1048; δ_H (400 MHz, $CDCl_3$) 2.54 (2H, t, ^3J = 7.6 Hz), 2.84 (2H, t, ^3J = 7.6 Hz), 2.87 (2H, t, ^3J = 7.2 Hz), 3.69 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 4.23 (2H, t, ^3J = 7.2 Hz), 6.65(5) (1H, d, ^3J = 8.4 Hz), 6.67 (1H, s), 6.71 (1H, d, ^3J = 8.4 Hz), 7.19 - 7.32 (5H, m); δ_C (67.8 MHz, $CDCl_3$) 26.2 (CH_2), 34.2 (CH_2), 35.1 (CH_2), 55.7 (OCH_3), 55.7(5) (OCH_3), 64.9 (OCH_2), 111.0 (CH), 111.4 (CH), 126.3 (CH), 126.5 (CH), 128.5 (2C, CH), 128.9 (2C, CH), 130.0 (C_{quat}), 137.9 (C_{quat}), 151.7 (C_{quat}), 153.3 (C_{quat}), 173.2 (Cquat, CO).

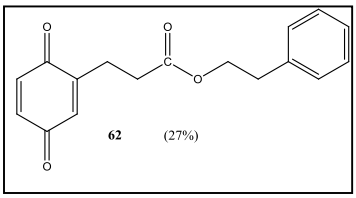
Ethyl 3-(1,4-dimethoxyphen-2-yl) propionate (**61-Et**)



As a colorless oil; (KBr/cm^{-1}) ν_{max} 2937, 2834, 1732, 1591, 1502, 1464, 1372, 1224, 1123, 1049, 867, 803, 710; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, ^3J = 7.2 Hz), 2.58 (2H, t, ^3J = 8.0 Hz), 2.90 (2H, t, ^3J = 8.0 Hz), 3.74 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.11 (2H, q, ^3J =

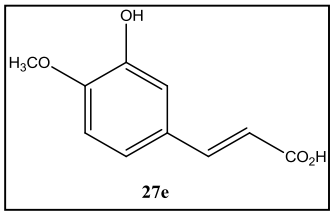
7.2 Hz), 6.69 (1H, dd, ^3J = 8.8 Hz, ^4J = 2.8 Hz), 6.73 (1H, d, ^4J = 2.8 Hz), 6.75 (1H, d, ^3J = 8.8 Hz); δ_C (100.5 MHz, $CDCl_3$) 14.2 (CH_3), 26.2 (CH_2), 34.2 (CH_2), 55.6 (OCH_3), 55.7 (OCH_3), 60.3 (OCH_2), 111.0 (CH), 111.4 (CH), 116.3 (CH), 130.0 (C_{quat}), 151.7 (C_{quat}), 153.3 (C_{quat}), 173.3 (C_{quat}, CO).

2-Phenylethoxycarbonylethyl-*p*-benzoquinone (**62**)



As a dark orange solid; MP. 43 – 44 ^oC; ν_{max} (KBr/cm^{-1}) 3060, 2964, 1736, 1666, 1598, 1303, 1183, 1170, 1091, 701, 428; δ_H (400 MHz, $CDCl_3$) 2.54 (2H, t, ^3J = 7.2 Hz), 2.69 – 2.73 (2H, m), 2.91 (2H, t, ^3J = 7.2 Hz), 4.29 (2H, t, ^3J = 7.2 Hz), 6.52 (1H, m), 6.69 (1H, dd, ^3J = 10.4 Hz, ^4J = 2.4 Hz), 6.74 (1H, d, ^3J = 10.4 Hz), 7.17 – 7.31 (5H, m); δ_C (67.8 MHz, $CDCl_3$) 24.5 (CH_2), 31.9 (CH_2), 35.0 (CH_2), 65.2 (OCH_2), 126.6 (CH), 128.5 (2C, CH), 128.8 (2C, CH), 133.0 (CH), 136.6 (CH), 136.7 (CH), 137.6 (C_{quat}), 147.4 (C_{quat}), 171.8 (Cquat, CO), 187.1 (Cquat, CO), 187.4 (Cquat, CO).

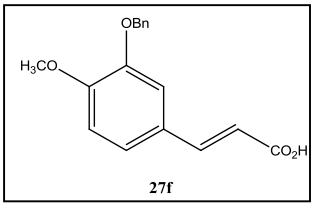
3-Hydroxy-4-methoxycinnamic acid (**27e**).



A solution of ethyl 3-hydroxy-4-methoxycinnamate (**28a**, 3.65 g, 16.4 mmol) in a mixture of aq. NaOH (5g NaOH in 50 mL H_2O) and CH_3OH (10 mL) was stirred at 95 ^oC for 14h. The cooled solution was acidified with half-conc. aq. HCl and extracted with $CHCl_3$ (3 X 35 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give compound **27e** (2.83 g, 89%) as a colorless solid, MP. 235 ^oC [Lit. 230 – 232 ^oC (Prachayasittikul et al. 2009)]; ν_{max} (KBr/cm^{-1}) 3404 (bs, OH), 3200 – 2587 (bs, OH), 2943, 2846, 1671 (CO), 1629, 1514, 1443, 1322, 1265, 1208, 1136, 1024, 947, 857, 817, 762, 572, 506; δ_H (400

MHz, $CDCl_3$) 3.93 (3H, s, OCH3), 6.28 (1H, d, ^3J = 16.0 Hz), 6.85 (1H, d, ^3J = 8.4 Hz), 7.05 (1H, dd, ^3J = 8.4 Hz, ^4J = 2.4 Hz), 7.15 (1H, d, ^4J = 2.4 Hz), 7.67 (1H, d, ^3J = 16.0 Hz).

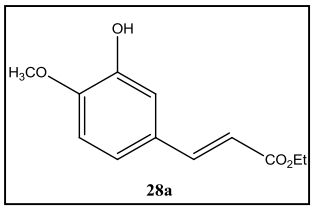
(*E*)-3-Benzyloxy-4-methoxycinnamic acid (**27f**).



27f

A suspension of **28b** (2.65 g, 8.5 mmol) in a mixture of aq. NaOH (3.5 g NaOH in 35 mL H_2O), EtOH (10 mL) and MeOH (10 mL) was stirred at 90 ^oC for 12h.The cooled solution was acidified with half-conc. aq. HCl. Thereafter, the mixture was extracted with $CHCl_3$ (3 X 35 mL). The organic extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give compound **27f** (1.75 g, 73%) as a colorless solid; ν_{max} (KBr/cm^{-1}) 3550 – 2450 (bs, OH), 2942, 1679, 1624, 1593, 1519, 1266, 1138, 1012, 849, 807, 741, 699; δ_H (400 MHz, $CDCl_3$) 3.91 (3H, s, OCH_3), 5.17 (2H, s, OCH_2), 6.22 (1H, d, ^3J = 16.0 Hz), 6.88 (1H, d, ^3J = 8.0 Hz), 7.08 (1H, d, ^4J = 1.6 Hz), 7.13 (1H, dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz), 7.29 – 7.48 (5H, m), 7.64 (1H, d, ^3J = 16.0 Hz); δ_C (67.8 MHz, $CDCl_3$) 56.0 (OCH_3), 71.0 (OCH_2), 111.4 (CH), 112.5 (CH), 114.7 (CH), 123.4 (CH), 127.3 (2C, CH), 128.1 (CH), 128.7 (2C, CH), 132.1 (Cquat), 136.5 (Cquat), 146.8 (CH), 148.3 (Cquat), 152.1 (Cquat), 171.5 (Cquat, CO).

A mixture of ethyl (*E/Z*)-3-hydroxy-4-methoxycinnamates (**28a**).

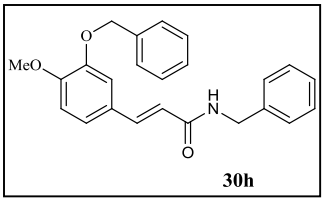


28a

A mixture of 3-hydroxy-4-methoxybenzaldehyde (**24a**, 1.39 g, 9.14 mmol) and ethoxycarbonylmethylidenetriphenyl phosphorane (4.44 g, 12.8 mmol) was heated under stirring at 135 ^oC for 90 min. The reaction took place in a melt of the mixture. After the reaction, the mixture was subjected directly to column chromatography on silica gel (CH_2Cl_2) to

give compound **28a** (1.30 g, 64%) as a colorless oil; ν_{max} (neat/cm^{-1}) 3550 – 3100 (bs, OH), 2980, 2842, 1699, 1633, 1583, 1513, 1441, 1266, 1179, 1132, 857, 806, 762, 724, 695; δ_H (400 MHz, $CDCl_3$) for *E* - **28a**: 1.31 (3H, t, ^3J = 7.2 Hz, CH_3), 3.90 (3H, s, OCH_3), 4.23 (2H, q, ^3J = 7.2 Hz, OCH_2), 6.27 (1H, d, ^3J = 16.0 Hz), 6.82 (1H, d, ^3J = 8.8 Hz), 7.01 (1H, dd, ^3J = 8.8 Hz, ^4J = 1.6 Hz), 7.12 (1H, d, ^4J = 1.6 Hz), 7.57 (1H, d, ^3J = 16.0 Hz); for *Z*-**28a**: 1.26 (3H, t, ^3J = 7.2 Hz, CH_3), 3.89 (3H, s, OCH_3), 4.18 (2H, q, ^3J = 7.2, OCH_2), 5.81 (1H, d, ^3J = 13.2 Hz), 6.78 (1H, d, ^3J = 13.2 Hz), 6.80 (1H, d, ^3J = 8.8 Hz), 7.21 (1H, dd, ^3J = 8.8 Hz, ^4J = 2.0 Hz), 7.30 (1H, d, ^4J = 2.0 Hz); δ_C (67.8 MHz, $CDCl_3$) for *E*-**28a**: 14.3 (CH_3), 56.0 (OCH_3), 60.4 (OCH_2), 110.5 (CH), 112.8 (CH), 116.3 (CH), 121.8 (CH), 128.0 (C_{quat}), 144.4 (CH), 145.8 (Cquat), 148.4 (Cquat), 167.3 (Cquat, CO).

N-Benzyl (*E*)-3-benzyloxy-4-methoxycinnamamide (**30h**).

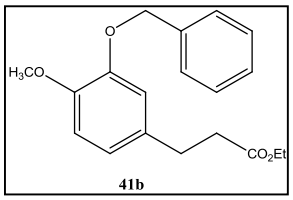


30h

A solution of triphenylphosphine (PPh_3, 980 mg, 3.74 mmol) and $BrCCl_3$ (775 mg, 3.91 mmol) in CH_3CN (10 mL) was stirred for 35 min. at RT, during which the solution became yellow-brown in color. Then, (*E*)-3-benzyloxy-4-methoxycinnamic acid (860 mg, 3.03 mmol) was added as a solid to the solution. The solution was stirred at 75 ^oC for 45 min. Then, benzylamine (800 mg, 7.48 mmol) was added drop-wise via syringe. The mixture was stirred for a further 14 hr at 75 ^oC. The cooled solution was evaporated *in vacuo* to dryness. The residue was submitted to column chromatography on silica gel (ether/$CHCl_3$ 1:1) to give compound **30h** (1.12 g, quant) as a colorless solid, MP. 162 ^oC; ν_{max} (KBr/cm^{-1}) 3412 (NH), 3312 (NH), 3064, 2917, 2870, 1651, 1620, 1515, 1259, 1134, 1012, 974, 751, 697; δ_H (400 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 4.52 (2H, s, NCH_2), 5.11 (2H, s, OCH_2), 5.98 (1H, m, NH), 6.21 (1H,

d, ^3J = 15.6 Hz), 6.84 (1H, d, ^3J = 8.4 Hz), 7.01 (1H, d, ^4J = 2.0 Hz), 7.06 (1H, dd, ^3J = 8.4 Hz, ^4J = 2.0 Hz), 7.25 – 7.42 (10H, m), 7.53 (1H, d, ^3J = 15.6 Hz); δ_C (67.8 MHz, $CDCl_3$) 43.8 (NCH_2), 56.0 (OCH_3), 71.0 (OCH_2), 111.5 (CH), 112.6 (CH), 118.2 (C_{quat}), 122.3 (CH), 127.3 (2C, CH), 127.5 (CH), 127.6 (C_{quat}), 127.9 (2C, CH), 128.0 (2C, CH), 128.6 (2C, CH), 128.7 (2C, CH), 136.7 (C_{quat}), 138.3 (C_{quat}), 141.2 (CH), 148.2 (CH), 151.2 (C_{quat}), 166.0 (C_{quat}, CO).

Ethyl 3-benzyloxy-4-methoxypropionate (**41b**).

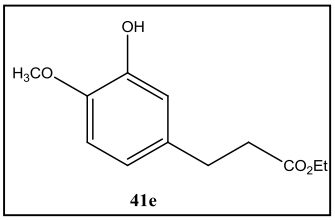


41b

To compound **28b** (3.20 g, 10.3 mmol) in toluene (20 mL) was added Pd/C (Aldrich 205680) (200 mg, 5 wt%) and AcOH (350 mg). Thereafter, finely ground $NaBH_4$ (500 mg) was added. After the mixture was stirred for 24h at RT, water (5 mL) was added slowly (drop-wise). Thereafter, half conc. HCl (3 mL) was added. The mixture was poured into water (70 mL) and extracted with $CHCl_3$ (3 X 30 mL). The separated organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was subjected to column chromatography on silica gel (eluent CH_2Cl_2) to give ethyl 3-benzyloxy-4-methoxypropionate (**41b**, 1.80 g, 56%) as a colorless solid; ν_{max} (KBr/cm^{-1}) 1731, 1515; δ_H (400 MHz, $CDCl_3$)1.22 (3H, t, ^3J = 7.2 Hz, CH_3), 2.53 (2H, t, ^3J = 7.2 Hz), 2.81 (2H, t, ^3J = 7.2 Hz), 3.85 (3H, s, OCH_3), 4.09 (2H, q, ^3J = 7.2 Hz, OCH_2), 5.11 (2H, s, OCH_2), 6.74 (2H, d, ^3J = 8.8 Hz), 6.80 (2H, d, ^3J = 8.8 Hz), 7.29 – 7.44 (5H, m); δ_C (67.8 MHz, $CDCl_3$) 14.2 (CH_3), 30.5 (CH_2), 36.1 (CH_2), 56.1 (OCH_3), 60.4 (OCH_2), 71.0 (OCH_2), 111.8 (CH), 114.4 (CH), 120.8 (CH), 127.3 (2C, CH), 127.8 (CH), 128.5 (3C, 2CH, C_{quat}), 133.1 (C_{quat}), 137.1 (C_{quat}), 148.0 (C_{quat}), 148.1 (C_{quat}), 173.0 (C_{quat}, CO), and ethyl 3-hydroxy-4-methoxypropionate (960 mg) (eluent:

CH_2Cl_2-ether 10:1) as a colorless solid, MP. 72 ^oC; ν_{max} (KBr/cm^{-1}) 3380 (bs, OH), 2981, 2960, 1727 (CO), 1588, 1517, 1300, 1270, 1179, 1147, 1126, 1007, 876, 804; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, ^3J = 7.2 Hz, CH_3), 2.56 (2H, t, ^3J = 8.0 Hz), 2.84 (2H, t, ^3J = 8.0 Hz), 4.11 (2H, q, ^3J = 7.2 Hz, OCH_2), 5.55 (1H, bs, OH), 6.65 (1H, dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 6.75 (1H, d, ^3J = 8.0 Hz), 6.76 (1H, d, ^4J = 2.0 Hz); δ_C (67.8 MHz, $CDCl_3$) 14.2 (CH_3), 30.4 (CH_2), 36.1 (CH_2), 56.0 (OCH_3), 60.4 (OCH_2), 110.6 (CH), 114.5 (CH), 119.6 (CH), 133.9 (C_{quat}), 145.0 (C_{quat}), 145.5 (C_{quat}), 173.0 (C_{quat}, CO). The reaction was carried out with 500 mg (1.60 mmol) starting material, 100 mg Pd/C (5 wt%), 255 mg AcOH, and 310 mg $NaBH_4$ in toluene (10 mL) to give the product in 87% yield.

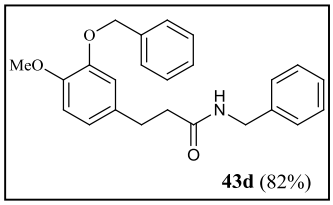
Ethyl 3-hydroxy-4-methoxypropionate (**41e**).



41e

To compound **28a** (960 mg, 4.32 mmol) in a solvent mixture of toluene (10 mL) and THF (5 mL) was added Pd/C (Aldrich 205680) (150 mg, 5 wt%) and AcOH (560 mg). Thereafter, finely ground $NaBH_4$ (680 mg) was added. After the mixture was stirred for 24h at RT, water (5 mL) was added slowly (dropwise). Thereafter, half conc. HCl (3 mL) was added. The mixture was poured into water (70 mL) and extracted with $CHCl_3$ (3 X 30 mL). The separated organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was subjected to column chromatography on silica gel (eluent CH_2Cl_2/Et_2O 10:1) to give ethyl 3-hydroxy-4-methoxypropionate (960 mg, quant.).

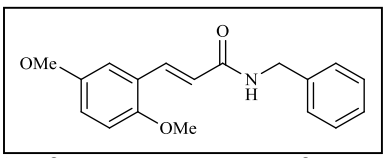
***N*-Octyl 3-benzyloxy-4-methoxypropionamide** (**43d**).



43d (82%)

A solution of triphenylphosphine (PPh_3, 1.06 g, 4.05 mmol) and bromotrichloromethane ($BrCCl_3$, 808 mg, 4.08 mmol) in dry CH_2Cl_2 (15 mL) was stirred at RT for 35 min., during which time the solution turned orange-brownish. Thereafter, 3-benzyloxy-4-methoxy phenylpropionic acid (**57a**, 1.0 g) was added (as a solid), and the mixture was stirred at reflux for 40 min. Then, *n*-octylamine (905 mg, 7.00 mmol) was added via syringe, and the resulting mixture was stirred at reflux for 14h. Then, the cooled solution was subjected to column chromatography on a silica gel (CH_2Cl_2/ether 40/3) to give compound **43d** (1.09 g, 62%) as a colourless solid, MP. 116- 188 ºC; ν_{max} (KBr/cm^{-1}) 3328 (s), 3038, 2953, 2929, 2850, 1642 (CO), 1536, 1516, 1255, 1136, 1017, 749, 700; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, ^3J = 6.8 Hz, CH_3), 1.34-1.37 (2H, m), 1.23-1.28 (10H, m), 2.37 (2H, t, ^3J = 7.6 Hz), 2.84 (2H, t, ^3J = 7.6 Hz), 3.10 – 3.15 (2H, m, NCH_2), 3.83 (3H, s, OCH_3), 5.12 (2H, s, OCH_2), 5.38 (1H, bs, NH),6.73 (1H, d, ^4J = 2.0 Hz), 6.73(5) (1H, dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 6.78 (1H, d, ^3J = 8.0 Hz), 7.28 – 7.44 (5H, m); δ_C (67.8 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 26.8 (CH_2), 29.2 (CH_2), 29.2(5) (CH_2), 29.5 (CH_2), 31.4 (CH_2), 31.8 (CH_2), 38.6 (CH_2), 39.6 (CH_2), 56.0 (OCH_3), 70.9 (OCH_2), 111.8 (CH), 114.3 (CH), 120.9 (CH), 127.4 (2C, CH), 127.8 (CH), 128.5 (2C, CH), 133.2 (C_{quat}), 137.2 (C_{quat}), 148.0 (C_{quat}), 148.1 (C_{quat}), 172.3 (C_{quat}, CO).

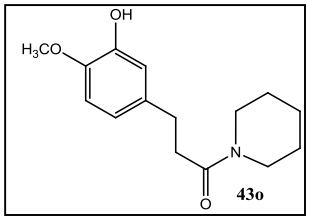
***N*-Benzyl 2,5-dimethoxycinnamamide**.



A mixture of PPh_3 (720 mg, 2.75 mmol) and CCl_4 (465 mg, 3.03 mmol) in CH_2Cl_2 (10 mL) was stirred at 45 ºC for 40 min. Thereafter, 2,5-dimethoxycinnamic acid (500 mg, 2.40 mmol, solid) was added to the mixture, and the

ensuing reaction mixture was stirred at 75 ^{o}C for 45 min. Then, benzylamine (515 mg, 4.81 mmol) was added dropwise, and the mixture was stirred additional 14h. The cooled mixture was subjected directly to column chromatography on silica gel (CH_2Cl_2, then CH_2Cl_2-ether 3:1) to give *N*-benzyl 2,5-dimethoxycinnamide (610 mg) as a colourless solid; MP. 104 ^{o}C; ν_{max} (KBr/cm^{-1}) 3288 (s, NH), 3076, 2989, 2923, 2831, 1652, 1615, 1556, 1496, 1214, 1042, 849, 711, 700; δ_H (400 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.57 (2H, d, ^3J = 6.0 Hz), 5.87 (1H, bs, NH), 6.52 (1H, d, ^3J = 15.6 Hz), 6.82 (1H, d, ^3J = 9.2 Hz), 6.86 (1H, dd, ^3J = 9.2 Hz, ^4J = 2.4 Hz), 6.99 (1H, d, ^4J = 2.4 Hz), 7.24 – 7.34 (5H, m), 7.85 (1H, d, ^3J = 15.6 Hz); δ_C (67.8 MHz, $CDCl_3$) 43.8 (NCH_2), 55.7 (OCH_3), 56.0 (OCH_3), 112.3 (CH), 113.9 (CH), 116.1 (CH), 121.6 (CH), 124.3 (C_{quat}), 127.6 (CH), 128.0 (2C, CH), 128.7 (2C, CH), 136.7 (CH), 138.3 (C_{quat}), 152.7 (C_{quat}), 153.4 (C_{quat}), 166.2 (C_{quat}, NCO).

***N*-Piperidinyl 3-hydroxy-4-methoxypropionamide** (**43o**).

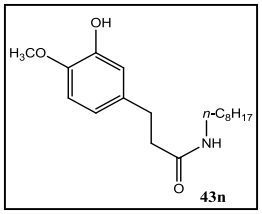


43o

A mixture of *N*-piperidinyl 3-benzyloxy-4-methoxy-propionamide (540 mg, 1.53 mmol), Pd/C (100 mg, Aldrich 205680, 5 wt%) in toluene (10 mL) and AcOH (270 mg) was added finely ground $NaBH_4$ (300 mg, 7.5 mmol). The resulting reaction mixture was stirred at RT for 24 h. Thereafter, AcOH (270 mg) was added. After 36 hr, further $NaBH_4$ (250 mg) and AcOH (300 mg) were added. After 48h, the reaction was stopped by adding dropwise H_2O (5 mL), thereafter half conc. aq. HCl (3 mL). The mixture was taken up with H_2O (25 mL). The mixture was extracted with CH_2Cl_2 (3 X 25 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to dryness. Column chromatography of the residue on silica gel (ether/CH_2Cl_2 1:2) gave compound **43o** (320

mg, 87%) as a slowly crystallizing oil; ν_{max} (neat/cm^{-1}) 2937, 2855, 1618, 1509, 1442, 1271, 1130, 1028; δ_H (400 MHz, $CDCl_3$) 1.46 – 1.51 (4H, m), 1.57 – 1.61 (2H, m), 2.58 – 2.65 (2H, m), 2.83 – 2.89 (2H, m), 3.49 (bs, 2H), 3.85 (3H, s, OCH_3), 6.68 – 6.81 (3H, m); δ_C (67.8 MHz, $CDCl_3$) 24.4, 26.0 (vbs), 31.1, 34.9, 43.0 (vbs), 46.2 (vbs), 56.0, 110.7, 114.5, 119.8, 134.3, 144.9(5), 145.5, 170.9 (C_{quat}, NCO).

***N*-Octyl 3-hydroxy-4-methoxypropionamide** (**43n**).



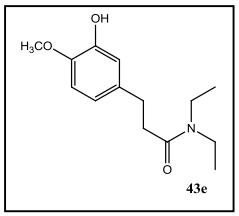
43n

To a mixture of *N*-octyl 3-benzyloxy-4-methoxy propion amide (1.06 g, 2.67 mmol), Pd/C (210 mg, Aldrich 205680, 5 wt%) in toluene (10 mL) and THF (5 mL) and AcOH (560 mg) was added finely ground $NaBH_4$ (400 mg, 10 mmol). The resulting reaction mixture was stirred atRTfor 24 h. Thereafter, AcOH (300 mg) was added; a further amount of AcOH (250 mg) was added after 48h. After 72 hr., further $NaBH_4$ (250 mg) and AcOH (300 mg) were added. Further AcOH (300 mg) was added to the mixture after 85 hr. After 96 hr., the reaction was stopped by adding dropwise H_2O (5 mL), thereafter half conc. aq. HCl (3 mL). The mixture was taken up with H_2O (25 mL) and extracted with ethyl acetate (25 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (first CH_2Cl_2 to remove residual toluene, then CH_2Cl_2/ether 3:1) to give *N*-octyl 3-hydroxy-4-methoxypropionamide (**43n**, 600 mg, 73%) as a colorless solid, MP. 125 ^oC; ν_{max} (KBr/cm^{-1}) 3513, 3302, 2957, 2924, 2850, 1640, 1537, 1518, 1283, 1223, 1023, 863, 807; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, ^3J = 6.8 Hz, CH_3), 1.23 – 1.29 (10H, m), 1.36 – 1.43 (2H, m), 2.42 (2H, t, ^3J = 7.6 Hz), 2.85 (2H, t, ^3J = 7.6 Hz), 3.15 – 3.20 (2H, m), 3.84 (3H, s, OCH_3), 5.46 (1H, bs), 6.65 (1H, dd, ^3J =

8.0 Hz, ^4J = 2.0 Hz), 6.75 (1H, d, ^3J = 8.0 Hz), 6.76 (1H, d, ^4J = 2.0 Hz); δ_C (67.8 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 26.8 (CH_2), 29.2 (CH_2), 29.

.2(5) (CH_2), 29.5 (CH_2), 31.2 (CH_2), 31.8 (CH_2), 38.6 (CH_2), 39.6 (CH_2), 55.9 (OCH_3), 110.6 (CH), 114.4 (CH), 119.8 (CH), 134.0 (C_{quat}), 145.01 (C_{quat}), 145.5 (C_{quat}), 172.3 (C_{quat}, CO).

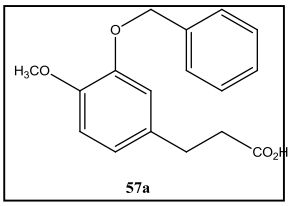
***N, N*-Bis(*n*-propyl) 3-hydroxy-4-methoxypropionamide** (**43e**).



43e

Reacted analogous to **43n**. (67%) as a pale pink oil; ν_{max} (neat/cm^{-1}) 3268 (bs, OH), 2963, 2875, 1622, 1513, 1438, 1375, 1273, 1129, 1029, 900, 869, 820, 760, 731; δ_H (400 MHz, $CDCl_3$) 0.86 (6H, t, ^3J = 7.2 Hz, 2 CH_3), 1.48 – 1.56 (4H, m, 2 CH_2), 2.58 (2H, t, ^3J = 8.0 Hz), 2.88 (2H, t, ^3J = 8.0 Hz), 3.10 (2H, bt, ^3J = 8.0 Hz, NCH_2), 3.26 (2H, bt, ^3J = 7.6 Hz, NCH_2), 6.69 (1H, dd, ^3J= 8.4 Hz, ^4J = 2.0 Hz), 6.75 (1H, d, ^3J = 8.4 Hz), 6.78 (1H, d, ^4J = 2.0 Hz); δ_C (67.8 MHz, $CDCl_3$) 11.2 (CH_3), 11.4 (CH_3), 20.9 (CH_2), 22.1 (CH_2), 31.2 (CH_2), 35.1 (CH_2), 47.9 (NCH_2), 49.2 (NCH_2), 56.0 (OCH_3), 110.7 (CH), 114.5 (CH), 119.8 (CH), 134.6 (C_{quat}), 144.9 (C_{quat}), 145.5 (C_{quat}), 172.2 (C_{quat}, CO).

3-[3-Benzyloxy-4-methoxyphenyl]propionic acid (**57a**).

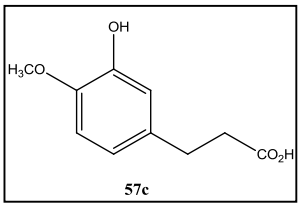


57a

A mixture of 3-[3-benzyloxy-4-methoxy-phenyl]-propionate (**41b**, 1.8 g, 5.7 mmol) in aq. NaOH (2.4 g NaOH in 24 mL H_2O) and CH_3OH (7 mL) was stirred at 90 ^oC for 14h. The cooled solution was acidified with half-conc. aq. HCl. The mixture was extracted with $CHCl_3$ (3 X 25 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give **57a** (1.47 g, 90%) as a colorless solid, MP. 125 – 127 ^oC; ν_{max} (KBr/cm^{-1}) 1700, 1521, 1241, 1146,

1013, 810; δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 5.12 (OCH_2), 6.73 – 6.76 (2H, m), 6.81 (1H, d, ^3J = 8.4 Hz), 7.27 – 7.37 (4H, m), 7.43 (2H, d, ^3J = 8.8 Hz); δ_C (67.8 MHz, $CDCl_3$) 30.1 (CH_2), 35.7 (CH_2), 56.0 (OCH_3), 71.0 (OCH_2), 111.9 (CH), 114.4 (CH), 120.8 (CH), 127.4 (2C, CH), 127.8 (CH), 128.5 (2C, CH), 132.7 (C_{quat}), 137.1 (C_{quat}), 148.0 (C_{quat}), 148.2 (C_{quat}), 178.7 (C_{quat}, CO).

3-Hydroxy-4-methoxyphenylpropionic acid (**57c**).



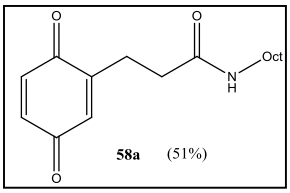
57c

Variation A: A solution of ethyl 3-hydroxy-4-methoxy-phenylpropionate (**41e**, 960 mg, 4.29 mmol) in a mixture of aq. NaOH (10 w% NaOH, 30 mL) and MeOH (5 mL) was stirred at 110 ^oC for 8 hr. To the cooled solution was added conc. aq. HCl (5 mL). The ensuing mixture was salted out, where acid started precipitating from the solution. The mixture was extracted with ethyl acetate (50 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to dryness. The solid was taken up with hexane/ether (10:1) and filtered.

The filter was air-dried to give 3-hydroxy-4-methoxyphenylpropionic acid (**57c**, 638 mg, 76%) as a colourless solid, MP. 149 ^oC; ν_{max} (KBr/cm^{-1}) 3398 (bs, OH), 2939, 2847, 1703, 1519, 1446, 1306, 1276, 1213, 1135, 809, 766; δ_H (400 MHz, $CDCl_3$)2.63 (2H, t, ^3J = 7.6 Hz), 2.85 (2H, t, ^3J = 7.6 Hz), 3.85 (3H, s, OCH_3), 5.90 (2H, bs), 6.67 (1H, dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 6.76 (1H, d, ^3J = 8.0 Hz), 6.77 (1H, d, ^4J = 2.0 Hz); δ_C (67.8 MHz, $CDCl_3$) 30.0 (CH_2), 35.7 (CH_2), 56.0 (OCH_3), 110.7 (CH), 114.5 (CH), 119.6 (CH), 133.4 (C_{quat}), 145.1 (C_{quat}), 145.5 (C_{quat}), 178.5 (C_{quat}, CO). **Variation B:** To a mixture of 3-hydroxy-4-methoxycinnamic acid (**27e**, 2.0 g, 10.3 mmol) and Pd/C (200 mg, 5 wt%, Aldrich 205680) in dioxane (10 mL) and toluene (15 mL) were added $NaBH_4$ (1.18 g in

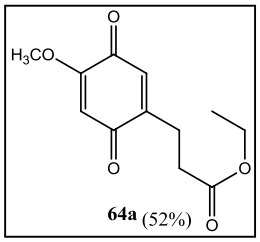
small portions) and acetic acid (1.33 g). After 36h, water (25 mL) was added carefully, followed by conc. aq. HCl (3 mL). The ensuing mixture was extracted with CH_2Cl_2 (3 X 35 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give compound **57c** (1.38 g, 69%).

***N*-Octyl 1,4-quinon-2-ylpropionamide** (**58a**).



To a stirred solution of compound **43g** (900 mg, 3.07 mmol) in CH_3CN (23 mL) was added at RT CAN (5.21 g, 9.50 mmol) in H_2O (20 mL). The reaction mixture was stirred at RT for 10 min. Thereafter, H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 X 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel (CH_2Cl_2/ether 10:1) gave compound **58a** (412 mg, 51%) as a red, slowly crystallizing oil; ν_{max} (KBr/cm^{-1}) 2925, 2854, 1662 (bs), 1541, 1492, 1466, 1286, 1039, 568; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, ^3J = 6.8 Hz, CH_3), 1.20-1.35 (10H, m), 1.54-1.61 (2H, m), 3.39 (2H, m), 6.78 (1H, d, ^3J = 10.0 Hz), 6.82 (1H, dd, ^3J = 10.0 Hz, ^4J = 2.4 Hz), 7.64 – 7.65 (1H, m), 8.31 (1H, bs, NH); δ_C (67.8 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 27.0 (CH_2), 29.1(5) (2C, CH_2), 29.2 (CH_2), 31.7 (CH_2), 40.1 (NCH_2), 134.7 (C_{quat}), 136.7 (CH), 137.1 (CH), 139.2 (CH), 160.8 (C_{quat}, NCO), 187.4 (C_{quat}, CO), 188.4 (C_{quat}, CO); UV (CH_2Cl_2) λ = 325 (ε = 590); UV (CH_3CN) λ= 325 nm, 247 nm (sh).

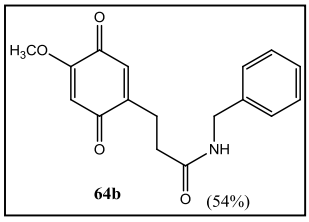
Ethyl 5-methoxy-1,4-quinon-2-ylpropionate (**64a**).



64a (52%)

To compound **63** (450 mg, 2.00 mmol) in CH_3CN (15 mL) was added dropwise a solution of CAN (3.47 g, 6.31 mmol) in H_2O (25 mL). The reaction mixture was stirred at RT for 15 min. Then, water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 X 25 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel (CH_2Cl_2/ether 2:1) gave compound **64a** (250 mg, 52.(5)%) as a yellow solid, MP. 114 ^oC; ν_{max} (KBr/cm^{-1}) 3065, 2985, 1728, 1671, 1644, 1603, 1299, 1268, 1234, 1194, 1179, 1058, 1027, 977, 914, 863, 786; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, ^3J = 7.2 Hz, CH_3), 2.54 (2H, t, ^3J = 7.2 Hz), 2.75 (2H, dt, ^3J = 7.2 Hz, ^4J = 0.9 Hz), 3.80 (3H, s, OCH_3), 4.11 (2H, q, ^3J = 7.2 Hz, OCH_2), 5.92 (1H, s), 6.51 (1H, t, ^4J = 0.9 Hz); δ_C (67.8 MHz, $CDCl_3$) 14.2 (CH_3), 24.5 (CH_2), 32.2 (CH_2), 56.3 (OCH_3), 60.8 (OCH_2), 107.7 (CH), 131.0 (CH), 148.5 (C_{quat}), 158.6 (C_{quat}), 172.0 (C_{quat}, CO), 182.1 (C_{quat}, CO), 187.0 (C_{quat}, CO). UV (CH_2Cl_2) λ = 265 nm, 360 nm; UV (CH_3CN) λ = 260 nm, 360 nm.

***N*-Benzyl 5-methoxy-1,4-quinon-2-ylpropionamide** (**64b**).

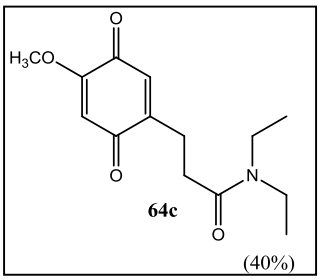


64b (54%)

To a stirred solution of compound **43m** (250 mg, 0.92 mmol) in CH_3CN (15 mL) was added dropwise a solution of CAN (1.58 g, 2.88 mmol) in H_2O (15 mL). The reaction mixture was stirred at RT for 15 min. Thereafter, H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 X 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel (CH_2Cl_2/ether 1:1) gave compound **64b** (104 mg, 54%) as a yellow solid, MP. 158 ^oC; ν_{max} (KBr/cm^{-1}) 3335, 1667,

1650, 1610, 1545, 1232, 1208, 1182; δ_H (400 MHz, $CDCl_3$) 2.44 (2H, t, ^3J = 7.6 Hz), 2.79 (1H, dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz), 3.79 (3H, s, OCH_3), 4.40 (2H, d, ^3J = 5.2 Hz), 5.78 (1H, bs, NH), 5.88 (1H, s), 6.54 (1H, t, ^4J = 1.6 Hz), 7.22 – 7.32 (5H, m); δ_C (67.8 MHz, $CDCl_3$) 25.4 (CH_2), 34.5 (CH_2), 43.7 (NCH_2), 56.3 (OCH_3), 107.7 (CH), 127.6 (CH), 127.9 (2C, CH), 128.8 (2C, CH), 131.3 (CH), 137.9 (C_{quat}), 148.5 (C_{quat}), 158.6 (C_{quat}), 170.7 (C_{quat}, NCO), 182.0 (C_{quat}, CO), 187.3 (C_{quat}, CO); UV (CH_2Cl_2) λ= 265 nm (ε = 5670 $M^{-1}cm^{-1}$), 351 nm (ε = 220 $M^{-1}cm^{-1}$); UV (CH_3CN) λ= 260 nm (ε = 8140 $M^{-1}cm^{-1}$), 350 nm (ε = 490 $M^{-1}cm^{-1}$).

***N, N*-Dipropyl 5-methoxy-1,4-quinon-2-ylpropionamide** (**64c**).

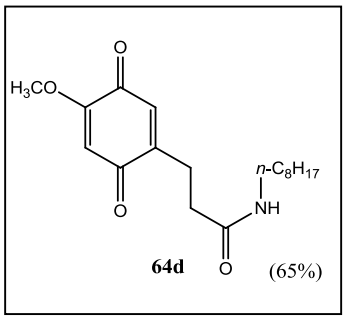


64c
(40%)

To compound **43e** (225 mg, 0.81 mmol) in CH_3CN (10 mL) was added dropwise a solution of CAN (1.39 g, 2.53 mmol) in H_2O (15 mL). The reaction mixture was stirred at RT for 15 min. Then, water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 X 25 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel (CH_2Cl_2/ether 2:1) gave compound **64c** (95 mg, 40%) as a yellow solid, MP. 85 ^oC; ν_{max} (KBr/cm^{-1}) 3064, 2962, 2931, 2873, 1674, 1647, 1605, 1455, 1423, 1239, 1207, 1180, 1145, 1049, 982, 920, 868; δ_H (400 MHz, $CDCl_3$) 0.83 – 0.91 (6H, m), 1.47 – 1.58 (4H, m), 2.53 (2H, dd, ^3J = 7.6 Hz, ^4J = 2.4 Hz), 2.76 (2H, t, ^3J = 7.6 Hz), 3.15 (2H, t, ^3J = 7.6 Hz), 3.23 (2H, t, ^3J = 7.6 Hz), 3.79 (3H, s, OCH_3), 5.90 (1H, s), 6.53 (1H, bs); δ_C (67.8 MHz, $CDCl_3$) 11.3 (CH_3), 11.4 (CH_3), 20.9 (CH_2), 22.2 (CH_2), 25.3 (CH_2), 31.4 (CH_2), 47.7 (NCH_2), 49.5 (NCH_2), 56.2 (OCH_3), 107.7 (CH), 131.1 (CH), 149.4 (C_{quat}), 158.6 (C_{quat}), 170.5 (C_{quat}, NCO), 182.2 (C_{quat}, CO), 187.4 (C_{quat}, CO); UV (CH_2Cl_2) λ = 265 nm (ε = 5670 M^{-}

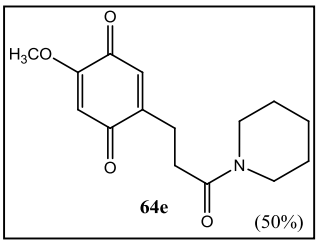
$^{1}cm^{-1}$), 351 nm (ε = 220 $M^{-1}cm^{-1}$); UV (CH_3CN) λ = 265 nm (ε = 13730 $M^{-1}cm^{-1}$), λ = 355 nm (ε = 550 $M^{-1}cm^{-1}$).

***N*-Octyl 5-methoxy-1,4-quinon-2-ylpropionamide** (**64d**).



To a stirred solution of compound **43n** (200 mg, 0.65 mmol) in CH_3CN (15 mL) was added dropwise a solution of CAN (1.12 g, 2.04 mmol) in H_2O (10 mL). The reaction mixture was stirred at RT for 15 min. Thereafter, H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 X 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel (CH_2Cl_2/ether 1:1) gave compound **64d** as (137 mg, 65%) as a yellow solid; MP. 160 ^{o}C; ν_{max} (KBr/cm^{-1}) 3337 (NH), 3062, 2918, 2849, 1669, 1654 (s), 1614, 1530, 1242, 1207, 1184; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, ^{3}J = 6.8 Hz, CH_3), 1.22 – 1.27 (10H, m), 1.42 – 1.48 (2H, m), 2.34 (2H, t, ^{3}J = 7.6 Hz), 2.76 (2H, dt, ^{3}J = 7.6 Hz, ^{4}J = 1.2 Hz), 3.20 – 3.22 (2H, m), 3.80 (3H, s, OCH_3), 5.54 (1H, bs, NH), 5.90 (1H, s), 6.54 (1H, t, ^{4}J = 1.2 Hz); δ_C (67.8 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 25.3 (CH_2), 26.9 (CH_2), 29.1(5) (CH_2), 29.2 (CH_2), 29.5 (CH_2), 31.8 (CH_2), 34.5 (CH_2), 39.7 (NCH_2), 56.3 (OCH_3), 107.7 (CH), 131.2 (CH), 148.7 (C_{quat}), 158.6 (C_{quat}), 170.9 (C_{quat}, NCO), 182.0 (C_{quat}, CO), 187.3 (C_{quat}, CO); UV (CH_2Cl_2) λ = 355 nm, 265 nm; UV (CH_3CN) λ = 351 nm, 260 nm.

***N*-Piperidinyl 5-methoxy-1,4-quinon-2-ylpropionamide** (**64e**).

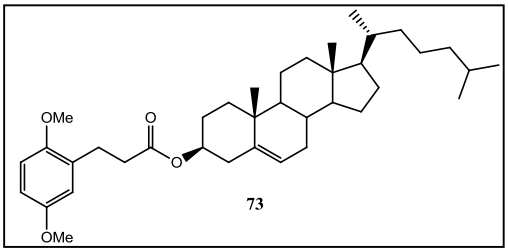


To a stirred solution of **43o** (250 mg, 0.95 mmol) in CH_3CN (15 mL) was added at RT CAN (1.64 g, 3.00 mmol) in H_2O (15 mL). The reaction mixture was stirred at RT for 10 min. Thereafter, H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 X 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel gave compound **64e** (130 mg, 50%) as a bright yellow solid; MP. 154 ^oC; ν_{max} (KBr/cm^{-1}) 2931, 2860, 1671, 1648 (s), 1634, 1625, 1458, 1234, 1203, 1178, 1008, 916; δ_H (400 MHz, $CDCl_3$) 1.50 – 1.56 (4H, m), 1.60 – 1.64 (2H, m), 2.56 (2H, t, ^3J = 7.2 Hz), 2.75 (2H, dd, ^3J = 7.2 Hz, ^4J = 1.4 Hz), 3.45 (4, bs), 3.80 (3H, s, OCH_3), 5.90 (1H, s), 6.55 (1H, t, ^4J = 1.4 Hz); δ_C (67.8 MHz, $CDCl_3$) 24.4 (CH_2), 25.2 (CH_2), 31.5 (CH_2), 56.3 (OCH_3), 107.7 (CH), 131.2 (CH), 149.3 (C_{quat}), 158.6 (C_{quat}), 169.3 (C_{quat}, CO), 182.2 (C_{quat}, CO), 187.4 (C_{quat}, CO).

Silver (I) oxide.

Ag_2O was prepared from $AgNO_3$ according to the procedure by D. E. Janssen and C. D. Wilson (Janssen and Wilson 1956): To an aq. solution of $AgNO_3$ (crystalline, 27.4 g, 16.1 mmol in 50 mL H_2O) is added dropwise under stirring an aq. NaOH solution (NaOH [6.6 g, 0.165 mol] in H_2O [200 mL]). Immediately black-brown solid Ag_2O developed. After the addition, the solid was collected on a sintered fritte and washed with water (3 X 50 mL). The moist solid was used in the following reaction.

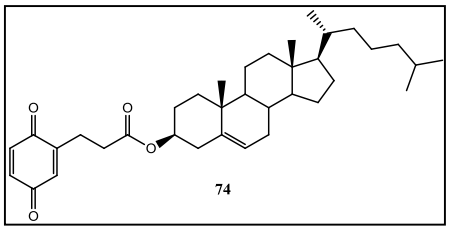
3-Cholesteryl 2,5-dimethoxyphenylpropionate (**73**).



73

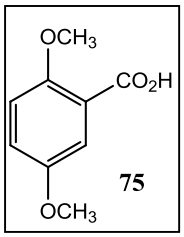
A solution of triphenylphosphine (PPh_3, 910 g, 3.47 mmol) and bromotrichloromethane ($BrCCl_3$, 720 mg, 3.63 mmol) in dry CH_2Cl_2 (10 mL) was stirred at RT for 35 min., during which time the solution turned yellow-orange. Thereafter, 2,5-dimethoxyphenylpropionic acid (**57b**, 510 mg, 2.43 mmol) was added (as a solid), and the mixture was stirred at reflux for 40 min. Then, cholesterol (**55**, 940 mg, 2.43 mmol) was added as a solid, and the resulting mixture was stirred at reflux for 14 hr. The mixture was subjected directly to column chromatography on silica gel (CH_2Cl_2-hexane 3:1) to give compound **73** (890 mg, 63%) as a slowly crystallizing oil; MP. 70 ^oC; ν_{max} (neat/cm^{-1}) 2954, 1733, 1502, 1465, 1375, 1222, 1163, 1051, 1030, 799, 738, 709; δ_H (400 MHz, $CDCl_3$) 0.65 (3H, s, CH_3), 0.83 (3H, d, ^3J = 6.4 Hz), 0.84 (3H, d, ^3J = 6.4 Hz), 0.89 (3H, d, ^3J = 6.4 Hz), 0.92 – 2.00 (26H, m), 0.99 (3H, s, CH_3), 2.26 – 2.28 (2H, m), 2.55 (2H, t, ^3J = 7.6 Hz), 2.88 (2H, t, ^3J = 7.6 Hz), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3),4.55 – 4.63 (1H, m), 5.34 (1H, bd, ^3J = 5.2 Hz), 6.68 (1H, dd, ^3J = 8.8 Hz, ^4J = 3.2 Hz), 6.72 (1H, d, ^4J = 3.2 Hz), 6.73 (1H, d, ^3J = 8.8 Hz); δ_C (67.8 MHz, $CDCl_3$) 11.8, 14.1 19.3, 21.0, 22.5, 22.6, 22.8, 23.8, 24.3, 26.3, 27.7, 28.0, 28.2, 31.8, 31.9, 34.5, 35.8, 36.1, 36.6, 37.0, 38.1, 39.5, 39.7, 55.6, 55.7, 56.1, 56.6, 73.8 (CH), 111.0 (CH), 111.4 (CH), 116.3 (CH), 122.5 (C_{quat}), 130.1 (CH), 139.7 (C_{quat}), 151.7 (C_{quat}), 153.3 (C_{quat}), 172.7 (C_{quat}, CO).

3-Cholesteryl 1,4-quinon-2-ylpropionate (**74**).



To a mixture of **73** (980 mg, 1.69 mmol) in CH_3CN (20 mL) was added a solution of CAN (2.87 g, 5.23 mmol) in H_2O (20 mL). Due to the very low solubility of crystalline **73** in CH_3CN, CH_2Cl_2 (0.5 mL) was added during the reaction. The reaction mixture was stirred at RT for 30 min. Thereafter, H_2O (30 mL) was added and the mixture was extracted with $CHCl_3$ (3 X 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (CH_2Cl_2-hexane 3:1) to give compound **74** (407 mg, 44%) as a yellow solid; MP. 148 ^oC; ν_{max} (KBr/cm^{-1}) 2934, 2868, 1732, 1655, 1302, 1188, 1163, 997, 924; δ_H (400 MHz, $CDCl_3$) 0.65 (3H, s, CH_3), 0.83 (3H, d, ^3J = 6.8 Hz, CH_3), 0.84 (3H, d, ^3J = 6.4 Hz, CH_3), 0.89 (3H, d, ^3J = 6.4 Hz, CH_3), 0.92 – 2.00 (26H, m), 0.99 (3H, s, CH_3), 2.27 (2H, bd, ^3J = 8.0 Hz), 2.53 (2H, t, ^3J = 7.2 Hz), 2.73 (1H, dd, ^3J = 7.2 Hz, ^4J = 1.2 Hz), 4.55 – 4.63 (1H, m), 5.34 (1H, bd, ^3J = 5.2 Hz), 6.57 (1H, d, ^4J = 2.0 Hz), 6.71 (1H, dd, ^3J = 10.0 Hz, ^4J = 2.0 Hz), 6.75 (1H, d, ^3J = 10.0 Hz), δ_C (67.8 MHz, $CDCl_3$) 11.8 (CH_3), 18.7, 19.3, 21.0, 22.5, 22.8, 23.8, 24.3, 24.6, 27.7, 28.0, 28.2, 31.8, 31.8(5), 32.3, 35.8, 36.1, 36.5, 38.1, 39.5, 39.7, 42.3, 49.9, 56.1, 56.6, 77.3 (CH), 122.8 (CH), 133.0 (CH), 136.4 (CH), 136.8 (CH), 139.4 (C_{quat}), 147.6 (C_{quat}), 171.3 (C_{quat}, CO), 187.1 (C_{quat}, CO), 187.4 (C_{quat}, CO); UV (CH_3CN) λ = 305.0 nm (ε = 656), 249.9 nm (ε = 14960); (CH_2Cl_2) λ = 310.0 nm, 249.9 nm.

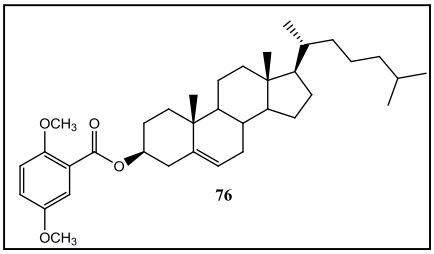
2,5-Dimethoxybenzoic acid (**75**).



75

To freshly prepared Ag_2O (moist, 7.5 g) in an aq. NaOH solution (NaOH [1.5 g, 37.5 mmol] in H_2O [40 mL]) was added under stirring 2,5-dimethoxybenzaldehyde (5.0 g, 30.1 mmol). After an induction time of 20-25 min., the solution became warm. After 14 hr., the solution was filtered through a paper filter. The filter cake was washed diligently with water (3 X 25 mL). The filtrate was acidified with half-conc. HCl.The mixture was extracted with ethyl acetate (75 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give compound **75** (4.72 g, 86%) as colorless needles, MP. 70 ^oC (Lit. 74.5 – 76.5 ^oC [Henton et al. 1980]); ν_{max} (KBr/cm^{-1}) 3428 (bs, OH), 2950, 2836, 1732, 1500, 1434, 1295, 1215, 1179, 1045, 1013, 812, 727; δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 6.98 (1H, d, ^3J = 8.8 Hz), 7.10 (1H, dd, ^3J = 8.8 Hz, ^4J = 3.2 Hz), 7.67 (1H, d, ^4J = 3.2 Hz); δ_C (67.8 MHz, $CDCl_3$) 55.9 (OCH_3), 57.2 (OCH_3), 113.2 (CH), 116.2 (CH), 117.9 (C_{quat}), 122.1 (CH), 152.2 (C_{quat}), 154.4 (C_{quat}), 165.2 (C_{quat}, CO).

Cholesteryl 2,5-dimethoxybenzoate (**76**).

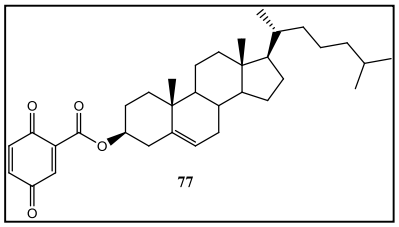


76

A solution of triphenylphosphine (PPh_3, 910 g, 3.47 mmol) and bromotrichloromethane ($BrCCl_3$, 720 mg, 3.63 mmol) in dry CH_2Cl_2 (10 mL) was stirred at RT for 35 min., during which time the solution turned yellow-orange. Thereafter, 2,5-dimethoxybenzoic acid (**75**, 500 mg, 2.80 mmol) was added (as a solid), and the mixture was stirred at reflux for 40 min. Then, cholesterol (940 mg, 2.43 mmol) was added as a solid, and the resulting mixture was stirred at reflux for 14h. Direct column

chromatography of the reaction mixture on silica gel (CH_2Cl_2-hexane 3:1) gave compound **76** (878 mg, 64%) as a colorless solid, MP. 119 ^oC; δ_H (400 MHz, $CDCl_3$)0.67 (3H, s, CH_3), 0.84 (3H, d, ^3J = 6.0 Hz, CH_3), 0.85 (3H, d, ^3J = 6.4 Hz, CH_3), 0.90 (3H, d, ^3J = 6.4 Hz, CH_3), 0.92 – 2.00 (26H, m), 1.03 (3H, s, CH_3), 2.42 – 2.48 (2H, m), 3.78 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.79 – 4.87 (1H, m), 5.39 (1H, bd, ^3J = 5.6 Hz), 6.89 (1H, d, ^3J = 8.8 Hz), 6.98 (1H, dd, ^3J = 8.8 Hz, ^4J = 3.6 Hz), 7.28 (1H, d, ^4J = 3.6 Hz); δ_C (67.8 MHz, $CDCl_3$) 11.8 (CH_3), 18.7 (CH_3), 19.4 (CH_3), 21.0, 22.6, 22.8, 23.8, 24.3, 27.8, 28.0, 28.2, 31.8, 31.9, 35.8, 36.2, 36.6, 37.0, 38.1, 39.4, 39.7, 42.3, 50.0, 55.8, 56.1, 56.7, 56.9, 74.6 (CH), 113.9 (CH), 116.0 (CH), 118.8 (CH), 121.4 (C_{quat}), 122.7 (CH), 139.7 (C_{quat}), 153.0 (C_{quat}), 153.4 (C_{quat}), 165.4 (C_{quat}, CO).

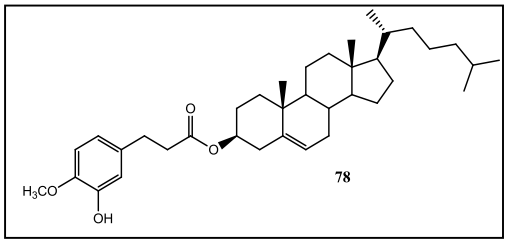
3-Cholesteryl quinonylcarboxylate (**77**).


77

To a stirred solution of compound **76** (870 mg, 1.54 mmol) in a solvent mixture of CH_2Cl_2 (5 mL) and CH_3CN (15 mL) was added CAN (2.67 g, 4.86 mmol) in H_2O (10 mL). The reaction mixture was stirred for 1h at RT. Then, H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 X 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel (CH_2Cl_2 – hexane 3:1) yielded compound **77** as an orange solid, MP. 158 ^oC; ν_{max} (KBr/cm^{-1}) 3051, 2933, 2867, 2850, 1740 (s), 1663 (s), 1467, 1252, 1040, 842; δ_H (400 MHz, $CDCl_3$) 0.66 (3H, s, CH_3), 0.84 (3H, d, ^3J = 6.4 Hz), 0.84(5) (3H, d, ^3J = 6.4 Hz), 0.90 (3H, d, ^3J = 6.0 Hz), 0.92 – 2.02 (26H, m), 1.01 (3H, s, CH_3), 2.40 – 2.42 (2H, m), 4.78 – 4.86 (1H, m), 5.40 (1H, bd, ^3J = 5.2 Hz), 6.80

(2H, m), 7.02 – 7.04 (2H, m); δ_C (67.8 MHz, $CDCl_3$) 11.8 (CH_3),18.7, 19.3, 21.0, 22.5, 22.8, 23.8, 24.3, 27.6, 28.0 (2C), 28.2, 31.8, 31.9, 35.8, 36.1, 36.5, 39.5, 39.7, 42.3, 49.9,56.1, 56.6, 76.5 (CH), 123.3 (CH), 135.7 (CH), 136.1 (CH), 136.9 (CH), 137.7 (C_{quat}), 139.0 (C_{quat}), 162.1 (C_{quat}, CO), 183.2 (C_{quat}, CO), 187.0 (C_{quat}, CO); UV (CH_3CN) λ = 325.0 nm, 244.9 nm; (CH_2Cl_2) λ = 325.0 nm, 249.9 nm.

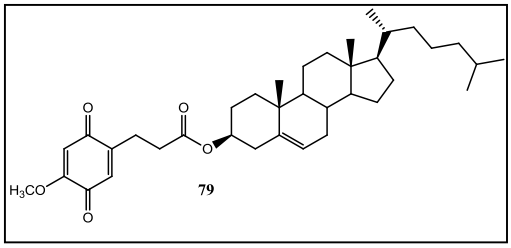
3-Cholesteryl 3-hydroxy-4-methoxy phenyl propionate (**78**).



A solution of triphenylphosphine (PPh_3, 854 mg, 3.26 mmol) and tetrachloromethane (CCl_4, 550 mg, 3.58 mmol) in dry CH_2Cl_2 (12 mL) was stirred at reflux for 50 min. Then, 3-hydroxy-4-methoxy phenylpropionic acid (**57c**, 535 mg, 2.73 mmol) was added, and the mixture was stirred at reflux for 1h. Then, cholesterol (**55**, 1.585 g, 4.1 mmol) was added, and the resulting mixture was stirred at reflux for 14 hr. The mixture was subjected directly to column chromatography on silica gel (eluant: CH_2Cl_2) to give compound **78** (960 mg) as a colorless solid, MP. 130 ^oC; ν_{max} (KBr/cm^{-1}) 3922 (ds, OH), 2939, 2903, 2866, 2850, 1698, 1592, 1536, 1465, 1437, 1364, 1255, 1213, 1129, 1032, 875, 801; δ_H (400 MHz, $CDCl_3$) 0.65 (3H, s, CH_3), 0.84 (3H, d, ^3J = 6.0 Hz, CH_3), 0.84(5) (3H, d, ^3J = 6.4 Hz, CH_3), 0.89 (3H, d, ^3J = 6.4 Hz, CH_3), 0.92 – 2.01 (26H, m), 0.99 (3H, s, CH_3), 2.27 (2H, bd, J = 8.0 Hz), 2.54 (2H, t, ^3J = 7.6 Hz), 2.83 (2H, d, ^3J = 7.6 Hz), 3.84 (3H, s, OCH_3), 4.55 – 4.63 (1H, m), 5.34 (1H, bd, ^3J = 4.0 Hz), 5.53 (1H, bs, OH), 6.65 (1H, dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 6.75 (1H, d, ^3J = 8.0 Hz), 6.76 (1H, d, ^4J = 2.0 Hz); δ_C (67.8 MHz, $CDCl_3$) 11.8 (CH_3), 18.7, 19.3, 21.0, 22.6, 22.8, 23.8, 24.3, 27.7, 28.0, 28.2, 30.4, 31.8

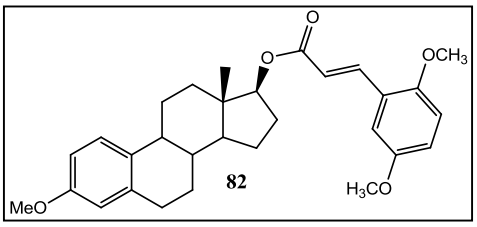
(2C), 31.9, 35.8, 36.1 (5), 36.4, 36.6, 36.9 (5), 38.1, 39.5, 39.7, 42.3, 50.0, 55.9 (5), 56.1, 56.6, 74.0 (CH), 110.6 (CH), 114.5 (CH), 119.6 (CH), 122.6 (CH), 133.9 (C_{quat}), 139.6 (C_{quat}), 144.9 (C_{quat}), 145.4 (C_{quat}), 172.4 (C_{quat}, CO).

Cholesteryl 5-methoxy-1,4-quinon-2-ylpropionate (**79**).



To a stirred solution of compound **78** (265 mg, 0.47 mmol) in a solvent mixture of CH_2Cl_2 (5 mL) and CH_3CN (10 mL) was added CAN (810 mg, 1.47 mmol) in H_2O (10 mL). The reaction mixture was stirred for 15 min. at RT. Then, H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2(3 X 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel (CH_2Cl_2/ ether 5:1) yielded **79** (145 mg) as a yellow-brown solid, MP. 202 ^oC; ν_{max} (KBr/cm^{-1}) 2938, 2867, 1732, 1671, 1649, 1606, 1465, 1374, 1172, 980; δ_H (400 MHz, $CDCl_3$) 0.65 (3H, s, CH_3), 0.84 (3H, d, ^3J = 6.8 Hz), 0.84(5) (3H, d, ^3J = 6.4 Hz), 0.89 (3H, d, ^3J = 6.8 Hz), 0.86 – 1.85 (24H, m), 0.99 (3H, s, CH_3), 1.92 – 2.01 (2H, m), 2.27 (2H, d, ^3J = 7.6 Hz), 2.52 (2H, t, ^3J = 7.2 Hz), 2.74 (2H, dt, ^3J = 7.2 Hz, ^4J = 0.8 Hz), 3.80 (3H, s, OCH_3), 4.55 – 4.63 (1H, m), 5.35 (1H, d, ^3J = 3.6 Hz), 5.92 (1H, s), 6.51 (1H, t, ^4J = 0.8 Hz); δ_C (67.8 MHz, $CDCl_3$) 11.8 (CH_3), 18.7 (CH_3), 19.3 (CH_3), 21.0, 22.5, 22.8, 23.8, 24.3, 24.6, 27.7, 28.0 (2C), 28.2, 31.8, 31.9, 32.5, 35.8, 36.1, 36.5, 36.9, 38.1, 39.5, 39.7, 42.3, 50.0, 56.1, 56.3, 56.6, 74.4 (CH), 107.7 (CH), 122.8, 131.0, 139.4, 148.5, 158.6, 171.3 (C_{quat}, CO), 182.1 (C_{quat}, CO), 187.0 (C_{quat}, CO); UV (CH_2Cl_2) λ = 360 nm (ε = 585), λ = 249.9 nm (ε = 12850).

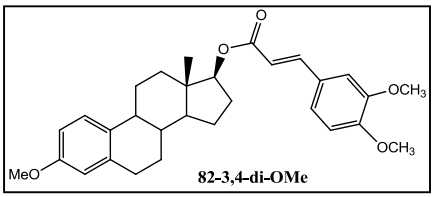
3-Methoxyestra-1,3,5(10)-trien-17*β*-yl 2,5-(*E*)-dimethoxycinnamate (**82**)



82

To a solution of triphenylphosphine (PPh_3, 582 mg, 2.22 mmol) in dry CH_2Cl_2 (7 mL) was given $BrCCl_3$ (460 mg, 2.32 mmol). The ensuing mixture was stirred at RT for 30 min., during which time it turned dark orange. Thereafter, 2,5-methoxycinnamic acid (420 mg, 2.02 mmol) was added portionwise, and the resulting reaction mixture was stirred under reflux for 45 min. Then, 3-*O*-methylestra-1,3,5(10)-trien-3,17*β*-diol (**81**, 275 mg, 0.96 mmol) was added, and the mixture was stirred under reflux for another 12h. At certain intervals, the reaction vessel is set under slight vacuum (alternatively, 0.96 mmol dry DBU or dry Et_3N can be added to the reaction 15 min. after the addition of the steroid). Direct column chromatography of the cooled, concentrated solution on silica gel ($CHCl_3$/ Et_2O/ hexane 1:1:1) 2,5-methoxyestra-1,3,5(10)-trien-17*β*-yl 4-(*E*)-methoxycinnamate (**82**) (330 mg, 72%)as a colorless solid, MP. 139-140 ^oC; ν_{max} (KBr/cm^{-1}) 3008, 2923, 2867, 2835, 1709, 1629, 1499, 1464, 1447, 1335, 1294, 1258, 1227, 1178, 1040, 997, 859, 819, 702, 560; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, s, CH_3), 1.32 – 2.32 (13H, m), 2.84 – 2.87 (2H, m), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.84 (1H, dd, ^3J = 8.8 Hz, ^3J = 8.0 Hz, OCH), 6.50 (1H, d, ^3J = 16.0 Hz), 6.63 (1H, d, ^4J = 2.8 Hz), 6.71 (1H, dd, ^3J = 8.8 Hz, ^4J = 2.8 Hz), 6.84 (1H, d, ^3J = 9.2 Hz), 6.90 (1H, dd, ^3J = 9.2 Hz, ^4J = 3.2 Hz), 7.06 (1H, d, ^4J = 3.2 Hz), 7.21 (1H, d, ^3J = 8.8 Hz), 7.97 (1H, d, ^3J = 16.0 Hz); δ_C (100.5 MHz, $CDCl_3$) 12.2, 23.3, 26.3, 27.3, 27.7, 29.8, 37.0, 38.6, 43.2, 43.8, 49.8, 55.2 (OCH_3), 55.8 (OCH_3), 56.1 (OCH_3), 82.7 (OCH), 111.5, 112.4, 113.2, 113.8, 117.0, 119.2, 124.0, 126.4, 132.6, 137.9, 139.6, 152.8 (C_{quat}), 153.5 (C_{quat}), 157.4 (C_{quat}), 167.5 (C_{quat}, CO).

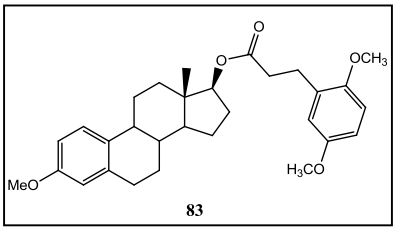
3-Methoxyestra-1,3,5(10)-trien-17*β*-yl 3,4-(*E*)-dimethoxycinnamate(82-3,4-di-OMe)



82-3,4-di-OMe

As a colorless solid, MP. 162-165 ^{o}C; ν_{max} (KBr/cm^{-1}) 3010, 2953, 2863, 2843, 2805, 2698, 1612, 1596, 1510, 1445, 1417, 1294, 1257, 1155, 1139, 1024, 848, 812, 782, 616, 570; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, s, CH_3), 2.84 – 2.88 (2H, m), 1.25 – 2.31 (13H, m), 3.77 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.83 (1H, dd, ^3J = 8.0, ^3J = 7.6 Hz, OCH), 6.32 (1H, d, ^3J = 16.0 Hz), 6.63 (1H, d, ^4J = 2.8 Hz), 6.70 (1H, dd, ^3J = 8.4 Hz, ^4J = 2.8 Hz), 6.86 (1H, d, ^3J = 8.4 Hz), 7.05 (1H, d, ^4J = 2.0 Hz), 7.10 (1H, dd, ^3J = 8.4 Hz, ^4J = 2.0 Hz), 7.20 (1H, d, ^3J = 8.4 Hz), 7.61 (1H, d, ^3J = 16.0 Hz); δ_C (100.5 MHz, $CDCl_3$) 12.2, 23.3, 26.2, 27.2, 27.7, 29.8, 37.0, 38.6, 43.2, 43.8, 49.8, 55.2 (OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 82.7 (OCH), 109.5, 111.0, 111.5, 113.8, 116.2, 122.6, 126.4, 127.5, 132.5, 137.9, 144.3, 149.2 (C_{quat}), 151.0 (C_{quat}), 157.4 (C_{quat}), 167.3 (C_{quat}, CO). Found: C, 75.76%; H, 7.32%. Calcd. for $C_{30}H_{36}O_5$ ·(476.60): C, 75.60%; H, 7.61%.

3-Methoxyestra-1,3,5(6)-trien-17-yl 3-(2,5-dimethoxyphenyl) propionate (**83**).

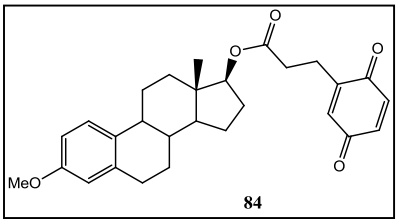


83

To a solution of 3-methoxyestra-1,3,5(6)-trien-17-yl 2,5-dimethoxycinnamate (**82**, 500 mg, 1.05 mmmol) and Pd/C (100 mg, 5wt%, Aldrich 205680) in toluene (10 mL) was added AcOH (235 mg, in successive portions of 150 mg and 85 mg) and $NaBH_4$ (280 mg, in successive portions of 150 mg and 130 mg). The mixture was stirred for 36 hr. at RT. Thereafter, H_2O (3 mL) was added carefully, followed by half-conc. aq. HCl (3 mL). The mixture was taken up in water (25

mL) and extracted with CH_2Cl_2 (3 X 30 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (CH_2Cl_2-hexane 3:1, then CH_2Cl_2) to give compound **83** (500 mg, quant.) as a slowly crystallizing colorless oil; ν_{max} (neat/cm^{-1}) 2928, 1727, 161, 1502, 1049, 869, 808; δ_H (400 MHz, $CDCl_3$) 0.77 (3H, s, CH_3), 1.25 – 2.28 (13H, m), 2.61 (2H, t, ^3J = 8.0 Hz), 2.83 – 2.85 (2H, m), 2.91 (2H, t, ^3J = 8.0 Hz), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.68 (1H, dd, ^3J = 8.8 Hz, ^3J = 7.6 Hz), 6.62 (1H, d, ^4J = 2.8 Hz), 6.68 – 6.77 (4H, m), 7.19 (1H, d, ^3J = 8.4 Hz); δ_C (67.8 MHz, $CDCl_3$) 12.0, 23.7, 26.2, 26.4, 27.2, 27.6, 29.8, 34.4, 36.8, 38.6, 42.9, 43.8, 49.7, 55.2, 55.7, 55.8, 82.6, 111.0, 111.4, 111.4 (5), 113.7, 116.3, 126.4, 130.0, 132.5, 137.9, 151.7, 153.3, 157.4, 173.4.

3-*O*-Methylestra-1,3,5(6)-trien-17-yl 3-(1.4-quinon-2-yl) propionate (**84**).



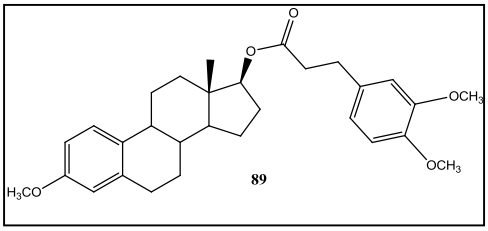
84

To a solution of **73** (370 mg, 0.775 mmol) in a solvent mixture of CH_3CN (10 mL) and CH_2Cl_2 was added dropwise CAN (1.34 g, 2.44 mmol) in water (10 mL), and the resulting reaction mixture was stirred for 35 min. at RT. Column chromatography on silica gel (CH_2Cl_2-ether 20:1) gave compound **74** (120 mg, 35%) as a yellow-orange, slowly crystallizing oil; ν_{max} (neat/cm^{-1}) 2926, 1727, 1659, 1610, 1502, 1444, 1255, 1081, 1038, 911, 870, 816, 728, 648; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, s, CH_3), 1.24 – 2.28 (13H, m), 2.57 (2H, t, ^3J = 7.0 Hz), 2.76 (2H, t, ^3J = 7.0 Hz), 2.82 – 2.84 (2H, m), 3.75 (3H, s, OCH_3), 4.67 (1H, dd, ^3J = 8.8 Hz, ^3J = 7.6 Hz),

6.58 - 6.59 (1H, m), 6.61 (1H, d, ^4J = 2.8 Hz), 6.68 (1H, dd, ^3J = 8.4 Hz, ^4J = 2.8 Hz), 6.72 (1H, d, ^4J = 2.0 Hz), 6.76 (1H, d, ^3J = 10.0 Hz), 7.17 (1H, d, ^3J = 8.4 Hz); δ_C (100.5 MHz, $CDCl_3$) 12.1 (CH_3), 23.2, 24.7, 26.2, 27.2, 27.6, 29.8, 32.2, 36.9, 38.5, 42.9, 43.7, 49.6, 55.2 (OCH_3), 83.2 (OCH), 111.5, 113.8, 126.3, 132.4, 132.9, 136.4, 136.8, 137.8, 147.6, 157.4, 172.0 (C_{quat}, CO), 187.1 (C_{quat}, CO), 187.4 (C_{quat}, CO); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 449 (M^+, 3).

3-Methoxyestra-1,3,5(6)-trien-17-yl 3-(3,4-dimethoxyphenyl)propionate) (**89**).

To a solution of3-methoxyestra-1,3,5(6)-trien-17-yl 3,4-dimethoxycinnamate (**82-3,4-di-OMe**, 314 mg, 0.66 mmmol) and Pd/C (100 mg, 5wt%, Aldrich 205680) in toluene (10 mL) was

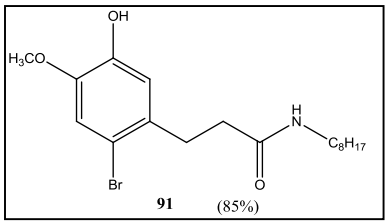


89

added AcOH (235 mg, in successive portions of 150 mg and 85 mg) and $NaBH_4$ (280 mg, in successive portions of 150 mg and 130 mg). The mixture was stirred for 36h at RT. Thereafter, H_2O (3 mL) was added carefully, followed by half-conc. aq. HCl (3 mL). The mixture was taken up in water (25 mL) and extracted with CH_2Cl_2 (3 X 30 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (CH_2Cl_2-hexane 3:1, then CH_2Cl_2) to give compound **89** (315 mg, quant.) as a slowly crystallizing colorless oil; ν_{max} (neat/cm^{-1}) 2932, 1732, 1609, 1516, 1456, 1257, 1031, 962, 890, 849, 809, 754, 667; δ_H (400 MHz, $CDCl_3$) 0.77 (3H, s, CH_3), 1.25 – 2.28 (13H, m), 2.61 (2H, t, ^3J = 8.0 Hz), 2.83 – 2.85 (2H, m), 2.90 (2H, t, ^3J = 8.0 Hz), 3.76 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.68 (1H, dd, ^3J = 8.8 Hz, ^3J = 7.6 Hz), 6.62 (1H, d, ^4J = 2.4 Hz), 6.68 –

6.80 (4H, m), 7.18 (1H, d, ^3J = 8.4 Hz); δ_C (67.8 MHz, $CDCl_3$) 12.1, 23.3, 26.2, 27.2, 27.5, 29.8, 30.7, 36.4, 36.8, 38.5, 42.9, 43.8, 49.7, 55.2, 55.8, 55.9, 82.7, 111.2, 111.4, 111.5, 113.7, 120.1, 126.4, 132.4, 133.2, 137.9, 147.4, 148.8, 157.4, 173.1.

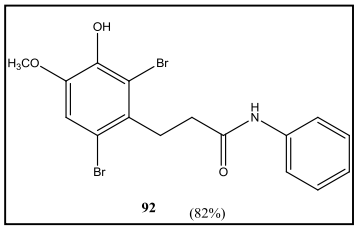
***N*-Octyl 2-bromo-5-hydroxy-4-methoxyphenylpropionamide** (**91**).



91 (85%)

To a solution of *N*-octyl 5-hydroxy-4-methoxyphenyl propionamide (**43n**, 220 mg, 0.66 mmol) in DMF (3 mL) was given at RT *N*-bromosuccinimide (150 mg, 0.83 mmol, 1.25 eq.) in multiple portions over a period of 24 h. The reaction mixture was stirred a total of 36h. Then, H_2O (25 mL) was added and the mixture was extracted with $CHCl_3$ (3 X 20 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. Remaining DMF was co-evaporated with ether. The residue was subjected to column chromatography on silica gel (CH_2Cl_2-ether 5:1) to give compound **91** (216 mg, 85%) as a colorless solid; ν_{max} (KBr/cm^{-1}) 3303 (bs, OH), 2929, 2856, 1644, 1556, 1504, 1441, 1280, 1208, 1161, 1034, 870, 795; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, ^3J = 7.0 Hz, CH_3), 1.23 – 1.27 (10H, m), 1.40 – 1.46 (2H, m), 2.43 (2H, t, ^3J = 7.8 Hz), 2.95 (2H, t, ^3J = 7.8 Hz), 3.18 – 3.23 (2H, m), 3.84 (3H, s, OCH_3), 5.45 (1H, bs), 6.82 (1H, s), 6.96 (1H, s); δ_C (67.8 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 26.8 (CH_2), 29.2 (CH_2), 29.2(5) (CH_2), 29.5 (CH_2), 31.7 (CH_2), 31.8 (CH_2), 36.8 (CH_2), 39.7 (CH_2), 56.2 (OCH_3), 112.8 (C_{quat}), 114.9 (CH), 116.2 (CH), 132.6 (C_{quat}), 145.0 (C_{quat}), 145.7 (C_{quat}), 171.9 (C_{quat}, CO).

***N*-Benzyl 2,6-dibromo-5-hydroxy-4-methoxyphenylpropionamide** (**92**).



To a solution of *N*-octyl 5-hydroxy-4-methoxyphenyl propionamide (**43m**, 120 mg, 0.42 mmol) in DMF (1.5 mL) was given at RT *N*-bromosuccinimide (160 mg, 0.9 mmol, 2.05 eq.) in multiple portions over a period of 24 hr. The reaction mixture was stirred a total of 48h. Then, H_2O (25 mL) was added and the mixture was extracted with $CHCl_3$ (3 X 20 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. Remaining DMF was co-evaporated with ether. The residue was subjected to column chromatography on silica gel (CH_2Cl_2-ether 5:1) to give compound **92** (185 mg, 82%) as a colorless solid, MP. 208 ^oC; ν_{max} (KBr/cm^{-1}) 3415, 3297, 1638, 1033 (s), 696; δ_H (400 MHz, $CDCl_3$) 2.42-2.44 (2H, m), 3.27-3.31 (2H, m), 3.87 (3H, s, OCH_3), 4.45 (2H, d, ^3J = 5.2 Hz, NCH_2), 5.71 (1H, bs), 7.00 (s), 7.24-7.33 (5H, m). The product is only very sparingly soluble in $CHCl_3$.

Chapter 3: Results and Discussion

3.1 Preparation of Cinnamic Acids As Starting Materials

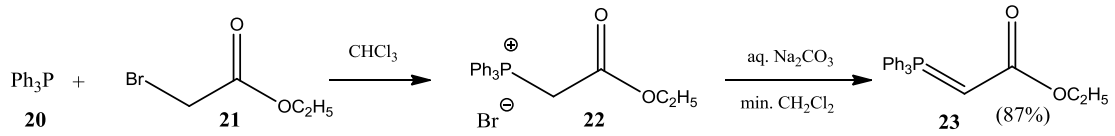
As it was planned to derive the quinone moiety from a hydroxylated or methoxylated arene, it is necessary to have a good access to hydroxylated or methoxylated phenylpropionic acids. It is planned to prepare the phenylpropionic acids by hydrogenation of the respective cinnamic acids. Thus, it became essential to find an easy access to cinnamic acids. Cinnamic acids are well-studied compounds that are produced industrially as well as cinnamic acid and derivatives find uses in the food industry (Cirigliano et al. 1997; Shahadi and Zhong 2010), and the cosmetic industry (L. Breton et al. 1997), among others. Additionally, cinnamic acids are important starting materials for a number of industrial syntheses, such as for the industrial preparation of phenylalanine and of aspartame (via phenylalanine) (Szmant 1989). Thus, a larger number of syntheses of cinnamic acids have been carried out. Among them are the reaction of benzaldehydes with malonic acid ester (Knoevenagel reaction with subsequent decarboxylation) (Mobinikhaledi et al. 2008; Gupta and Wakhloo 2007), of benzaldehydes with acetic anhydride/sodium acetate (Perkin reaction) (Johnson 1942), and of iodoarenes with acrylates via Heck reaction (Carmichael et al. 1999) with subsequent hydrolysis in a two-step sequence. Recently, Knoevenagel type reaction has also been carried out with Meldrum's acid (Zolfigol 2015).

In Thiemann group the Heck reaction to cinnamates has only been used once (Burmester et al. 2010), and the yields of Knoevenagel and Perkin reactions have been found to be unpredictable, often. On the other hand, the Wittig reaction of benzaldehydes

with alkoxycarbonylmethylidenetriphenylphosphoranes gives cinnamates in dependable and good yields. While the reaction even with conjugated phosphoranes have been carried out in benzene or chloroform as solvents and oftentimes under an inert atmosphere, it has been found more recently that the alkoxycarbonylmethylidenetriphenylphosphoranes react selectively with the keto and aldehyde carbonyl function, but not with oxygen or water, even under slightly elevated temperatures. This has led to carrying out the Wittig reactions of aldehydes with alkoxycarbonylmethylidenetriphenylphosphoranes under various conditions (Odinets and Matveeva 2010, Al Jasem et al. 2014), including under solventless conditions (Thiemann 2007; Watanabe et al. 2005; Thiemann et al. 2004) and in aqueous medium (Dambacher et al. 2005; Wu et al. 2005A; Wu et al. 2005B; Yamamoto et al. 2005; Watanabe et al. 2005; Wu et al. 2006; Orsini et al. 2006; El Batta et al. 2007; Tiwari and Kumar 2008; McNulty and Das 2009). Apart from running Wittig reactions of benzaldehydes with alkoxycarbonylmethylidenetriphenylphosphorane with minimal solvent to acquire the alkyl cinnamates with a subsequent hydrolysis of the cinnamates with aq. NaOH/MeOH, this led the Thiemann group to try and synthesize cinnamic acids by a one-pot Wittig olefination – hydrolysis, when running the Wittig reactions in 2M aq. NaOH solutions (Thiemann et al. 2010; Thiemann et al. 2016). The cinnamic acids could be isolated by simple fitration after acidification of the reaction mixture with half-conc. aq. HCl. The filtered, air-dried products could be used for the next reaction step (**Table 1**). Here, both strategies were followed.

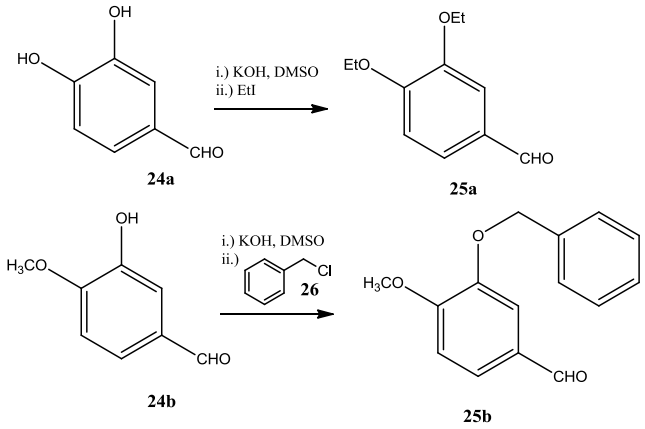
First, the stabilized ethoxycarbonylmethylidenetriphenylphosphorane (**23**) had to be prepared (Considine 1962). For this, triphenylphosphine was reacted with ethyl bromoacetate in $CHCl_3$. The product ethoxycarbonylmethyltriphenylphosphonium

bromide could be crystallized from ether. After decanting the solvent, the phosphonium bromide was dehydrobrominated in aq. Na_2CO_3. For the reaction, a small amount of CH_2Cl_2 was added so that the phosphorane would collect in the CH_2Cl_2 phase as the reaction proceeds. Afterwards, the CH_2Cl_2 phase was evaporated to give the phosphorane which slowly crystallized (**Scheme 6**).

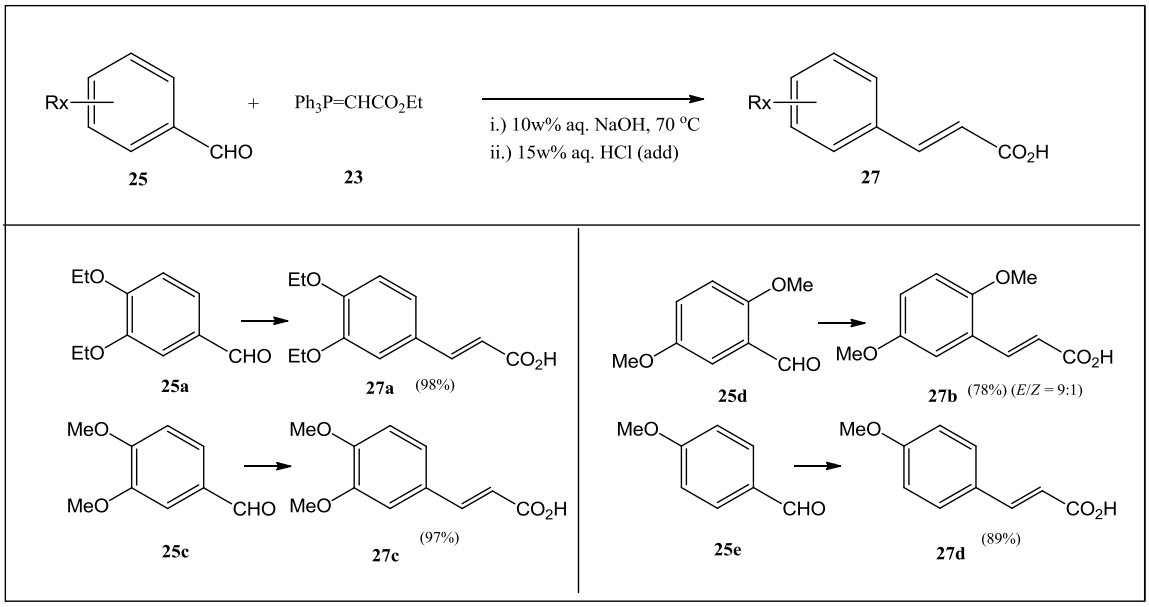


Scheme 6 : Preparation of ethoxycarbonylmethylidenetriphenylphosphorane

Next, some the alkoxylated aldehydes had to be synthesized from the corresponding hydroxybenzaldehydes by Williamson type ether synthesis (Johnstone and Rose 1979, **Scheme 7**).



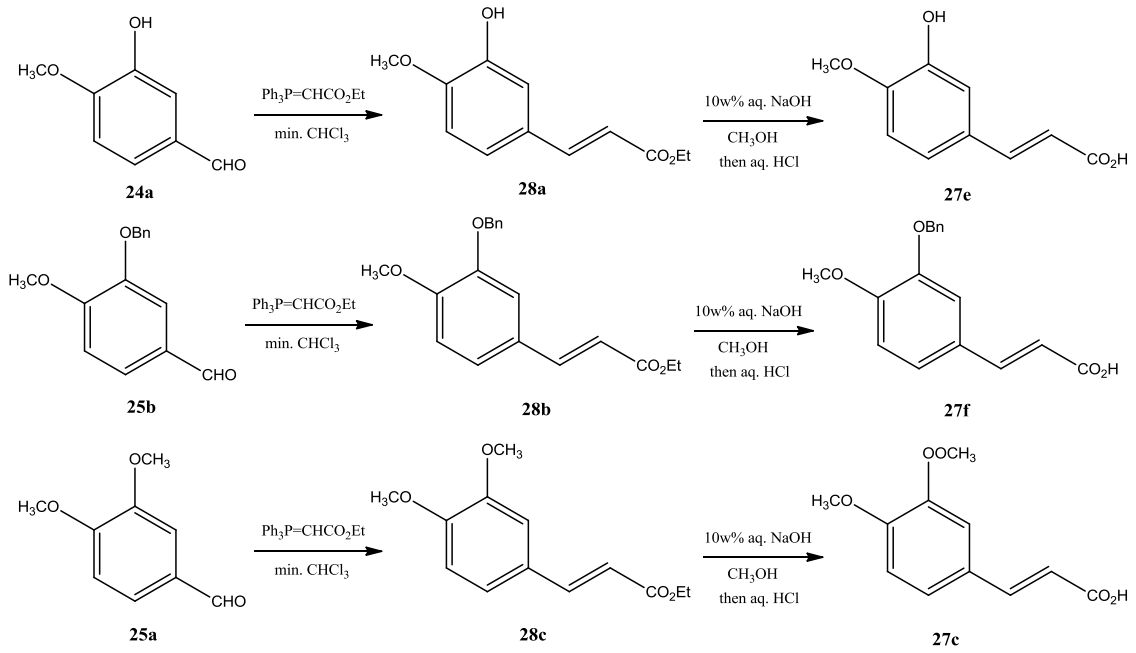
Scheme 7: Preparation of alkoxylated benzaldehydes by Williamson-type synthesis (Johnstone & Rose 1979)



Scheme 8: One step synthesis of cinnamic acids using Wittig olefination hydrolysis

For the two step Wittig olefination (**Scheme 9**) – hydrolysis, first benzaldehyde and phosphorane were reacted in a minimum amount of solvent (Thiemann et al. 2006). The cinnamate gained as product was isolated by column chromatography. Then, the alkyl cinnamate was reacted in a mixture of aq. NaOH/MeOH at 90 ^{o}C to the respective cinnamic acids. For the one-pot Wittig olefination – hydrolysis reaction, an aq. solution of 2M aq. NaOH was added to a mixture of benzaldehyde and phosphorene, and the resulting mixture was heated to 95 ^{o}C. After the reaction was complete, it was cooled to RT. During this time two phases could be seen, that is oil droplets in water. As the reaction cooled and the stirring stopped the oil droplets partially coalesced. At some point, crystallization set in. The crystallized triphenylphosphine oxide was filtered off, washed diligently with 2M aq. NaOH and water, dried and collected. The aqueous phase was acidified with half conc. aq. HCl. The warm acidified solution was allowed to cool and stand for some time for the crystallization of the respective cinnamic acids to be complete.

Sometimes it was beneficial to salt out for a complete crystallization. The cinnamic acids had to be dried carefully for the next step as the Appel type transformations are very sensitive towards water/moisture.



Scheme 9: Two step synthesis of hydroxylated/alkoxylated cinnamic acids

It is known that some benzaldehydes do not give the cinnamic acids under the one-pot conditions. 4-Nitrobenzaldehyde and 2-nitrobenzaldehyde are two described examples (Thiemann et al. 2010, Thiemann et al., 2016). 2-Hydroxybenzaldehydes, such as 2,4-dihydroxybenzaldehyde do not undergo the reaction successfully. So, the hydroxy group in 2-hydroxybenzaldehyde was protected with a benzyl group (Johnstone and Rose 1979).

3.2 The Reactions of Linking Alcohols and Amines to Carboxylic Acids Under Mild Conditions Utilizing a Modified Appel-Type Reaction

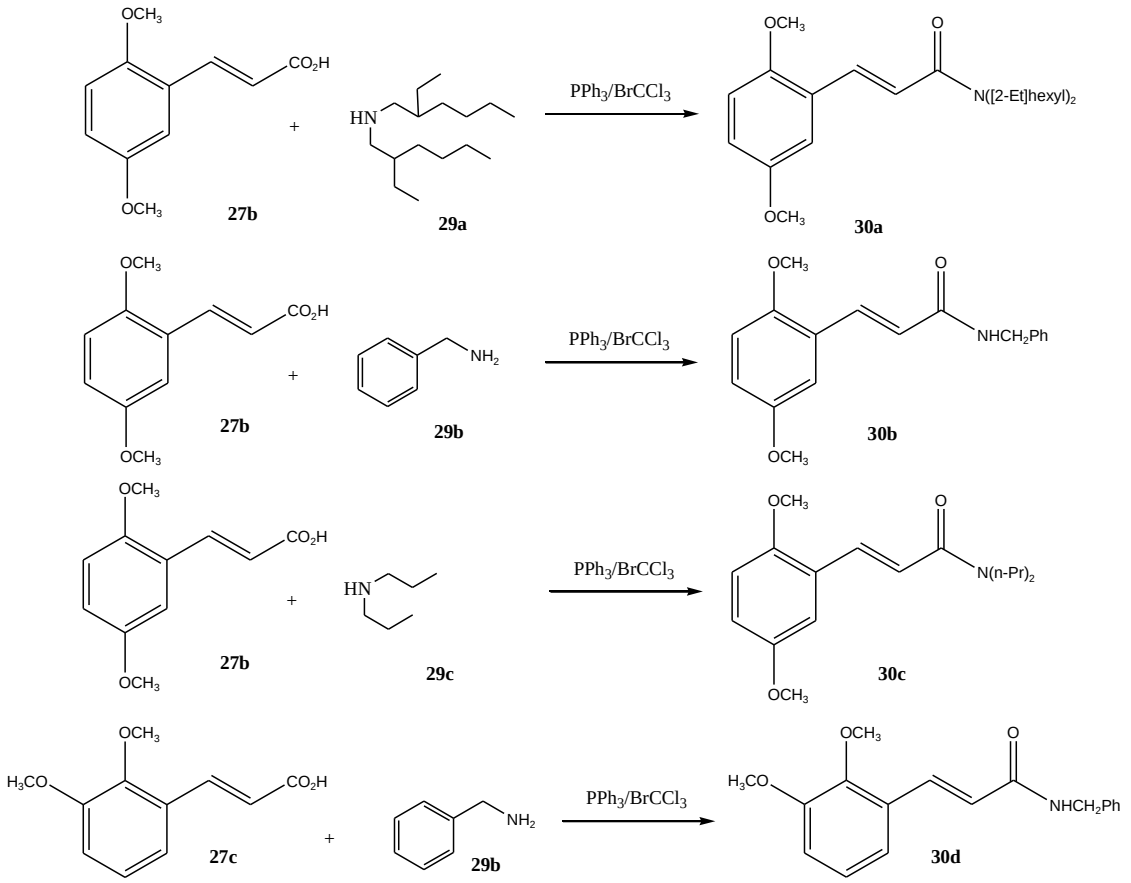
For the linking of the steroid to the precursor of the bioactive moiety or the halogen containing moiety in form of an ester or an amide, a simple reaction was looked for that would not need the preparation and isolation of a reactive acyl species such as an acyl halide (conversion of each acid component to the respective acyl halide), which our laboratory is not equipped for. The Fischer esterification needs in most of its variants elevated temperatures (Ishihara et al. 2005, Komura et al. 2008, Chakraborti et al. 2009), mostly above 80 ^{o}C, which was not suitable for our purposes. An interesting alternative is the Steglich esterification (Neises and Steglich), which uses *p*-*N*,*N*-dimethylamino pyridine (DMAP) and dicyclohexylcarbodiimide (DCC). The reaction can be altered and used for amidations of acids as well. In Thiemann group, this reaction has often been found difficult to perform as remainders of dicyclohexylcarbodiimide cannot be separated adequately from the product. Lastly, the Yamaguchi esterification (Inanaga et al. 1979, Dhimitruka and SantaLucia 2006) utilizes only one, commercially available acid chloride, namely the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride), together with DMAP, without having to convert each carboxylic acid to be converted to the corresponding acyl chloride. Because of lack of our experience with this reaction, it was decided to rather use a variation of the Appel-type esterification/amidation. It was also used to link acids to oximes in form of *O*-acyloximes (Al Azani et al. 2016).

The Appel name reaction is connected to the transformation of an alcohol to an alkyl chloride (Calzada and Hooz 1974, Appel 1975) using a combination of triphenylphosphine (PPh_3) and tetrachlorocarbon (CCl_4). The reagent PPh_3/CCl_4,

however, is also useful as a dehydrating reagent and transforms carboxylic acids into activated forms *in situ* such as to acyl chlorides. These can then be reacted with amines to carboxamides (Barstow and Hruby 1971). Mechanisms of Appel-type reactions can be complex and more than one pathway can operate at the same time. The use of an Appel-type reaction for the esterification of carboxylic acids has been mentioned in reviews (Appel 1975) without a clear reference to an original research article in this respect. Tetrachlorocarbon (CCl_4) is listed as an ozone class 1 depletor (UNEP 1996) and has been phased out for many applications. Therefore, it seemed important to look for a substitute for CCl_4. This was found in $BrCCl_3$. The C-Br bond exhibits a lower dissociation energy than the C-Cl bond, and so the photochemically induced homolytic cleavage, producing the bromo radical, occurs at a longer wavelength than the C-Cl cleavage in CCl_4. Also, $BrCCl_3$ has a small dipole, so that it would be expected that $BrCCl_3$is removed from the atmosphere more quickly than CCl_4. Still, $BrCCl_3$ has a half-life of 44 years in the atmosphere (Atkinson R. et al. 1992, Orkin and Kasimovskaya 1995), but it is not listed as a class 1 or class 2 ozone depletor. The Thiemann group started using $BrCCl_3$ in 2010. In 2010, the Lautens group published the use of $BrCCl_3/PPh_3$ in the Appel reaction itself and in the transformation of alkanones and alkanals into the corresponding dichlorovinyl compounds (Newman et al. 2011). Before that, Clement and Soulen had shown that the reaction of acyl cyanides with $PPh_3/BrCCl_3$ leads to the corresponding 3,3-dichloroacrylonitriles (Clement and Soulen 1976). Later, Thiemann et al. reported on the use of $BrCCl_3/PPh_3$ in the transformation of aldoximes and amides to nitriles (Y. Al Jasem et al. 2014) and on the use of $BrCCl_3/PPh_3$ in amidation reactions and the preparation of anhydrides from carboxylic acids (T. Thiemann et al. 2011, M. Al Azani et al. 2016). The

reaction could also be used to prepare esters and acyloximes. The reaction was utilized to prepare a number of cinnamyl esters, propionates, cinnamyl amides, and propionamides needed for as starting materials for further reactions (see below).

When $BrCCl_3$ was mixed with PPh_3 in CH_2Cl_2 or in CH_3CN a dark yellow solution developed after 20 min. of stirring at RT. When the acid component was added, the color disappeared rapidly. Addition of amine often led to a strongly exothermic reaction. When an alcohol was added for an esterification, the smell of hydrogen chloride emanated. A tertiary amine was not used as a proton scavenger. Initially, DBU was used, but the results were notbetter. Therefore, liberated HCl was driven off from time to time by putting a little vacuum onto the system. As the lab ran out of $BrCCl_3$, also CCl_4 was used in some of the experiments, as CCl_4 was used in the classical type of Appel reaction. For the esterification, it was noted, however, that the yield was lower than when using $BrCCl_3$. $BrCCl_3$ reacts with PPh_3 relatively quickly at RT., which can be followed by the change of color during the reaction. For a change of color in the reaction of CCl_4 with PPh_3, elevated temperature was needed, and this part of the Appel-type reaction was carried out in refluxing CH_2Cl_2, necessitating 45 min. Some of the cinnamic acids have poor solubility in CH_2Cl_2 – then CH_3CN was used as solvent. In those cases CH_3CN had to be removed completely before the separation of the product by column chromatography.



Scheme 10: Examples of the amidation of alkoxylated cinnamic acids in a modified Appel-type reaction

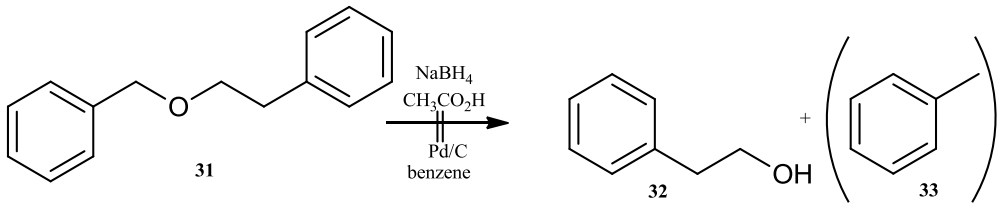
3.3 Exploratory Reactions to Hydroxylated/Alkoxylated Phenylpropionic Acids

The reaction from a cinnamic acid, a cinnamate, or a cinnamamide to a respective phenylpropionic acid, phenylpropionate or phenylpropionamide should proceed easily through hydrogenation of the double bond using hydrogen gas and a platinum or palladium catalyst (O'Connor 2011). There had been however a small fire in our laboratory in January 2013 resulting from the use of hydrogen gas and its exposure to dry catalyst. Normally, it is strongly recommended to flush the solution to be hydrogenated with inert gas before adding hydrogen.

As this was complicated with the current infrastructural setup, it was sought to derive the hydrogen *in-situ*, in the solution that was to be hydrogenated. Additionally, we wanted to use benzylic protective groups (PGs) in some of our synthetic strategies. These were to be removed at the end by hydrogenation, also. Most welcome was a selective, controlled hydrogenation process (double bond vs. debenzylation) with *in situ* generated hydrogen. From the literature, it could be seen that *in-situ* hydrogen production through the decomposition of formic acid (Garcia-Verdugo et al. 2006) had been explored previously. In addition, "hydrogen transfer" reactions (Zassinovich et al. 1997; Brieger and Nestrick 1975) are known, where no externally added hydrogen gas is necessary. Typical "hydrogen donors" can be ammonium formate (Paryzek et al. 2003), formic acid (Brunel 2007; Berthold 2002, Soltani et al. 2009), hydrazine (Imada et al. 2010) or silanes (Mandal and McMurray 2007).

Many of the hydrogen transfer reactions, however, need specific catalysts that are not easy to obtain. When screening the literature, the most promising system for hydrogenating alkenes with *in situ* produced hydrogen seemed to be the one forwarded by D. B. Cordes et al. (Russo et al. 2011; Rousslang et al. 2011; Tran et al., 2009). D. B. Cordes used $NaBH_4$, acetic acid (AcOH) in the presence of Pd/C with toluene as the solvent. From their work it was clear that halo substituents such as bromo and chloro substituents would be reductively removed, but the work did not investigate whether the system $NaBH_4$, AcOH, Pd/C (cat.) would reductively cleave benzyl esters, benzyl ethers or benzyl amides to produce the free acids, alcohols and amines, respectively.

When $NaBH_4$, CH_3CO_2H, Pd/C in the first *O*-debenzylation reactions, the *O*-debenzylation, *eg.* From **31** to **32**, did not proceed, even with an excess of reagent (**Scheme 11**).

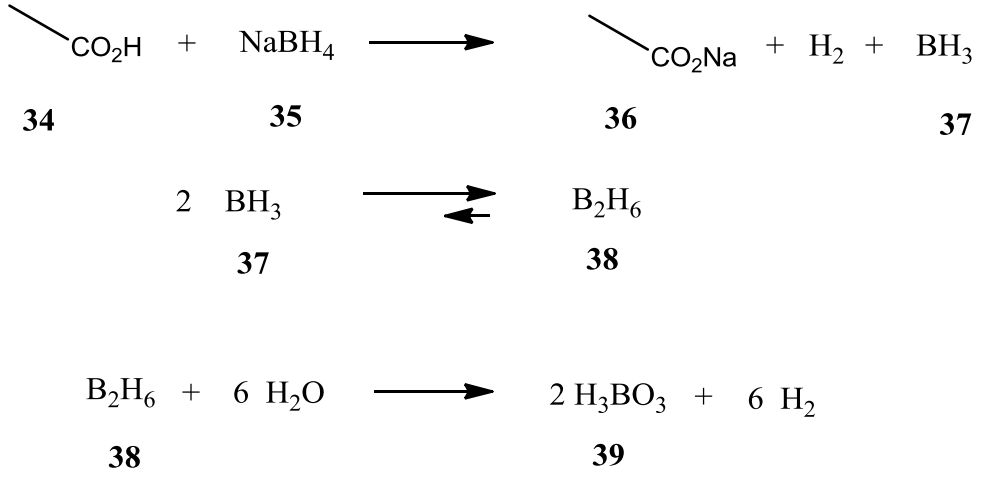


Scheme 11: O-Debenzylation of (2-(benzyloxy)ethyl)benzene does not proceed under the conditions

This result gave an indication that $NaBH_4$, CH_3CO_2H, Pd/C could be used as a reaction system that would allow to hydrogenate double bonds in the presence of benzyl ethers and benzyl esters. In order to assure this, hydrogenations of alkenes carrying *O*-benzyl ether, *O*-benzyl ester and *N*-benzyl amide functions with this reducing agent.

When a finely ground powder of $NaBH_4$ is added to a mixture of alkene, acetic acid and Pd/C in toluene or benzene, fine gas bubbles appear immediately. The sodium borohydride reacts with the acetic acid, giving, apart from sodium acetate (**36**), hydrogen and borane. Borane (**37**), or its formed dimer, diborane (**38**), would then hydrolyse with the water introduced with the acetic acid and solvents to form boric acid (**39**) and further hydrogen (**Scheme 12**). The hydrogen thus produced *in situ* provides the reagent in the Pd/C catalyzed hydrogenation reaction of the alkenes. The life-time of the borane (**37**)/ diborane (**38**) produced in the reaction has not been ascertained and so great care must be

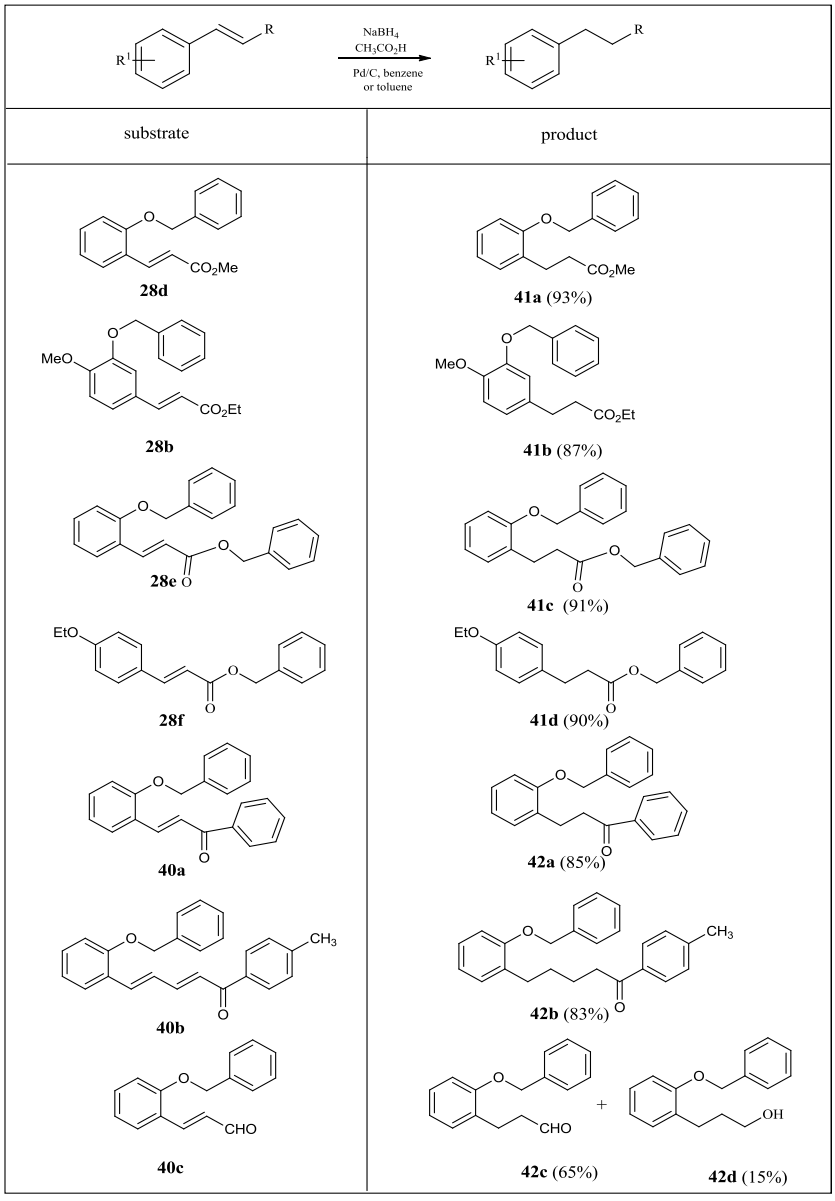
taken, as borane (**37**)/ diborane (**38**) are highly toxic, and a complete hydrolysis of the borane with completion of the hydrogenation of the alkenes has not been established.



Scheme 12: Reaction sequences of NaBH4 in presence of CH_3CO_2H and water

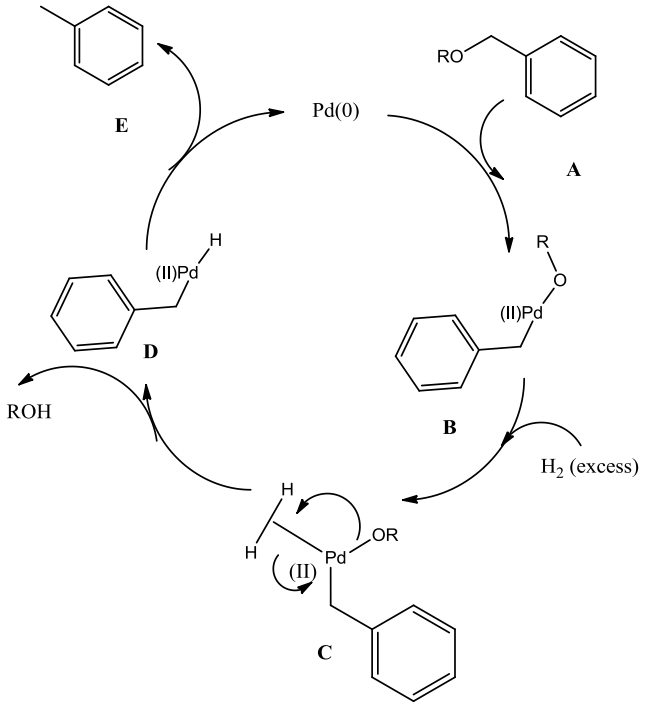
With $NaBH_4$, CH_3CO_2H, Pd/C in toluene or benzene, alkenes **28** and **40**, carrying *O*-benzyl ether functions and/or *O*-benzyl ester groups could be hydrogenated effectively without loss of the *O*-benzyl function. Multiple double bonds in a substrate are completely hydrogenated under the conditions as can be seen in the transformation of compound **40b** to compound **42b**. Ketones are not reduced with $NaBH_4$, CH_3CO_2H, (cat.) Pd/C, evident in the conversions of **40a**/**40b** to **42a**/**42b**. Upon careful handling, even a carbaldehyde-function can be retained in the reaction as can be seen in the transformation of 2-benzyloxycinnamaldehyde (**24**) to 2-benzyloxyphenylpropionaldehyde (**40c**) with only relatively small amounts of 3-(2-benzyloxyphenyl) propanol (**42d**) evident as by-product (**Table 1**).

Table 1: Reduction of alkenes carrying O-benzyl ester and/or O-benzyl ether functions

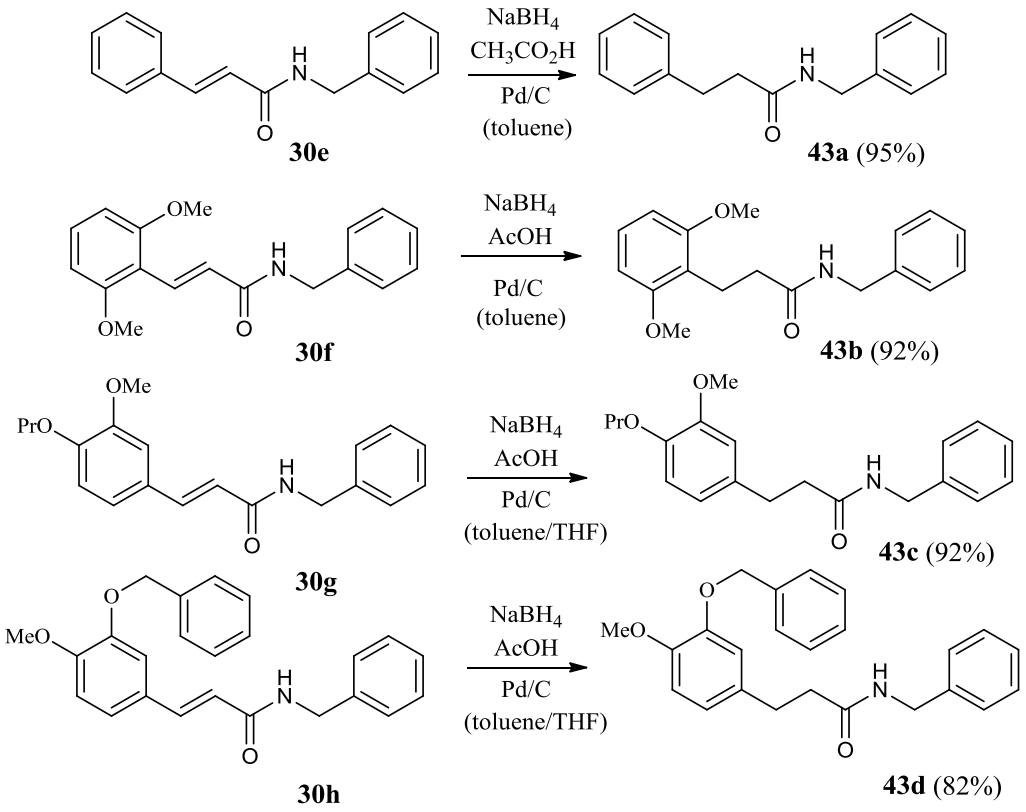


It is known that also ammonia, ammonium acetate and pyridine suppress reductive *O*-debenzylation with hydrogen in the presence of Pd/C, while the hydrogenation of alkenes proceeds under the conditions (Sajiki 1995, Sajiki et al. 1997, Sajiki et al. 1998A, Sajiki et al. 1998B, Sajiki and Hirota 1998, Sajiki and Hirota 2003).

Also, Bartsch 1984, Pennings and Reinhoudt 1983, Fleet and Smith 1985). Shortly, the mechanistic reasoning behind the suppression of the *O*-debenzylation in our case is not clear. The accepted mechanism for the Pd (0) hydrogenative *O*-debenzylation is shown in **Scheme 13**. It must be noted that the reaction is taken place under heterogeneous conditions, while the mechanism does not consider this. It is believed that the reductive step **D** to **E** is significantly important to determine the character of the "Pd(0)" species and may depend on the reactive system (**Scheme 13**).



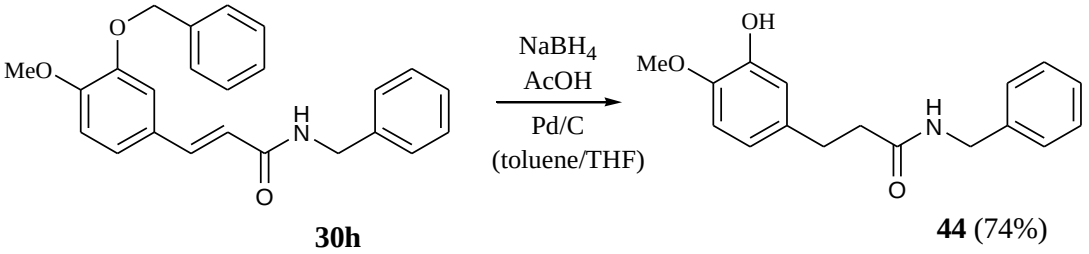
Scheme 13: Accepted mechanism for Pd(0) catalysed hydrogenative O-debenzylation.



Scheme 14: Hydrogenation of N-benzyl cinnamamides to N-benzyl phenylpropionamides

Also, *N*-benzyl cinnamamides **30e** – **30h** were subjected to hydrogenation with $NaBH_4$, CH_3CO_2H in the presence of cat. Pd/C to afford the corresponding *N*-benzyl phenylpropionamides **43a – 43d** (**Scheme 14**). Due to the poor solubility of both **30g** and **30h** compounds in toluene or benzene, their hydrogenation was carried out in a mixture of toluene and THF (1/1 *v*/*v*). No *N*-debenzylation was observed in the reactions. Overall, the stability of the benzyl protective group (Bn-PG) was found to be -NHBn; -CH_2OCH_2Ph > $PhOCH_2Ph$ > -CO_2CH_2Ph, under the reaction conditions used. This could be seen when *N*-benzyl 4-methoxy-3-benzyloxycinnamamide **30h** was subjected to prolonged reaction more than 36 hrs. with $NaBH_4$, CH_3CO_2H, Pd/C in a solvent mixture

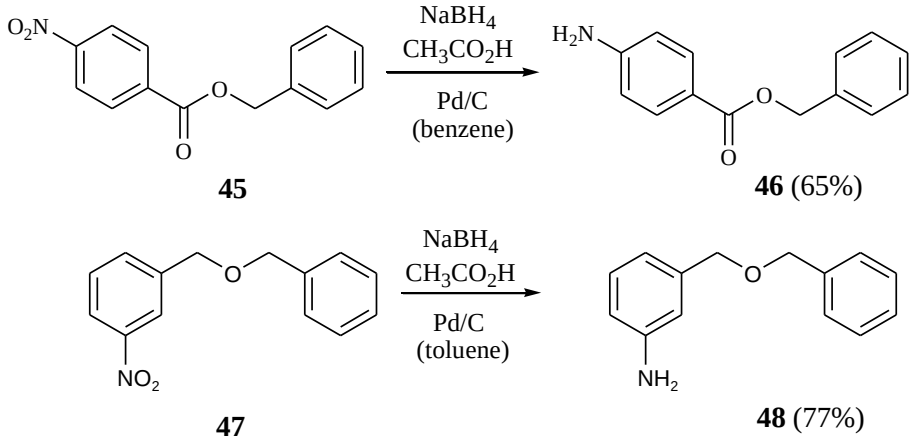
of toluene and THF (1:1 *v*/*v*), where the O-benzyl function was reductively cleaved as well to give phenol **44** (**Scheme 15**).



30h **44** (74%)

Scheme 15: The hydrogenation of N-benzyl 4-methoxy-3-benzyloxycinnamide

While we found that 2,5-dimethoxycinnamamides with secondary amines have low melting points, 2,5-dimethoxypropionamides with secondary amines are oils. 2,5-Dimethoxypropionamides with primary amines such as with *n*-octylamine have higher melting points as they exhibit intermolecular hydrogen bonding. With *N*-benzyl 4-benzyloxypropionamide as substrate, the debenzylation does not proceed even after 2.5 days.



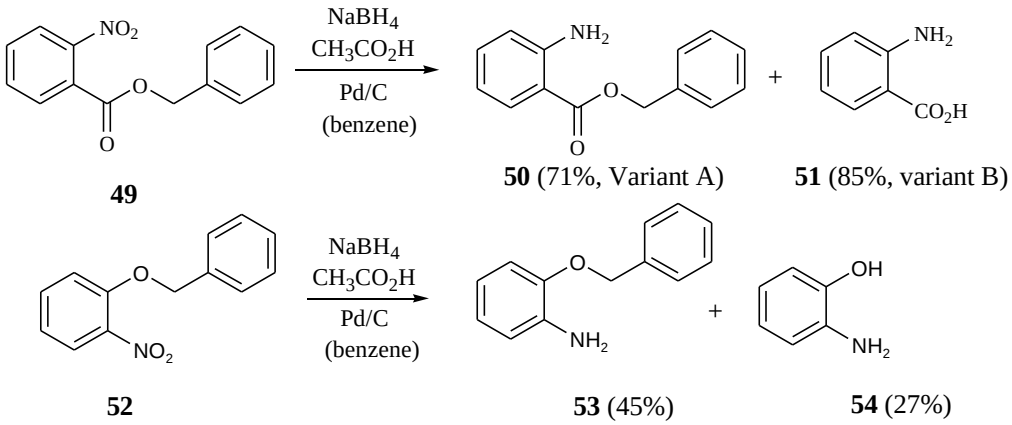
45 **46** (65%)

47 **48** (77%)

Scheme 16: Reductive transformation of nitroarenes to anilines with $NaBH_4$, AcOH, cat. Pd/C.

Finally, the use hydrogen in presence of Pd/C is an often used method to convert nitroarenes to anilines (Vanier 2007). Other hydrogen sources such as formic acid and decaborane with Pd/C have been used in the transformation (Berthold et al. 2002, Bae et al. 2000). Although it would not benefit our final target, some nitrated benzyl ethers and benzyl esters were subjected to the conditions used above. It was found that nitroarenes are reduced to anilines also with the system $NaBH_4$ and CH_3CO_2H in the presence of cat. Pd/C. Here, benzyl 4-nitrobenzoate (**45**) could be converted cleanly to benzyl 4-aminobenzoate (**46**). Furthermore, benzyl 3-nitrobenzyl ether (**47**) could be transformed to 3-aminobenzyl benzyl ether (**48**) (Scheme 10). However, in the case of both benzyl 2-nitrobenzoate (**49**) and benzyl 2-nitrobenzyl ether (**52**), the benzyl group was removed reductively to give mixtures of anthranilic acid (**51**) and benzyl 2-aminobenzoate (**50**) and of 2-aminobenzyl benzyl ether (**53**) and 2-aminophenol (**54**), respectively (Scheme 11).

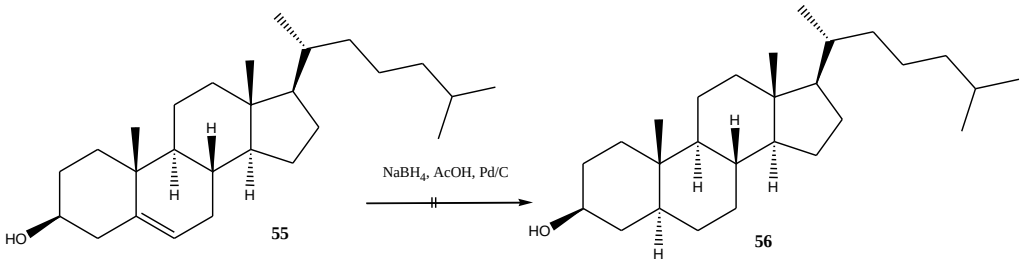
Here, close proximity of the nitro group to the benzyl function leads to partial reductive cleavage of the latter. While the reduction of the nitro group can pass through a number of intermediates and can be mechanistically complex, it is believed that a reactive intermediate along the pathway from nitro- to amino-function leads to the reductive cleavage of the benzyl ether in **53** and benzyl ester in **50**.



Scheme 17: Reductive transformations of nitroarenes with benzyl functions in close proximity to the nitro group.

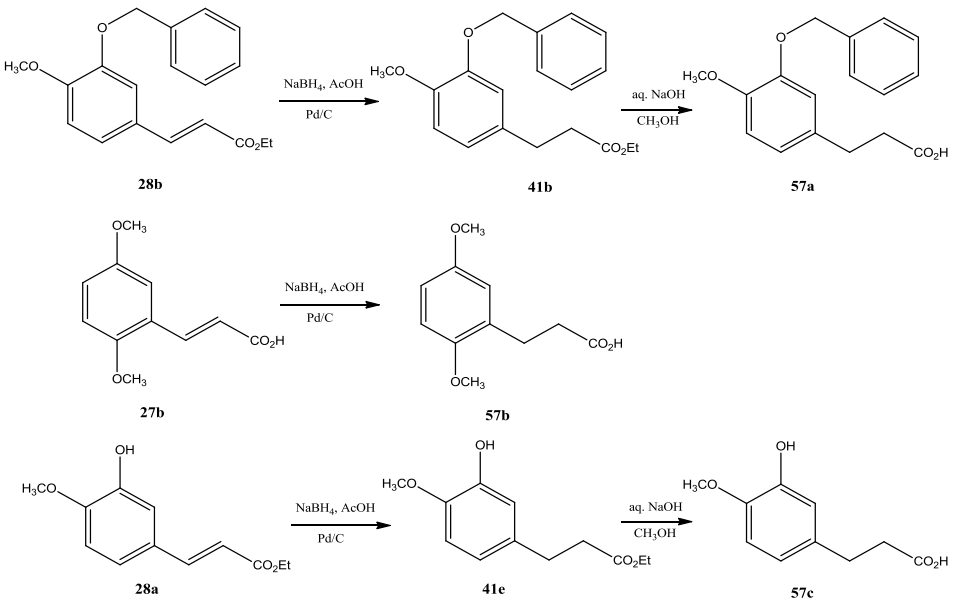
In all, a way was found that could be used in our laboratory to hydrogenate alkenes without reduction of ester functionalities and with a control over whether a debenzylation would take place at the same time or not. The reaction was used later to perform clean two step reactions: hydrogenation of the double bond and subsequent debenzylation. The hydrogenation step was used for all phenylpropionates and phenylpropionamides produced in this thesis. The two-step reaction was used to prepare all the 3-hydroxy-4-propionates and 3-hydroxy-4-methoxypropionamides in this thesis (see below). Interestingly, recently, P. R. Sultane et al. also reported on the use of $NaBH_4$ in CH_3OH in the presence of Pd/C as a convenient protocol for the deprotection of benzyl esters (Sultane et al. 2015). In the paper, it is noted that H_2 is produced when $NaBH_4$ is allowed to react with CH_3OH. However, it is also well-known that $NaBH_4$ in CH_3OH reduces ketones and aldehydes, maybe predominantely in the form of $NaBH_x(OCH_3)_y$ (X = 1-3; Y = 1-3), so that here a combination of mechanisms can operate: hydrogenation with *in situ* created H_2, reduction with *in situ* created BH_3 or B_2H_6, and hydride transfer.

The combination of $NaBH_4$ and a ruthenium salt such as $RuCl_3 \cdot 3H_2O$ has also been used successfully in the hydrogenation of olefins in the presence of ester functions and benzyl ether groups, which are not affected (Sharma et al. 2007, Babler et al. 2011, Babler and White 2010). Also the combination of $NaBH_4$ and catalytic amounts of cobalt salts are known to reduce alkenes to alkanes, but here also ester groups are reduced, so that these cases involve a completely mechanism of reduction as compared to the one operating when using $NaBH_4$, AcOH, Pd/C. It must also be noted that our system does not hydrogenate trisubstituted alkenes such as cholesterol (**55**) (**Scheme 18**).



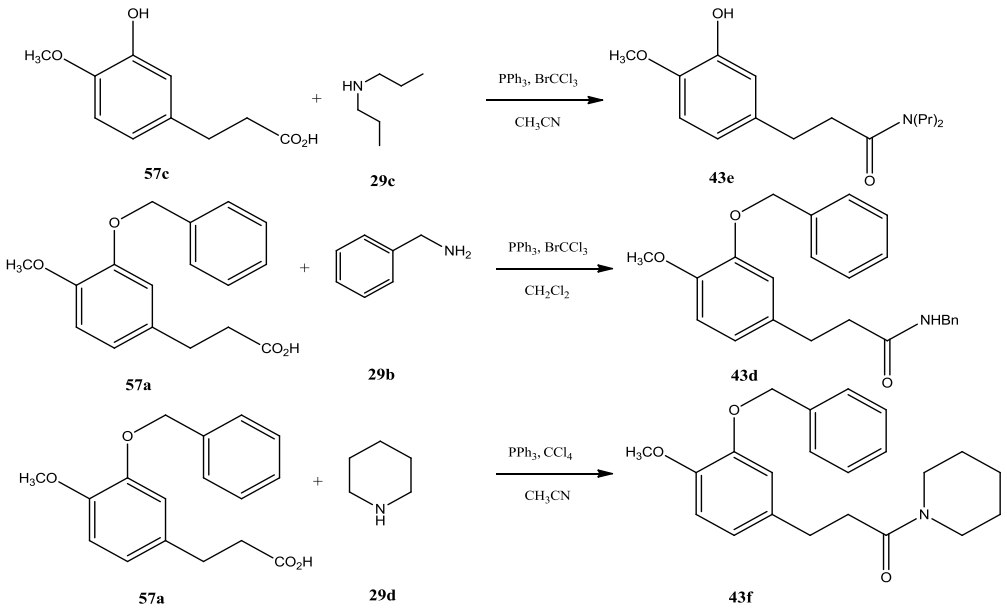
Scheme 18: Attempted hydrogenation of cholesterol with NaBH4, AcOH in the presence of Pd/C.

Importantly, however, also the cinnamates and cinnamic acids could hydrogenated with NaBH4, AcOH in the presence of Pd/C to the corresponding phenylpropionates and phenylpropionic acids, where the hydrogenation of the cinnamates could be achieved readily, while the cinnamic acids were sluggish in the reaction and reaction times were long (up to 3 days). So, it was beneficial to hydrogenate the cinnamate first, and then to hydrolyse the ester (**Scheme 19**).



Scheme 19: Hydrogenation of cinnamates and cinnamic acids to phenyl- propionates and phenylpropionic acids with NaBH4, AcOH in presence of Pd/C.

The phenylpropionic acids could then be transformed into amides or esters utilizing the modified Appel reaction (**Scheme 20**).



Scheme 20: Amidation of phenylpropionic acids by modified Appel reaction

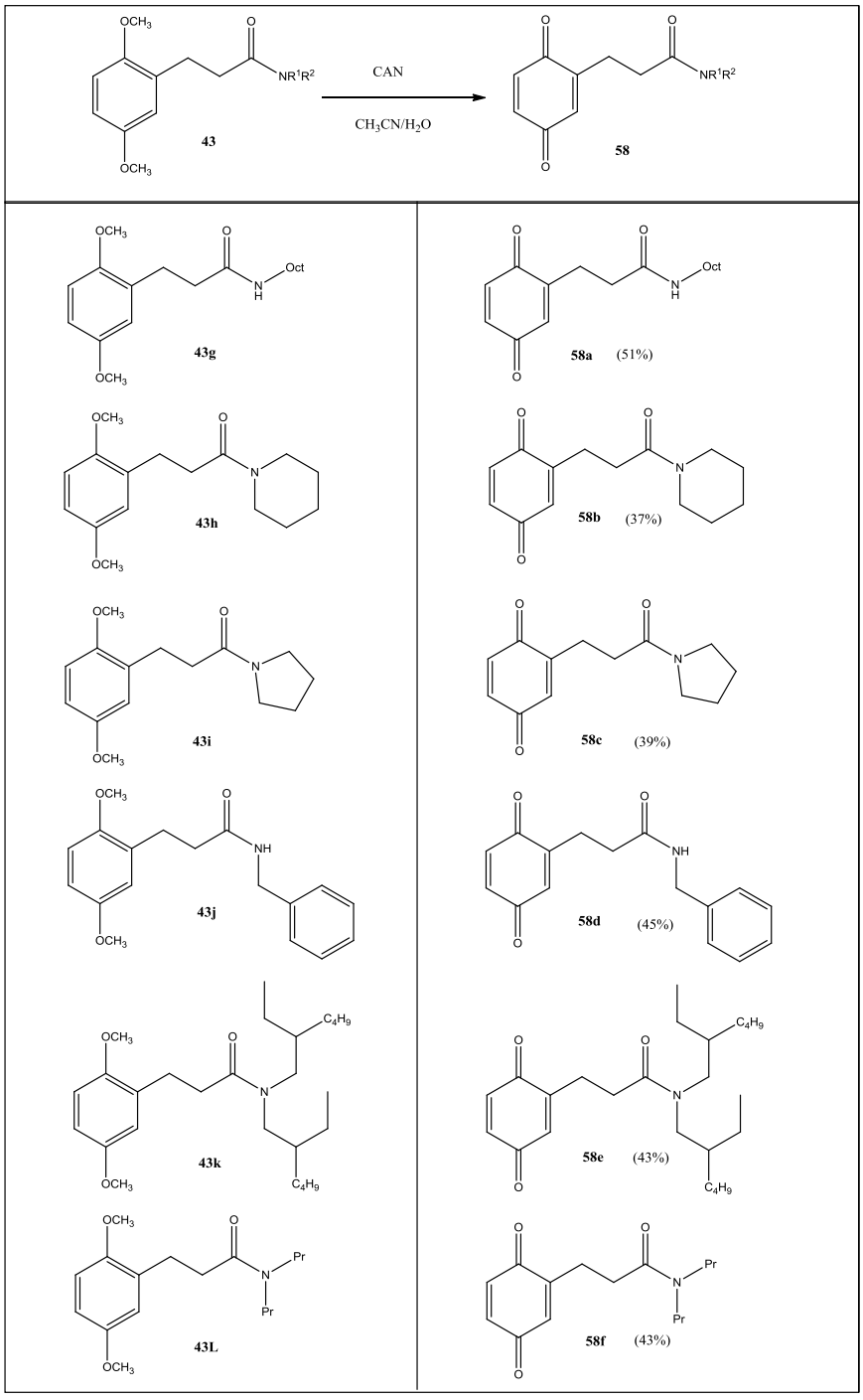
3.4 Exploratory Reactions of Converting 1,4-dimethoxyphenylpropionates and 1,4-dimethoxyphenylpropionamides

A number of different synthetic approaches are known to quinones from alkoxylated/hydroxylated benzenes (Abraham et al. 2011, Weaver and Pettus 2014). Common reagents used are cerium ammonium nitrate (CAN) (Jacob et al. 1976) and potassium dinitrosodisulfonate (Fremy's salt) (Weaver and Pettus 2014).

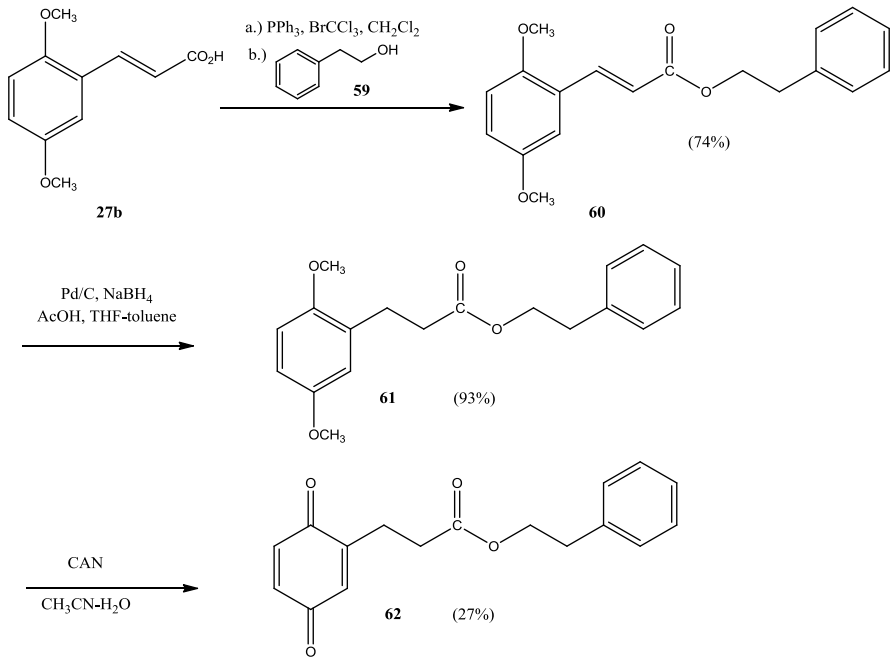
The conversion of 1,4-dimethoxybenzene to *para*-benzoquinones is almost always carried out with CAN, often using a mixture of CH_3CN and H_2O as solvent. The 2,5-dimethoxypropionates and 2,5-dimethoxypropionamides facilely reacted to the corresponding *para*-benzoquinones (**Table 2**). Upon addition of the yellow, aqueous solution of CAN to the product in acetonitrile, the reaction mixture immediately turned orange-reddish. The orange-reddish component of the reaction mixture is a by-product, however, from which the oftentimes yellow (in solution) quinone can be separated by column chromatography.

Sometimes, R_f values of starting material and product can be similar, but the product can be seen as more "UV intense" on the TLC. Also, the product, initially showing a faint yellow color on the TLC will turn brownish upon standing, probably due to a redox reaction of the quinone. From the column, the quinones are obtained as pale-yellow to orange solids in the case of the secondary amides and as orange to reddish oils in case of the tertiary amides. Both carbonyl functions of the quinones invariably show a peak in the range of δ187.0 – 188.0 ppm in the ^{13}C-NMR spectrum.

Table 2: Preparation of amidoethylquinones



(Source: Al-Azani et al. 2015)



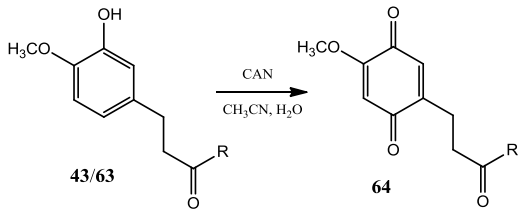
Scheme 21: Example of the preparation of a quinonylpropionate (Al-Azani et al. 2015)

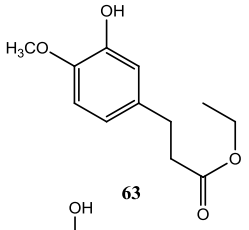
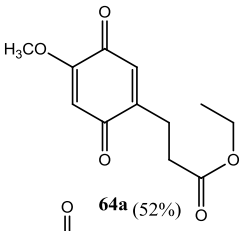
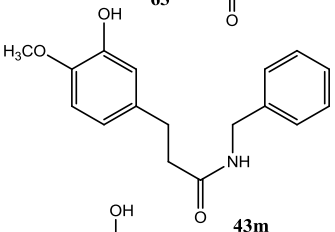
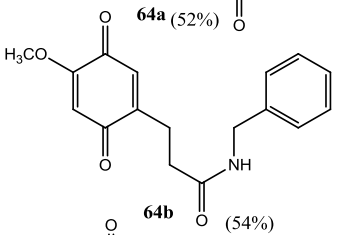
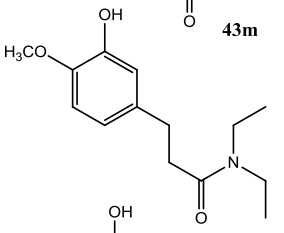
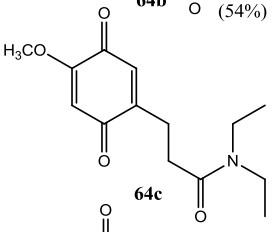
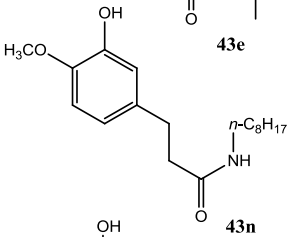
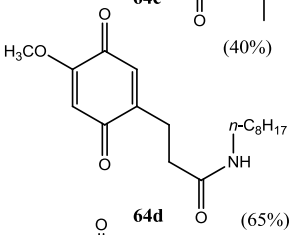
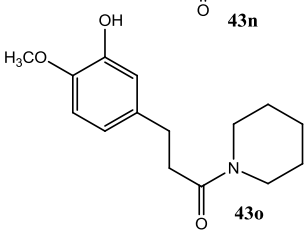
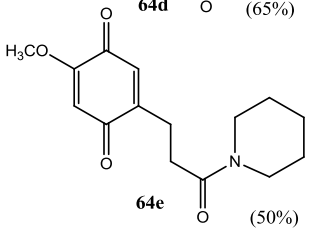
The process of Appel type reaction with 2,5-dimethoxycinnamic acid (**27b**) using $PPh_3/BrCCl_3$ as the reagent, hydrogenation of the Appel-type product using $NaBH_4$-AcOH-THF-toluene and subsequent oxidative demethylation with CAN in AcCN-H_2O can also be used nicely to prepare quinones bound to a substructure by ester linkage as shown in **Scheme 21**.

3.5 Exploratory Reactions of Converting 3-hydroxy-4-methoxyphenyl propionates and 3-hydroxy-4-methoxyphenylpropionamides

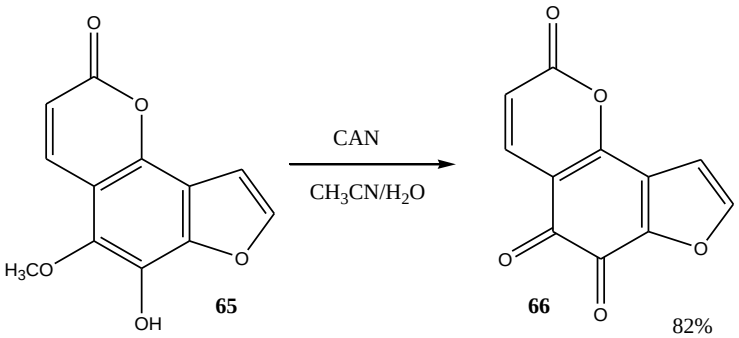
When, the 3-hydroxy-4-methoxyphenylpropionamides were treated with CAN in H_2O-AcCN, methoxyquinonylpropionamides **64** were produced (**Table 3**).

Table 3: Conversion of 3-hydroxy-4-methoxyphenylpropionate and 3-hydroxy-4-methoxy phenylpropionamides to alkoxycarbonylethyl-methoxy-quinone and amidoethyl-methoxy-quinones



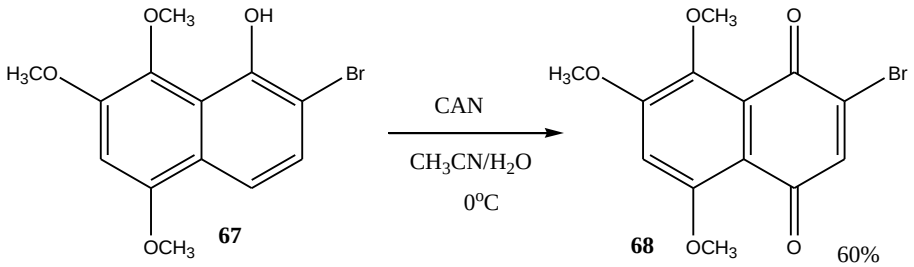
Starting material	Product (Yield)
 **63**	 **64a** (52%)
 **43m**	 **64b** (54%)
 **43e**	 **64c** (40%)
 **43n**	 **64d** (65%)
 **43o**	 **64e** (50%)

The conversion of the hydroxyl-methoxyarene to the methoxyquinone system is of interest and not trivial. Equally well, it could have been envisaged that an *ortho*-quinone (minus methoxy group) would form, as there is some precedence for this as in the synthesis of isopsoralenquinone **66** (**Scheme 22**) (Reed & Moore 1988).

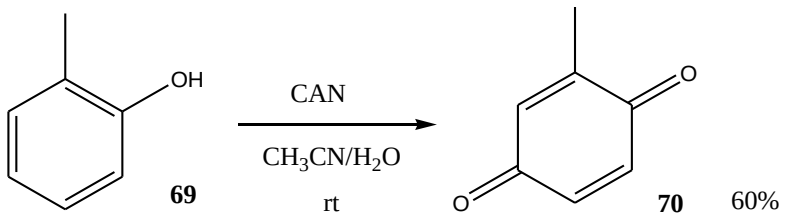


Scheme 22: Synthesis of isopsoralenquinone (Reed and Moore 1988).

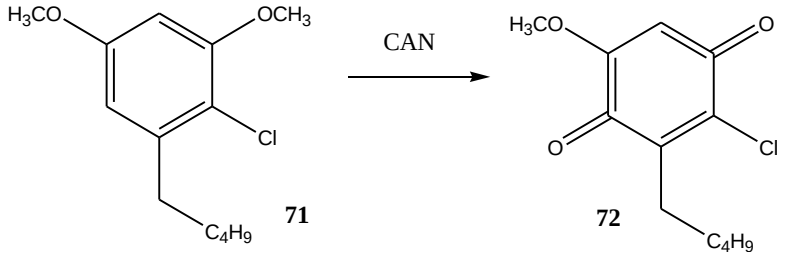
There are some examples, however, where an oxo group is introduced *para* to a hydroxy- or methoxy group upon reaction with CAN, if the *para*-position is available. Examples are given in **Schemes 17** and **18**.



Scheme 23: Oxidation of bromonaphthol to naphthoquinone (Wu et el. 2011)



Scheme 24: Oxidation of 2-methylphenol to 2-methyl-p-benzoquinone (Rao et al. 1985)



Scheme 25: Oxidation to chloromethoxybenzoquinone (Spyroudis 2000, Bruner et al. 1995)

Scheme 25 shows a typical example, where an oxo group is introduced by CAN into the 1,4-position to a methoxy group to give a *p*-quinone is the chloro-methoxy-substituted arene **71**, which is transformed to **72** (Spyroudis 2000, Bruner et al. 1995). The direct oxidation of phenols to *para*-quinones can also be achieved with salcomine/O_2(Podlesny and Kozlowski 2012) and with O_2 itself in the presence of a base (Danheiser et al. 1992) such as TBAF or KOBu^t. In all, the transformation from 3-hydroxy-4-methoxyphenylpropionamides and 3-hydroxy-4-methoxyphenylpropionates to the corresponding methoxyquinones, pursued in this thesis, is worth a more comprehensive study.

The UV-VIS spectra of the acquired quinones were measured in CH_2Cl_2 and CH_3CN. No appreciable solvent effect was noted, however. Isolated quinones show an

intense absorption at λ = 250 nm and a weaker absorption band at λ = 305-310 nm (see **Scheme 26**). Quinones with a carbonyl substituent exhibit an intense absorption at λ = 245 nm and a weaker absorption band at λ = 325 nm. The methoxy substituted quinones display an intense absorption at λ = 265 nm and a weaker absorption band at λ = 350 - 360 nm, meaning that both absorption bands are shifted towards lower energy versus the isolated quinone systems.

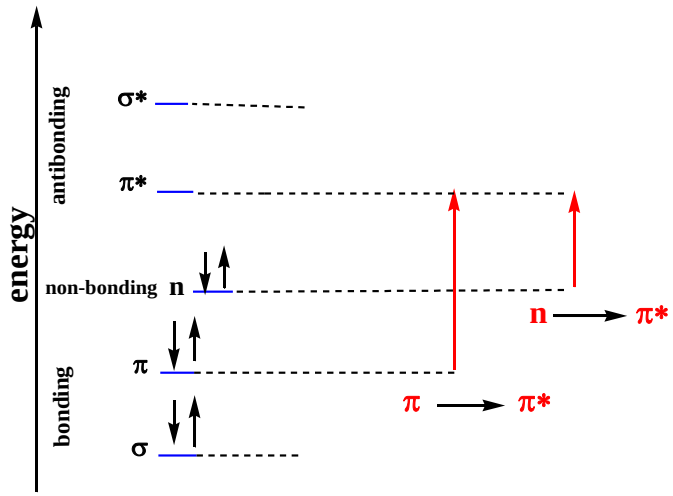
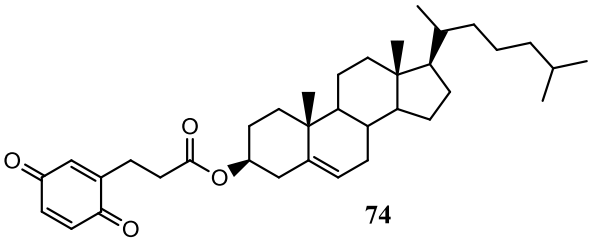


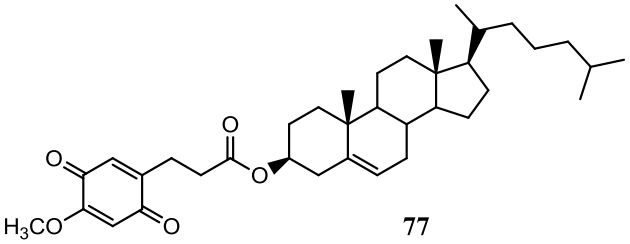
Figure 1: Electronic scheme of a p-quinone

According to the literature, both absorptions that were observed are related to π-π* transitions. n-π* Transitions have been reported to be very weak and at longer wavelengths (400-500 nm and 650 nm, respectively) (Orlando et al. 1968, Kuboyama 1962). These were not specifically looked for in our case.



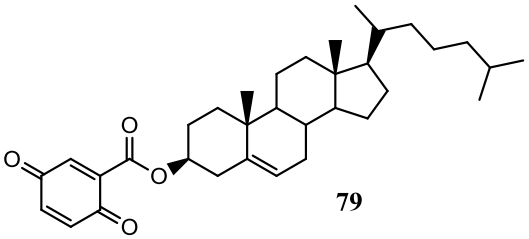
74

CH_2Cl_2: λ = 310 nm (ε = 642 $mol^{-1}cm^{-1}$); λ = 250 nm (ε = 22570 $mol^{-1}cm^{-1}$)
CH_3CN:λ = 305 nm (ε = 646 $mol^{-1}cm^{-1}$); λ = 250 nm (ε = 14950 $mol^{-1}cm^{-1}$)



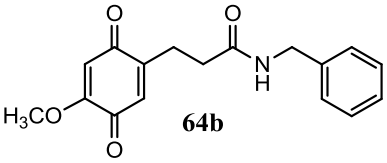
77

CH_2Cl_2: λ = 360 nm (ε = 595 $mol^{-1}cm^{-1}$); λ = 265 nm (ε = 12500 $mol^{-1}cm^{-1}$)



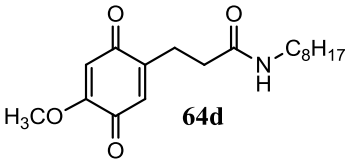
79

CH_2Cl_2: λ = 325 nm (ε = 1072 $mol^{-1}cm^{-1}$); cnd
CH_3CN:λ = 325 nm (ε = 1025 $mol^{-1}cm^{-1}$); λ = 245 nm (ε = 17710 $mol^{-1}cm^{-1}$)



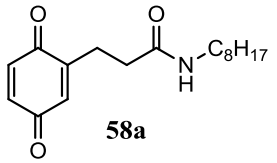
64b

CH_2Cl_2: λ = 351 nm (ε = 220 $mol^{-1}cm^{-1}$); λ = 265 nm (ε = 5665 $mol^{-1}cm^{-1}$)
CH_3CN:λ = 351 nm (ε = 490 $mol^{-1}cm^{-1}$); λ = 260 nm (ε = 8150 $mol^{-1}cm^{-1}$)



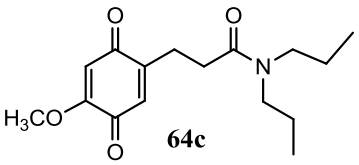
64d

CH_2Cl_2: λ = 355 nm (ε = 598 $mol^{-1}cm^{-1}$); λ = 265 nm (ε = 15020 $mol^{-1}cm^{-1}$)



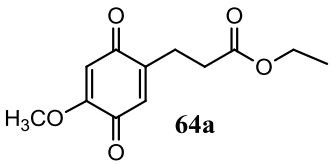
58a

CH_3CN:λ = 325 nm (ε = 1500 $mol^{-1}cm^{-1}$); cnd



64c

CH_2Cl_2: λ = 355 nm (ε = 547 $mol^{-1}cm^{-1}$); λ = 265 nm (ε = 13730 $mol^{-1}cm^{-1}$)
CH_3CN:λ = 351 nm (ε = 718 $mol^{-1}cm^{-1}$); λ = 260 nm (ε = 25480 $mol^{-1}cm^{-1}$)



64a

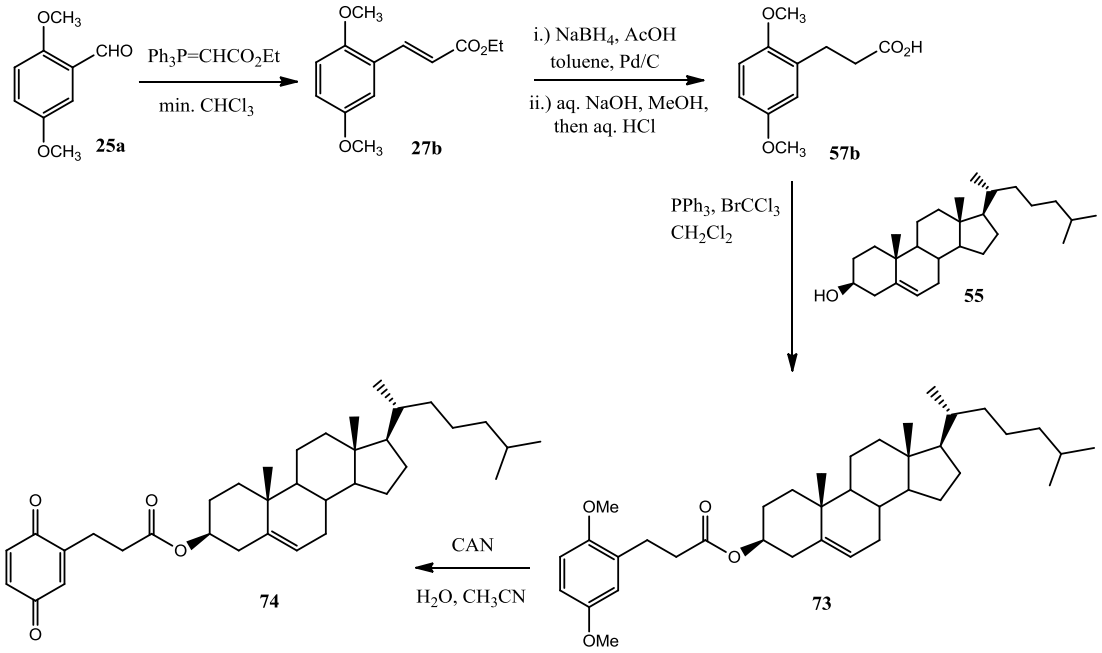
CH_3CN: λ = 360 nm (ε = 595 $mol^{-1}cm^{-1}$); λ = 260 nm (ε = 15100 $mol^{-1}cm^{-1}$)

Scheme 26: UV-VIS absorption data for selected quinones.

3.6 Preparation of Cholesteryl and Estradiol Derived Steroid Quinone Hybrids Utilizing the Above Reactions

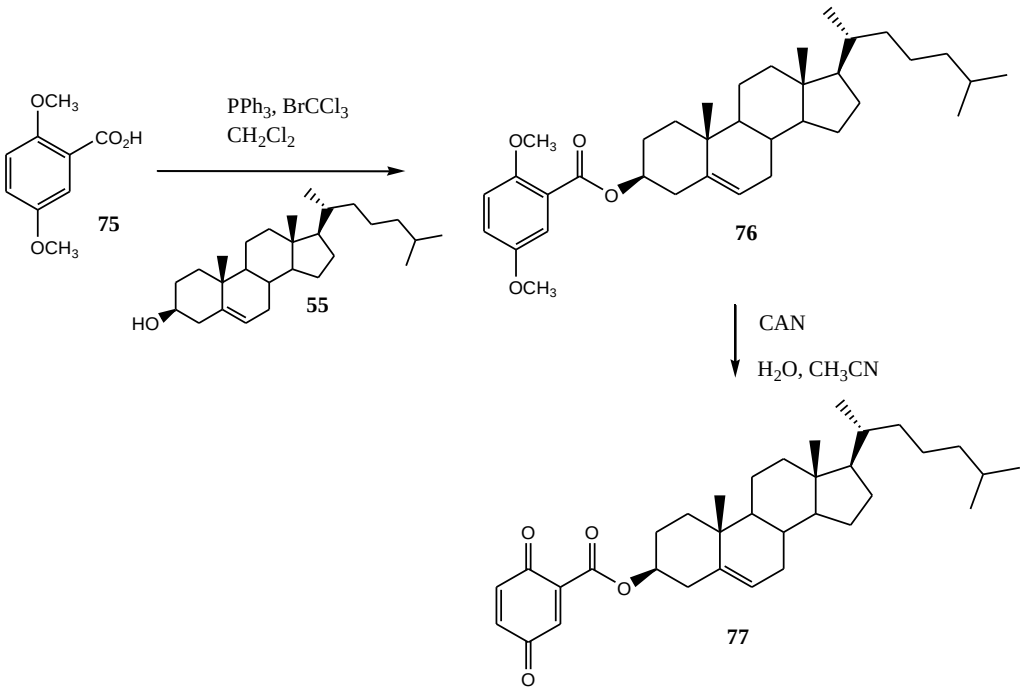
Finally, a number of steroid-quinone conjugates were prepared using the reactions studied and optimized above. Starting from 2,5-dimethoxybenzaldehyde (**25a**), a Wittig reaction produced dimethoxycinnamate **27b**. **27b** was subjected to hydrogenolysis using $NaBH_4$, AcOH, Pd/C. The dimethoxyphenylpropionate obtained was hydrolysed to **57b** (aq. NaOH, MeOH). It must be noted that during hydrolysis sodium salts can be obtained that are not completely soluble in the solvents mixture. One needs to take care not to lose this precipitated part. For instance, when hydrolyzing ethyl 4-benzyloxypropionate, which itself is an oil, in 10w%aq. NaOH/MeOH (2:1 v/v), it can be seen that after some time a solid forms which is the sodium 4-benzyloxypropionate. 2,5-Dimethoxypropanoic acid (**57b**) does not crystallize well from the aqueous solution, so that the ensuing mixture was extracted with ether and chloroform. A short column followed. Then, the 2,5-dimethoxyphenylpropionic acid (**57b**) was esterified with cholesterol (**55**) using the modified Appel type reaction. Finally, the cholesteryl dimethoxyphenylpropionate **73** was oxidized with CAN in H_2O/CH_3CN to the cholesterol quinone hybrid **74**. 3-Cholesteryl 2,5-dimethoxypropionate (**73**) crystallizes slowly. Once crystallized, however, it is hard to dissolve in acetonitrile. Nevertheless, it is possible to add a small amount of dichloromethane that helps dissolves the steroidal ester, but is not detrimental to the progress of the reaction. More problematic is the reaction with 3-cholesteryl 2,5-dimethoxybenzoate (**76**). Here, the addition of a small amount of CH_2Cl_2 still leads to an incomplete oxidation of the starting material. As reactions with CAN have been reported to proceed in CH_3CN, THF, CH_2Cl_2 and even in alcohols, it was decided to run the

reaction in a mixture of CH_3CN/CH_2Cl_2 that would be able to solubilize the starting material. Also, the reaction time was lengthened to 1h as the product seemed to be reasonably stable in the reaction medium (**Scheme 27**).



Scheme 27: Overall reaction sequence to 3-cholesteryl 1,4-quinon-2-ylpropionate

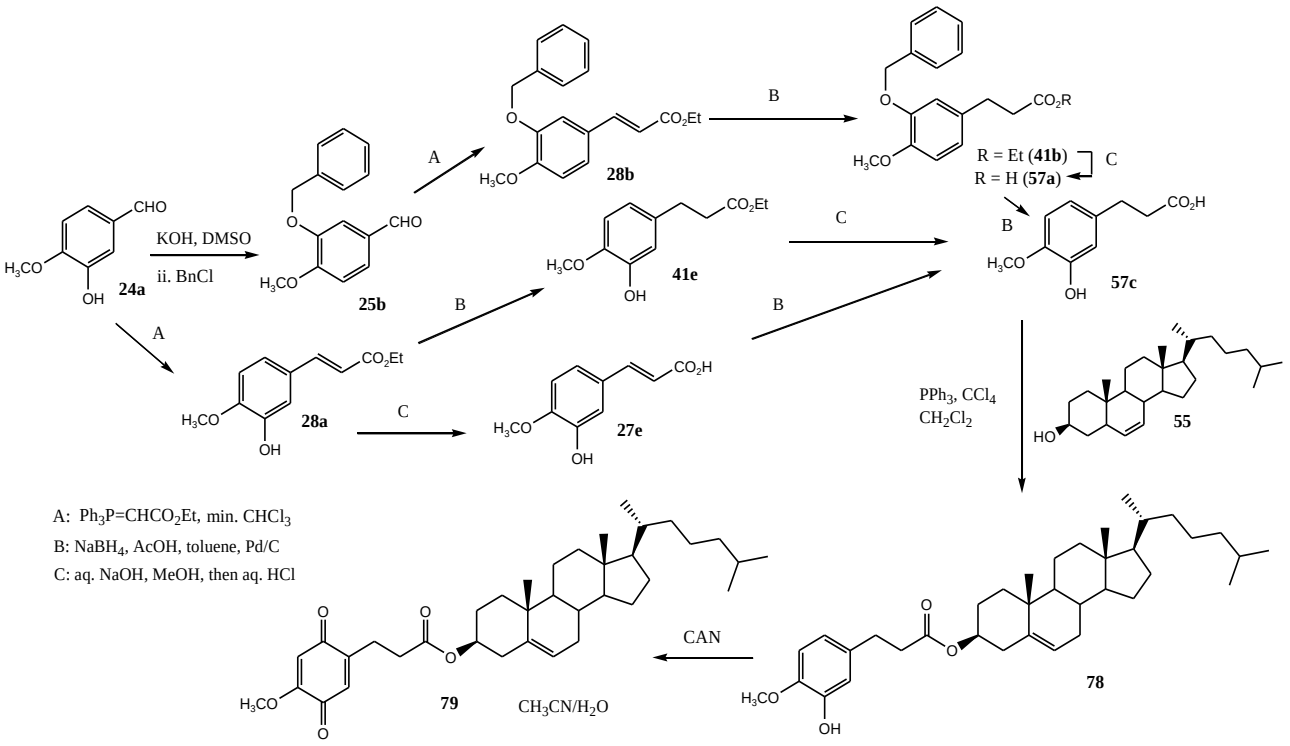
A similar sequence was carried out with 2,5-dimethoxybenzoic acid (**75**). Dimethoxybenzoic acid (**75**) was prepared by oxidation of 2,5-dimethoxybenzaldehyde (**25a**) with Ag_2O (Janssen and Wilson 1956). Again, the esterification was carried out by modified Appel-type reaction. The oxidative demethylation reaction to the steroidal quinone **77** proceeded readily, but the compound was less stable during the column chromatographic separation than **74** (**Scheme 28**).



Scheme 28: Overall reaction sequence to 3-cholesteryl quinonylcarboxylate

The reaction to the methoxyquinone-steroid conjugate was pursued through a number of synthetic routes. Initially, hydroxy group in 3-hydroxy-4-methoxy benzaldehyde (**24a**) was protected as the *O*-benzyl ether **25b**. With the protected benzaldehyde, the Wittig reaction was carried out, the double bond hydrogenation of the cinnamate **28b**, the hydrolysis to the cinnamic acid **41b** and finally the hydrogenative debenzylation to 3-hydroxy-4-methoxyphenylpropionic acid (**57c**). Later on, a more direct route was taken without benzylation of the hydroxyl group. Initially, the benzylation was chosen as an early experiment of esterifying directly 3-hydroxy-4-methoxycinnamic acid and 3-hydroxy-4-methoxyphenylpropionic acid gave only poor yields. This was to be circumvented by chosing the benzyl group. It was seen later on that the poor yield of the direct esterification of the non-protected phenolic acids was due to

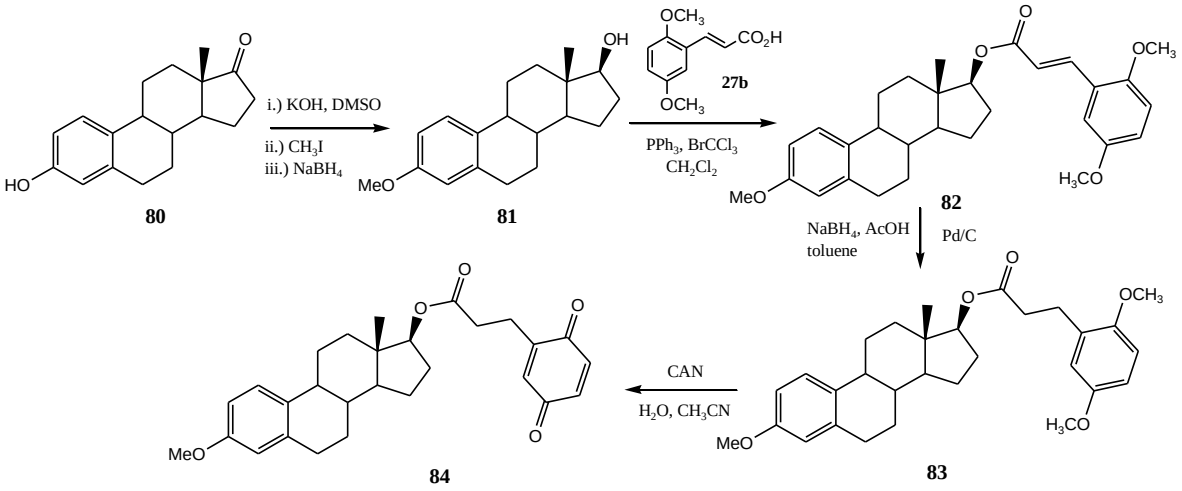
moisture that they had retained as at the time they had been produced directly from their respective esters and had been obtained by acidification, filtration and air-drying of the product. Later, it was seen that the esterification of non-protected phenolic acids under the modified Appel reaction conditions proceeded in acceptable yields. The oxidative demethylation of compound **78** with CAN went without problem, and **79** was reasonably stable to be separated by column chromatography (**Scheme 29**).



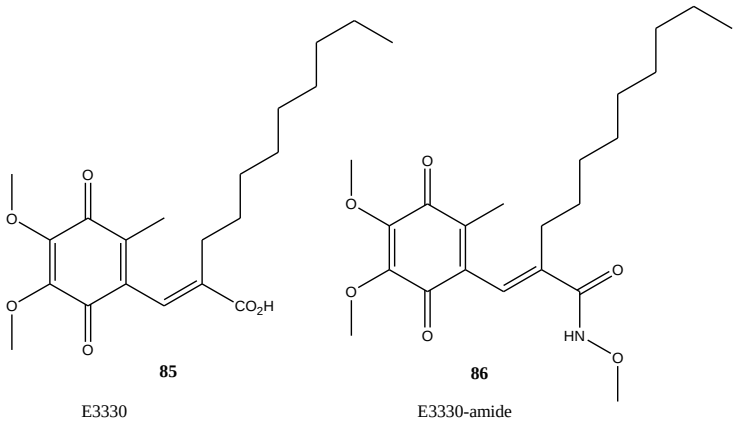
Scheme 29: Overall reaction sequence to cholesteryl 5-methoxy-1,4-quinon-2-ylpropionate with different synthetic routes

Similarly, the 3-methoxyestran-17β-yl 1,4-quinon-2-ylpropionate was produced. Estrone (**80**) was *O*-methylated at C3 (KOH, DMSO, CH_3I) and then reduced to the 3-*O*-methylestradiol ($NaBH_4$, MeOH-Et_2O). Modified Appel reaction with 2,5-dimethoxycinnamic acid (**27b**) produced the steroidal cinnamate **82**, which could be

hydrogenated ($NaBH_4$, AcOH, Pd/C) to the steroidal phenylpropionate **83**, which was oxidatively demethylated to steroidal quinone **84**.



Scheme 30: Overall reaction sequence to 3-O-methoxyestra-1,3,5(6)-trien-17-yl 3-(1,4-quinon-2-yl)propionate



Scheme 31: Structures of quinonylacrylic acid E3330 and quinonylacrylamide E3330-amide (Zhang et al. 2013, Nyland et al. 2010).

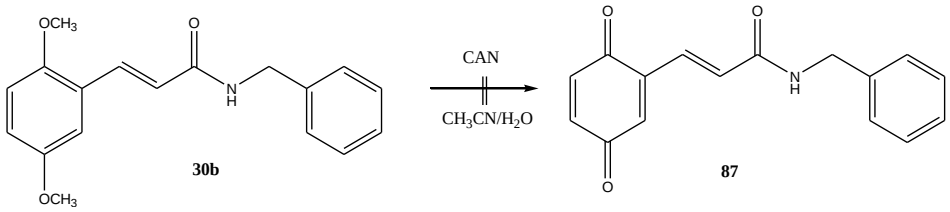
Lastly, it was tried to transform the dimethoxycinnamates and cinnamamides to the corresponding quinonylacrylates and quinonylacrylamides. Recently, some quinonylacrylates and quinonylacrylamides, such as quinonylacryl acid E3330 (**85**) and

E3330-amide (**86**) (**Scheme 31**), have been synthesized and found to be strong apurinic/apyrimidinic endonuclease 1 inhibitors. These proteins play a role in cellular redox regulation (Zhang et al. 2013). Nyland et al. had published a recent synthetic strategy to these via CAN oxidation the tetramethoxycinnamates. We have subjected the benzyl dimethoxycinnamamide **30b** to CAN oxidation in CH_3CN/H_2O (Scheme 24). While the reaction proceeded as with the dimethoxypropionamides, showing in the TLC a pronounced strongly UV active product, column chromatographic separation only gave two small fractions, one yellowish one reddish, both of which showed to be a mixture, most likely of oligomers, where the vinylic moiety was no longer in evidence, but where methoxy groups could still be observed.

It may be that the main fraction reacted during the chromatographic separation on the column, which would speak for the slow diminishing of the intensity of a strongly yellow fraction associated with the created quinone. Nevertheless, the result also shows that there is at least some oligomerization during the oxidative reaction and that also there is no complete demethylation/oxidation. Why these results are different from those obtained by Nyland et al. is not yet clear, but perhaps the additive methoxy group in Nyland's subtrate/productand/or the trisubstitution of the alkene moiety suppress oligomerization and the reactive decomposition of the product on silica. CAN is used as a polymerization initiator of polymerization reactions of acrylates and methacrylates (Deng et al. 2016, Yalinca et al. 2016, Xu et al. 2015), so that a possibility of oligomerization might have been expected. The polymerizations using CAN as an initiator, however, are usually run under less mild conditions than those used in the

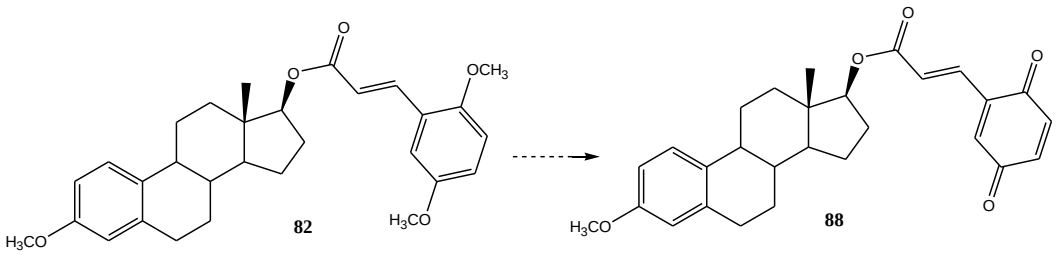
attempted oxidation of **30b**. Methyl quinonylacrylate, prepared electrochemically, has been shown to be quite reactive (Irngartiner and Stadler 1998).

Quinonyl acrylates have also been synthesized from the corresponding dimethoxycinnamates with the combination of 4-iodophenxyacetic acid and Oxone® (Yakura et al. 2010). As oxone is known also to hydroxylate tertiary carbons in steroidal frameworks, this was not attempted in this thesis.



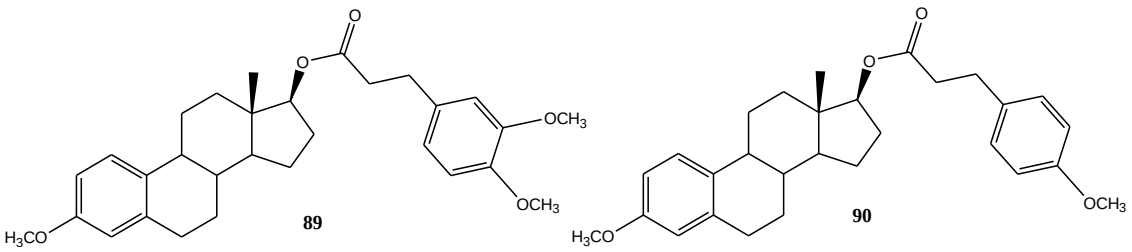
Scheme 32: 2,5-Dimethoxycinnamamide 30bdoes not oxidize smoothly of quinonylacrylate

3-*O*-Methoxyestra-1,3,5(10)-trien-17β-yl 2,5-dimethoxycinnamate is still left as a substrate as its conversion to the corresponding quinone has not yet been attempted (**Scheme 33**).



Scheme 33: Further, future target molecule

Also, with 3-*O*-methoxyestra-1,3,5(10)-trien-17β-yl 3.4-dimethoxyphenyl propionate (**89**) and 4-methoxyphenylpropionate (**90**), there are two further possible substrates in stock, of which compound **90** might submit to oxidation with Fremy's salt (**Scheme 34**).



Scheme 34: Further molecules in stock.

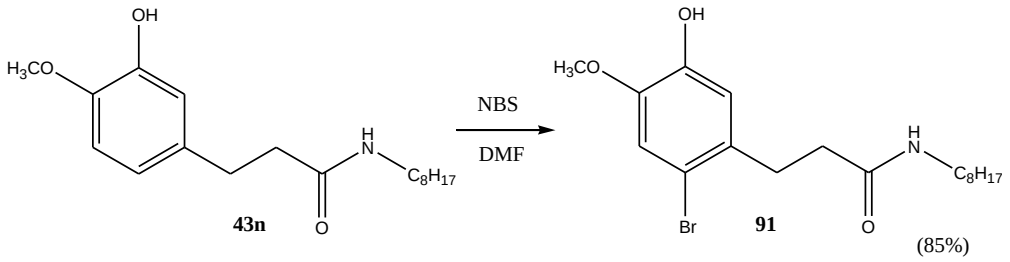
3.7 Bromination of The 3-hydroxy-4-methoxyphenylpropionamide and 3-hydroxy-4-methoxyphenylpropionate Moieties As Prosthetic Groups of Steroids

In the radiohalogenation of steroids, the selectivity of the reaction is important as well as the ease of manipulation and work-up of the product. In the most direct way, estrone and 3-*O*-methylestrone themselves have been brominated and iodinated. Here, it came to mixtures of 2-halo, 4-halo and 2,4-dihaloestrones, where the 3-hydroxy and the 3-methoxy groups directed the halogen substituent into the *ortho*-position, the *para*-position not being available. No halogenation of C16, *α*- to the 17-keto group could be noted, however. The mixture of compounds led to a complicated separation process at that time, where the dehalogenated estrones were selectively dehalogenated under

reductive conditions (Numazawa et al. 1985, Shiine 2009, Burmester et al. 2013). Clearly, a leaving group on the steroidal frame, including on the aromatic A-ring of an estradiol derived steroid, can lead to very selective halogenations (Oliveira el al. 2012, Oliveira et al. 2013, Thiemann et al. 2016). On the other hand, often it is of advantage and easier to halogenate a prosthetic group linked to the steroid (Neto et al. 2012) or a substituent on the steroid (Neto 2011, Melo e Silva 2001).

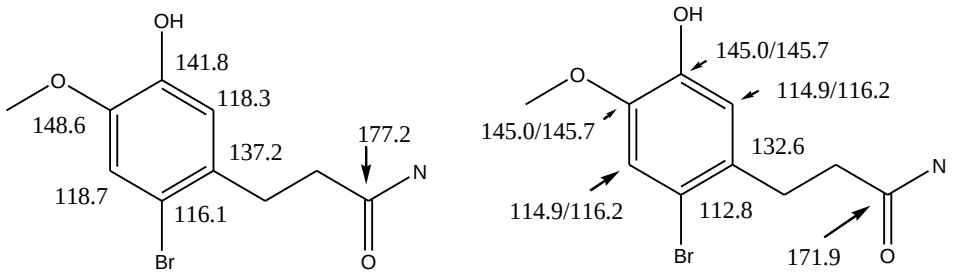
The 3-hydroxy-4-methoxyphenylpropionamides and 3-hydroxy-4-methoxy phenylpropionates, prepared and utilized above, seemed a suitable system to tag with a halogen as these are very electron rich systems. It would be very beneficial to use the same immediate structural precursor for a potential therapeutic (quinone system) and diagnostic (radiolabeled) chemical structure. The importance of the substitution pattern in **43** is the hydroxyl function, which should have a very strong activating effect and should direct a further substituent into the ortho/para positions. The bromination of phenols has been achieved in a number of ways such as by direct bromination with bromine (de la Mare 1974), which, however, often produces polybrominated by-products and mixtures of regioisomers. N-Bromosuccinimide (NBS), bromination has been described under different conditions such as NBS/$HBF_4{\cdot}Et_2O$ in CH_3CN (Oberhauser 1997) and NBS in DMF (Mitchell et al. 1979). Thus, it was decided to try the bromination of the 3-hydroxy-4-methoxyphenylpropionamides with *N*-bromosuccinimide (NBS). Radiolabelled *N*-bromosuccinimide is known. R. Otto has communicated the use of ^{82}Br-NBS (Otto 1985). The question remained how the directive effects of the methoxy, the hydroxyl and the alkyl function would balance each other. Work of the group of Carreño (Carreño et al. 1997) has shown that in the bromination with *N*-bromosuccinimide (NBS), the phenolic

hydroxyl group in polar solvents such as CH_3CN is *para*-directing, in non-polar solvents such as CS_2 ortho-directing. Also, Carreño et al. showed that the hydroxyl group's directivity was more important than that of the methoxy group. As the Thiemann group had some success using DMF as a solvent for bromination of arenes with NBS, DMF was used here, also. When *N*-octyl 3-hydroxy-4-methoxyphenylpropionamide (**43n**) was reacted with NBS in DMF at RT, mono-brominated compound **91** was produced, where the bromo function is situated para to the hydroxyl function (**Scheme 35**).



Scheme 35: Monobromination of N-octyl 3-hydroxy-4-methoxyphenylpropionamide

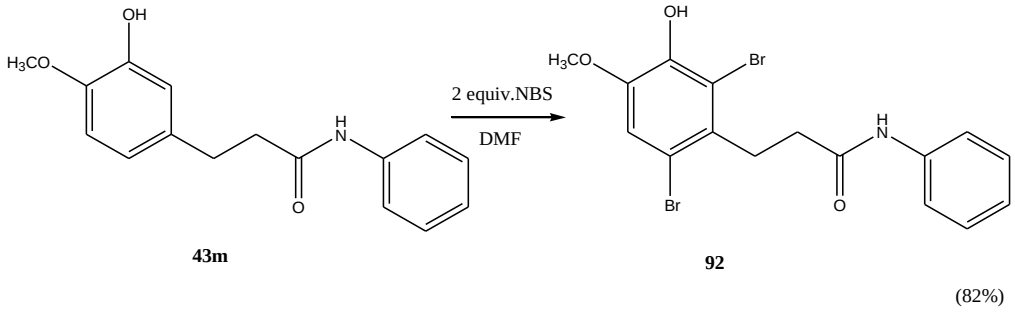
The ^1H NMR spectrum shows two singlets at δ 6.82 ppm and 6.96 ppm, respectively. The ^{13}C NMR spectrum agrees with that predicted by the algorithm embedded in the ChemDraw Ultra software (**Scheme 36**).



calculated (with software embedded in ChemDraw Ultra) experimental ^{13}C NMR data

Scheme 36: Predicted and measured 13C-NMR data of the aromatic ring system in N-octyl 2-bromo-5-hydroxy-4-methoxyphenylpropionamide

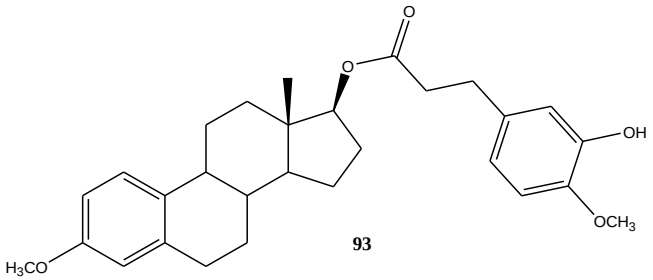
With an excess of NBS, dibromination takes place as can be seen in the reaction of *N*-benzyl 3-hydroxy-4-methoxyphenylpropionamide (**43m**), which could be transformed selectively to N-benzyl 2,6-dibromo-3-hydroxy-4-methoxyphenylpropion amide (**92**). Nevertheless, the non activated benzyl group was not brominated under the conditions so that selective mono- and subsequently dibromination of the more activated ring system can be achieved.



43m **92** (82%)

Scheme 37: Selective dibromination of N-benzyl 3-hydroxy-4-methoxyphenylpropionamide

It has not been tried to connect the 3-hydroxy-4-methoxyphenylethyl moiety to an estradiol derived system, yet, *eg*., by ester or amide bond, as in compound **93** (**Scheme 38**). Here, the monobromination has to be carried out with great care as a second bromo substituent would then choose between the estradiol A ring and the monobrominated 3-hydroxy-4-methoxyphenylethyl moiety.



93

Scheme 38: Future substrate for NBS bromination

Chapter 4: Conclusions and Outlook

In this study, four steroidalquinone conjugates were prepared: 3-Cholesteryl 1,4-quinon-2-ylpropionate (**74**), 3-Cholesteryl quinonylcarboxylate (**77**), Cholesteryl 5-methoxy-1,4-quinon-2-ylpropionate (**79**) and 3-Methoxyestra-1,3,5(10)-trien-17*β*-yl 2,5-(*E*)-dimethoxycinnamate (**82**)

To achieve this, hydroxylated and alkoxylated cinnamic acids were prepared, either in a one-step Wittig-olefination-hydrolysis reaction or by a two-step procedure of Wittig reaction and subsequent hydrolysis (aq. NaOH-CH_3OH).

Next, the esterification and amidation of these cinnamic acids were studied under modified Appel reaction conditions, where *O*-benzyl and *N*-benzyl protective groups were introduced into the molecules. It was found that $PPh_3/BrCCl_3$ could be used effectively for the amidation and esterifications of carboxylic acids in general. This study must be seen as a continuation of ongoing research into this reaction in Thiemann group.

Then, the hydrogenation of the cinnamates and cinnamides was studied, where the hydrog en needed for the reaction was produced *in situ*. The reactions were investigated in regard to the selectivity of the hydrogenation reaction over the reductive debenzylation. Thereafter, it was studied under which conditions the hydrogenative debenzylation would succeed using the same system ($NaBH_4$, AcOH, Pd/C, toluene or benzene). It was found that alkene hydrogenation of activated double substituted alkenes works selectively over *O*-debenzylation. With an excess of reagent and under longer reaction times, *O*-debenzylation proceeds, also, while *N*-debenzylation does not succeed.

Further, the oxidation of 2,5-dimethoxyphenylpropionamides and 2,5-dimethoxy phenylpropionates, prepared above, to the respective quinones was carried out. Thereafter, the focus was on the use of the 3-hydroxy-4-methoxyphenylpropionamides and 3-hydroxy-4-methoxypropionates, prepared above. Dealkylation/oxidation with CAN was found to lead to methoxy-substituted quinones. These reactions were combined to synthesize four steroidal quinone conjugates.

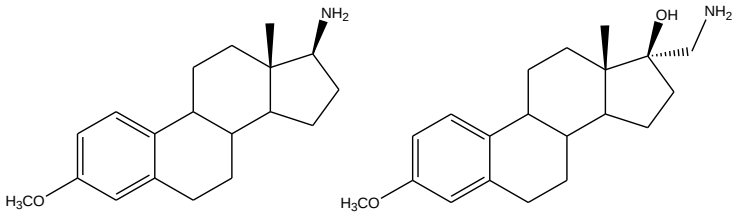
Finally, the selective bromination of the 3-hydroxy-4-methoxypropionamides was studied, where the 3-hydroxy-4-methoxypropionamide is seen as a potential prosthetic group joined to the steroids. It was found that the bromine enters the molecule selectively para to the hydroxyl function. With excess NBS, a second bromination of the 3-hydroxy-4-methoxypropionamide is achieved. No bromination is found in the N-benzyl group or on the carbon α to the amide function.

The strategies that were finally followed and the reactions that were used were governed by the laboratory infrastructure in place and the type of reactions that the laboratory was laid out for. So, the work with and purification of strongly corrosive reagents such as acid halides, thionyl chloride, sulfuryl chloride or phosphorus halides were avoided as much as possible. Therefore, the work on the Appel type reactions with $PPh_3/BrCCl_3$ had to be expanded upon to use it to furnish ester and amide linkages. The employment of external hydrogen gas was avoided – therefore the use of the reaction system $NaBH_4$, AcOH, Pd/C had to be studied further in view of deprotection of O-benzyl protective groups (PGs) in relation to alkene hydrogenation. Also, the utilization of

bromine was to be avoided in our laboratory – therefore, the use of NBS was studied exclusively in the bromination reactions.

Difficulties to modify some reactions to the available infrastructure and which would have been important for a better success of the thesis, could not be overcome. One such critical reaction was the preparation of steroidal amines, which would have involved the reduction of steroidal oximes (Ribeiro Morais 2006, Ribeiro Morais and Thiemann 2012), the addition of trimethylsilyl cyanide with subsequent reduction (Ribeiro Morais 2006, Ribeiro Morais and Thiemann 2012) or the work and purification of azides and subsequent reduction. Some of this was not attempted, some of this did not lead to good results. Thus, 3-*O*-methylestrone oxime was synthesized. Other oximes were prepared as test compounds for the reduction to amines, including cinnamaldehyde oxime, of which an X-ray crystal structure was published (Bugenhagen et al. 2015).

It would very important to expand the work to include more estrane-derived steroidal-quinone conjugates. Here, it would be beneficial to proceed via the 17β-aminoestranyl compounds **94** or the 17α-aminomethylestradiols **95** (Ribeiro Morais 2006, Ribeiro Morais and Thiemann 2012) to end with a steroid-quinone conjugate where the quinone is linked to the steroid via an amide bond. Also, it would be essential to study the bromination of steroidal 5-hydroxy-4-methoxyphenylpropionamides and steroidal 5-hydroxy-4-methoxyphenylpropionates, where the estradiol derived structure should either have the 3-hydroxy function either non-protected or protected with an easily removable PG function.



94 **95**

Scheme 39: Interesting aminoestranes as future starting materials for steroid-quinone conjugates and steroid-conjugates with a prosthetic group that can be halogenated in the final step.

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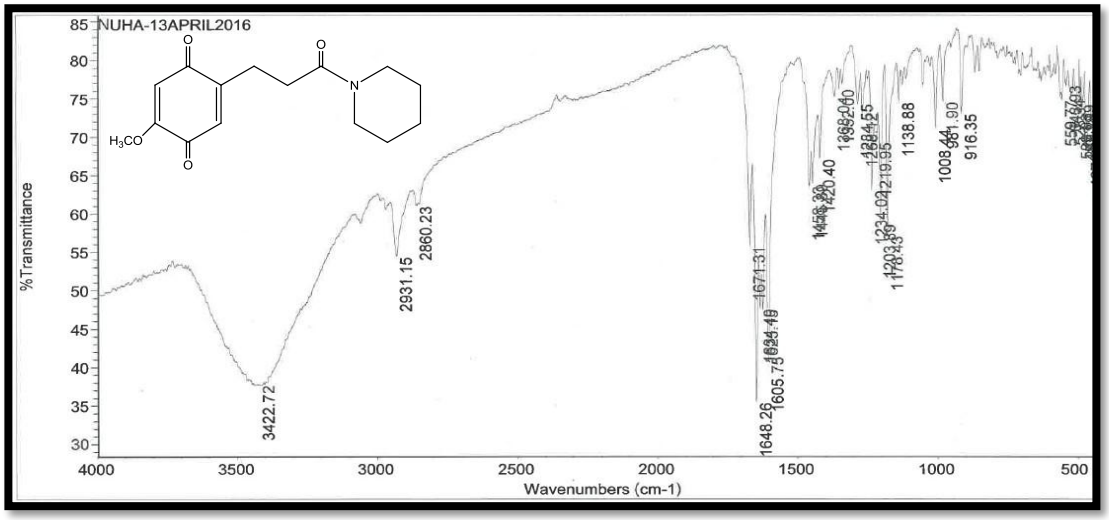
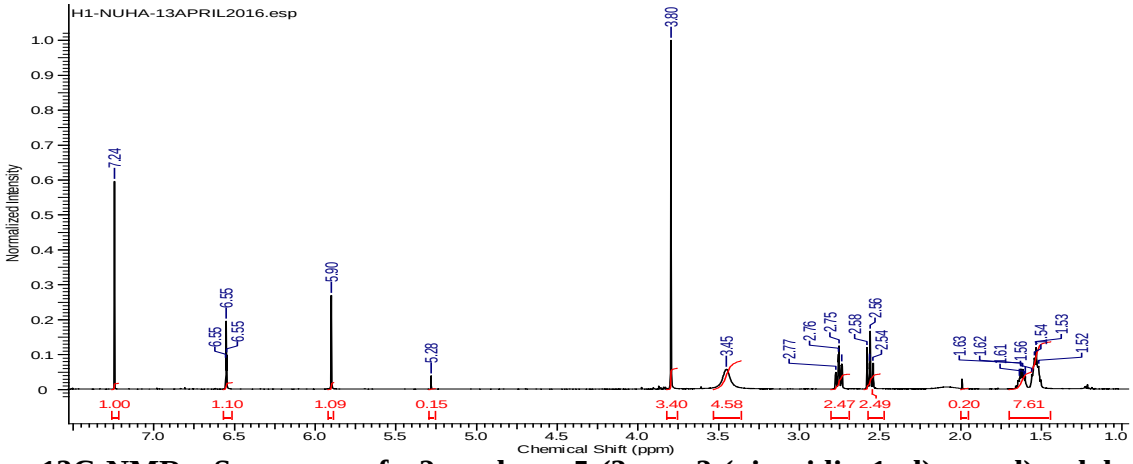
Appendix

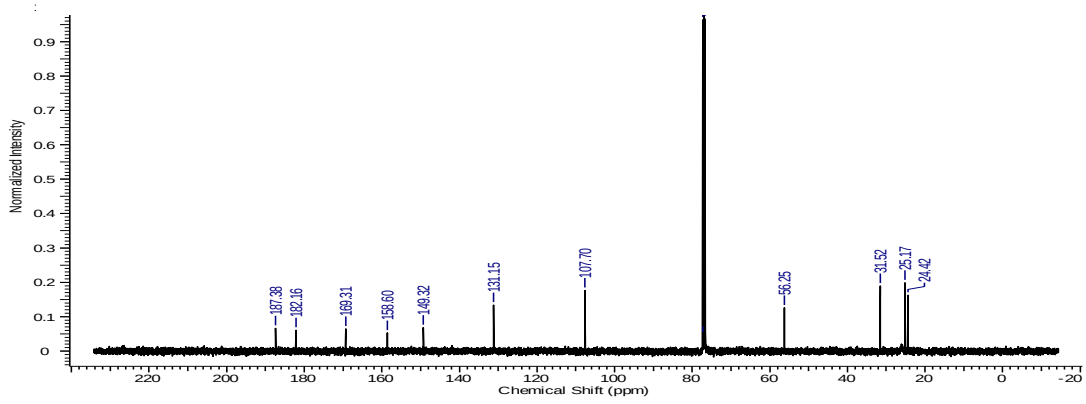
IR Spectrum of 2-methoxy-5-(3-oxo-3-(piperidin-1-yl)propyl)cyclohexa-2,5-diene-1,4-dione



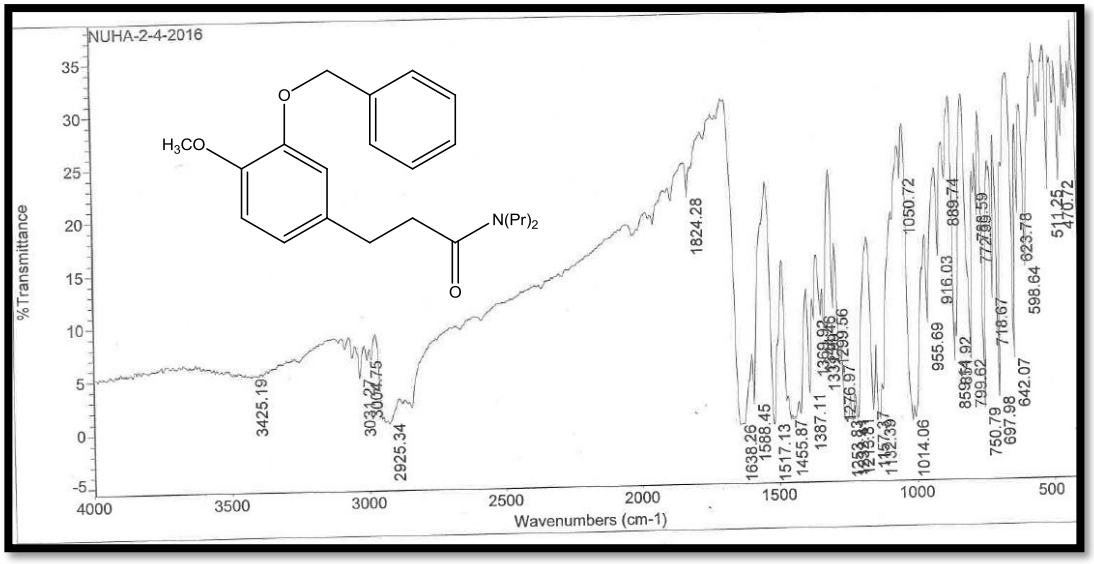
1H-NMR spectrum for 2-methoxy-5-(3-oxo-3-(piperidin-1-yl)propyl)cyclohexa-2,5-diene-1,4-dione



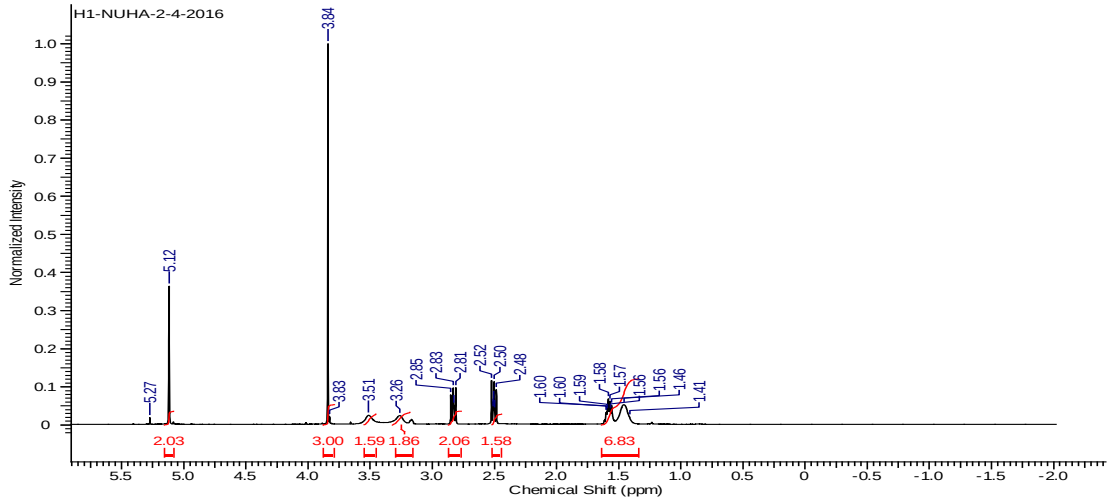
13C-NMR Spectrum for2-methoxy-5-(3-oxo-3-(piperidin-1-yl)propyl)cyclohexa-2,5-diene-1,4-dione



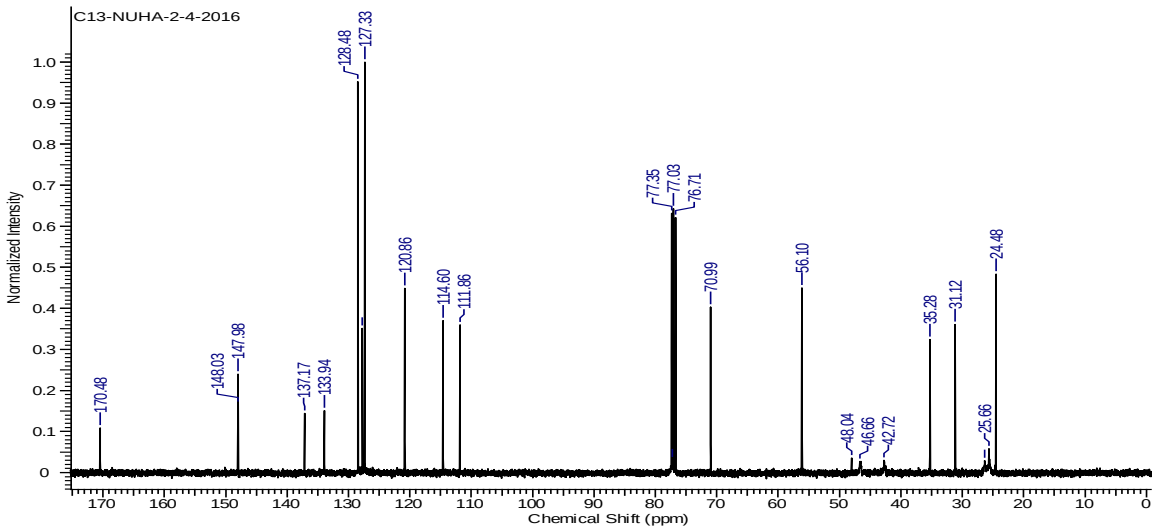
IR spectrum of 3-(3-(benzyloxy)-4-methoxyphenyl)-N,N-dipropylpropanamide



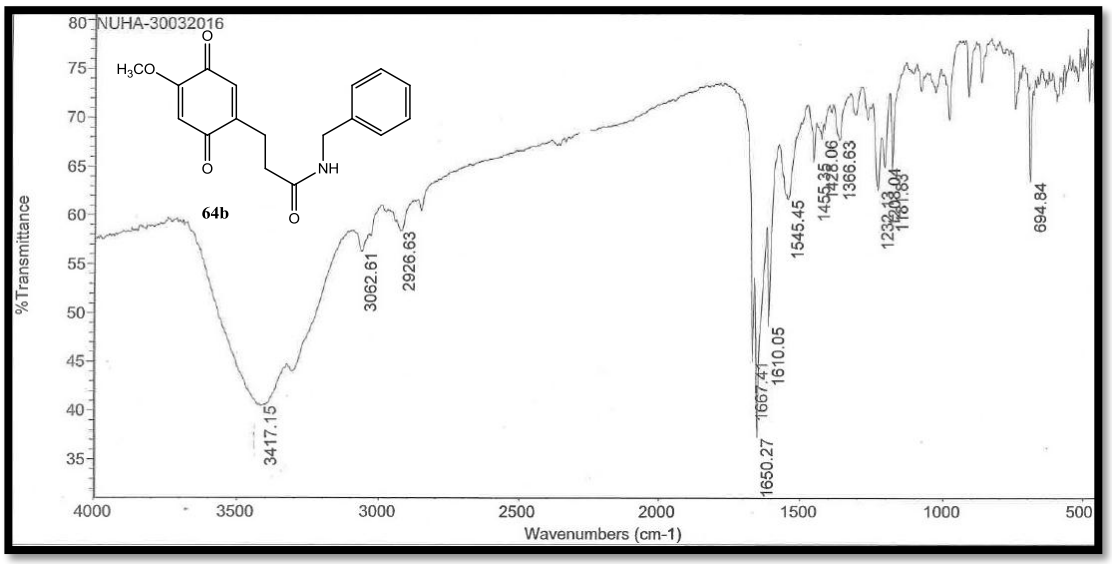
1H-NMR spectrum for 3-(3-(benzyloxy)-4-methoxyphenyl)-N,N-dipropylpropanamide



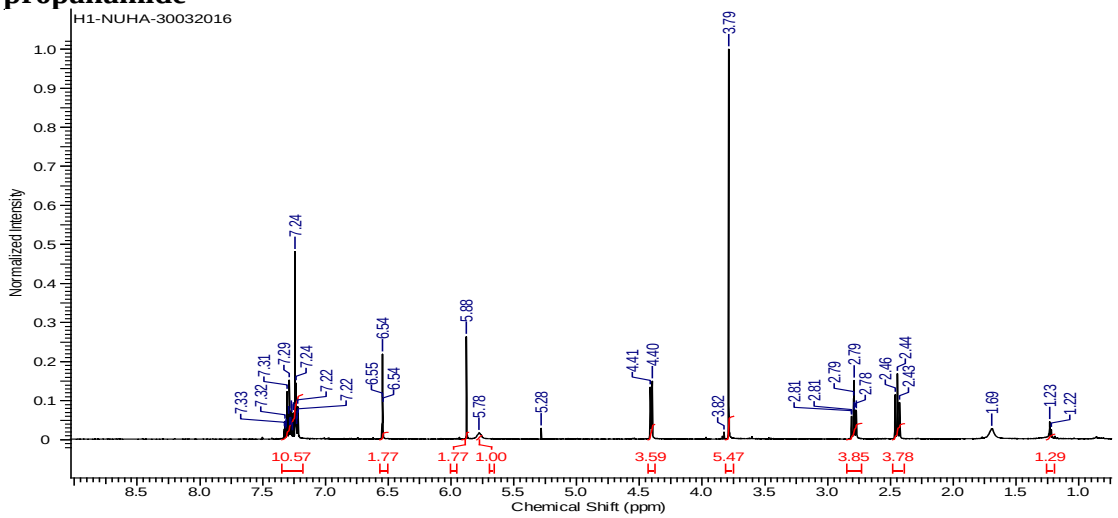
13C-NMR for 3-(3-(benzyloxy)-4-methoxyphenyl)-N,N-dipropylpropanamide



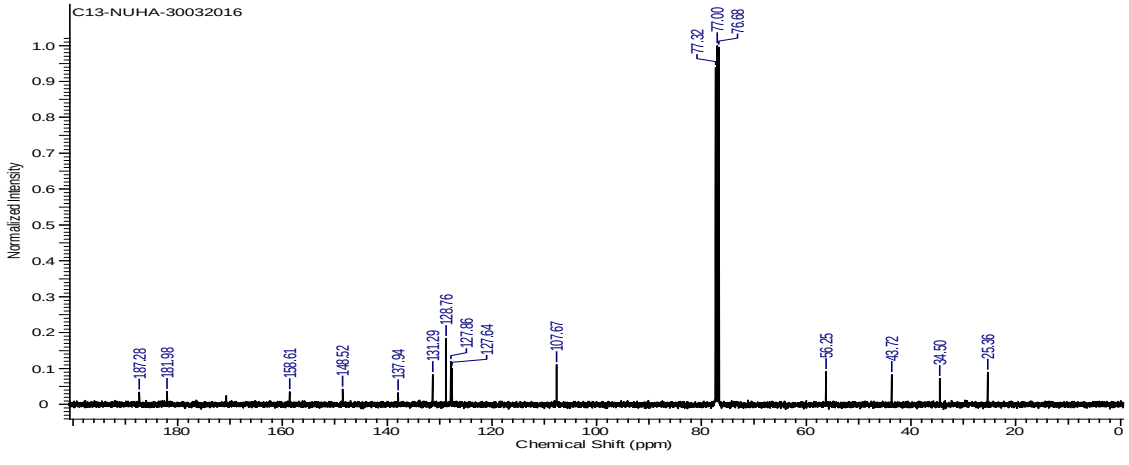
IR spectrum of N-benzyl-3-(4-methoxy-3,6-dioxocyclohexa-1,4-dien-1-yl) propanamide



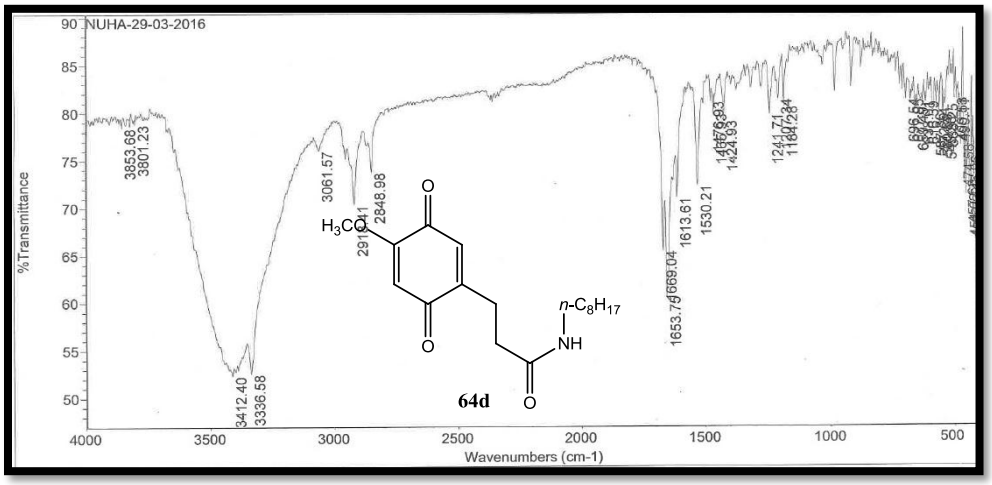
1H-NMR spectrum for N-benzyl-3-(4-methoxy-3,6-dioxocyclohexa-1,4-dien-1-yl) propanamide



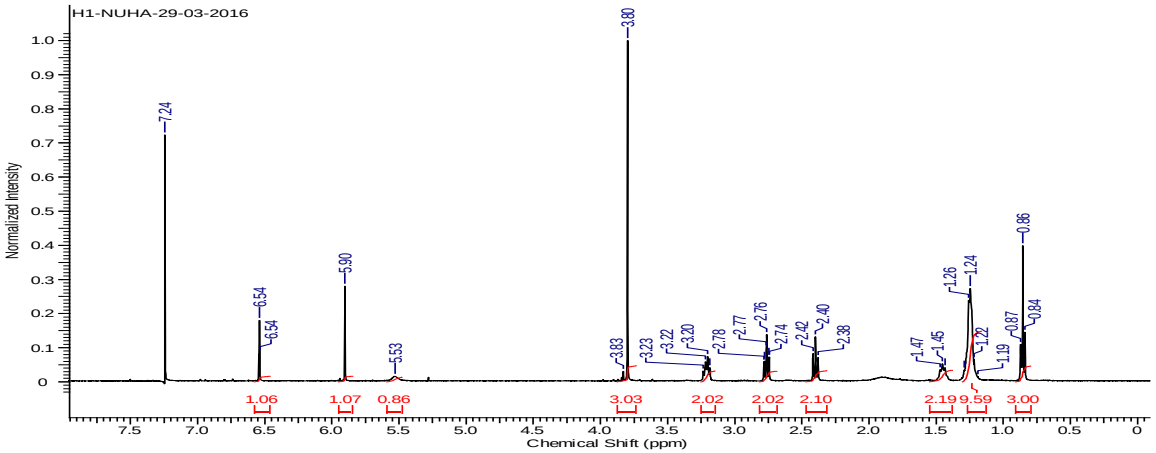
13C-NMR spectrum for 1H-NMR spectrum for N-benzyl-3-(4-methoxy-3,6-dioxo cyclohexa-1,4-dien-1-yl) propanamide



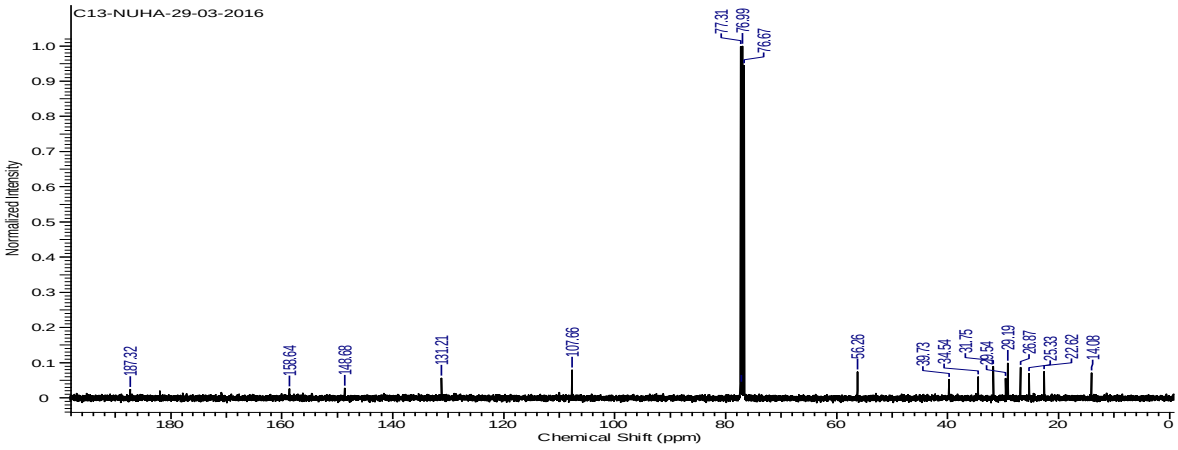
IR spectrum of *N*-Octyl 5-methoxy-1,4-quinon-2-ylpropionamide 64d



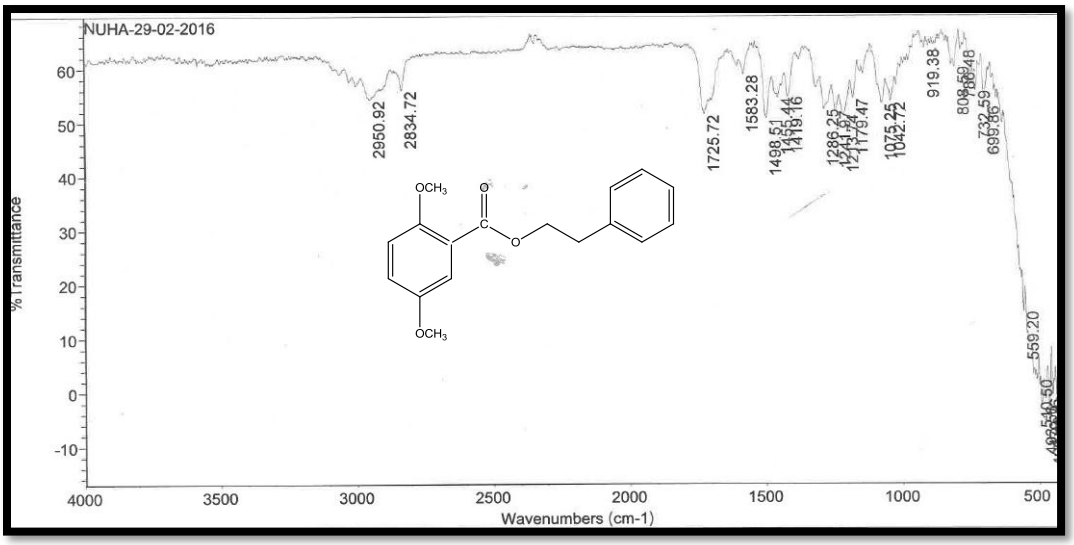
H1-1H-NMR spectrum of *N*-Octyl 5-methoxy-1,4-quinon-2-ylpropionamide 64d



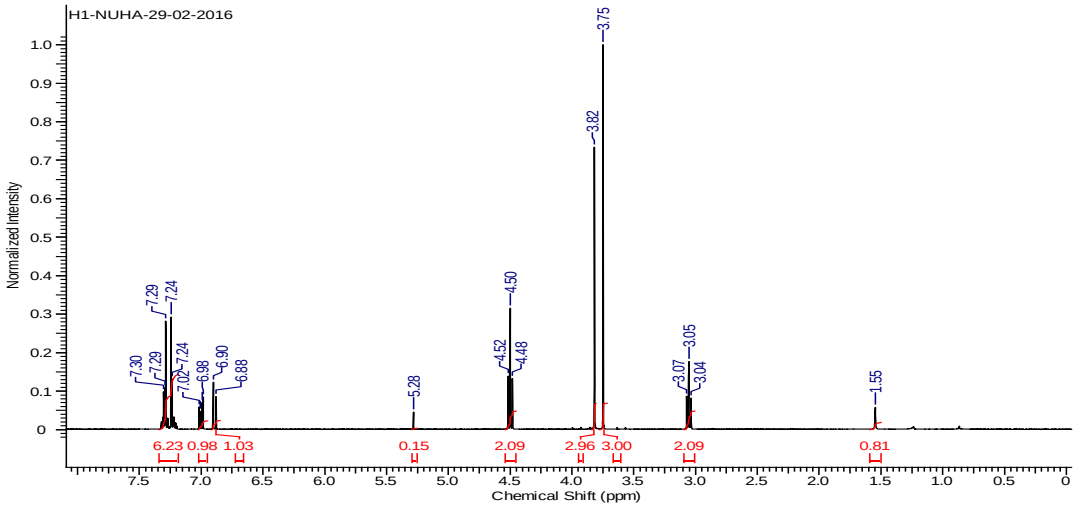
13C-NMR spectrum for *N*-Octyl 5-methoxy-1,4-quinon-2-ylpropionamide 64d



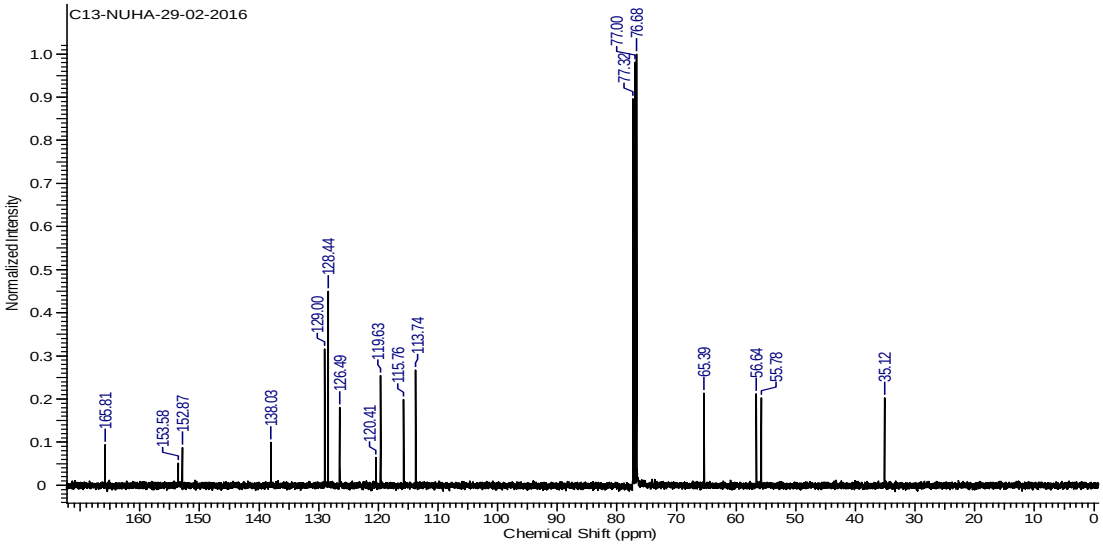
IR spectrum of phenethyl 2,5-dimethoxybenzoate



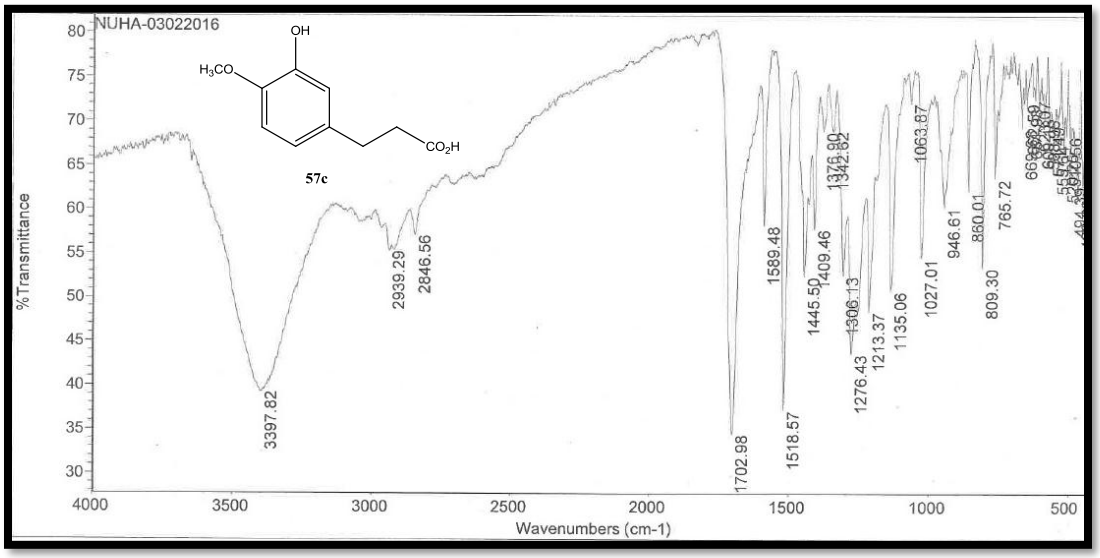
1H-NMR spectrum of phenethyl 2,5-dimethoxybenzoate



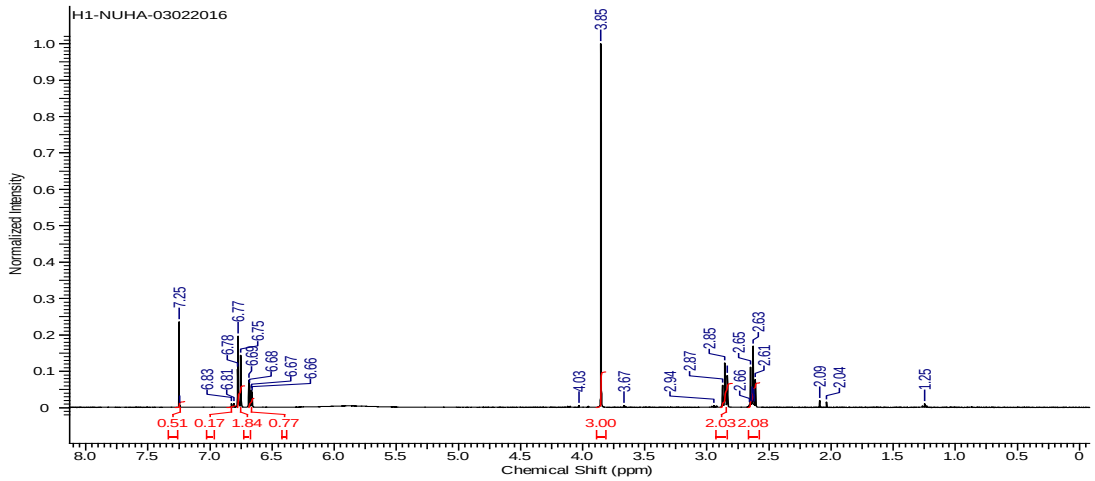
13C-NMR spectrum of phenethyl 2,5-dimethoxybenzoate



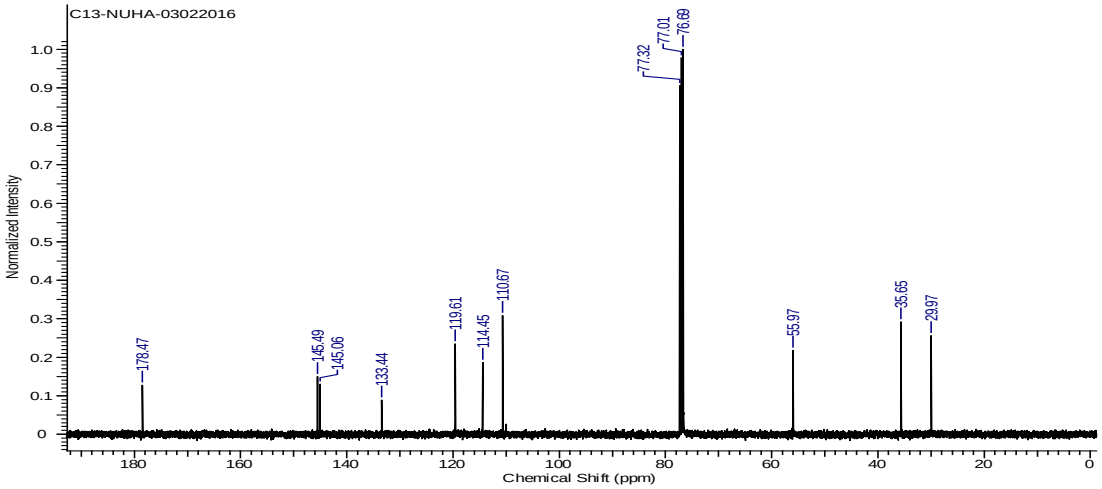
IR spectrum for 3-Hydroxy-4-methoxyphenylpropionic acid 57c



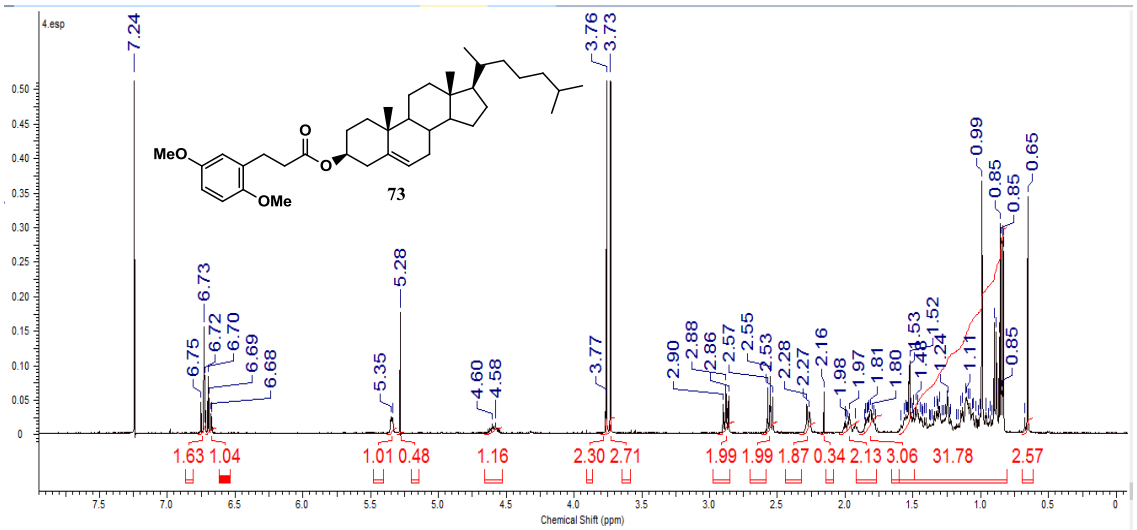
1H spectrum for 3-Hydroxy-4-methoxyphenylpropionic acid 57c



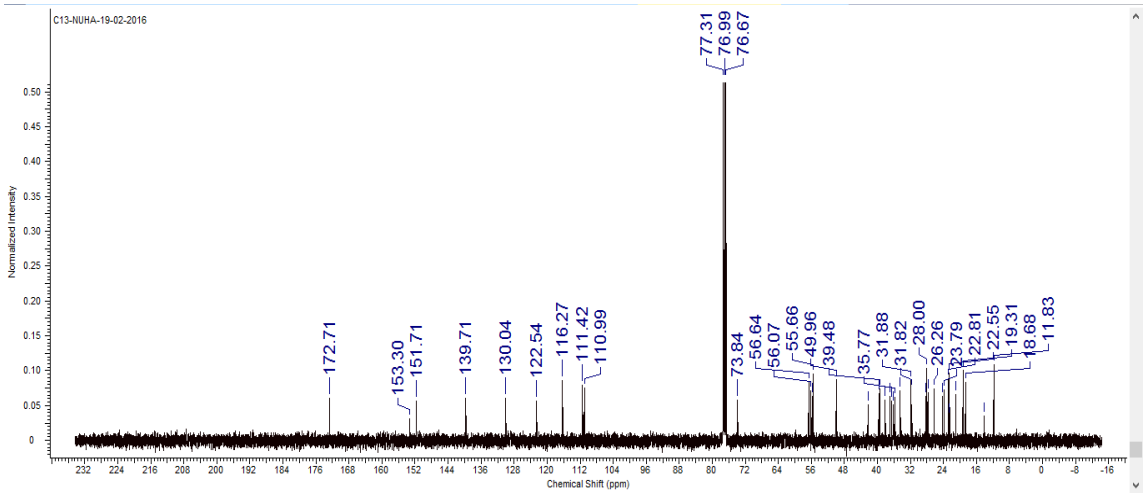
13C spectrum for 3-Hydroxy-4-methoxyphenylpropionic acid 57c



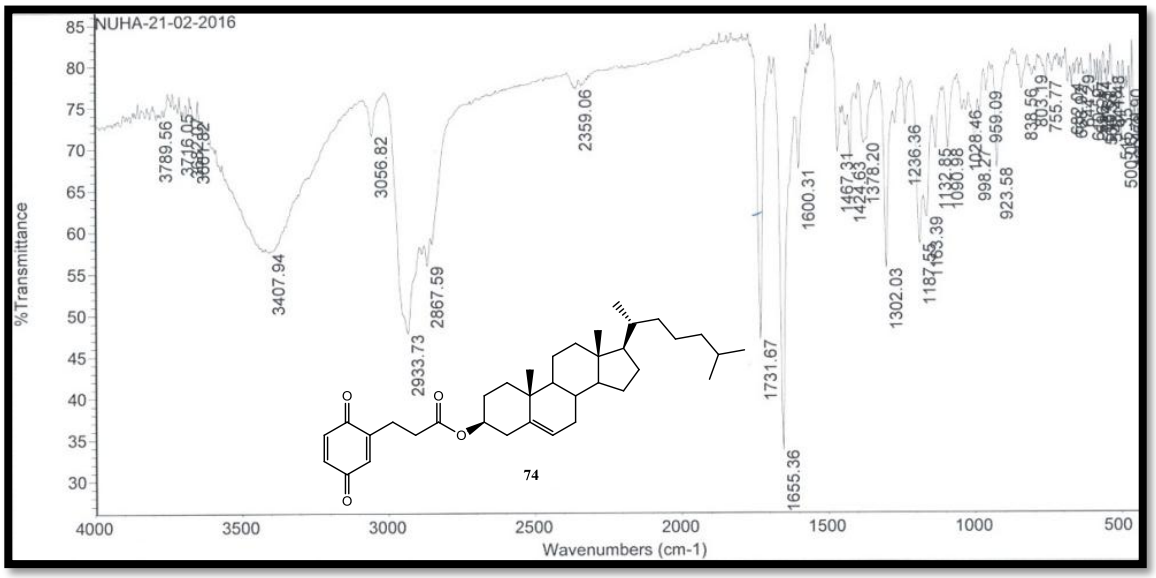
1H-NMR spectrum for 3-Cholesteryl 2,5-dimethoxyphenylpropionate 73



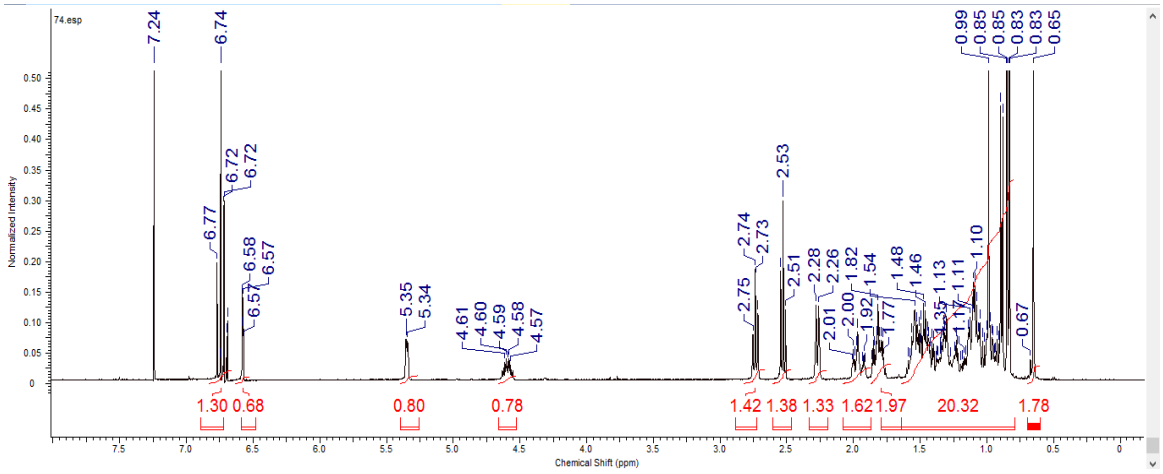
13C-NMR spectrum for 3-Cholesteryl 2,5-dimethoxyphenylpropionate 73



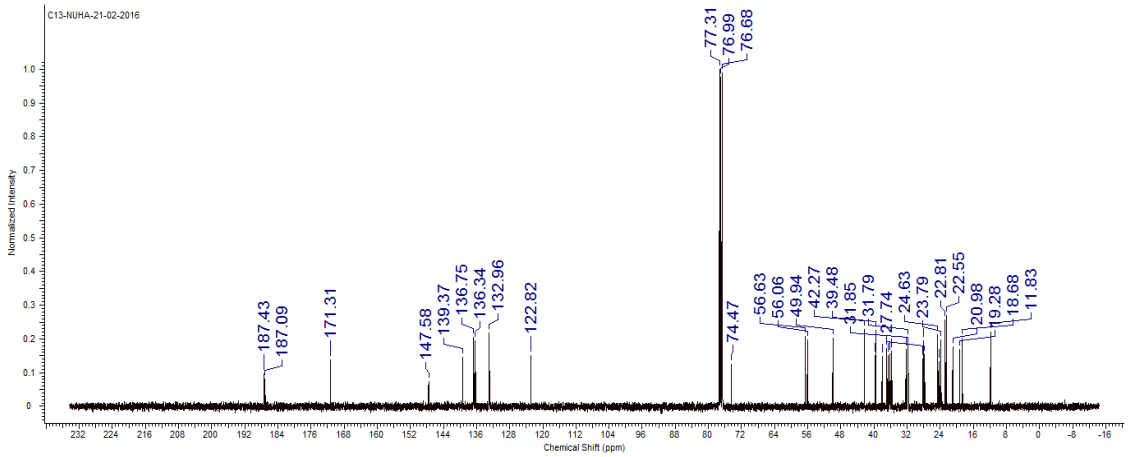
IR spectrum of 3-Cholesteryl 1,4-quinon-2-ylpropionate 74



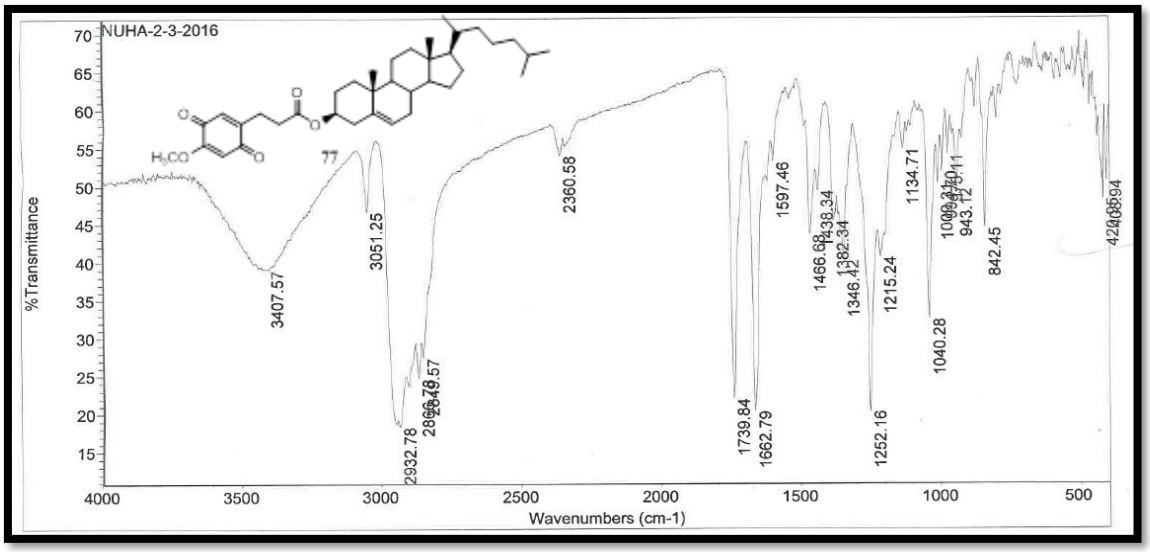
1H-NMR spectrum for 3-Cholesteryl 1,4-quinon-2-ylpropionate 74



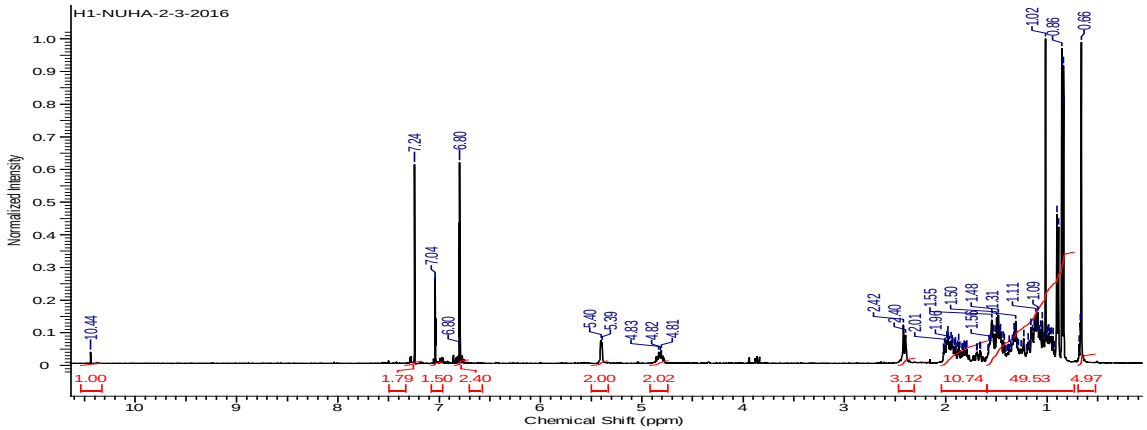
13C-NMR spectrum for 3-Cholesteryl 1,4-quinon-2-ylpropionate 74



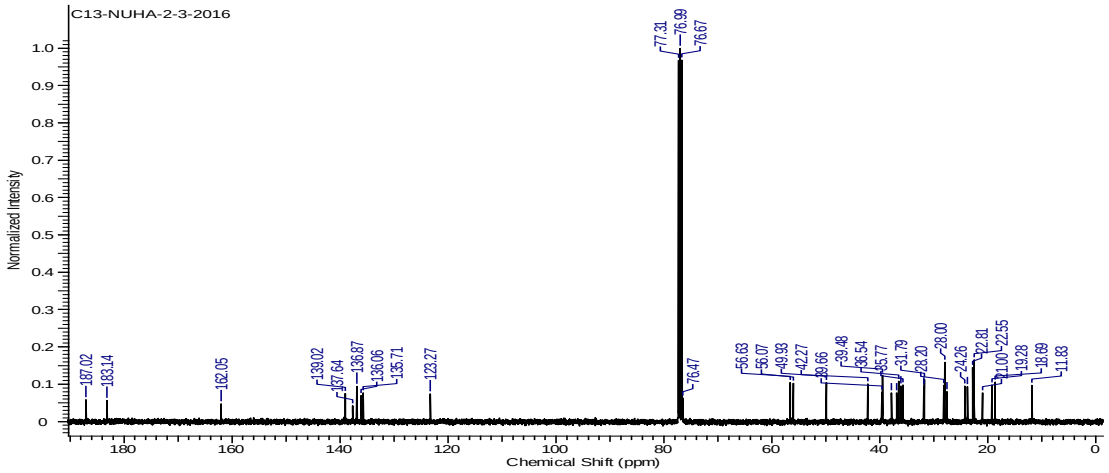
IR spectrum for 3-Cholesteryl quinonylcarboxylate 77



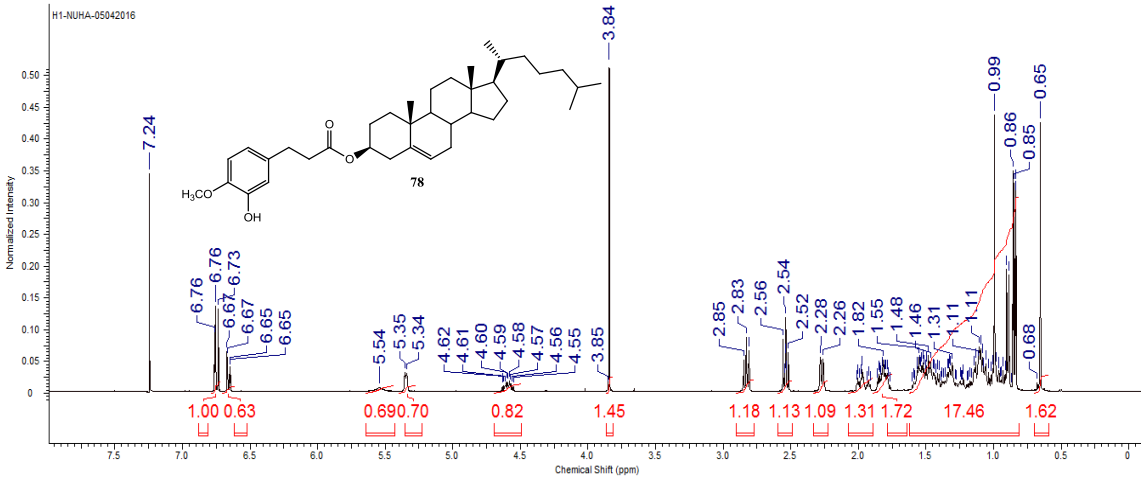
1H- NMR spectrum for 3-Cholesteryl quinonylcarboxylate 77



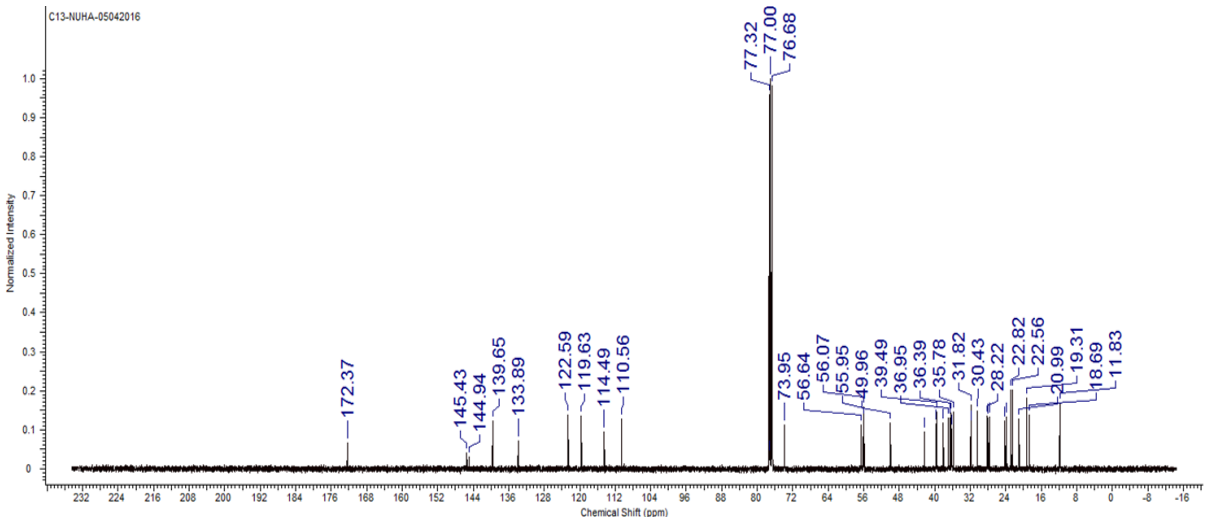
13C- NMR spectrum for 3-Cholesteryl quinonylcarboxylate 77



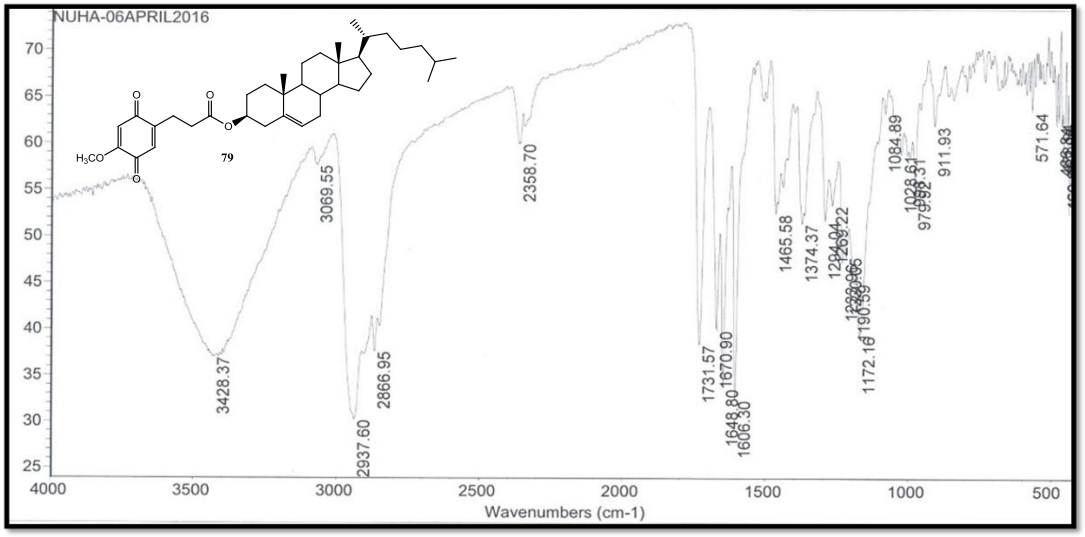
1H-NMR spectrum for 3-Cholesteryl 3-hydroxy-4-methoxy phenyl propionate 78



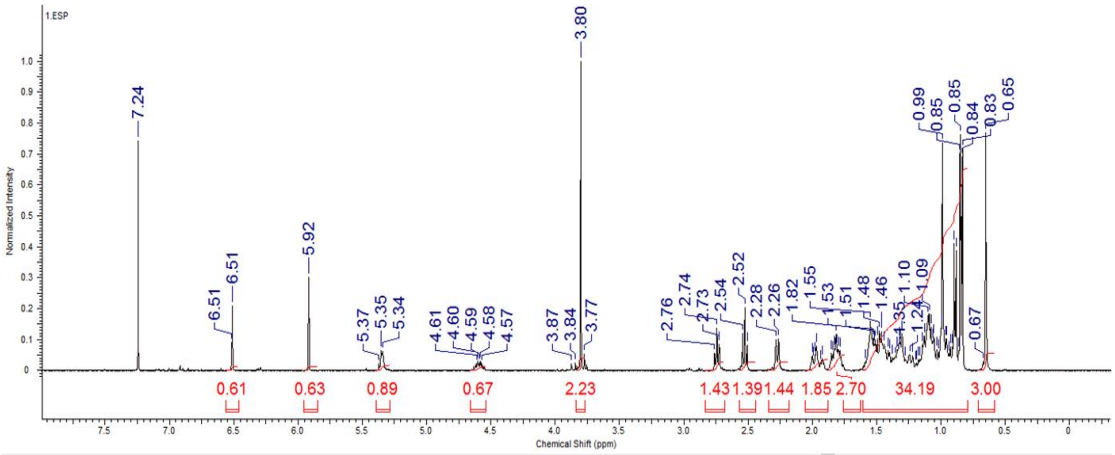
13C-NMR spectrum for 3-Cholesteryl 3-hydroxy-4-methoxy phenyl propionate 78



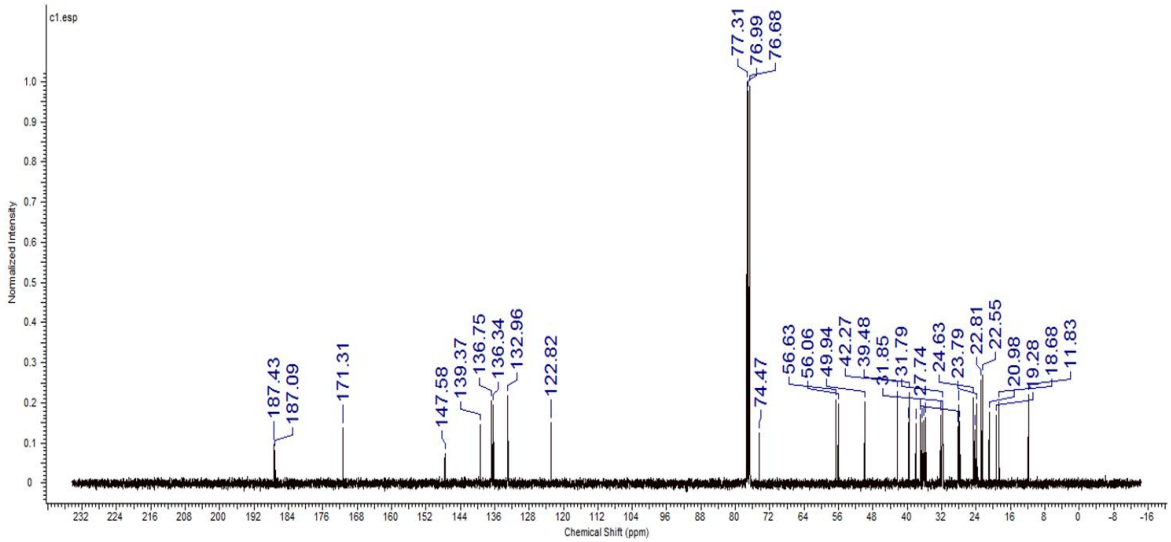
IR spectrum of 3-Cholesteryl Cholesteryl 5-methoxy-1,4-quinon-2-ylpropionate79



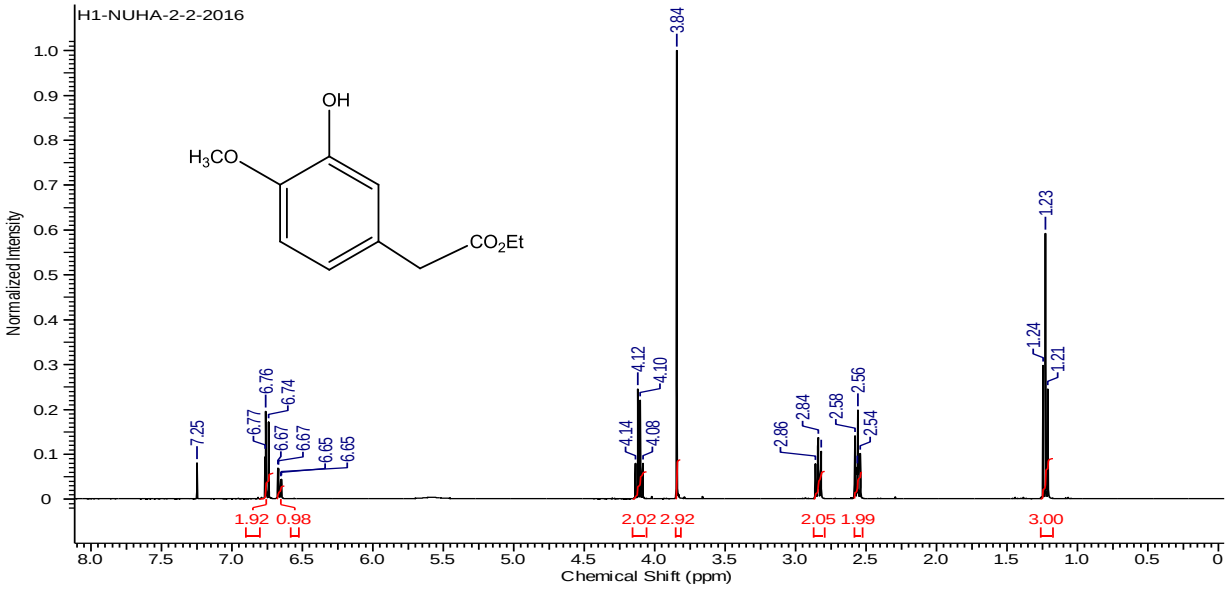
1H-NMR spectrum for 3-Cholesteryl -5-methoxy-1,4-quinon-2-ylpropionate 79



13C- NMR spectrum for 3-Cholesteryl -5-methoxy-1,4-quinon-2-ylpropionate 79



1H-NMR spectrum for ethyl 2-(3-hydroxy-4-methoxyphenyl) acetate



1H spectrum for 3-(3-(benzyloxy)-4-methoxyphenyl)-N-octylpropanamide