FUNCTIONALIZATION OF 2-NITROINDOLE AND (+)-ESTRONE VIA PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS

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Declaration

I hereby declare that this thesis has been written without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Anton Ivanov

Rostock, 26.11.2015

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Abstract

This thesis deals with the functionalization of naturally occurring frameworks via palladium-catalyzed cross-coupling reactions. This includes arylation of indoles via CH-activation reaction, alkynylation of (+)-estrone via Sonogashira reaction and arylation of (+)-estrone via Suzuki-Miyaura reaction. In this way the methods were optimized for the corresponding substrates, series of new substances were synthesized and the scope and limitations of the reactions were studied. Synthesized compounds are of pharmacological relevance due to their structural similarity to bioactive natural products and synthetic drugs. Certain compounds showed significant activity as alkaline phosphatases inhibitors.

Kurzbeschreibung

Die vorliegende Arbeit beschäftigt sich mit der Funktionalisierung von natürlich auftretenden Substanzen durch Palladium-katalysierte Kreuzkupplungsreaktionen. Sie beinhaltet Arylierungen von Indolen durch CH-Aktivierungsreaktionen, Alkinylierungen von (+)-Estron mittels Sonogashira Reaktion sowie Arylierungen von (+)-Estron unter Anwendung der Suzuki-Miyaura Reaktion. In diesem Zusammenhang wurden die Methoden für die entsprechenden Substrate optimiert, eine Vielzahl neuer Verbindungen wurde synthetisiert und die Möglichkeiten und Einschränkungen der angewendeten Synthesemethoden wurden untersucht. Die synthetisierten Produkte sind von einer gewissen pharmakologischen Bedeutung, aufgrund der strukturellen Ähnlichkeiten mit bekannten natürlichen bioaktiven Verbindungen und mit synthetisch hergestellten Medikamenten. Einige Produkte haben erhebliche Aktivitäten als Inhibitoren von alkalischen Phosphatasen gezeigt.

List of used abbreviations

2D	Two-dimensional
Ar	Aryl
ATR	Attenuated total reflection
Arg	L-Arginin
Asp	L-Asparagin
CDP-Star®	Disodium 2-chloro-5-(4-methoxyspiro[1,2-dioxetane-3,2′-(5-chloro-tricyclo[3.3.1.1$^{3.7}$]decan])-4-yl]-1-phenyl phosphate
CN	Nitrile
CNS	Central nervous system
Cy	Cyclohexyl
d	Day
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EA	Ethyl acetate
EI	Electron ionization
ESI	Electrospray ionization
Et	Ethyl
GC	Gas chromatography
GCAP	Germ cell alkaline phosphatase
h	Hour
His	L-Histidine
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
Hz	Hertz
IC_{50}	Half maximal inhibitory concentration
i-Pr	Isopropyl
IR	Infrared spectroscopy
IAP	Intestinal alkaline phosphatase
J	Coupling constant

λ	Wavelength
*K*i	Inhibitory constant
Me	Methyl
MS	Mass spectrometry
mp	Melting point
NEt_3	Triethylamine
n-BuLi	*n*-Butyllithium
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
n-Pr	*n*-Propyl
Ph	Phenyl
Pi	Inorganic phosphate
PPi	Pyrophosphate
PivOH	Pivalic acid
PLAP	Placental alkaline phosphatase
Py	Pyridine
R	Organic moiety
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SAR	Structure-activity relationship
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
STS	Steroid sulfatase
t-BuLi	*tert*-Butyllithium
OTf	Triflate
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TNAP	Tissue nonspecific alkaline phosphatase
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Contents

1 Introduction

Широко распространяет химия руки свои в дела человеческие.
М. В. Ломоносов

Chemistry has widely spread his hands in human affairs.
M. V. Lomonosov

1.1 Natural products in drug discovery

Natural products are substances produced by living cells. They are either produced as primary metabolites, which are used by the cells for their own function or biosynthesized as secondary metabolites for various purposes, most of which unknown to us. Natural products remain a major source of drugs even today. In fact natural products, their derivatives (semi-synthetic compounds derived directly from natural products by chemical or biological methods) and natural-product-mimics constitute over 50% of all drugs that are used clinically.[1]

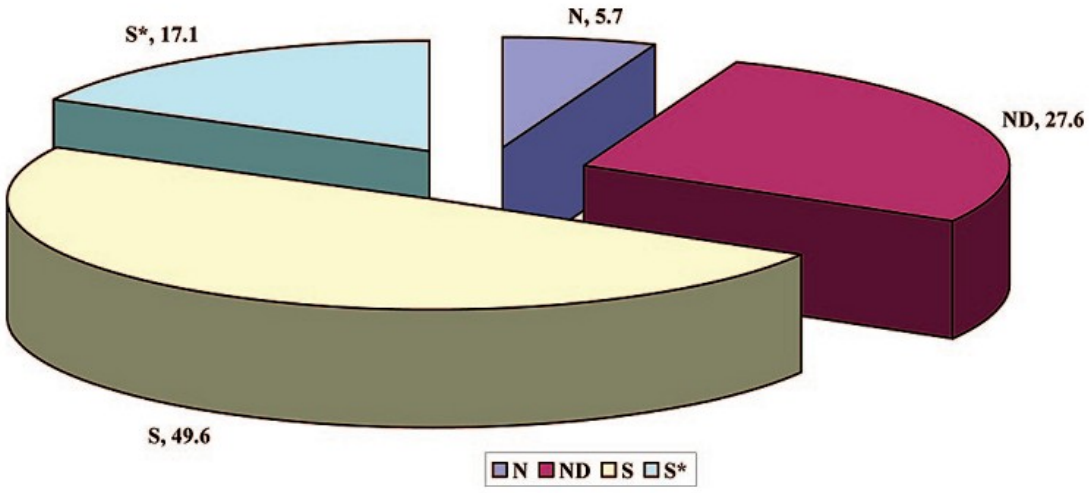


***Figure 1**: Source of small molecule drugs, 1981–2006: major categories, in percentages (total amount of sources n = 983). Major categories are as follows: "N", natural product; "ND", derived from a natural product and usually a semisynthetic modification; "S", totally synthetic drug often found by random screening/modification of an existing agent; "S*", made by total synthesis, but the pharmacophore is/was from a natural product.*[1]

The use of natural products as medicines has been described throughout history in the form of traditional medicines, remedies, potions and oils with many of these bioactive natural products still unidentified. The dominant source of knowledge of natural product uses from medicinal plants is a result of man experimenting by trial and error over hundreds of centuries through palatability trials or untimely deaths, searching for available foods for the treatment of diseases.[2]

Traditional medicinal practices have formed the basis of most early medicines, followed by subsequent clinical, pharmacological and chemical studies. Probably the most famous and well known example to date would be the synthesis of the anti-inflammatory agent, acetylsalicylic acid (Aspirin®) derived from the natural product, salicin, isolated from the bark of the willow tree Salix alba L. Investigation of Papaver somniferum L. (opium poppy) resulted in the isolation of several alkaloids including morphine, a commercially important drug, first reported in 1803. It was in the 1870s that crude morphine was boiled in acetic anhydride to yield diacetylmorphine, or heroine, and found to be readily converted to the painkiller codeine.[3]

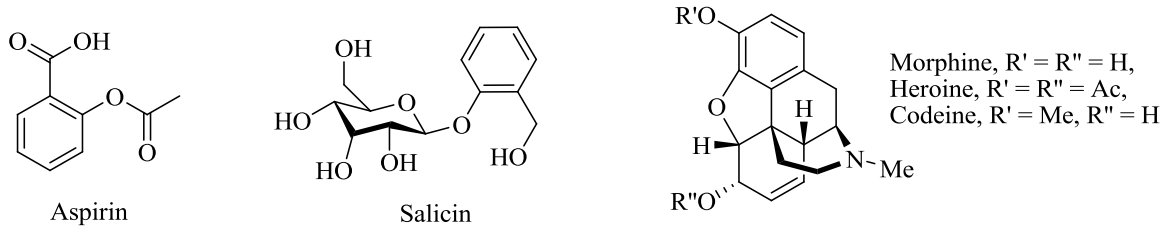


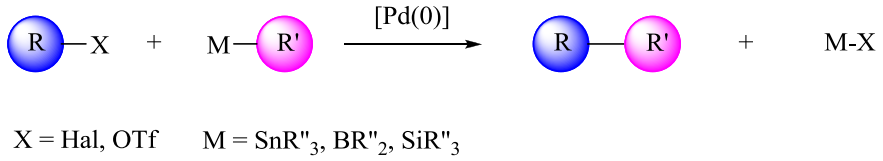
Figure 2: *Natural products.*

As outlined above, pharmaceutical research into natural products is of great significance in an era of advanced and cheap methods of synthesis. It has experienced, however, a slow decline during the past two decades.[4] This may be due to success in combinatorial chemistry, which allowed synthesizing and testing for activity of a vast number of compounds. Nevertheless, it was soon recognized that the combinatorial libraries lacked diversity. Hence, new approaches were applied to design compounds that allowed the introduction of many points of diversity, such as chiral centers, to mimic natural products.[3] Thus, the importance of the latter has been acknowledged once more.

The synthesis of natural-product-like compounds in all their complexity demands new advanced methods. Nowadays it is equally important that these methods are economically efficient and minimize the use and generation of hazardous substances. Possible transformations of natural scaffolds are numerous, whereas one of the most interesting, challenging and promising field is the formation of new carbon-carbon (C-C) bonds. Chemistry of transition metals, in particular, of palladium complexes, plays a key role here.

1.2 Modern methods of new C-C bond construction

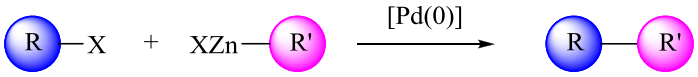
Cross-coupling reactions comprise of a group of transformations leading to the formation of C-C bonds based on the transmetallation of nucleophilic organometallic compounds with organic electrophiles in the presence of late-transition metals as catalysts. In most cases, cross-coupling reactions are based on palladium catalysis (Scheme 1).[5] These reactions are nowadays one of the most powerful methods for the creation of a C-C bond. Their development undoubtedly modified retro-synthetic strategies of organic chemists for the preparation of many important organic molecules, including biologically active compounds and industrially relevant starting materials.[6]



Scheme 1: *Representative palladium-catalyzed cross-coupling reactions.*

The majority of cross-coupling reactions were discovered in the second half of the twentieth century and bear the name of their inventors and developers. A brief description of the most important examples of C-C bond formation methods is presented below.

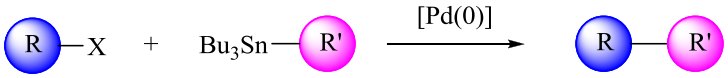
The Negishi coupling. The development of synthetically useful methods for the preparation of polyfunctional organozinc reagents of general structure RZnX has attracted much interest from organic chemists (Scheme 2). However, the reactivity of organozinc compounds as nucleophiles towards various electrophiles is lower than that of the corresponding Grignard or organolithium reagents, but it can be increased in the presence of an appropriate catalyst. Thus, the use of palladium as a catalyst and a phosphine ligand affords a convenient, general and selective method of versatile organozincs with organohalides coupling within a couple of hours.[7]



R = alkenyl, aryl, benzyl, propargyl
R' = alkenyl, aryl, alkyl, benzyl, allyl
X = Hal

Scheme 2:*The Negishi coupling.*

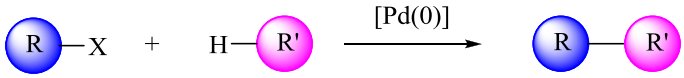
The Stille coupling.[8] The Stille protocol is defined as the carbon-carbon bond formation by Pd-catalyzed coupling of organic electrophiles (usually halides or triflates) with organotin reagents of general structure $RSnAlk_3$ (Scheme 3). Organotin reagents tolerate a variety of functional groups that many other reactive organometallics do not. Moreover, since most organotin reagents are sensitive to neither moisture nor oxygen, they can easily be isolated and stored. Many functionalities on the electrophiles can also survive the cross-coupling reaction due to its mild conditions. Thus, organic chemists can easily handle them but with special care because of their toxicity, e.g. tributyltin compounds are recently suspected of being endocrine disrupters. In consequence, a number of preparation techniques for such reagents have been developed and this protocol has widely been applied to syntheses of a vast number of densely functionalized substances such as biologically intriguing compounds.[9]



R = alkenyl, aryl, benzyl, acyl
R' = alkenyl, aryl, alkyl, benzyl, allyl
X = Hal, OTf

Scheme 3:*The Stille coupling.*

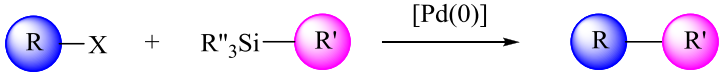
The Heck coupling. The palladium-catalyzed arylation and vinylation of olefins is known worldwide as the Heck reaction (Scheme 4). It is attractive from a synthetic point of view because high chemoselectivity and mild reaction conditions are associated with low toxicity and low cost of the reagents.[10] Typical reagents for the reaction are unsaturated halides or triflates, while simple alkenes act as substrates.[11] Aryl iodides are usually more reactive than bromides and triflates, and aryl chlorides are notoriously unreactive unless special catalysts or ligands and elevated temperatures are used to enhance the reaction rate. The Heck reaction is compatible with a variety of substituents; only strong oxidizing agents such as quinones are not tolerated. Today, efficient methods have been developed that also make possible regiocontrolled functionalizations of electron-rich alkenes, and frequently efficient double bond migration control has been achieved with both cyclic and acyclic systems. Powerful catalytic systems have emerged after considerable experimentation with palladium salts, ligands, and solvents; very high turnover numbers and short reaction times have been accomplished.[9]



R = alkenyl, aryl, alkyl
R' = alkenyl
X = Hal, OTf

Scheme 4: *The Heck coupling.*

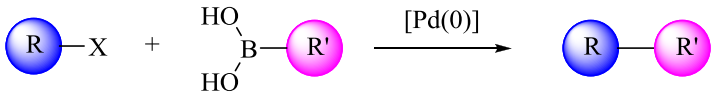
The Hiyama coupling. Organosilicon compounds of general structure $RSiR'_3$ react with unsaturated organic halides or triflates in the presence of palladium catalysts and fluorine anions to give corresponding products (Scheme 5).[12] Recent studies expand an application area of organosilanols and their salts overcoming the need to use fluorine and making the reaction a valuable alternative to boron- and tin-based methods.[13]



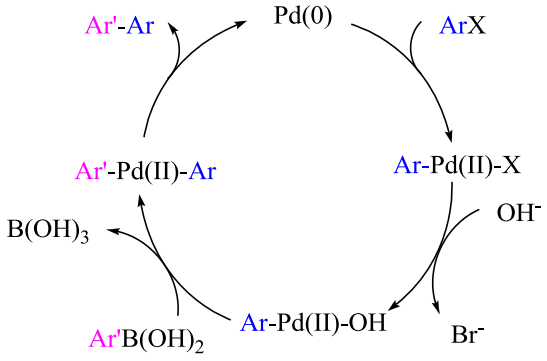
R = alkenyl, aryl, alkynyl, alkyl
R' = alkenyl, aryl, alkynyl
R" = Cl, F, Alkoxy
X = Hal, OTf

Scheme 5:*The Hiyama coupling.*

The Suzuki-Miyaura coupling. Cross-coupling reactions of organoboron compounds with organic halides or triflates were developed by Suzuki and Miyaura[14] and present one of the most convenient paths to biaryls or, in other words, arylation procedures (Scheme 6). However, not only aryls can act as organoboron compounds. Alkyls, alkenyls and alkynes are among other suitable substrates. The organoborons often used are boronic acids of general structure $RB(OH)_2$, their properties, such as thermal stability and inactivity with regard to oxygen and water, make them extremely useful and convenient reagents. The most commonly used palladium catalyst for the reaction is $Pd(PPh_3)_4$, but depending on the reaction various catalytic systems can be used, for example, $Pd(OAc)_2$, Pd_2dba_3 or $PdCl_2$ with or without phosphine ligands. The cross-coupling reactions of organoboronic acids, in general, require the presence of a negatively charged base, such as sodium or potassium carbonate, phosphate or hydroxide. Suitable solvents are toluene, dioxane, DME or DMF, moreover, in some cases even water can be used as a solvent.[15]



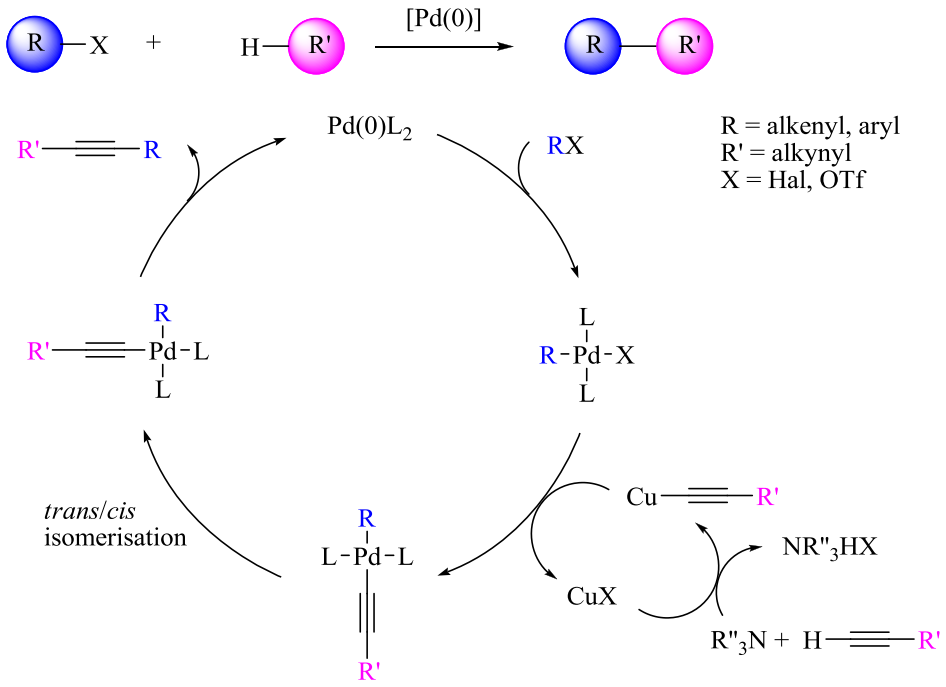
R = alkenyl, aryl, alkynyl, alkyl
R' = alkenyl, aryl, alkynyl, alkyl
X = Hal, OTf



Scheme 6:*The Suzuki-Miyaura coupling and the possible reaction mechanism.*

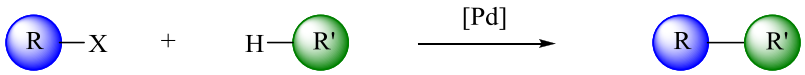
The Sonogashira coupling. The palladium catalysed C-C bond formation process which is able to couple a terminal sp hybridized carbon from an alkyne with a sp^2 carbon of an aryl or vinyl halide (or triflate) is commonly termed as a Sonogashira coupling (Scheme 7). The reaction name arises from the discovery in 1975 by Sonogashira, Tohda, and Hagihara[16] that this

process could be performed easily at room temperature using a palladium source such as $PdCl_2(PPh_3)_2$ as catalyst, combined with a catalytic amount of CuI in an amine as a solvent. Nowadays, the term "Sonogashira reaction" comprises the palladium(0)-catalyzed coupling of a sp^2 (or even sp^3) halide or triflate with a terminal alkyne, regardless of whether copper(I) salts are present.[17] The Sonogashira reaction is usually performed using a palladium-phosphine ligand complex as catalyst in the presence of a catalytic amount of a copper(I) salt and an amine (as a solvent or in large excess) under homogeneous conditions. The traditionally used catalysts are triphenylphosphine-related complexes, $Pd(PPh_3)_4$, with the more stable and soluble $PdCl_2(PPh_3)_2$ being the most common, although catalysts with bidentate ligands have also been employed.[18] The addition of copper is crucial in terms of increasing the reactivity of the system. It added, however, some shortcomings, e.g. the necessity of avoiding the presence of oxygen in order to block the undesirable formation of alkyne homocoupling.[17] In the last time, the use of more active catalysts, though, has allowed coupling procedures which work in the absence of copper co-catalysis and has even made the presence of an amine and a phosphine unnecessary. These copper- and amine-free procedures can be driven closer to environmental perfection when aqueous solvents or even neat water are employed.[18]



Scheme 7: *The Sonogashira coupling and the reaction mechanism.*

C-H activation reactions. Nowadays, reactions discussed above (namely, Negishi, Stille, Hiyama and Suzuki-Miyaura) are considered as classical methods for creating aryl-aryl C-C bonds. They all require functionalization of both coupling components. For example, in the Suzuki-Miyaura coupling, aryl halides react with organoboron compounds; in the Stille coupling, they react with organotin compounds and so on. In contrast, using a carbon-hydrogen (C-H) bond as a functional group in cross-coupling reactions is beneficial since prefunctionalization of one or both of the coupling components is not required. Since aryl halides and aryl metals are typically made in one or more steps from hydrocarbons, the use of carbon-hydrogen bonds as a functional group would result in the shortening of synthetic schemes and overall increased efficiency of chemical processes. Increased efficiency in its turn makes the chemical processes more "green" by reducing the amount of byproducts and solvent waste. General methods, useful in synthetic applications, were first studied and developed just in last decades, and the field is now one of the most extensively researched among organic chemists.[19]



X = Hal for CH-activation reaction;
X = H for double CH-activation reaction

***Scheme 8**: Representative CH- and double CH-activation reactions.*

A double CH-activation is the most atomically economical way of C-C bond formation. In this case, both reagents provide for the reaction only C-H bonds. However, regioselectivity issues usually occur due to multiple C-H bonds in both coupling components. A simple CH-activation reaction could be thus considered as a compromise between classical methods of C-C bond formation and double CH-activation. In this case, common reaction partners are presented by aryl halides, usually iodides or bromides, less often chlorides, from the one side and C-H bonds bearing compounds from the other side. The latter can additionally have directing groups, such as anilides or carboxylates that promote the reaction and increase regioselectivity. Various palladium catalysts with or without phosphine ligands can be used as catalytic systems.[19]

1.3 Task and motivation

For hundreds of years chemistry has served us as a powerful tool in creating new useful substances such as dyes, medicines, pesticides and compounds used in machines and electronics amongst other things. The development of synthetic methods allows us nowadays to produce any determined structure. However, the search for more effective, fast, beneficial and ecologically friendly approaches never ends. There is moreover an endless need for new drugs, particularly antimicrobial and antiviral. They inevitably become inefficient due to the mutation of microbes and viruses which makes the latter resistant to known remedies. Natural products, as an inexhaustible source of diverse new molecules, together with improving synthetic strategies to modify them, is one solution for the struggle between mankind with infection.

Therefore, in this work, the modern and classical palladium-catalyzed cross-coupling protocols will be applied in order to modify natural product's scaffolds and to obtain new potentially biologically active products. When possible, the latter will be tested for their biological action.

2 Arylation of indoles via CH-activation reaction at position 3

2.1 Introduction

2.1.1 Biological importance of indoles

Indole was first synthesized by Adolf von Bayer almost 150 years ago in the course of his studies of indigo dye.[20] In the following years it was found to be a part of many naturally occurring compounds.[21] Among them are alkaloids, such as toxins gramin, strychnine and psilocybin that is also known for its psychedelic activity; plant hormones auxins, such as heteroauxine that coordinates growth and behavioral processes in the plant's life cycle; neuromodulators and neurotransmitters, such as serotonin that plays an important role in regulation of the human CNS and many others. Indole is probably the most widely distributed heterocyclic compound in nature, since it is a core of an essential amino acid tryptophan and as such a constituent of almost all proteins (Figure 3).[22]

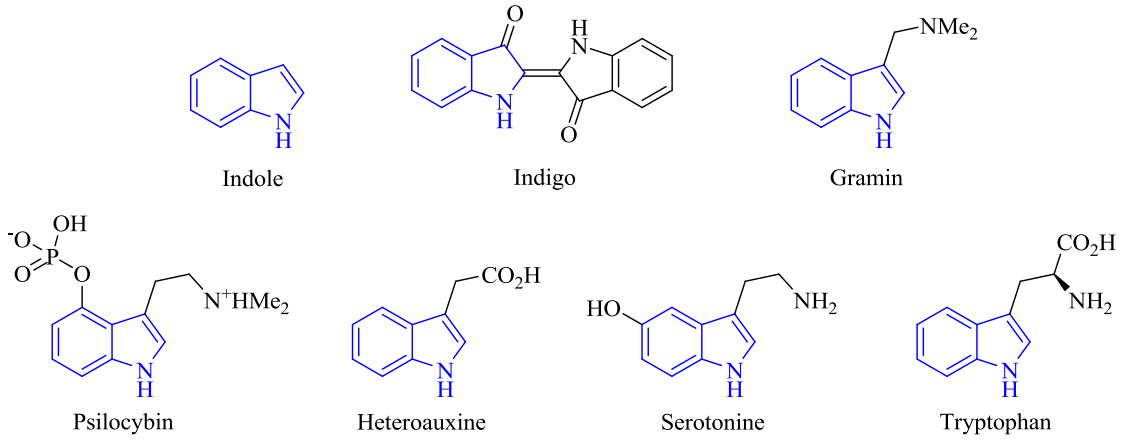
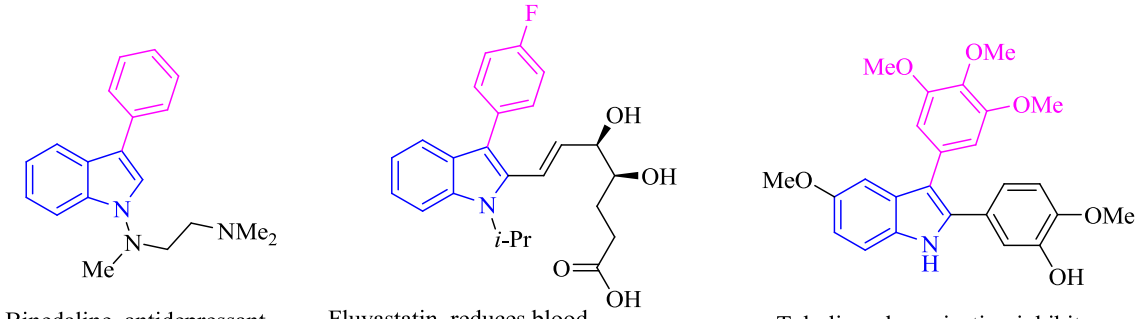


Figure 3: *Natural compounds containing indole skeleton.*

Naturally, such diversity in biological properties of indoles attracted attention of synthetic and pharmaceutical chemists. The variety of indole-ring containing marketed drugs have been reported to exhibit anticancer,[22] immunomodulatory,[23] vasodilator,[24]

antihypertensive,[25] antipsychotic,[22] antidepressant,[26] anti-inflammatory,[27] antiviral,[28] and antimicrobic[29] properties. It was recently found that simple 3-arylated indoles show significant activity against Gram-positive pathogens.[30] Furthermore, they exhibit antidepressant,[22] anticancer,[31] antimicrobic and other properties (Figure 4).[32]



Binedaline, antidepressant

Fluvastatin, reduces blood cholesterol level

Tubulin polymerization inhibitor

Figure 4: *Biologically active 3-arylated indoles.*

Concerning further modifications of the indole core, nitro-derivatives of indole should be mentioned. A big study of 9,600 structurally diverse drug-like compounds as potential inhibitors of the bacterial membrane transporter NorA showed that a quarter of all active indole compounds were containing a nitro group in their structure.[33] Further studies confirmed a range of 2-aryl-5-nitroindoles to be effective inhibitors of the NorA multiple drug resistance pump.[34] Differently nitro-substituted indoles also showed significant anti-inflammatory activity.[35]

Although the indole family is very well studied, its potential seems to be limitless. There is still a need to access a greater range of indole derivatives with a variety of functionalization in the aryl substituent group. Such derivatives would be of value in establishing new potent drugs and their structure-activity relationships.

2.1.2 Task and motivation

As described above, numerous indole derivatives show interesting physiological properties, among them 3-arylated indoles and nitro-indoles. Due to the literature, however,

indoles containing both of the said moieties are only scarcely described. There is, moreover, no synthetic method towards 3-aryl-2-nitroindoles. Thus, it is an intriguing challenge to find the way to obtain these compounds and test their biological activity.

2.1.3 Synthesis of 3-aryl-2-nitroindoles

Figure 5 shows three possible retrosynthetic paths to design 3-aryl-2-nitroindoles. First, an indole core can be assembled from non-cyclic parts through cyclization reaction (Figure 5, Path A). Then, 3-arylindole can be nitrated at position 2 (Path B). Finally, an indole bearing a nitro group at position 2 can be arylated at position 3 (Path C).

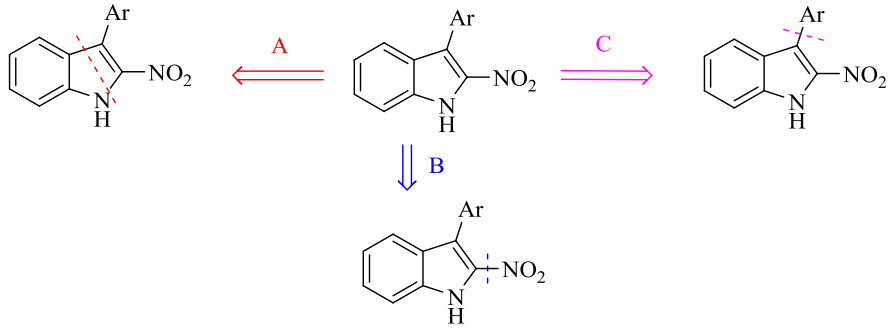
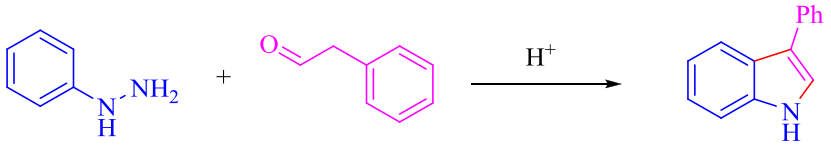


Figure 5: *Retrosynthetic analysis for synthesis of 3-aryl-2-nitroindoles.*

Path A. Fischer indole synthesis is a classical route towards substituted indoles.[36] Invented more than a century ago,[37] it remains a versatile method for the preparation of indoles and its numerous modifications are constantly being developed.[38] In the reaction appropriate hydrazines and aldehydes or ketones react under acidic conditions (Scheme 9). This method, however, is unsuitable if 3-aryl-2-nitroindoles are target molecules, because needed 1-nitro-2-phenyl-ethanone does not exist. Numerous further synthetic strategies of combining acyclic building block to obtain an indole core also give no possibility to directly obtain 3-aryl-2-nitroindoles.



Scheme 9: *Fischer synthesis of 3-phenylindole.*

Path B. Nitration of indoles occurs depending on the nitration agent in the pyrrole ring or in the benzene ring, but is in both cases mostly not selective. This results in lower yields and/or products of disubstitution. Furthermore, oxidation or dimerisation of the indole can take place.[39]

Path C. Arylation of 2-nitroindole is unknown in the literature. However, there is plenty of information for a simple indole and its derivatives. Unsubstituted and *N*-methyl indole can be easily arylated selectively at position 3 reacting with diaryliodonium salts in the presence of copper salts[40] or even in the absence of metal catalysis.[41] An interesting approach of selective palladium-catalyzed 3-arylation of indoles was published recently.[42] In the publication, various cyclohexanones acted as aryl sources via an alkylation and dehydrogenation sequence using molecular oxygen as the hydrogen acceptor. Further, it was shown that aryl hydrazines also act as suitable reagents.[43] 3-Aryl substituted indoles were also prepared by Suzuki-Miyaura reactions of 3-brominated indoles as the starting material.[44] Although this synthetic strategy is very efficient, it is limited by its requirement of additional synthetic steps, such as the synthesis of the required 3-bromoindoles. All these methods demand the employment of relatively expensive compounds as starting materials. In other studies some uncommon and expensive catalysts[45] or ligands[46] were used.

In some cases, however, simple catalytic systems together with cheap reagents were employed. Thus, a simple heating of indole with arylbromides in toluene in the presence of palladium acetate, a ligand and a base gave 3-arylated products with good yields.[47] Arylation at positions 1 and 2 can be excluded using 1,2-disubstituted indoles as substrates. It was shown, for example, for 2-chloroindole,[48] where the chlorine group additionally acts as an activating group and provides a possibility for further functionalization.

A direct arylation of nitro-group containing substrates was studied in Prof. Langer's group.[49] In the study, a transition-metal catalyzed arylation of 4-nitropyrazoles was developed. A catalytic system consisting of $PdCl_2(PPh_3)_2$, CuI and PivOH provided the arylation of substrates with excellent yields.

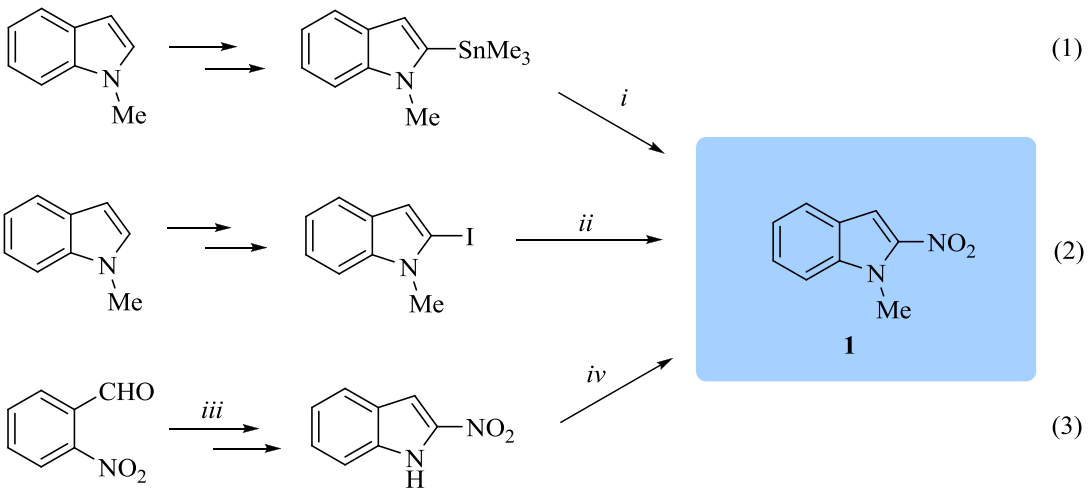
Thus, a comparison of known in the literature pathways for the synthesis of 3-aryl-2-nitroindoles showed the following: the most rational and efficient strategy for the synthesis would be the use of direct arylation of 2-nitroindole (CH-activation reaction, section **1.2**). This approach tolerates the use of non-functionalized substrates (with simple C-H bonds) and minimizes the production of waste. To exclude some possible side-reactions *N*-methylated indole will be used as a substrate.

2.2 Results and discussion

2.2.1 Synthesis of starting material

Several routes towards 1-methyl-2-nitroindole can be found in the literature. Direct nitration cannot be used, as it proceeds at more electron-rich position 3. However, it is possible to perform the reaction in a two step manner. For example, at the first step trimethylstannane derivative of indole can be obtained[50] and then transformed into the corresponding 2-nitroindole through reaction with tetranitromethane (Reaction 1, Scheme 10).[51] A disadvantage of this method is a need of use of toxic and dangerous compounds. Using another method, 2-halogenated[52] *N*-protected indoles can be treated with $AgNO_2$ giving corresponding nitro-derivatives.[53] Unfortunately, in case of *N*-methylindole, the yield is only insignificant (Reaction 2, Scheme 10).

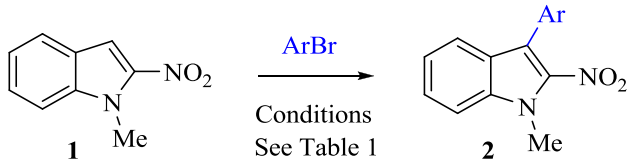
Alternatively, a four-step reaction sequence starting with *o*-nitrobenzaldehyde can be used (Reaction 3, Scheme 10).[54] The method gives the desired 2-nitroindole in relatively good overall yield and allows working with cheap and safe reagents. Subsequent methylation with methyliodide[55] afforded the starting material. Thus, 1-methyl-2-nitroindole (**1**) was obtained using this method.



Scheme 10: *Reagents and conditions: i, tetranitromethane, DMSO, 20°C; ii, $AgNO_2$, acetone/water, 65°C; iii, 1) NaN_3, DMF, 60°C; 2) CH_3NO_2, KOH, EtOH, 0°C; 3) Ac_2O, Py, 0-20°C; 4) xylenes, 140°C; iv, NaH, CH_3I, DMF, 25 °C.*

2.2.2 CH-Activation reaction of 1-methyl-2-nitroindole with aryl bromides

Having in hand 1-methyl-2-nitroindole as a starting material, I started to search for suitable conditions for the arylation reaction. Based on the experience of Prof. Langer's working group,[49] first, a catalytic system comprising of $PdCl_2(PPh_3)_2$ as a catalyst and CuI and PivOH as additives was used. Utilizing the system, however, gave no product. Therefore, a number of catalysts, ligands and additives was tested, until it was found, that applying a simple $Pd(OAc)_2$ alongside with an additional equivalent of aryl bromide afforded the desired product in a good yield (Scheme 11, Table 1). Surprisingly, the use of ligands like PPh_3 and PCy_3, and CuI or PivOH as well as increased concentration of the catalyst resulted in lower yields. This can be explained by a possible formation of solvent-stabilized nanoparticles of palladium.[56] This catalytic species are known to be active with an absence of ligands. Whereas higher concentrations of a catalyst lead to the rapid precipitation of palladium black and catalyst deactivation.[57]



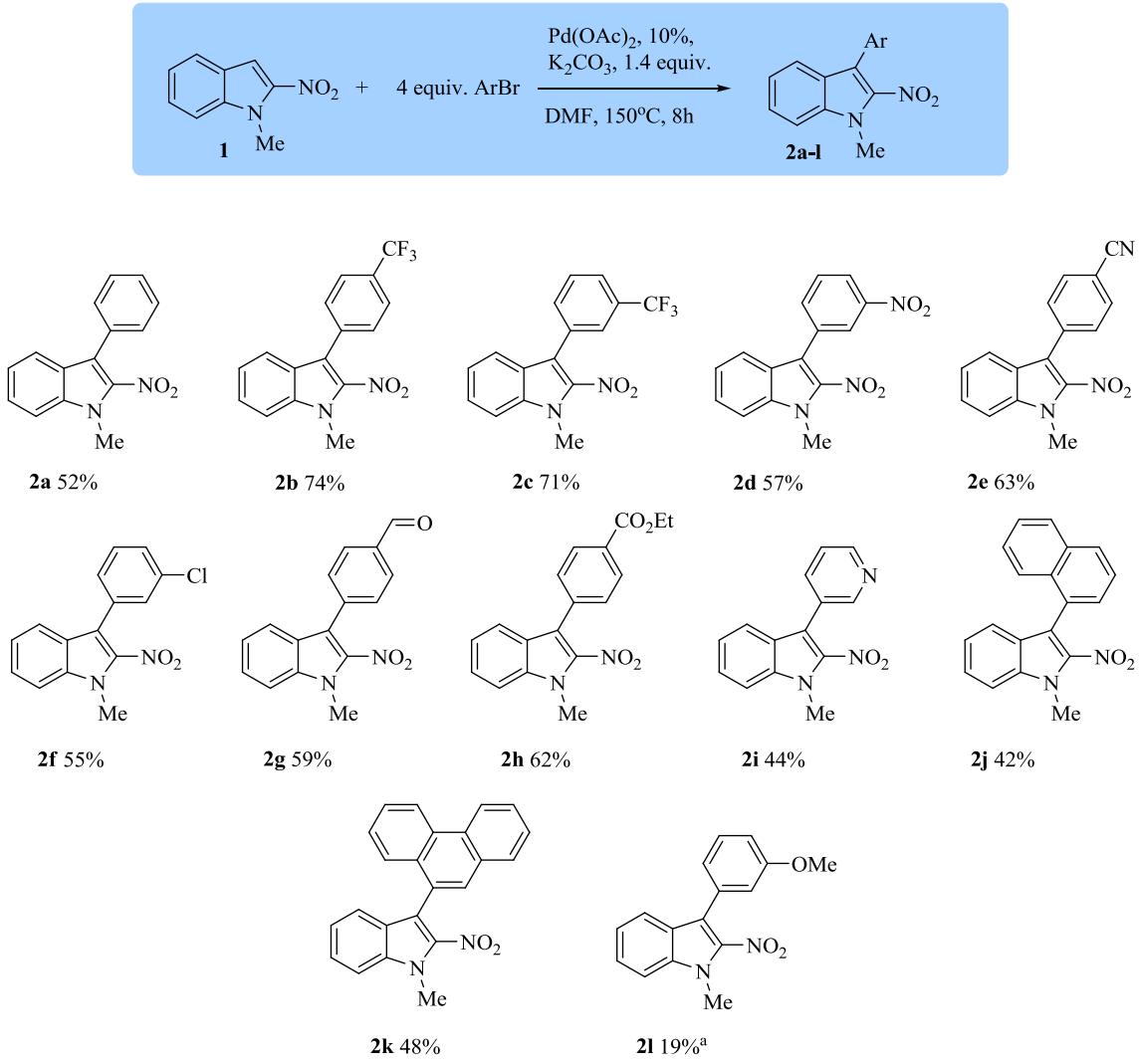
Scheme 11: *Synthesis of 3-aryl-1-methyl-2-nitroindoles* ***2****.*

Table 1: *Optimization of the synthesis of* ***2c****.*

Entry	Catalyst	Ligand	Additive	%[a]
1	$PdCl_2(PPh_3)_2$, 10%	-	PivOH, CuI	-[c]
2	$Pd(PPh_3)_4$, 10%	-	-	-[c]
3	$Pd(OAc)_2$, 10%	-	-	57
4	$Pd(OAc)_2$, 10%	PCy_3	-	60
5	$Pd(OAc)_2$, 10%	-	PivOH, CuI	54
6	**$Pd(OAc)_2$, 10%**	**-**	**-[b]**	**74**
7	$Pd(OAc)_2$, 10%	PPh_3	-	56
8	$Pd(OAc)_2$, 20%	-	-	55
9	$Pd(OAc)_2$, 10%	-	PivOH	62
10	$Pd_2(dba)_3$, 10%	-	-	-[c]

[a] Isolated yields. Conditions: catalyst (see Table), ArBr [Ar = 3-$(F_3C)C_6H_4$] (3.0 equiv), K_2CO_3 (1.4 equiv.), 150 °C, 8 h, DMF; [b] 4.0 equiv. of ArBr; [c] low conversion of starting material.

Using optimized conditions a range of 3-aryl-1-methyl-2-nitroindoles **2a-l** was synthesized (Scheme 12). Best results were obtained for electron-deficient arenes, bearing groups such as CF_3, NO_2, CN, CO_2Et and others. Electron-neutral arenes were obtained with moderate yields, and in the case of electron-rich arenes reactions gave products only in low yields or were not successful at all. In all cases, after completion of the reaction significant amounts of the unreacted substrate could be observed. Unfortunately, attempts to increase the conversion by using longer reaction times were fruitless. Mostly, this fact did not affect the isolation of products by a simple column chromatography, due to diverse polarity of the substrate and products. In case of products **2d** and **2e**, however, HPLC was applied for the isolation.



Scheme 12: *Synthesized 3-aryl-1-methyl-2-nitroindoles* ***2a-l*** *with isolated yields.* [a] *Yield determined by HPLC.*

2.2.3 Structure identification

The structure of all products was characterized by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry. Moreover, the structure of compounds **2a** and **2b** was independently confirmed by X-Ray diffraction analysis (Figure 6). All bond lengths match corresponding theoretical values. The torsion angles between the indole core and aryl rings are between 54 – 59°.

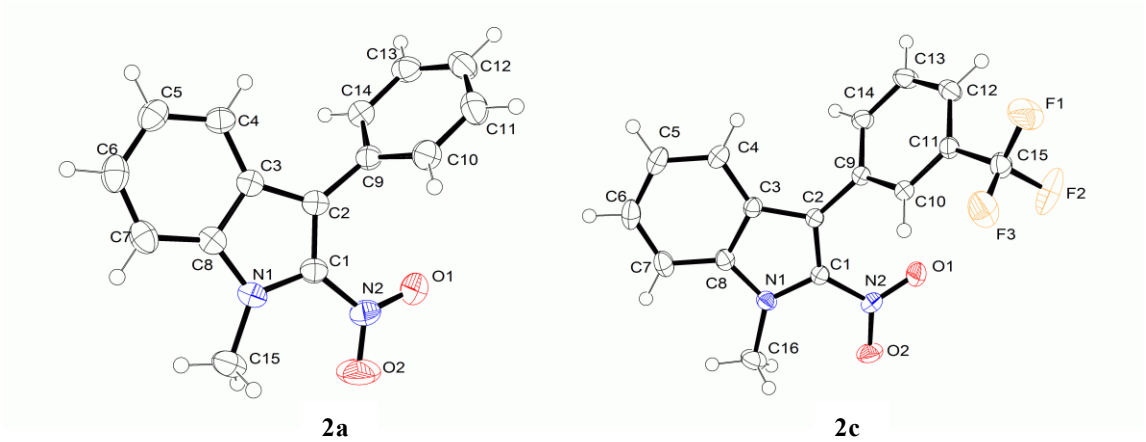


Figure 6: *Crystallographic structures of compounds* ***2a*** *and* ***2c****, oxygen atoms red, nitrogen atoms blue, fluorine atoms yellow.*

2.2.4 Biological studies

The obtained compounds were tested for their activity as inhibitors of alkaline phospatases (see section **3.2.4.1**) in the Centre for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad, Pakistan. Unfortunately, no significant activity was observed.

2.3 Conclusion

A method for the synthesis of new 3-aryl-1-methyl-2-nitroindoles was developed through a palladium-catalyzed cross-coupling CH-activation reaction of 1-methyl-2-nitroindole with various aryl- and heteroarylbromides. The method is suitable for electron rich and electron neutral reagents and provides target products in good yields. The products obtained during this study might be of pharmacological relevance.

3 Alkynylation of (+)-estrone

3.1 Introduction

3.1.1 Biological importance of (+)-estrone

Steroid skeleton is a wide spread constituent among biologically important molecules. Thus, cholesterol is an essential structural component of all animal cell membranes, whereas steroid hormones are a part of the signal system of organisms.[58] Female primary sex hormones – estrogens – present a hormone family that promotes the development of female secondary sexual characteristics and regulates the menstrual cycle.[59]

The term estrogens denotes a subgroup of steroids with an aromatic A ring (Figure 7) as a characteristic part of the tetracyclic molecular framework. The most prominent members of this class are the follicular hormone estradiol and its main metabolites (+)-estrone (**3**, further simply estrone) and estriol together with their sulfated and glucuronidated counterparts.[60]

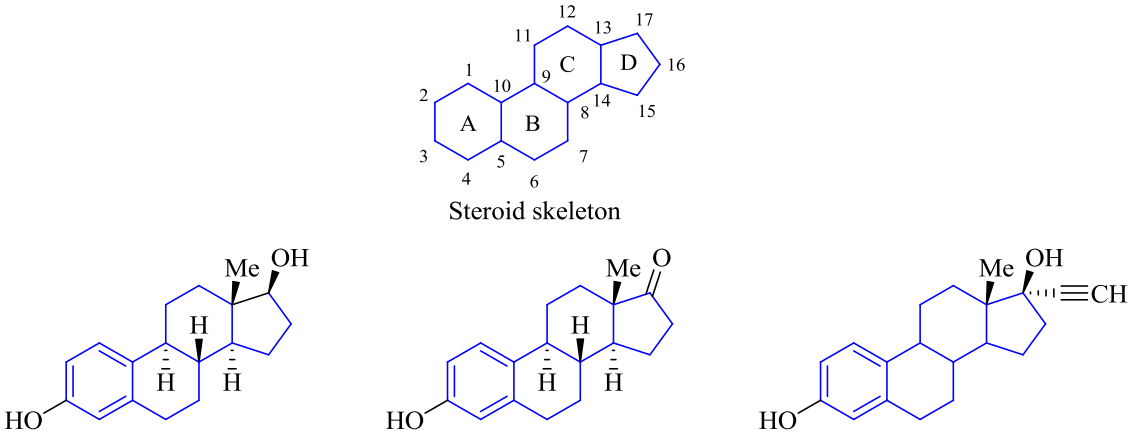


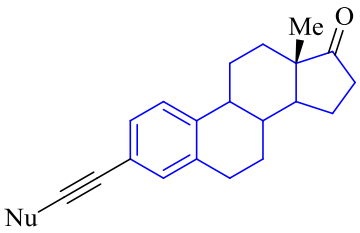
Figure 7: *Estrogen steroids.*

The rapid oxidation of estradiol with the formation of estrone observed after oral administration and first liver passage stimulated early synthetic variations of the natural

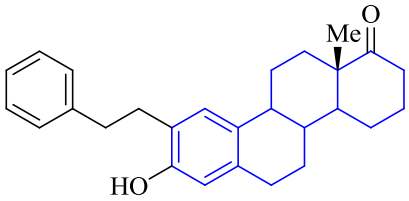
hormone. As a result, 17α-ethynylestradiol was synthesized and found to be highly effective by the oral route.[61] With the advent of an estrogen/progestogen combination as a regimen for oral contraception in the early 1950s, 17α -ethynylestradiol became the estrogenic component of contraceptive preparations and has maintained its dominant position, despite the synthesis and investigation of numerous analogues since then (Figure 7).[60]

It was further found that 3-alkynylestrones (for example, nucleoside containing 3-ethynyl-estra-1,3,5(10)-trien-17-one (**4**)) show antiviral properties and can be used as prophylactic agents against various virus infections.[62] 2-Phenylethynylestrone was applied for the synthesis of 2-phenylethyl-D-homo-estrone (**5**), which is a highly active inhibitor of steroidogenic human 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD 1). The IC_{50} values of this compound are in the nanomolar range and are seven-fold higher than that of estrone (Figure 8).[63]

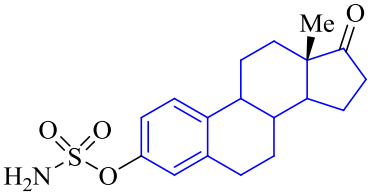
A recent study showed that estrone sulfamate (**6**, EMATE) inhibits steroid sulfatase (STS) and, therefore, can be successfully used for the treatment of hormone-dependent breast cancer.[64,65] EMATE was further functionalized at position 2- and 4- in order to search for STS inhibitors lacking the undesired estrogenic effect, displayed by EMATE.[64]



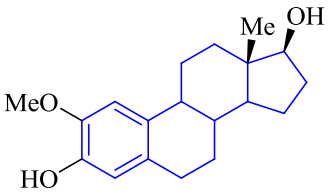
4, Nu = nucleoside



5, 2-Phenylethyl-D-homo-estrone



6, EMATE



7, 2ME2

Figure 8: *Biologically active estrone derivatives.*

Furthermore, it was shown that 3-functionalized derivatives of 2-methoxyestradiols **7** (2ME2) show high antiproliferative and antiangiogenic activity. Investigations on their structure-activity relationships indicate high antitumor activity for functional groups at position 3, containing hydrogen donors with π-electrons (such as hydroxyl, amino, formamide, etc.), while relatively bulky substituents (such as tertiary amines) suppress the undesired estrogenic activity.[66]

3.1.2 Task and motivation

Despite the potentially high biological and pharmacological activity of alkynylated or differently functionalized in position 3 estrone derivatives, there are only a few reports on their synthesis, mostly lacking a preparative scope. Thus, I decided to study the synthesis of 3-alkynylated estrone derivatives and to investigate the scope and limitations of the follow up chemistry of the new introduced triple bond.

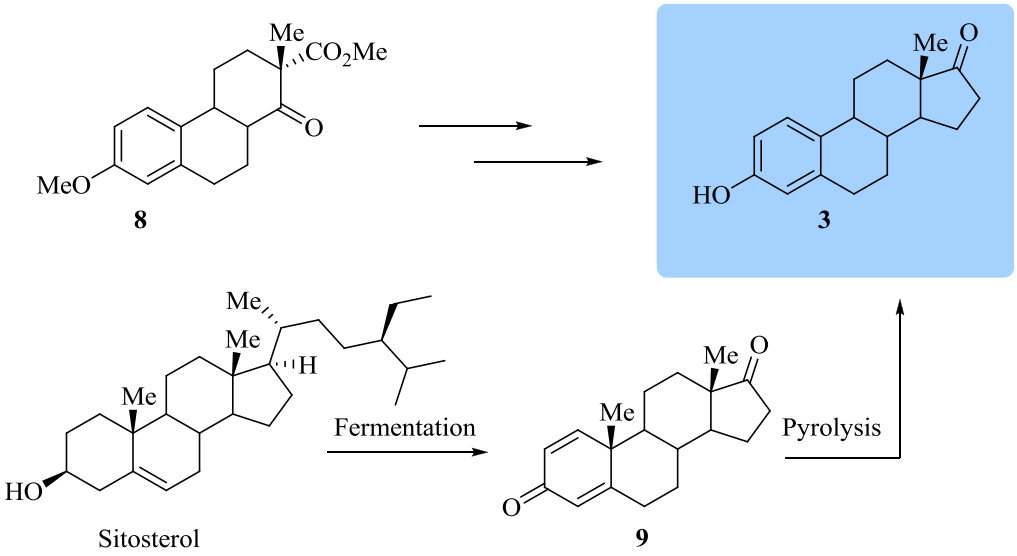
3.1.3 Synthesis of estrone

Being a female primary sex hormone, estrone can be isolated from the urine of pregnant women or animals.[67] These methods, however, are time-consuming and ineffective. Therefore, the following synthetic methods were developed.

The first total synthesis of estrone was completed in 1948 by Anner and Miesher.[68] The readily available racemate of tricyclic ketoester **8** (Scheme 13) was used as a starting material. The nine-step reaction sequence lacks stereoselectivity and, therefore, a racemate separation is needed that significantly reduces the reaction yield. The following attempts were focused on trying to increase the selectivity of the reaction, where a key strategy was a cyclization of various chiral reagents via Diels-Alder reaction.[69] These approaches, though, still did not exclude the necessity of a racemate separation. Finally, the most modern methods combine

achievements of the previous works and the use of microorganisms as a source of highly selective enzymes, for example, as reduction promoters.[70]

Currently, the most economic process combines microbial degradation of abundant cholestane derivatives (e.g. sitosterol) with pyrolytic methane extrusion from androsta-1,4-diene-3,17-dione (**9**) to form estrone (Scheme 13).[60]



Scheme 13: *Total synthesis of estrone.*

3.1.4 3-Alkynylation of estrone

The Sonogashira cross-coupling reaction is a convenient way to create new carbon-carbon bonds between arenes and alkynes (Section **1.2**). Estra-1,3,5(10)-trien-17-one-3-yl triflate (**10**, estronyl triflate) can be used as a substrate and is easily accessible by triflation of the phenolic OH-group of estrone.[71] Some examples of the Sonogashira reaction of estrone are known. Conditions of the reactions are common and include the use of copper(I) iodide as co-catalyst, NEt_3 as base and DMF as solvent. $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ can be used as catalysts.[62,72] However, the latter afforded only a moderate yield.

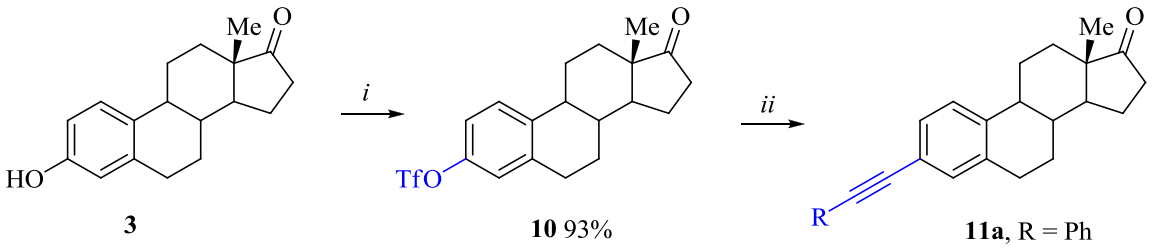
Additionally the use of imidazol-1-yl-sulfonates instead of triflate as effective electrophilic partners in copper-free palladium-catalyzed Sonogashira reactions has been suggested in the literature[73]. Such modification is reasonable when standard conditions deliver unsatisfying results. Otherwise, the use of expensive reagents is undesirable. Finally, it was shown that phenols can be directly transformed into alkynylated aryls, without isolation of intermediate triflate, using fluoroalkanesulfonyl fluoride as a co-reagent.[74]

3.2 Results and discussion

3.2.1 Sonogashira reaction of estra-1,3,5(10)-trien-17-one-3-yl triflate

Estronyl triflate (**10**) was obtained with an excellent yield of 93% from commercially available (+)-estrone (**3**) using triflyl chloride as a triflating agent.[71] Using triflic anhydride for this purpose resulted in a less pure reaction and strongly decreased the yield.[72]

With estrone triflate in hand, suitable conditions for the subsequent Sonogashira reaction were studied. Following a known procedure,[62] I soon realized that described conditions are only applicable for the electron rich trimethylsilylacetylene. Other acetylenes gave diminished yields. Therefore, the reaction conditions were optimized. Using phenylacetylene as a model compound, it was found that best results were obtained using DMF as a solvent in the presence of diisopropylamine as a base at 100 °C for 8h. 10 mol% of $Pd(PPh_3)_4$ and 10 mol% of copper(I) iodide are required to achieve high yields (Scheme 14, Table 2).



***Scheme 14**: Synthesis of **11a**: Conditions: i, **3** (1.0 equiv.), TfCl (1.2 equiv.), NEt_3 (1.2 equiv.), DCM, 0 to 20°C; ii, **10** (1.0 equiv.), phenylacetylene (1.2 equiv.), catalyst, co-catalyst, base (3 equiv.), DMF, T°C.*

Table 2: *Optimization of the Sonogashira reaction.*

Entry	Catalyst	Co-catalyst	Base	T, °C	Time, h	Yield[a], %
1	$Pd(PPh_3)_4$,10%	CuI,20%	NEt_3	20	8	0
2	$Pd(PPh_3)_4$,10%	CuI,20%	NEt_3	60	8	0
3	$Pd(PPh_3)_4$,10%	CuI,20%	NEt_3	100	8	64
4	$Pd(PPh_3)_4$,10%	CuI,20%	$HN(i\text{-}Pr)_2$	100	8	82
5	**$Pd(PPh_3)_4$,10%**	**CuI,10%**	**$HN(i\text{-}Pr)_2$**	**100**	**8**	**87**
6	$Pd(PPh_3)_4$, 5%	CuI,10%	$HN(i\text{-}Pr)_2$	100	16	55

Proceeding reaction at relatively low temperatures afforded no product, while heating the reaction mixture at 100°C gave the target alkyne **11** in a good yield. Changing NEt_3 to $HN(i\text{-}Pr)_2$ resulted in yield improvement, whereas lowering the amount of the catalyst used led to dramatically yield decrease.

Using conditions, developed by Chen et al. for the direct alkynylation of estrone[74] in a one-pot reaction provided products with lower yields, compared to the overall yields of the present two-step procedure. Thus, phenyl derivative **11a** was obtained with 63% and 81% respectively, *tert*-butylphenyl derivative **11d** with 75% and 85% respectively.

Taking this into account, optimized conditions were used to obtain alkynylestrones **11a-i** with good to excellent yields (Figure 9). As already mentioned, electron-donating substituents on the phenylacetylene resulted in higher yields and vice versa. Additionally, problems during the purification process of products containing strong electron-withdrawing groups reduced the isolated yields due to high amounts of impurities. Accordingly, it was not possible to obtain the *p*-cyanophenylethynyl derivate at all.

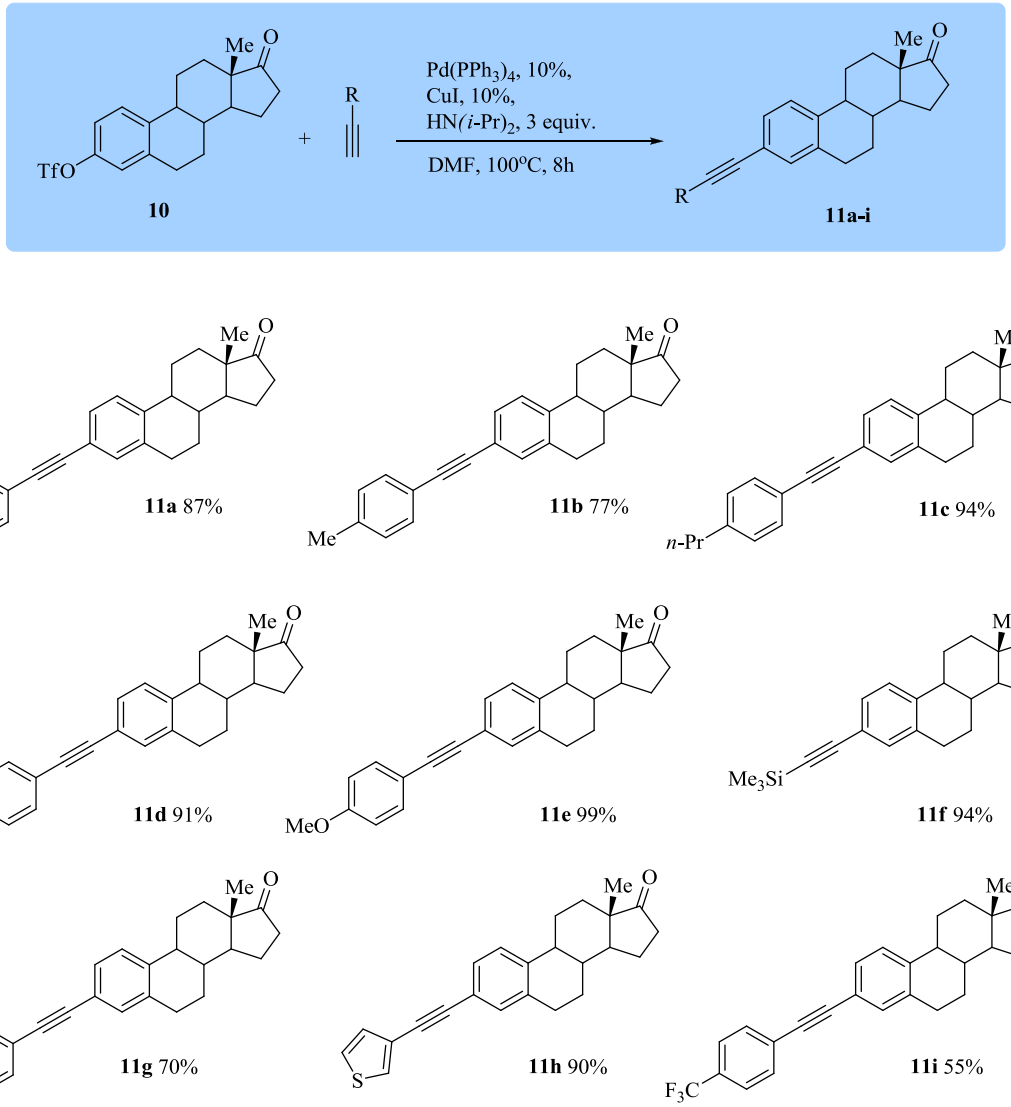


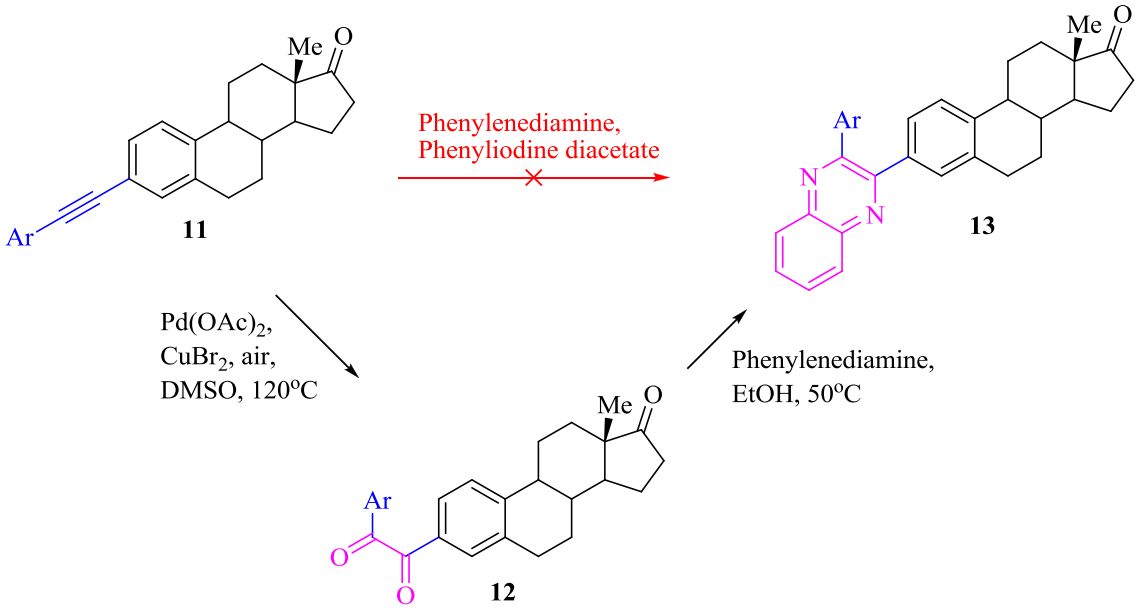
Figure 9: *Synthesized alkynylated estrones* ***11a-i*** *with isolated yields.*

3.2.2 Further functionalization of alkynylated estrones

Having in hand the alkynylated products, further transformation possibilities were studied. As a particular focus of interest was to obtain heterocyclic derivatives as they are often connected with diverse biological activity. For example, quinoxaline, easily accessible from the triple bond, is a wide-spread structure element in biologically active compounds, exhibiting

herbicide,[75] anti-microbial,[76] anti-depressant,[77] anti-cancer,[78] anti-inflammatory[79] and anti-HIV[80] activity.

According to the literature, a pyrazine ring can be formed either in a one-pot reaction of an acetylene substrate **11**, in the presence of phenylenediamine and phenyliodine diacetate;[81] or through a two-step reaction comprising an oxidation step and subsequent cyclization (Scheme 15). For the compounds of the present study the former method afforded no product, therefore, alkyne **11** was first oxidized in the presence of $Pd(OAc)_2$ and $CuBr_2$ to dione **12**.[82] The concentration of the used catalytic system seems to be crucial, as the attempts to decrease it resulted in diminished yields. In the final step quinoxalines were obtained in high yields under mild conditions using phenylenediamine (Scheme 15, Table 3).[83]



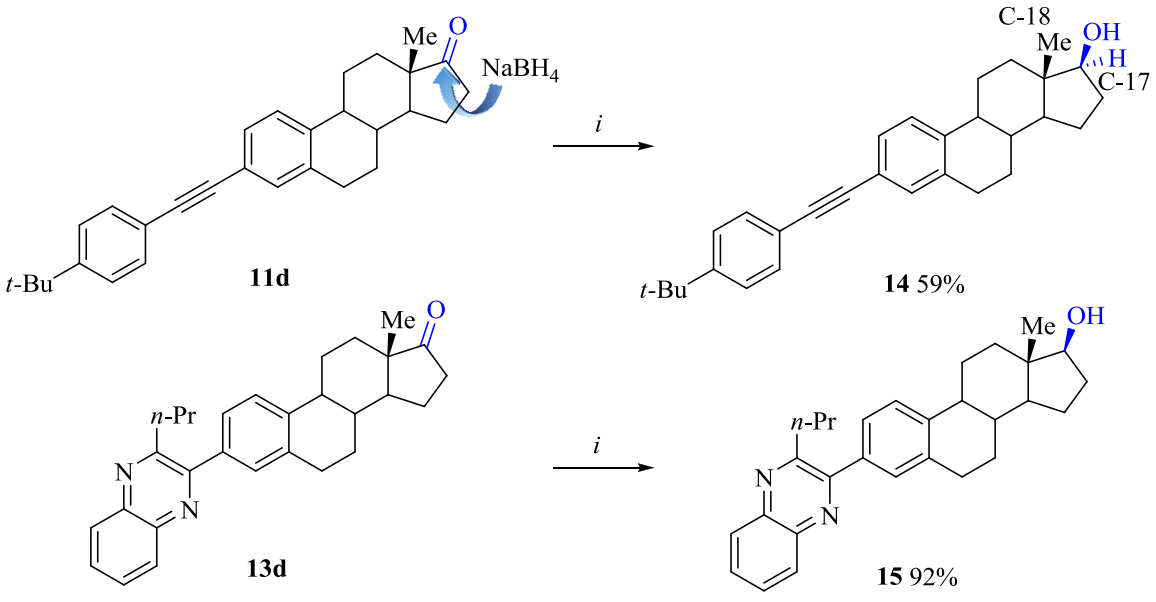
Scheme 15: *Paths to quinoxalines **13**.*

*Table 3: Synthesis of **12a-d** and **13a-d**.*

Compound	Ar	12 [%][a]	13 [%][a]
a	C_6H_5	58	92
b	4-*tert*-BuC_6H_4	65	88
c	thiophen-3-yl	59	82
d	4-*n*-PrC_6H_4	79	96

[a] Isolated yields.

Finally, 3-alkyne-3-deoxyestrone **11d** and quinoxaline **13d** were transformed in the corresponding 17-hydroxy derivatives **14** and **15** respectively, by reduction of the carbonyl group using $NaBH_4$ at room temperature (Scheme 16).[84] Products **14** and **15** were obtained diastereomerically pure due to NMR spectra which showed only one set of chemical shift data and absence of doubled signals. These diastereomers are assumed to have structures depicted in Scheme 16 with β-position of the hydroxyl group, as NOESY-spectra showed only insignificant interaction between protons of the methyl-group C-18 and proton at position C-17. This corresponds to theoretical expectations that an attack of $NaBH_4$ occurs from the back side relative to the location of the methyl group due to the steric hindrance (Scheme 16).



***Scheme 16:** Synthesis of **14** and **15**. Conditions: i, $NaBH_4$ (2 equiv.), MeOH/DCM 1:1, 20°C, 1h.*

3.2.3 Structure identification

The structure of all products was characterized by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry. Moreover, the structure of compound **11c** was independently confirmed by X-Ray diffraction analysis (Figure 10). The triple bond C7-C8 perfectly corresponds with a theoretical value of 120 pm.

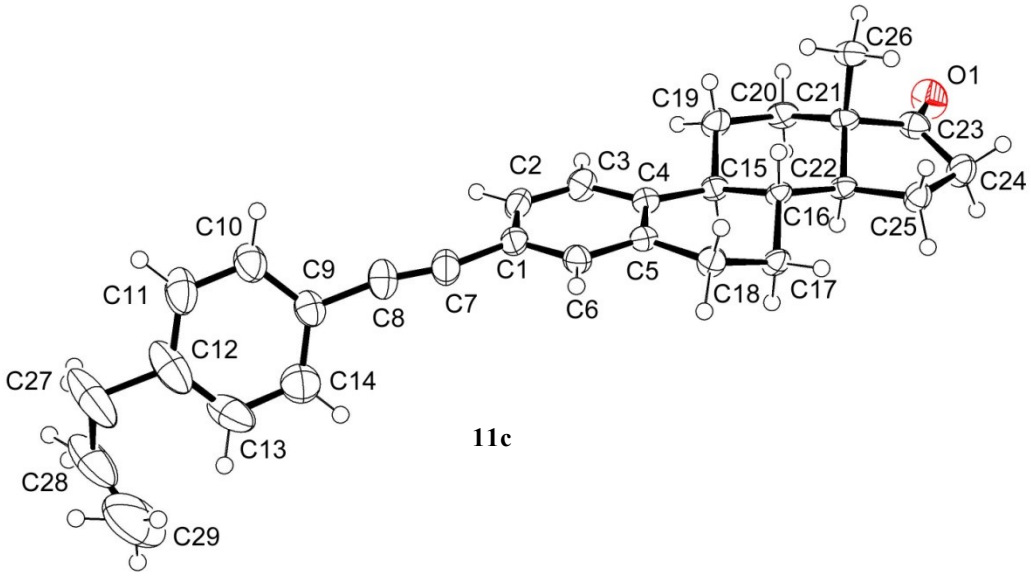


Figure 10: *Crystallographic structure of compound* ***11c****, oxygen atom red.*

3.2.4 Biological studies

3.2.4.1 Alkaline phosphatases inhibitors

Alkaline phosphatases (APs) are metalloenzymes expressed in a wide variety of tissues and exist as four different isoenzymes, each coded by a different gene. With few exceptions, APs are homodimeric enzymes and each catalytic site contains three metal ions, i.e., two Zn and one Mg, necessary for enzymatic activity.[85] The enzymes catalyze the hydrolysis of monoesters of

phosphoric acid and also catalyze a transphosphorylation reaction in the presence of large concentrations of phosphate acceptors. Catalytic roles of APs involve breakdown of various nucleotides to liberate inorganic phosphate (Pi).[86] Mammalian APs have optimum activities at alkaline pH and exhibit a wide range of substrate specificity ranging from phosphomonoesters to an assortment of phosphate containing compounds, such as inorganic polyphosphates, glucose-phosphates, phosphatidates (containing fatty acid side chains), and bis(*p*-nitrophenyl) phosphate.[87]

Alkaline phosphatases are categorized into two groups, the tissue nonspecific alkaline phosphatase (TNAP) and tissue-specific APs that include placental AP (PLAP), intestinal AP (IAP), and germ cell AP (GCAP). The tissue specific APs (PLAP, GCAP and IAP) share 90 – 98% sequence identity, whereas TNAP shares only 50% sequence identity with these tissue-specific APs.[88]

PLAP is important in the diagnosis of a variety of germ-cell (e.g seminoma) and non germ-cell tumors including lung, ovarian, gastrointestinal and uterine carcinomas.[89] The human tissue non-specific alkaline phosphatase (TNAP) is found in liver, kidney, and bone. TNAP hydrolyzes PPi (a potent inhibitor of mineralization) and is responsible for maintaining sufficient levels of extracellular PPi. TNAP acts as a potentially useful therapeutic target for the treatment of soft tissue ossification abnormalities including ankylosis, osteoarthritis and arterial calcification. IAP has also been suggested to be involved in lipid absorption as a parallel increase has been observed in triacylglycerol concentration and IAP activity, during fat absorption in thoracic duct lymph.[87]

Inhibitors of APs can help map out the exact mechanisms and origins of pathological conditions, thus, defining footsteps that can lead to novel therapies based on inhibition of APs. The most well known and commonly used inhibitors of APs are levamisole (Ki =16 μM) and theophylline (Ki = 82 μM).[90]

3.2.4.2 Alkaline phosphatase inhibition studies

The studies were accomplished in the Centre for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad, Pakistan, as a part of a cooperation project.

For the determination of inhibition activity of compounds against bovine kidney alkaline phosphatase (TNAP) enzyme and calf intestine alkaline phosphatase (IAP) a luminescence assay using CDP-star® (1,2-dioxetane based substrate) was used.

All synthesized compounds (estrone and quinoxaline derivatives, **11a-i** and **13a-d**) showed potent inhibition activity against b-TNAP and c-IAP. Some of them were selective potent inhibitors, comparable to the respective reference standards used in the study. It is clear from Table 4 that compounds **11b**, **11f-i** were found to be selective TNAP inhibitors with the inhibitory values IC_{50} 0.32±0.001 to 2.83±0.20 µM and they showed more inhibition potential than the known reference inhibitor i.e. Levamisole having IC_{50} value of 19.21±0.001 µM. The compound **11i** displayed potent activity against b-TNAP with IC_{50} value 0.32 ±0.001 µM.

Further, **11a** was found to be selective c-IAP inhibitor with the IC_{50} value of 7.35±0.71 µM and was more potent than the known reference inhibitor i.e. L-Phenylalanine having IC_{50} value of 80.21±0.001 µM.

The compounds **11e** and **13a-d** showed dual inhibition against the both isoenzymes. All of the compounds showed activity with the IC_{50} values ranging from 0.25 ±0.001 to 2.44±0.10 µM and 0.32±0.005 to 1.95±0.08 µM, against b-TNAP and c-IAP respectively.

Table 4: *Tissue non-specific alkaline phosphatase (b-TNAP) and intestinal alkaline phosphatase (c-IAP) inhibition data for the synthesized compounds.*

Compound	b-TNAP	c-IAP
	IC_{50} [a] (µM) ± SEM or (% inhibition)[b]	IC_{50} [a] (µM)± SEM or (% inhibition)[b]
11a	34.90% [b]	7.35±0.71 [a]
11b	2.83±0.20 [a]	30.15% [b]
11c	29.39% [b]	16.2±0.64 [a]
11d	37.82% [b]	19.8±0.96 [a]
11e	0.91±.005[a]	0.71±.002 [a]
11f	1.08±.052 [a]	37.10% [b]
11g	0.90±0.01 [a]	30.42% [b]
11h	0.38±.002 [a]	48.85% [b]
11i	0.32±.001[a]	30.35% [b]
13a	0.52±0.004[a]	0.32±0.005[a]
13b	0.48±.003 [a]	1.95 ±0.08 [a]
13c	2.44±0.10 [a]	0.92 ±0.01 [a]
13d	0.25 ±0.001 [a]	0.44 ±0.003[a]
Levamisole	19.21±0.001[a]	-------
L-Phenyl alanine	-------	80.21±0.001[a]

[a] The IC_{50} is the concentration at which 50% of the enzyme activity is inhibited. [b] The % inhibition of the enzyme activity caused by 0.5 mM of the tested compound.

3.2.4.3 Molecular docking

The calculations were accomplished in the Centre for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad, Pakistan using FlexX utility of LeadIT v2.1.8 software from BioSolveIT GmbH, Germany.

As discussed above, the *in vitro* enzyme assay revealed high inhibition potency of 3-(*p*-trifluorophenylethynyl)-estra-1,3,5(10)-trien-17-one (**11i)** against b-TNAP as compared to that of c-IAP. To identify its putative binding mode, molecular docking study was performed (Figure 11). For this purpose the modeled homology models of the both enzymes were used.[91]

The following interactions between alkyne **11i** and the active site of b-TNAP were observed. The compound **11i** was able to form hydrogen bonds with amino acids His454 and

Arg335 using the carbonyl oxygen atom and one of the fluorine atoms of trifluoromethyl group respectively. The fluorine atom further formed conventional interaction with amino acid Asp294. Additionally, amino acid His341 took part in π-π stacking interaction with the aryl ring of the steroid skeleton.

The following interactions between alkyne **11i** and the active site of c-IAP were observed. The compound **11i** was able to form a hydrogen bond with amino acid Arg169 using one of the fluorine atoms of trifluoromethyl group. Further, the compound pose was stabilized by π-π stacking interactions of amino acid residues His336 and His339 with *p*-trifluorophenyl-group and His451 with the aryl ring of the steroid skeleton.

Due to the HYDE assessment (HYdrogen Bond and Dehydration Energies method, it allows the estimation of interaction energies of protein-substrate complexes),[92] the compound **11i** revealed higher binding affinity of -21 KJ/mol inside active site of b-TNAP as compared to that of -13 KJ/mol inside active site of c-IAP. The difference in binding affinity and the type of interactions with different amino acid residues is attributable for higher potency against b-TNAP as compared to that of c-IAP.

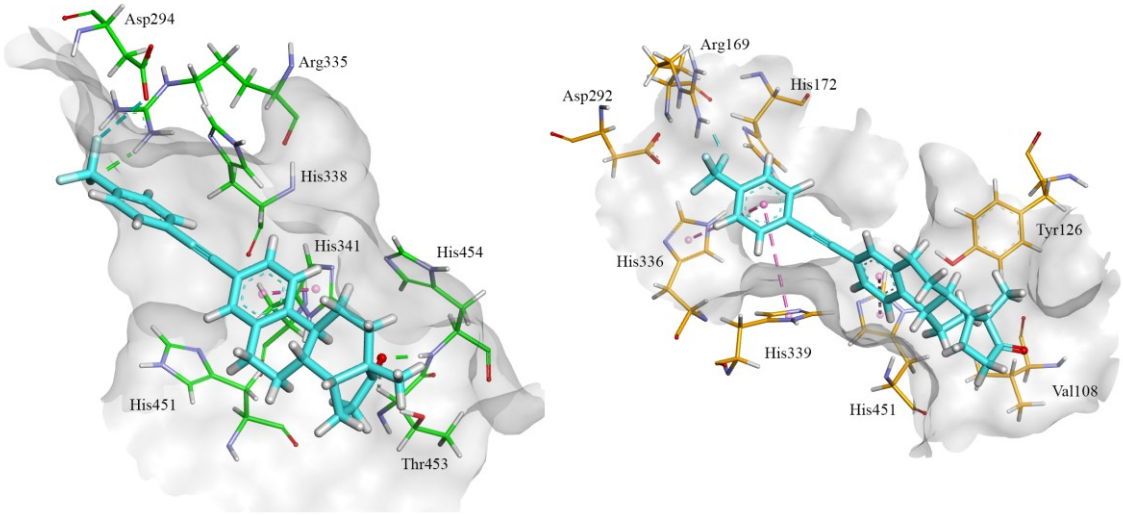


***Figure 11**: Binding mode of compound **11i** (colored cyan) inside active site of b-TNAP (colored green) and inside active site of c-IAP (colored brown). Hydrogen bonding interaction is shown as green dashed lines, π-π staking interactions as pink dashed lines, interaction of fluorine as cyan dashed lines.*

It can be thus assumed that substituents of phenylethynyl moiety that are able to form a hydrogen bond (such as CF_3, OMe, NH_2, etc.) would promote the binding of the substrate with active site of b-TNAP and, therefore, its selective inhibition.

3.3 Conclusions

During the present study, the Sonogashira reaction was successfully applied in order to synthesize alkynylated (+)-estrones. As a result, a series of new compounds was obtained, some of them were further functionalized towards corresponding diones, quinoxalines and estradiol derivatives. Biological studies showed inhibitory activity of the products against alkaline phosphatases of types TNAP and IAP.

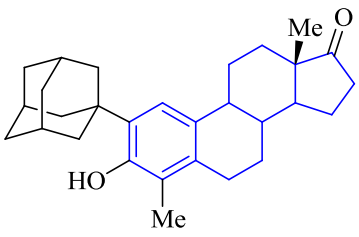
4 Arylation of (+)-estrone

4.1 Introduction

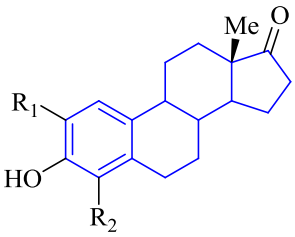
4.1.1 Recent studies of the biological activity of 2- and/or 4-substituted estrones

The importance of estrone and its derivatives as biological transmitters and building blocks for a range of drugs or drug candidates has been discussed in Section **3.1.1** of the previous chapter. That chapter was focused on 3-modified estrones and ways of synthesis and functionalization thereof. To build a more complete picture of estrone chemistry and derivatives, the present chapter is dedicated to 2- and 4-substituted estrones. The latter are scarcely studied, but exhibit some interesting properties.

For instance, it was recently shown that substitution at 2- and/or 4-position of estrone affected its biological activity.[93–97] Thus, derivatives with bulky substituents, such as 2-adamantyl compound ZYC-26 (Figure 12) can exhibit a neuroprotective activity against cerebral ischemia/reperfusion injury, while having a decreased feminizing activity.[93,94] Various simple substituents alter the ability of estrone to inhibit steroid sulfatase (STS) and thus its activity against breast cancer cells growth.[95–97]



ZYC-26



R_1 = H, F, CN, NO_2;
R_2 = H, NO_2

***Figure 12**: Biologically active 2,4-substituted estrones.*

Despite this, 2- and/or 4-aryl-substituted estrones are scarcely studied and only a few methods of their synthesis are described in literature. Among them, some non-specific methods

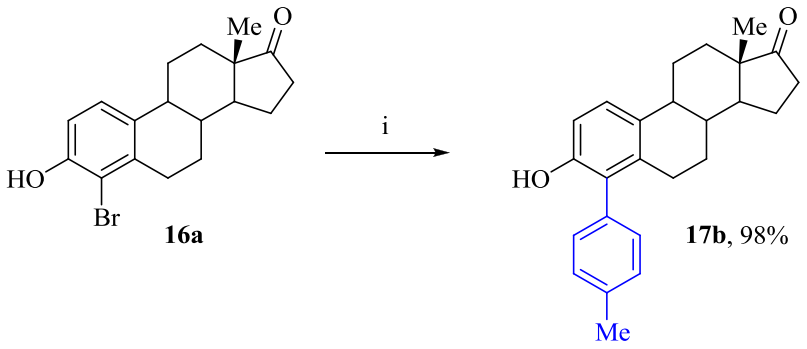
utilizing pentavalent organobismuth reagents that afford target products in vanishingly low yields.[98] Recently, an example of 2-arylation using diaryliodonium triflates with moderate yield was published.[99] This study, however, lacks a scope of products and, moreover, forces to work with expensive and not readily available reagents. 2- And 4-arylation of other members of steroid family is known in the literature, namely, of estrogen[100] and of estra-1,3,5(10)-trien-3-ol (17-deoxyestrone).[101] In both cases iodine derivatives of substrates were arylated via Suzuki-Miyaura protocol (see Section **1.2**).

It is, therefore, an interesting task to investigate the scope and limitations of the synthesis of further arylated estrone derivatives. The present research is performed in collaboration with colleagues from the University of Szeged, Hungary, that generously afforded brominated estrones as substrates. Suzuki-Miyaura protocol will be applied to arylate estrone at position 2- or 4-, or at both of them. A potential biological activity against b-TNAP and c-IAP of the new compounds will be studied.

4.2 Results and discussion

4.2.1 Arylation of 4-bromoestrone

I started with arylation of 4-bromoestrone (**16a**). Common conditions for the Suzuki cross-coupling reaction, using 5 mol% of $Pd(PPh_3)_4$ gave excellent 98% yield of the desired arylated product **17b**. The attempt to use a reduced amount of catalyst (2.5 mol%) resulted in a slightly diminished yield. While using DMF instead of dioxane resulted in a dramatically decreased yield of 15%. The optimized conditions are depicted in Scheme 17.



Scheme 17: *Synthesis of* ***17b****. Conditions: i,* ***16a*** *(1.0 equiv.), p-tolylboronic acid (1.5 equiv.), $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (2.0 equiv.), dioxane, 101°C, 8h.*

The optimized conditions were used to produce 4-arylestrones **17a-m**. All products were isolated in good to excellent yields (Figure 13). Application of boronic acids containing electron-donating as well as electron-withdrawing groups gave similar results, while more sterically hindered *o*-substituted boronic acids resulted in lower yields (products **17k-m**).

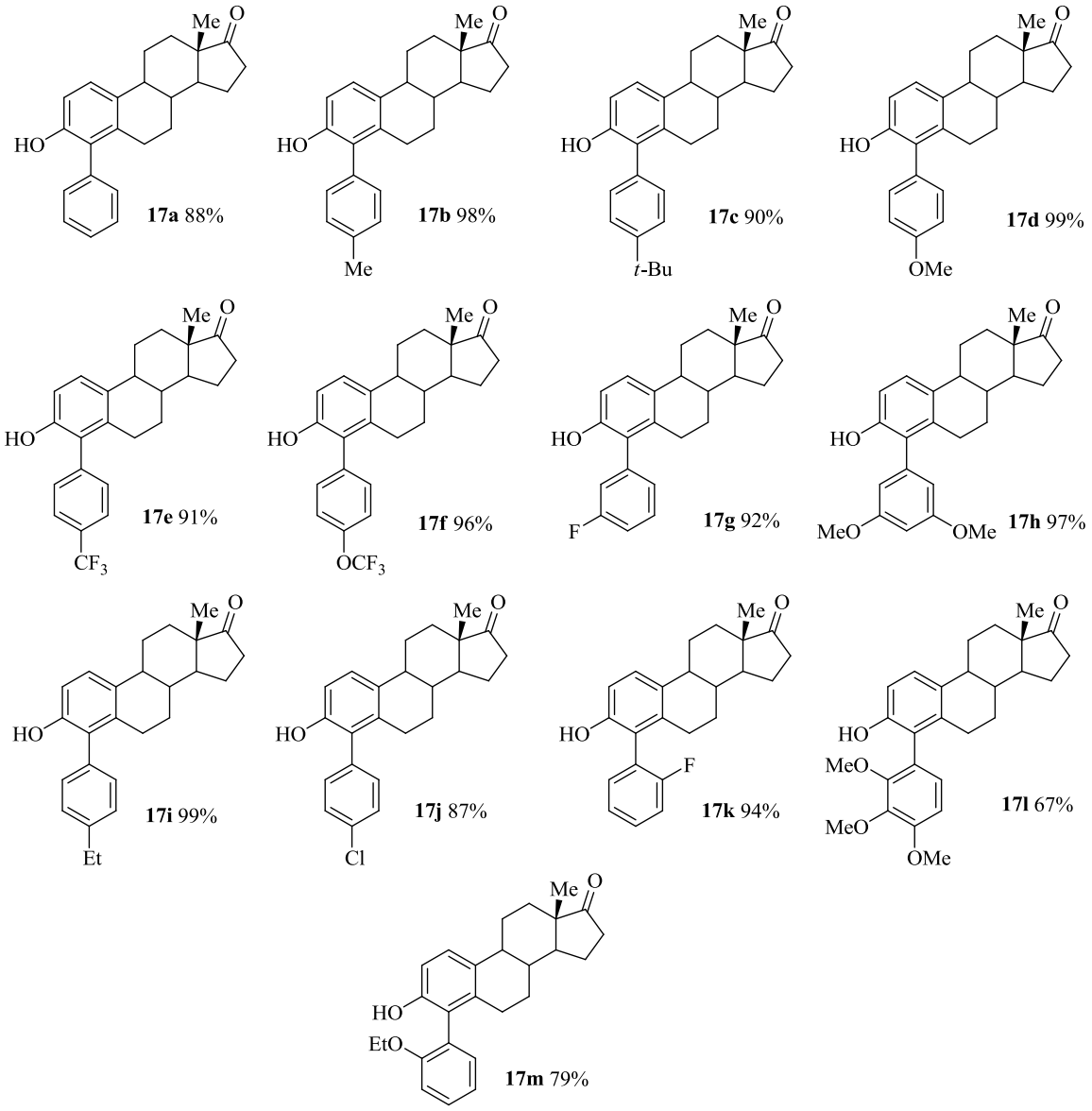
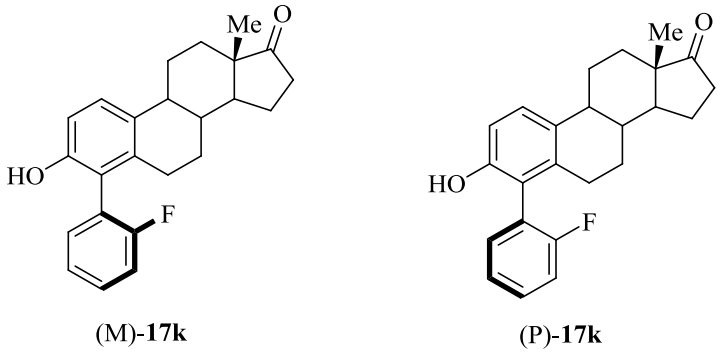


Figure 13: *Synthesized 4-arylestrones* ***17a-m*** *with isolated yields.*

In the case of *o*-substituted products **17k-m** (and even some *m*-products, e.g. **17g**), hindered rotation about the bond between the ring A and the aryl ring led to the formation of a new stereogenic center, thus forming a mixture of two diastereomers, proven by the observation of two sets of NMR signals. Interestingly, even such a small atom as fluorine was sufficient for occurrence of the described effect (Figure 14).

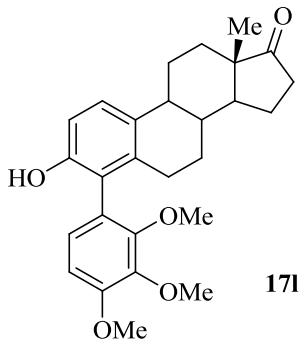


(M)-**17k** (P)-**17k**

Figure 14: *M- and P-atropisomers of* ***17k.***

This effect is called atropisomerisation[102] – it describes stereoisomers that result from restricted rotation about a single bond. It is mostly known for *o*-substituted biaryls, however, not all substituents cause the effect. Most tri- and tetra-ortho-substituted biphenyls are conformationally stable and can be conveniently resolved into enantiomers at room temperature.

The determination of the composition of enantiomeric or diastereomeric mixtures is routinely performed by NMR spectroscopy. Homotopic and enantiotopic groups have isochronous NMR signals, but diastereotopic nuclei are chemically nonequivalent and usually exhibit different (anisochronous) chemical shifts. Diastereoisomers have different chemical and physical properties and often afford distinguishable NMR spectra. The interconversion of stereoisomers exhibiting diastereotopic nuclei can be monitored by variable-temperature NMR spectroscopy. A particularly simple situation arises when two nuclei (AB case) provide sharp signals with equal intensity and undergo chemical exchange resulting in line broadening and coalescence upon heating. In other words, with the rise of temperature, a molecule receives more energy, and at a certain point with enough energy the rotation about the bond is less hindered and atropisomery disappears. Only one set of NMR signals can be observed, now.



17l

Figure 15: *The structure of 4-(2,3,4-trimethoxyphenyl)-estrone (**17l**).*

To study the atropisomery, a sample of 4-(2,3,4-trimethoxyphenyl)-estrone (**17l**) was applied for ^{1}H NMR spectra between 25°C and 130°C (Figures 15 and 16). At the stacked fragments of the spectra peaks of a methyl group (Me) at position 17 and peaks of three methoxy groups (MeO) can be seen. One methyl and two methoxy groups are presented as sets of two singlets, and the third methoxy group as a quasi-singlet consisted of two totally overlapped singlets. Due to the integration of the peaks, the mixture consists of two atropisomers in about 1:1 ratio. Considering the middle methoxy group peaks, as a most evident example, some observations can be made. First, with the temperature rise the peaks shift to low field, which is irrelevant in this case. Second, the peaks slowly shift to each other, and at 130°C a broadening of the singlets can be observed. Apparently, the atropisomers are relatively stable, as the effect can be observed only insignificantly. Theoretically, at higher temperatures, the peaks will coalesce, what could not be shown due to technical limitations.

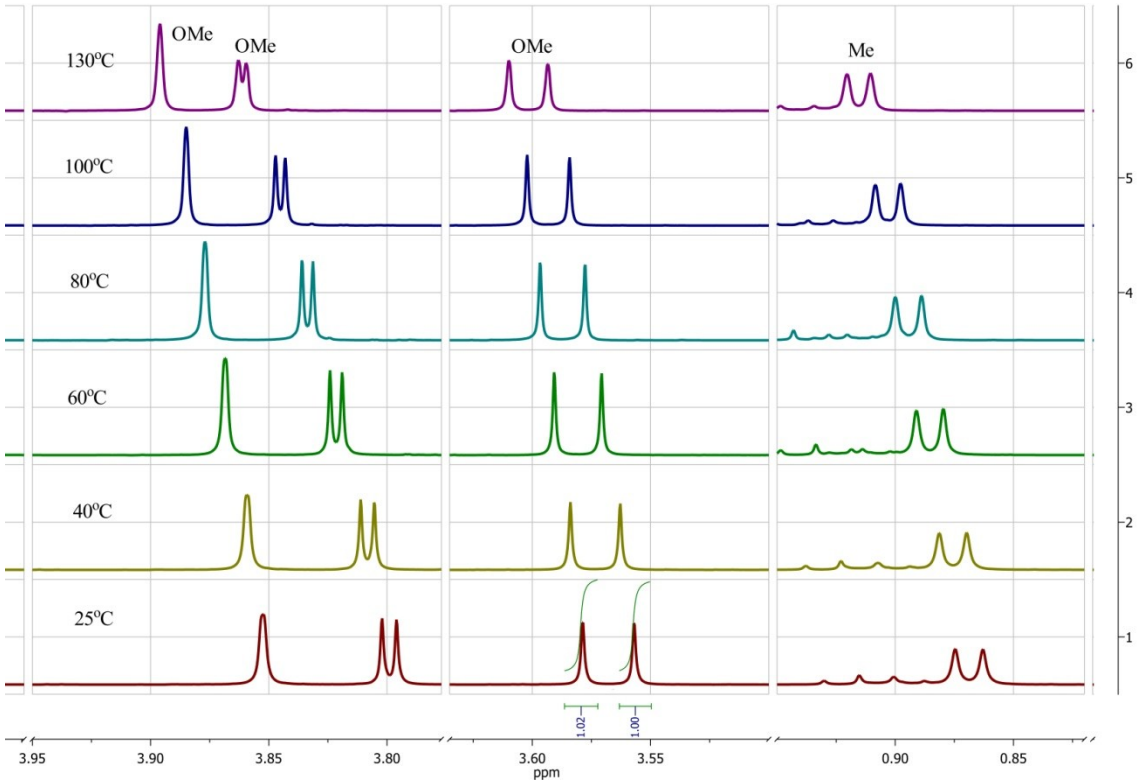
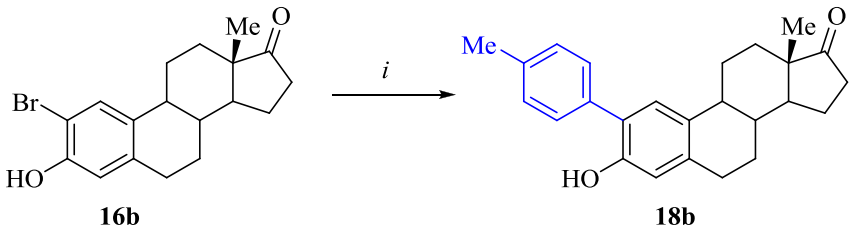


Figure 16: *Stacked fragments of ^{1}H NMR spectra for* ***17l*** *at different temperatures.*

4.2.2 Arylation of 2-bromoestrone

For the reaction of 2-bromoestrone (**16b)** with *p*-tolylboronic acid conditions applied for the 4-bromoestrone (**16a)** were first tested. However, the attempt was unsuccessful, whereas the reaction resulted in an inseparable mixture of undefined products. Afterwards, different catalysts, ligands, bases and solvents were applied to find appropriate conditions. Thus, Buchwald's ligands RuPhos and SPhos showed to be crucial for obtaining the desired arylated product, while RuPhos gave higher yields (Scheme 18, Table 5). The best results were obtained by using the highlighted conditions (Entry 7).



16b **18b**

Scheme 18: *Synthesis of* ***18b****, conditions in Table 5.*

Table 5: *Optimization of the Suzuki reaction for synthesis of 2-p-tolylestrone* ***18b****. Conditions: i,* ***16b*** *(1.0 equiv.), p-tolylboronic acid (1.5 equiv.), catalyst (5.0 mol%), ligand (5.0 mol%), base (2.0 equiv.), solvent, temperature (°C).*

Entry	Catalyst	Ligand	Base	Solvent	T [°C]	Time [h]	Yield [%]
1	$Pd(PPh_3)_4$	-	K_3PO_4	dioxane	101	20	-[b]
2	$Pd(PPh_3)_4$	-	Cs_2CO_3	dioxane	101	18	-[b]
3	$Pd(PPh_3)_4$	-	K_3PO_4	DMF	130	20	-[b]
4	$Pd(PPh_3)_4$	BINAP	K_2CO_3	DMF	130	20	-[b]
5	$Pd(PPh_3)_4$	SPhos	K_2CO_3	dioxane	101	22	66[a]
6	$Pd(PPh_3)_4$	XPhos	K_2CO_3	dioxane	101	22	-[b]
7	**$Pd(PPh_3)_4$**	**RuPhos**	**K_2CO_3**	**dioxane**	**101**	**22**	**75[a]**
8	$Pd(PPh_3)_4$	$PCy_3 \cdot HBF_4$	K_2CO_3	dioxane	101	22	35[a]
9	$Pd(PPh_3)_4$	RuPhos	K_3PO_4	dioxane	101	28	69[a]
10	$Pd(PPh_3)_4$	RuPhos	Cs_2CO_3	dioxane	101	28	40[a]
11	$Pd(PPh_3)_4$	RuPhos	KF	dioxane	101	28	63[a]
12	$Pd(PPh_3)_4$	RuPhos	K_2CO_3	toluene	105	20	73[a]
13	$Pd(PPh_3)_4$	RuPhos	K_2CO_3	DMF	105	20	-[c]
14	$Pd(OAc)_2$[d]	$PCy_3 \cdot HBF_4$	K_2CO_3	dioxane	101	20	-[b]
15	$PdCl_2(PPh_3)_2$	-	K_2CO_3	dioxane	101	20	-[b]

[a] Isolated yields. [b] Low conversion of starting material. [c] Inseparable mixture. [d] 10 mol%.

The optimized conditions were then used to obtain a list of 2-arylestrones **18a-h** in good yields (Figure 17). As expected, all yields were significantly lower in comparison with the corresponding values in case of 4-arylestrones **17a-m** due to the lower reactivity of this position. Electronic properties of the substituents did not affect the yield. Attempts to synthesize *o*-aryl

derivatives were unsuccessful, as well as the application of *p*-chlorophenylboronic acid. The latter can be explained by the occurrence of the competing cross-coupling reaction between two molecules of the boronic acid as well as participation of the product in further arylation reactions.

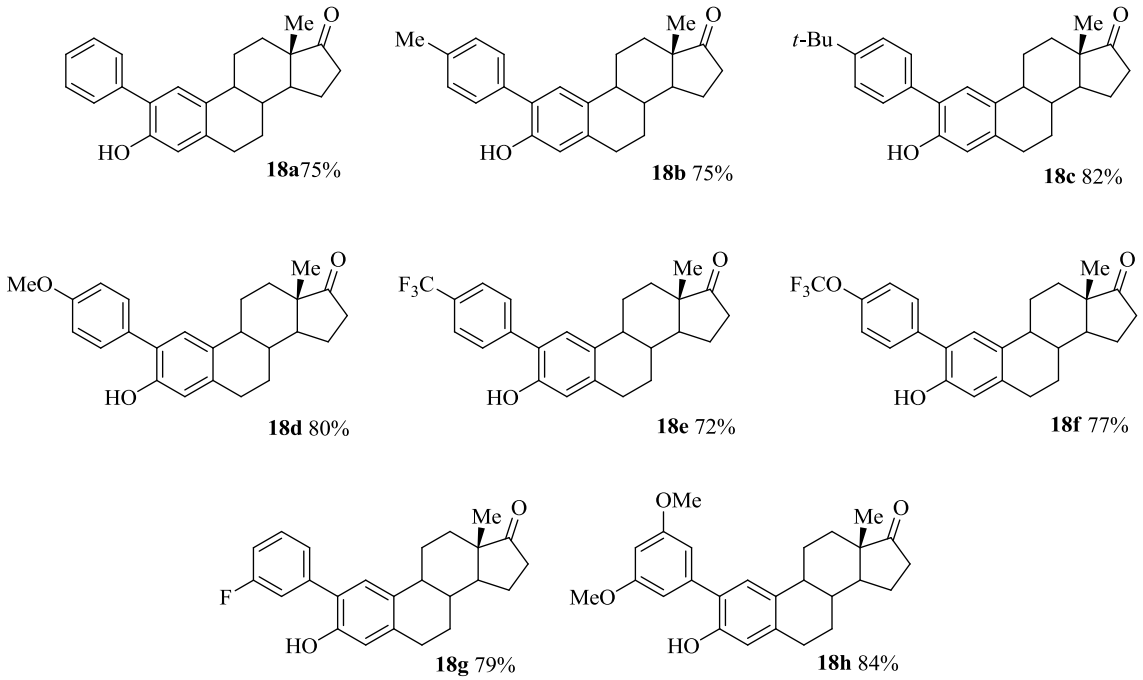


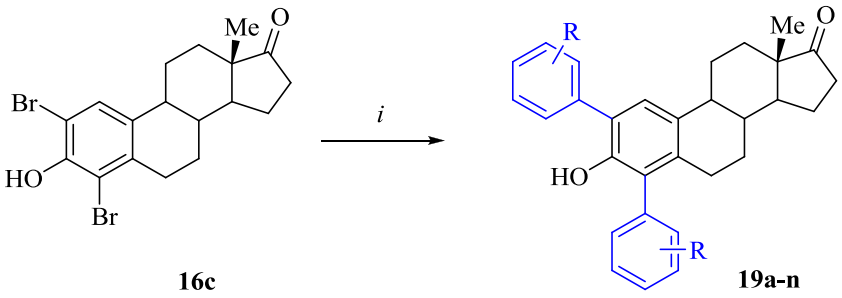
Figure 17: *Synthesized 2-arylestrones* ***18a-h*** *with isolated yields.*

4.2.3 Arylation of 2,4-dibromoestrone

Arylation of estrone at positions 4 and 2 was shown. While the former reaction proceeds at relatively mild conditions with relatively short reaction time giving products with excellent yields, the latter, in contrast, demands harsh reaction conditions and provides only moderate yields. Such diverse reactivity forced me to suggest that a site-selective Suzuki cross-coupling reaction starting from 2,4-dibromoestrone (**16c**) might be possible.

I started with the milder conditions used in case of 4-bromoestrone (**16a**), hoping they would deliver a product of selective 4-arylation leaving the bromine at position 2 unreacted. However, only an inseparable mixture of starting material, mono- and di-substituted products was observed. Some further mild conditions gave the same result, until adjusted conditions used for the coupling reaction of 2-bromoestrone (**16b**) were tried, which gave a disubstituted product. Thus, after testing a number of different catalysts, ligands, bases and solvents, I had to face the fact that the site-selective reaction was not possible for that substrate. Therefore, I quit my attempts and continued with the synthesis of 2,4-diarylestrones.

To exclude the formation of undesired mono-substituted side-products longer reaction time (40h), toluene as solvent and higher temperature (110°C) were used. That gave pure disubstituted products **19a-n** with excellent yields (Scheme 19, Figure 18). Once again electronic properties of boronic acids did not affect the yields, while sterically hindered *o*-boronic acids surprisingly gave corresponding products with good yields. In comparison with 2-arylestrones **18a-h** the products were obtained with 10-20% higher yields. It could be assumed that position 2 is strongly affected by bromine or aryl at position 4, which shifts reactivity of this position and eases the reaction. This also explains an unsuccessful effort to achieve the site-selectivity. It was not possible, though, to isolate some mono-substituted products to investigate the mechanism of the reaction.



16c **19a-n**

Scheme 19: *Synthesis of 2,4-diarylestrones* ***19a-n****. Conditions: i,* ***16c*** *(1.0 equiv.), boronic acid (3 equiv.), Pd(PPh$_3$)$_4$ (5 mol%), RuPhos (5 mol%), K$_2$CO$_3$ (4.0 equiv.), toluene, 110°C, 40h.*

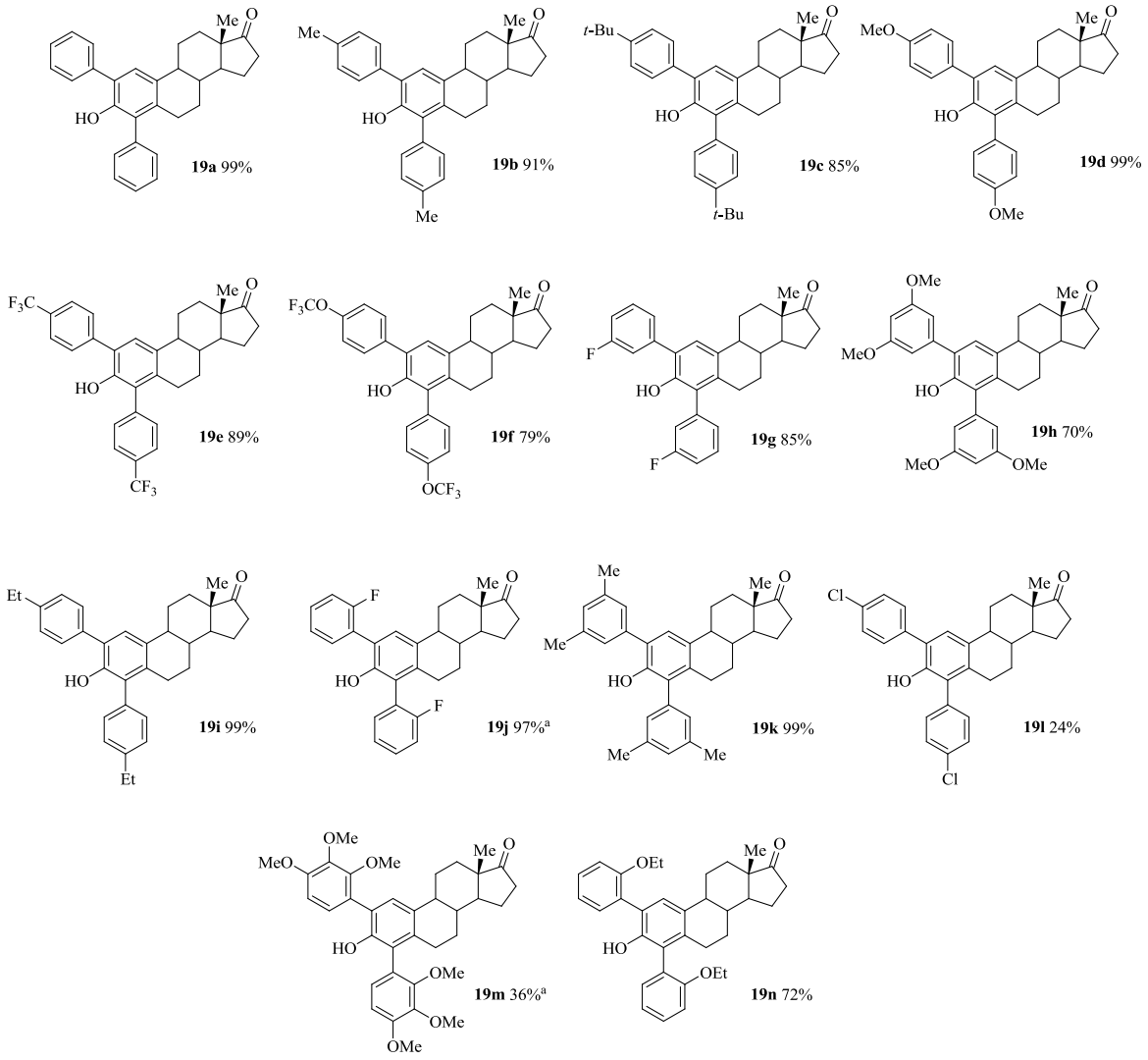
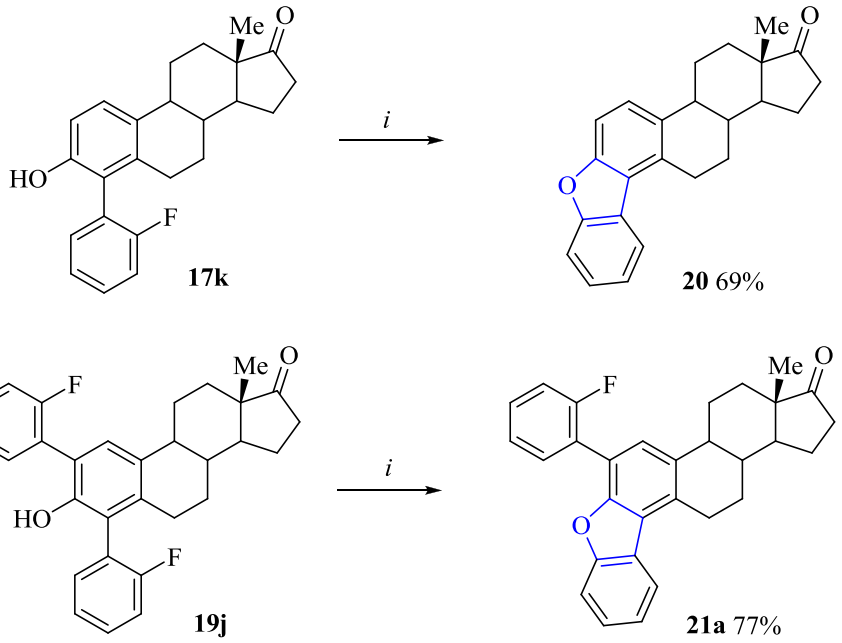


Figure 18: *Synthesized 2,4-diarylestrones* ***19a-n*** *with isolated yields. [a]Reaction time 72h.*

Similar to 4-arylestrones **17k-m** *o*-substituted products **19j**, **m** and **n** exist as a mixture of two diastereomers. Interestingly, *o*-substituted aryls at position 2 did not result in the formation of additional stereogenic center, which can be observed by NMR spectroscopy. Apparently, free position 1 of estrone enabled unhindered rotation about the C2-aryl bond at room temperature.

4.2.4 Further functionalization of estrone derivatives

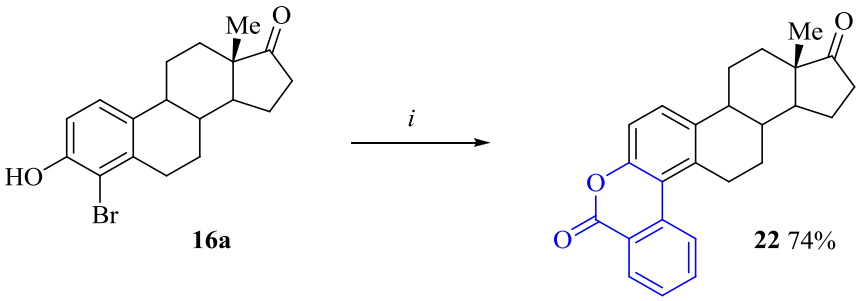
In order to prove the utility of the developed synthetic protocol, some of the obtained arylated estrone derivatives were used in further reactions. Thus, a cyclization of *o*-fluorophenyl derivatives **17k** and **19j** afforded corresponding dibenzofurans by nucleophilic aromatic substitution. A method described in a patent[103] was optimized, whereas DMF instead of *N*-methylpyrrolidone and a lower temperature of 150°C were used. Thus, cyclized products **20** and **21a** could be isolated in good yields (Scheme 20). Interestingly, dibenzofuran **21a** was obtained as a site-selective product, and cyclization by an attack at the fluorophenyl moiety attached at position 2 was not observed. The structure of the product was confirmed by means of NMR spectra (see **Section 4.2.5**). The attempts to obtain the dibenzofuran **20** directly from **16a** through one-pot two-step reaction were made. In this case, however, the yield was much lower than the overall yield for the two step process; 34% and 65% respectively.



Scheme 20: *Synthesis of cyclized products* ***20*** *and* ***21a****. Conditions: i,* ***17k*** *or* ***19j*** *(1.0 equiv.),* K_2CO_3 *(2.0 equiv.), DMF, 150°C, 4h.*

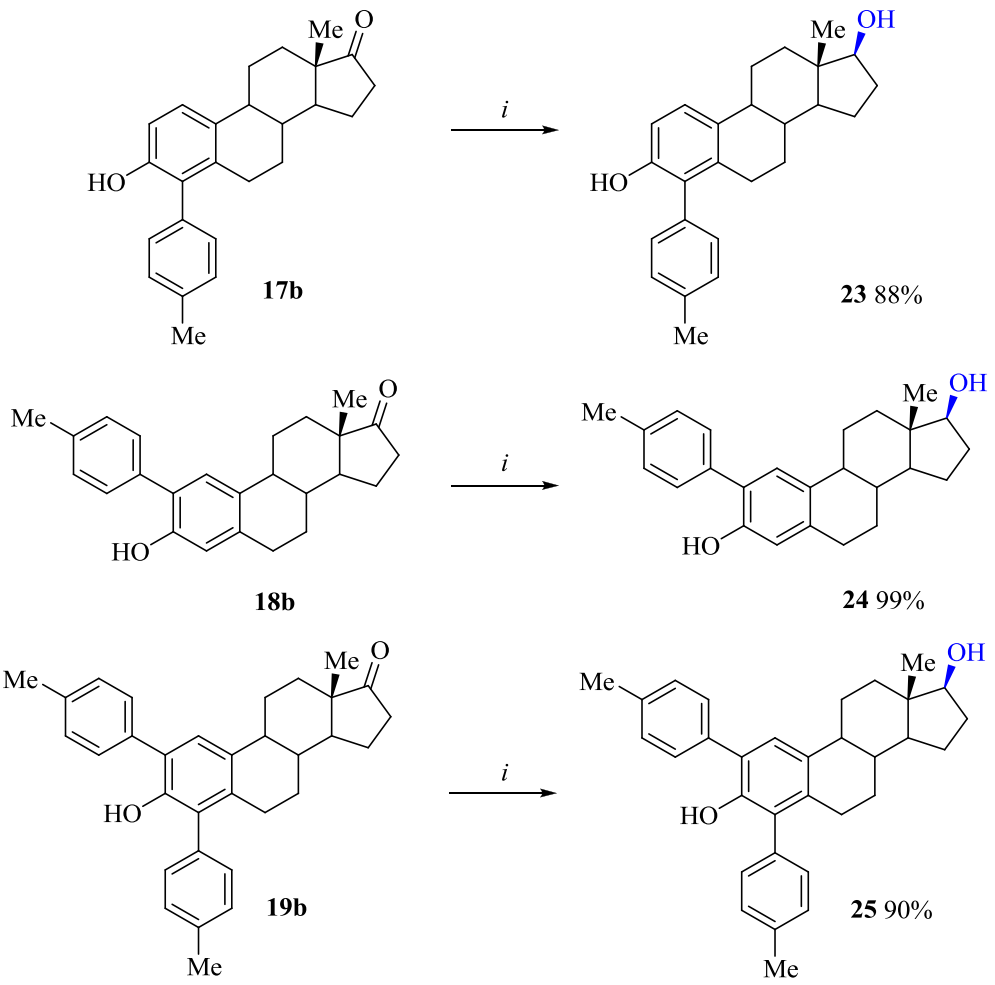
In a similar manner, synthesis of lactone **22** was planned. Unfortunately, it was not possible to obtain the required *o*-carboxyphenyl derivative of any of the three substrates and an

inseparable mixture of starting material and different products was observed in all cases. However, if the harsh conditions used for bisarylation of 2,4-bromoestrone (**16c**) were applied to 4-bromoestrone (**16a**) the target lactone **22** was formed in a one-pot procedure in a good yield (Scheme 21).



Scheme 21: *Synthesis of lactone **22**. Conditions: i, **16a** (1.0 equiv.), o-ethoxycarbonylboronic acid (3 equiv.), $Pd(PPh_3)_4$ (5 mol%), RuPhos (5 mol%), K_2CO_3 (4.0 equiv.), toluene, 110°C, 72h.*

Finally, *p*-tolylestrones **17b**, **18b** and **19b** were transformed in corresponding estradiol derivatives **23**, **24** and **25** respectively, using $NaBH_4$ as a reductant and NaOH as a base according to a common method (Scheme 22).[104] Similar to estradiols **14** and **15**, one set of chemical shifts in NMR spectra confirmed a diastereoselective reaction. It can be further assumed, that these diastereomers exist in a β-form, as NOESY-spectra showed only insignificant interaction between protons of the methyl-group attached at C-13 and the proton H-17 (cf. Scheme 16).



Scheme 22: *Synthesis of estradiols* ***23***, ***24*** *and* ***25****. Conditions: i,* ***17b***, ***18b*** *or* ***19b*** *(1.0 equiv.),* $NaBH_4$ *(2.7 equiv.), NaOH (3.0 equiv.), MeOH, 20°C, 1h.*

4.2.5 Structure identification

The structure of all products was characterized by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry. Moreover, the structures of compounds **17c**, **18e** and **22** were independently confirmed by X-Ray diffraction analysis (Figure 19). All bond lengths match corresponding theoretical values. The torsion angles between the steroid skeleton and the

aryl ring are about 67.9° for 4-(*p*-*tert*-butylphenyl)estrone (**17c**) and 34.5° for 2-(*p*-trifluoromethylphenyl)estrone (**18e**).

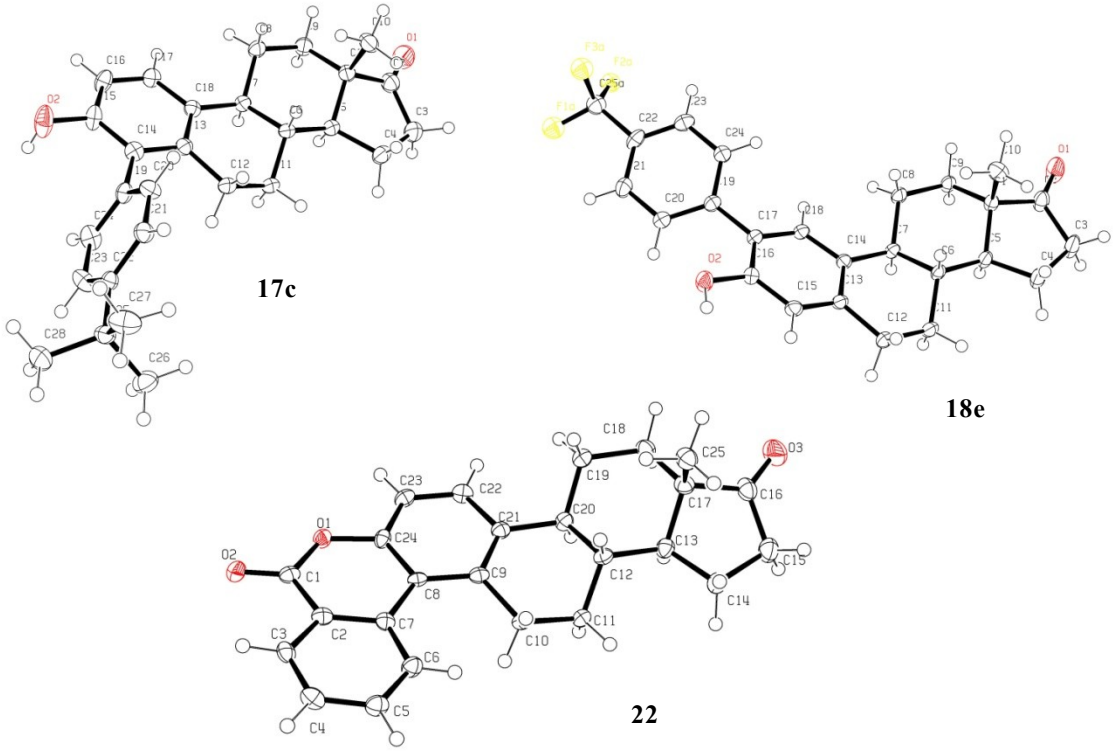


Figure 19: *Crystallographic structures of compounds **17c**, **18e** and **22**, oxygen atoms red, fluorine atoms yellow.*

As discussed above, cyclization of estrone **19j** (Scheme 20) could give in principle two isomers, depending which of the fluorine atoms is attacked. To determine which of the products was formed, NMR spectra (^{1}H, HMBC and NOESY) of compound **21** (product of **19j**) were compared with the same of benzofuran **20** with a solved and only possible structure. As can be seen in Figure 21, both benzofurans **20** and **21** have similar ^{1}H NMR spectra, therefore, all the following arguments are true for the both compounds. A doublet at about 8 ppm that is strongly shifted to lower field refers to the hydrogen atom H_M (magenta) of the benzofuran moiety. Such strong downfield shift can be explained by the deshielding effect of the phenyl ring A, lying in the same plain with H_M, due to anisotropy. HMBC spectrum helps to assign the two multiplet signals (≈ 3.3 ppm and 3.5 ppm) to the CH_2 hydrogen atoms H_G (green), showing correlations to

three aromatic carbon atoms (Figure 20). The multiplet signals at about 2.5 ppm correspond to the CH_2 hydrogen atoms H_B (blue). Here only one correlation to the carbon C-6 was observed.

For both products NOESY spectrum shows a correlation between H_M and H_G, which undoubtedly confirms the structure of the isomer **21a** (Figure 20).

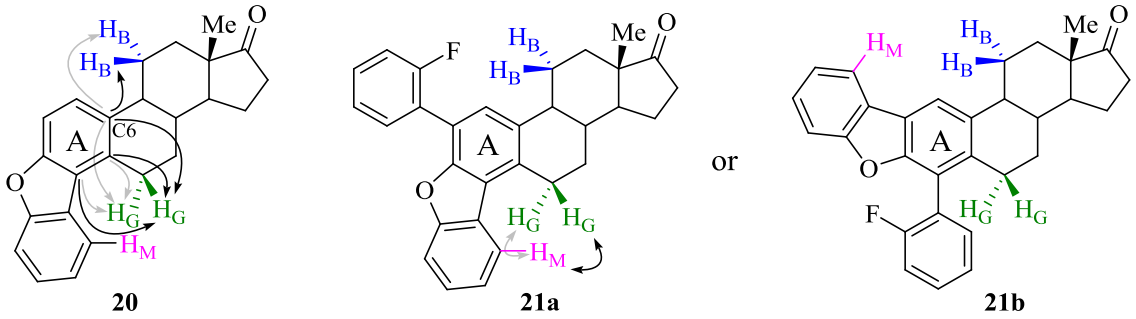


Figure 20: *Correlation of hydrogen with carbon atoms in the HMBC and hydrogen with hydrogen atoms in the NOESY showed in black and gray arrows for* ***20*** *and* ***21a****.*

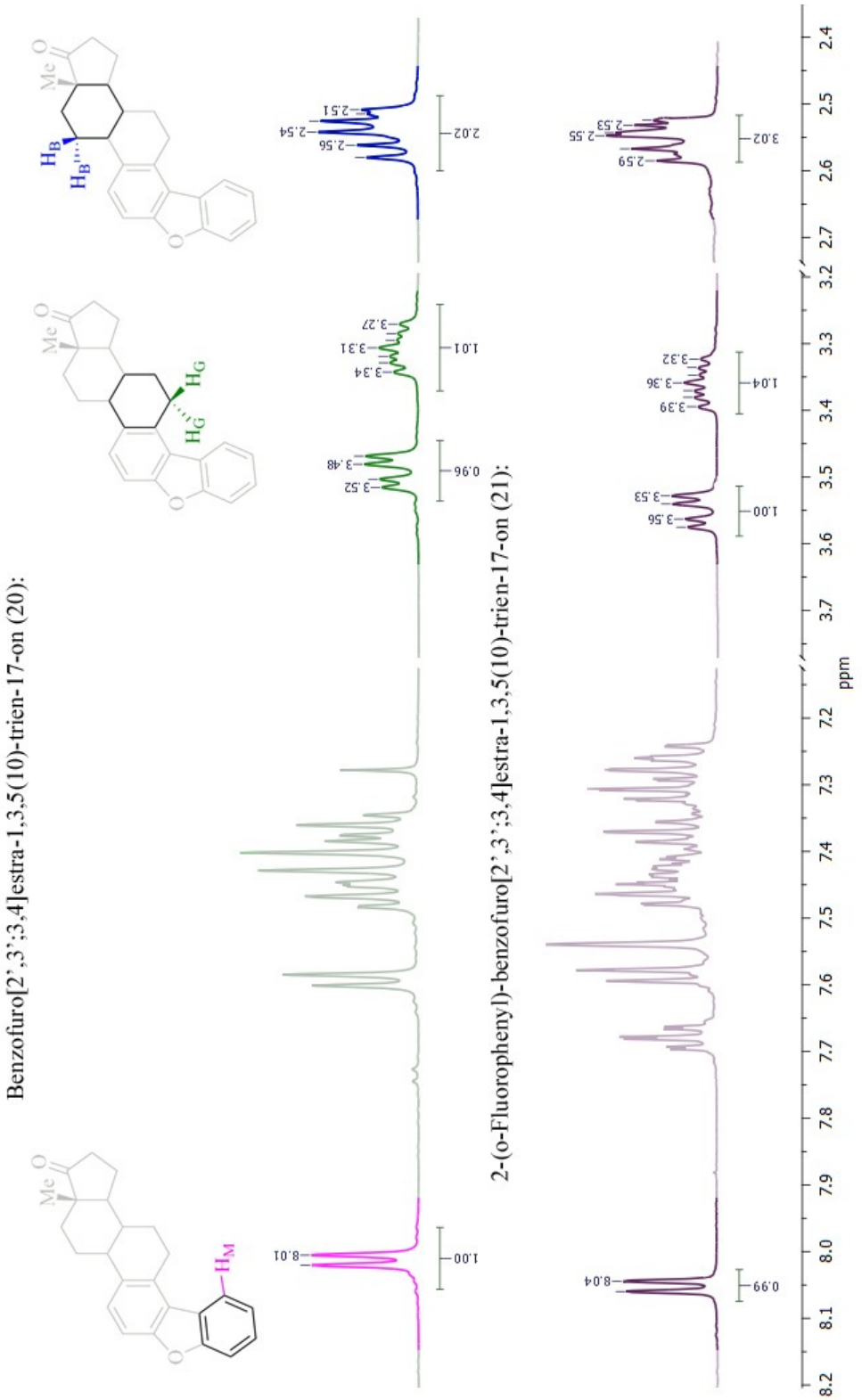


Figure 21: *Stacked fragments of ^{1}H NMR spectra for* ***20*** *and* ***21****.*

4.2.6 Biological studies

The biological evaluation of synthesized compounds is currently under investigation in the Centre for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad, Pakistan.

4.3 Conclusions

During the present study, the Suzuki-Miyaura reaction was successfully applied in order to arylate (+)-estrone derivatives. As a result, a series of new compounds was synthesized. Some of them were further functionalized towards corresponding dibenzofuran, benzocoumarin and estradiol derivatives. Biological studies are in progress.

5 Summary

In the present work, palladium-catalyzed cross-coupling reactions were successfully performed on derivatives of the naturally occurring frameworks comprising indole and (+)-estrone. Convenient synthetic pathways towards new compounds were developed. So, potential biological active compounds were synthesized in order to identify possible drug candidates.

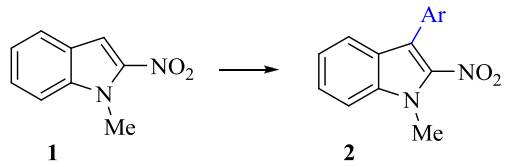
More specifically, an atom-efficient arylation of 2-nitroindoles at position 3 via CH-activation reaction was investigated. It afforded a series of new 3-aryl-1-methyl-2-nitroindoles in good yields. A simple catalyst $Pd(OAc)_2$ together with K_2CO_3 and DMF represent cheap and convenient reaction conditions.

Further, a modified Sonogashira reaction was used to alkynylate (+)-estrone at position 3. Oxidation of the obtained products and subsequent cyclization with *o*-phenylendiamine afforded interesting quinoxaline derivatives of 3-deoxyestrone. In its turn, a reduction with $NaBH_4$ afforded estradiol derivatives. All products were measured for an ability to inhibit alkaline phosphatases and showed significant activity.

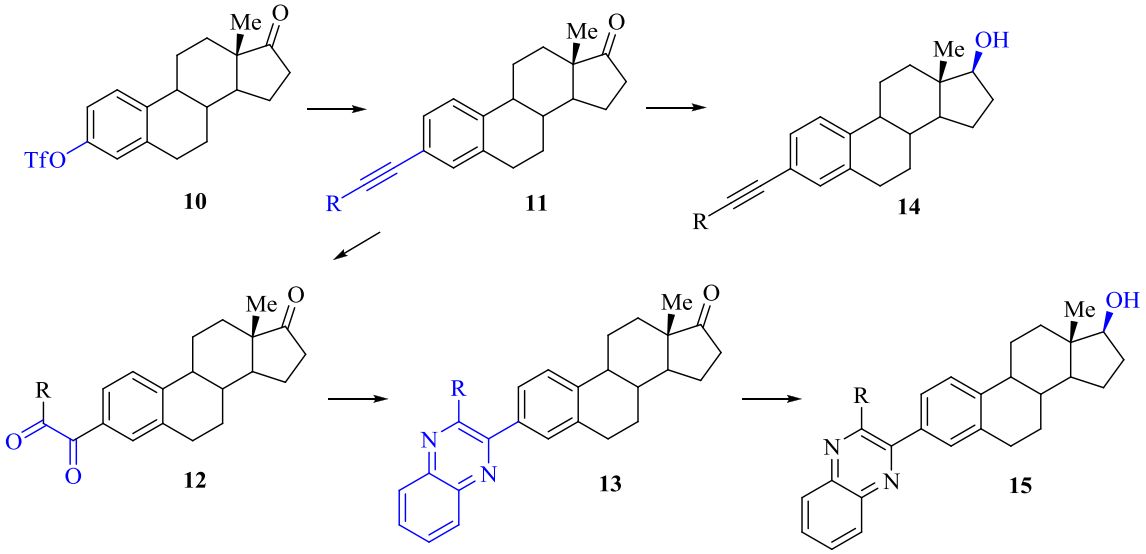
Finally, different derivatives of (+)-estrone were monoarylated at position 2 and 4 and also 2,4-bisarylated in excellent yields. Further transformations additionally afforded polycyclic compounds as well as estradiol derivatives. The biological evaluation of synthesized compounds is currently under investigation.

Figure 22 shows the overview of the obtained products.

Chapter 2: Arylation of *N*-methyl-2-nitroindole



Chapter 3: 3-Alkynylated (+)-estrones and derived products



Chapter 4: Arylation of (+)-estrone derivatives and following cyclisations

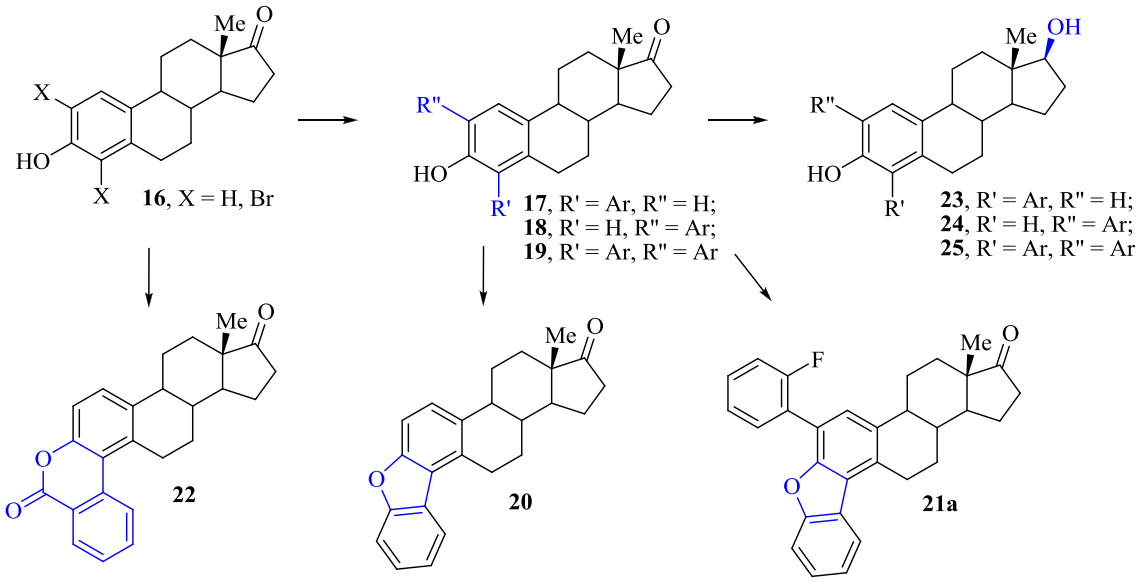


Figure 22: *General structures of the synthesized compounds.*

Supplement 1

Experimental part

1.1 Analytics

^{1}H NMR-Spectroscopy:
Bruker AVANCE 250 II (250 MHz), Bruker AVANCE 300 III (300 MHz), Bruker AVANCE 500 (500 MHz). The spectra were calibrated according to the solvent signals: 7.26 ppm for $CDCl_3$, 2.54 ppm for DMSO-d_6. Peak characterization: s = singlet, br.s = broad singlet, d = doublet, t = triplet, pt = pseudo triplet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets, q = quartet, m = multiplet.

^{13}C NMR-Spectroscopy:
Bruker AVANCE 250 II (63 MHz), Bruker AVANCE 300 III (75 MHz), Bruker AVANCE 500 (125 MHz). The spectra were calibrated according to the solvent signals: 77.00 ppm for $CDCl_3$, 39.5 ppm for DMSO-d_6. Peak characterization: t = triplet, q = quartet, m = multiplet. DEPT method was used for determining the presence of primary, secondary, tertiary and quaternary carbon atoms.

^{19}F NMR-Spectroscopy:
Bruker AVANCE 300 III (282 MHz).

All chemical shifts are given in ppm. All coupling constants *J* are indicated in Hz.

Mass spectrometry (MS):
GC 6890N / MSD 5973 (Agilent) or Finnigan MAT 95-XP (Thermo Electron).

High resolution MS (HRMS):
Finnigan MAT 95 XP (Thermo Electron) (electron ionisation EI, 70 eV) or 6210 Time-of-Flight LC/MS (Agilent) (electrospray ionization, ESI). Only the measurements with an average deviation from the theoretical mass of ± 2 μDa were accounted as correct.

Infrared spectroscopy (IR):
Nicolet 380 FT-IR spectrometer with ATR sampling technique for solids as well as liquids. Abbreviations for signal allocations: w = weak, m = medium, s = strong.

X-ray crystallography:
Bruker-Nonius Apex X8 or Bruker Apex Kappa-II diffractometers with CCD-Kamera (Mo-Kα and graphite monochromator, λ = 0.71073 Å).

Melting point determination (mp):
Microscope Laborlux 12 Pol S, Mettler FP90 central Processor, SNT 12 V 100 K. The melting points are uncorrected.

Thin layer chromatography (TLC):
Merck silica gel 60 F_{254}. Detection under UV light at 254 nm and 366 nm without dipping reagent or with vanillin/sulfuric acid visualization reagent.

Column chromatography:
Chromatography was performed over Merck silica gel 60 (0.063-0.200 mm, 70-230 mesh). All solvents were distilled before use.

High Performance Liquid Chromatography (HPLC):
HPLC system from KNAUER®. Analytical column: 250 x 4 mm with precolumn, Eurospher 100-7 C18. Preparative column: 250 x 20 mm, Eurospher 100-7 C18. Analytical pump 100 (2 x 10 ml). Preparative pump 1800 (2 x 250 ml). RI detector 2400. UV detector 2500.

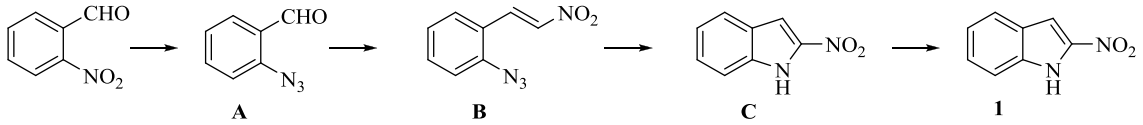
High-Precision Digital Automatic Polarimeter:
GYROMAT-HP, quartz cell 20 mm.

All chemicals and solvents for carrying out reactions were purchased from the standard chemical suppliers: Sigma-Aldrich®, Acros®, Merck®, TCI® and abcr®. All reactions were monitored by TLC using UV light to visualize the course of reaction.

1.2 General synthetic procedures and product characterization

1.2.1 Supplement to chapter 2

Synthesis of the starting material – 1-methyl-2-nitroindole (1):



A **B** **C** **1**

***o*-Azidobenzaldehyde (A):** To a two-neck round-bottom 500 ml flask, fitted with a thermometer and reflux condenser, *o*-nitrobenzaldehyde (5 g, 0.033 mol), sodium azide (4.5 g, 2.1 equiv.) and dry DMF (200 ml) were added under argon atmosphere. The mixture was stirred at 60°C for 30 h. The temperature of the reaction should be kept under 65 °C to avoid a formation of side-products. The reaction mixture was then evaporated to dryness at a rotor evaporator. Water was added to the residue, and the semi-product was extracted with DCM and purified by column chromatography (EA : Heptane = 1:5) to give 2.7 g (55%) of **A**.

***o*-Azido-β-nitrostyrene (B):** **A** (2.5 g, 0.017 mol) was added together with nitromethane (1.85 ml, 2.0 equiv.) and EtOH (50 ml) to a round-bottom 250 ml flask fitted with a dropping funnel. KOH (1.05 g, 1.1 equiv.) dissolved in EtOH (30 ml) was slowly added to the mixture via the dropping funnel at 0 °C (ice bath), whereas the mixture became an emulsion. After the addition the mixture was stirred at 0 °C for 1 h, and a solution of AcOH (10 ml) in water (50 ml) was added at once, after which the solution became clear. The semi-product was extracted with DCM, dried and used for the subsequent reaction without further purification. It was added to a round-bottom 250 ml flask and stirred with Ac_2O (34 ml) and pyridine (3.4 ml) one day at an ice bath. After it, the reaction mixture was poured into water and extracted with DCM. **B** was purified by column chromatography (DCM). Yield 2.5 g (80%).

2-Nitroindole (C): To a round-bottom 100 ml flask fitted with reflux condenser, **B** (2 g, 0.011 mol) and xylenes (50 ml) were added and stirred at 140 °C one day. The solvent was then evaporated to dryness, and the residue was purified by column chromatography (EA : Heptane = 1:10) to give 0.69 g (40%) of **C**.

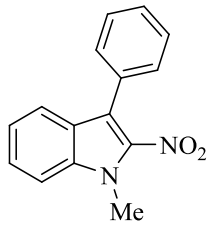
1-Methyl-2-nitroindole (1): In a round-bottom 50 ml flask **C** (0.5 g, 3.1 mmol) was dissolved in DMF (10 ml), and NaH (137 mg, 1.1 equiv., 60 % in mineral oil) was added portionwise to the mixture at 20 °C, whereas the mixture became red. After 15 min of stirring the mixture was

cooled at an ice bath to 0 °C, and CH_3I (0.21 ml, 1.1 equiv.) was added, whereas the color of the reaction changed to yellow. The mixture was left to stay at 20 °C overnight, then DMF was evaporated and the residue was purified by column chromatography (EA : Heptane = 1:15) to give 0.49 g (90%) of **1**.

General Procedure for the synthesis of compounds 2a-k:

In a Schlenk flask **1** (100 mg, 0.57 mmol), appropriate aryl bromide (2.28 mmol, 4.0 equiv.), $Pd(OAc)_2$ (0.057 mmol, 0.1 equiv.), K_2CO_3 (0.8 mmol, 1.4 equiv.) and DMF (5 ml) were added under argon atmosphere and stirred at 150 °C overnight. Reaction mixture was then evaporated to dryness, and a product was isolated by column chromatography (EA/H) or via semi-preparative HPLC (methanol/water).

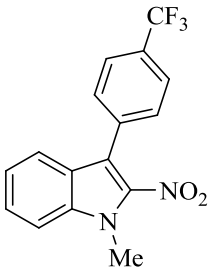
1-Methyl-2-nitro-3-phenylindole (2a):



According to the general procedure compound **2a** was isolated as a yellow solid (72 mg, 52%), mp = 119 – 120 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.09 (s, 3H, CH_3), 7.28 (pt, $^3J_{H\text{-}H}$= 7.5 Hz, 1H, Ar), 7.49 – 7.61 (m, 7H, Ar), 7.78 (d, $^3J_{H\text{-}H}$= 8.5 Hz, 1H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): 32.6 (CH_3), 111.8 (CH), 118.6 (C), 121.8 (CH), 122.4 (CH), 124.0 (C), 127.8 (CH), 127.9 (CH), 128.4 (2CH), 129.9 (2CH), 131.3 (C), 136.1 (C), 138.1 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1612 (w), 1548 (w), 1501 (m), 1458 (s), 1365 (s), 1303 (s), 1246 (s), 1208 (m), 1178 (m), 1157 (m), 1130 (m), 1113 (m), 1091 (m), 1069 (m), 1028 (m), 978 (w), 923 (m), 897 (m), 858 (w), 779 (m), 769 (m), 753 (s), 740 (s), 699 (s), 642 (m), 604 (s), 550 (m). MS (EI, 70 eV): m/z (%) = 253 (18), 252 (M^+, 100), 235 (15), 223 (10), 222 (20), 221 (10), 207 (25), 206 (12), 205 (21), 204 (20), 195 (12), 194 (15), 192 (10), 191 (24), 190 (36), 181 (21), 178 (12), 166 (10), 165 (49), 164 (19), 163 (20), 152 (15), 151 (10). HRMS (EI, 70 eV): Calcd. for $C_{15}H_{12}O_2N_2$: 252.08933; found: 252.08938.

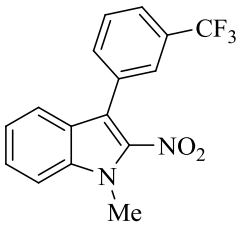
1-Methyl-2-nitro-3-(*p*-trifluoromethylphenyl)-indole (2b):



According to the general procedure compound **2b** was isolated as a yellow solid (135 mg, 74%), mp = 128 – 129 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.12 (s, 3H, CH_3), 7.27 – 7.33 (m, 1H, Ar), 7.54 (d, $^{3}J_{H\text{-}H}$ = 8.2 Hz, 1H, Ar), 7.58 – 7.64 (m, 1H, Ar), 7.75 (d, $^{3}J_{H\text{-}H}$ = 8.0 Hz, 2H, Ar), 7.82 (d, $^{3}J_{H\text{-}H}$ = 8.6 Hz, 1H, Ar), 7.90 (d, $^{3}J_{H\text{-}H}$ = 8.1 Hz, 2H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 32.8 (CH_3), 111.9 (CH), 116.9 (C), 121.4 (CH), 122.7 (CH), 123.7 (C), 124.3 (q, $^{1}J_{C\text{-}F}$ = 272.1 Hz, CF_3), 125.3 (q, $^{3}J_{C\text{-}F}$ = 3.7 Hz, 2CH), 128.0 (CH), 128.2 (q, $^{2}J_{C\text{-}F}$ = 32.0 Hz, C), 130.8 (2CH), 135.9 (C), 136.1 (C), 138.2 (C). ^{19}F NMR (282 MHz, DMSO-d_6): δ = -61.0 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929 (w), 1729 (w), 1612 (w), 1529 (w), 1503 (m), 1484 (m), 1409 (w), 1318 (s), 1311 (s), 1210 (s), 1209 (m), 1162 (s), 1106 (s), 1074 (s), 912 (m), 842 (m), 802 (m), 774 (w), 751 (m), 739 (s), 699 (s), 683 (m), 596 (m), 544 (m). MS (EI, 70 eV): m/z (%) = 321 (M^+, 18), 320 (M, 100), 303 (21), 301 (13), 290 (31), 275 (14), 274 (11), 273 (16), 272 (11), 233 (32), 221 (17), 205 (18), 204 (11), 190 (19). HRMS (EI, 70 eV): Calcd. for $C_{16}H_{11}O_2N_2F_3$: 320.07671; found: 320.07671.

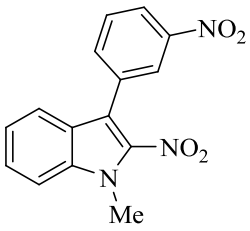
1-Methyl-2-nitro-3-(*m*-trifluoromethylphenyl)-indole (2c):



According to the general procedure compound **2c** was isolated as a yellow solid (130 mg, 71%), mp = 117 – 118 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.13 (s, 3H, CH_3), 7.32 (pt, $^{3}J_{H\text{-}H}$ = 7.5 Hz, 1H, Ar), 7.50 (d, $^{3}J_{H\text{-}H}$ = 8.1 Hz, 1H, Ar), 7.62 (pt, $^{3}J_{H\text{-}H}$ = 7.7 Hz, 1H, Ar), 7.80 – 7.89 (m, 5H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 32.8 (CH_3), 111.9 (CH), 116.9 (C), 121.4 (CH), 122.8 (CH), 123.8 (C), 124.1 (q, $^{1}J_{C\text{-}F}$ = 272.4 Hz, CF_3), 124.6 (q, $^{3}J_{C\text{-}F}$ = 3.7 Hz, CH), 126.4 (q, $^{3}J_{C\text{-}F}$ = 3.9 Hz, CH), 128.0 (CH), 129.2 (q, $^{2}J_{C\text{-}F}$ = 31.8 Hz, C), 129.5 (CH), 132.6 (C), 134.1 (CH), 136.1 (C), 138.2 (C). ^{19}F NMR (282 MHz, DMSO-d_6): δ = -61.0 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957 (w), 1723 (w), 1612 (w), 1548 (w), 1495 (m), 1464 (m), 1424 (w), 1373 (m), 1324 (s), 1298 (s), 1246 (s), 1202 (m), 1162 (s), 1106 (s), 1074 (s), 958 (m), 926 (m), 912 (m), 842 (m), 802 (m), 772 (w), 751 (m), 738 (s), 700 (s), 686 (m), 645 (m), 611 (m), 596 (m), 554 (m). MS (EI, 70 eV): m/z (%) = 321 (M^+, 18), 320 (M, 100), 303 (25), 301 (10), 290 (28), 273 (15), 233 (36), 205 (19), 204 (11), 190 (18). HRMS (EI, 70 eV): Calcd. for $C_{16}H_{11}O_2N_2F_3$: 320.07634; found: 320.07671.

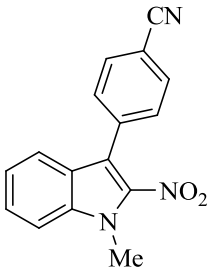
1-Methyl-2-nitro-3-(*m*-nitrophenyl)-indole (2d):



According to the general procedure compound **2d** was isolated as a yellow solid (97 mg, 57%), mp = 114 – 115 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.15 (s, 3H, CH_3), 7.34 (pt, $^3J_{H-H}$ = 7.6 Hz, 1H, Ar), 7.58 (d, $^3J_{H-H}$ = 8.2 Hz, 1H, Ar), 7.61 – 7.66 (m, 1H, Ar), 7.86 (d, $^3J_{H-H}$ = 8.0 Hz, 2H, Ar), 8.01 – 8.04 (m, 1H, Ar), 8.34 – 8.39 (m, 2H, Ar). ^{13}C NMR (63 MHz, DMSO-d_6): δ = 32.9 (CH_3), 111.9 (CH), 116.1 (C), 121.3 (CH), 122.76 (CH), 122.83 (CH), 123.7 (C), 124.7 (CH), 128.0 (CH), 130.0 (CH), 133.2 (C), 136.1 (C), 136.7 (CH), 138.2 (C), 147.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3119 (w), 2923 (w), 1703 (w), 1613 (w), 1546 (w), 1525 (m), 1495 (m), 1469 (m), 1374 (m), 1339 (s), 1308 (s), 1295 (s), 1251 (m), 1204 (m), 1158 (m), 1131 (m), 1100 (m), 1074 (m), 1024 (m), 1001 (m), 922 (m), 893 (w), 813 (m), 805 (m), 777 (w), 754 (m), 731 (s), 686 (s), 658 (m), 646 (m), 606 (m), 551 (m). MS (EI, 70 eV): m/z (%) = 298 (M^+, 18), 297 (M, 100), 280 (24), 267 (19), 221 (23), 206 (20), 205 (34), 204 (30), 192 (13), 191 (12), 190 (29), 177 (11), 165 (11), 164 (21), 163 (22), 151 (11). HRMS (EI, 70 eV): Calcd. for $C_{16}H_{11}O_2N_2F_3$: 297.07441; found: 297.07400.

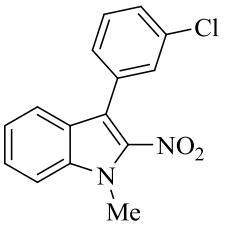
3-(*p*-Cyanophenyl)-1-methyl-2-nitroindole (2e):



According to the general procedure compound **2e** was isolated as a yellow solid (100 mg, 63%) with mp = 132 – 133 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.12 (s, 3H, CH_3), 7.31 (pt, $^3J_{H-H}$ = 7.6 Hz, 1H, Ar), 7.52 (d, $^3J_{H-H}$ = 8.2, 1H, Ar), 7.61 (pt, $^3J_{H-H}$ = 7.6 Hz, 1H, Ar), 7.73 (d, $^3J_{H-H}$ = 8.2 Hz, 2H, Ar), 7.82 (d, $^3J_{H-H}$ = 8.6 Hz, 1H, Ar), 8.01 (d, $^3J_{H-H}$ = 8.2 Hz, 2H, Ar). ^{13}C NMR (63 MHz, DMSO-d_6): δ = 32.8 (CH_3), 110.5 (C), 111.9 (CH), 116.6 (C), 118.7 (C), 121.3 (CH), 122.8 (CH), 123.5 (C), 128.0 (CH), 130.9 (2CH), 132.3 (2CH), 136.0 (C), 136.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3062 (w), 2230 (m), 1607 (w), 1553 (w), 1511 (m), 1486 (m), 1460 (s), 1409 (w), 1366 (s), 1309 (s), 1271 (m), 1253 (m), 1201 (w), 1163 (w), 1134 (m), 1086 (m), 1024 (w), 1012 (w), 940 (w), 906 (s), 856 (m), 817 (m), 777 (w), 763 (w), 749 (m), 734 (s), 670 (w), 642 (m), 617 (m), 546 (s). MS (EI, 70 eV): m/z (%) = 278 (M^+, 18), 277 (M, 100), 260 (27), 247 (32), 232 (17), 231 (16), 230 (26), 229 (19), 216 (21), 215 (28), 191 (10), 190 (53), 189 (15), 188 (18). HRMS (EI, 70 eV): Calcd. for $C_{16}H_{11}O_2N_2F_3$: 277.08458; found: 277.08452.

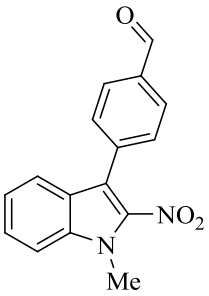
3-(*m*-Chlorophenyl)-1-methyl-2-nitroindole (2f):



According to the general procedure compound **2f** was isolated as a yellow solid (90 mg, 55%), mp = 106 – 107 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.10 (s, 3H, CH_3), 7.30 (pt, $^3J_{H-H}$ = 7.6 Hz, 1H, Ar), 7.47 – 7.53 (m, 2H, Ar), 7.56 – 7.62 (m, 3H, Ar), 7.80 (d, $^3J_{H-H}$ = 8.6 Hz, 2H, Ar). ^{13}C NMR (63 MHz, DMSO-d_6): δ = 32.7 (CH_3), 111.8 (CH), 117.0 (C), 121.5 (CH), 122.6 (CH), 123.8 (C), 127.90 (CH), 127.92 (CH), 128.6 (CH), 129.5 (CH), 130.2 (CH), 133.0 (C), 133.6 (C), 136.0 (C), 138.1 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3064 (w), 2918 (w), 1599 (w), 1553 (w), 1498 (m), 1462 (s), 1371 (s), 1304 (s), 1248 (m), 1207 (m), 1158 (m), 1131 (m), 1087 (m), 1073 (m), 955 (m), 916 (m), 899 (m), 847 (w), 833 (w), 787 (m), 776 (m), 763 (w), 735 (s), 723 (s), 693 (s), 606 (m). MS (EI, 70 eV): m/z (%) = 288 (M+, 31), 287 (M+, 16), 286 (M, 100), 269 (18), 256 (25), 224 (12), 221 (37), 206 (17), 205 (44), 204 (27), 199 (24), 195 (12), 193 (11), 192 (13), 191 (10), 190 (38), 188 (12), 177 (10), 176 (10), 165 (19), 164 (16), 163 (26), 151 (10). HRMS (EI, 70 eV): Calcd. for $C_{15}H_{11}O_2N_2Cl$: 286.05036; found: 286.05012; calcd. for $C_{15}H_{11}O_2N_2{}^{37}Cl$: 288.04741; found: 288.04782.

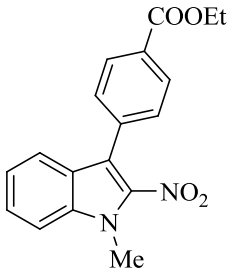
3-(*p*-Formylphenyl)-1-methyl-2-nitroindole (2g):



According to the general procedure compound **2g** was isolated as a yellow solid (96 mg, 59%), mp = 184 – 185 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.12 (s, 3H, CH_3), 7.23 – 7.34 (m, 1H, Ar), 7.54 – 7.63 (m, 2H, Ar), 7.91 (d, $^3J_{H-H}$ = 8.1 Hz, 2H, Ar), 7.97 (d, $^3J_{H-H}$ = 8.6 Hz, 1H, Ar), 8.23 (d, $^3J_{H-H}$ = 8.3 Hz, 2H, Ar), 10.13 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 32.7 (CH_3), 111.9 (CH), 117.2 (C), 121.4 (CH), 122.7 (CH), 123.6 (C), 127.9 (CH), 129.5 (2CH), 130.6 (2CH), 135.3 (C), 136.0 (C), 137.7 (C), 138.1 (C), 192.7 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2921 (w), 2849 (w), 1691 (m), 1603 (m), 1551 (w), 1512 (w), 1484 (w), 1461 (s), 1370 (s), 1253 (m), 1206 (m), 1172 (m), 1163 (m), 1135 (m), 1086 (m), 1009 (m), 941 (w), 906 (m), 827 (m), 804 (m), 760 (m), 732 (s), 671 (m), 652 (m), 611 (m). MS (EI, 70 eV): m/z (%) = 281 (M^+, 19), 280 (M, 100), 263 (12), 223 (14), 221 (15), 207 (16), 206 (14), 205 (18), 204 (19), 195 (12), 192 (10), 191 (16), 165 (43), 164 (19), 163 (21), 152 (10). HRMS (EI, 70 eV): Calcd. for $C_{16}H_{11}O_2N_2F_3$: 280.08424; found: 280.08427.

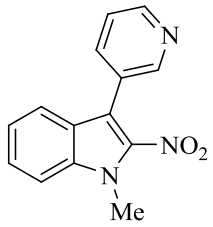
3-(*p*-Ethylcarboxyphenyl)-1-methyl-2-nitroindole (2h):



According to the general procedure compound **2h** was isolated as a yellow solid (115 mg, 62%), mp = 113 – 114 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.39 (t, $^3J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_2CH_3), 4.11 (s, 3H, NCH_3), 4.40 (q, $^3J_{H\text{-}H}$ = 7.1 Hz, 2H, CH_2CH_3), 7.30 (pt, $^3J_{H\text{-}H}$ = 7.4 Hz, 1H, Ar), 7.52 – 7.68 (m, 4H, Ar), 7.81 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 1H, Ar), 8.12 (d, $^3J_{H\text{-}H}$ = 8.3, 2H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.2 (CH_2CH_3), 32.7 (NCH_3), 60.8 (CH_2CH_3), 111.9 (CH), 117.3 (C), 121.5 (CH), 122.7 (CH), 123.6 (C), 127.9 (CH), 129.18 (2CH), 129.20 (C), 130.2 (2CH), 136.1 (C), 136.4 (C), 138.1 (C), 165.5 (COOEt). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2921 (w), 1717 (s), 1609 (w), 1571 (w), 1546 (w), 1503 (w), 1464 (s), 1407 (w), 1373 (m), 1309 (s), 1271 (s), 1204 (m), 1180 (m), 1156 (m), 1102 (s), 1020 (s), 939 (w), 908 (m), 855 (m), 813 (w), 771 (m), 752 (m), 737 (s), 705 (s), 667 (m), 636 (m), 621 (w), 612 (m), 555 (w). MS (EI, 70 eV): m/z (%) = 325 (M+, 20), 324 (M, 100), 294 (11), 279 (22), 266 (10), 251 (11), 223 (10), 222 (22), 221 (33), 207 (13), 206 (15), 205 (26), 204 (21), 190 (22), 165 (14), 164 (14), 163 (16). HRMS (EI, 70 eV): Calcd. for $C_{16}H_{11}O_2N_2F_3$: 324.11046; found: 324.11041.

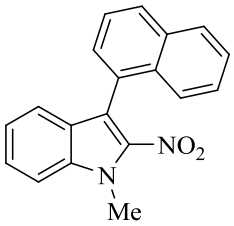
1-Methyl-2-nitro-3-(3-pyridyl)-indole (2i):



According to the general procedure compound **2i** was isolated as a yellow solid (64 mg, 44%), mp = 114 – 115 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.13 (s, 3H, CH_3), 7.23 – 7.34 (m, 1H, Ar), 7.52 – 7.64 (m, 3H, Ar), 7.82 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 1H, Ar), 7.96 – 8.00 (m, 1H, Ar), 8.69 (dd, $^3J_{H\text{-}H}$ = 4.8 Hz, $^4J_{H\text{-}H}$ = 1.6 Hz, 1H, Py), 8.73 (d, $^4J_{H\text{-}H}$ = 1.5 Hz, 1H, Py). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 32.8 (CH_3), 111.9 (CH), 115.2 (C), 121.4 (CH), 122.7 (CH), 123.4 (CH), 123.9 (C), 127.7 (C), 128.0 (CH), 136.1 (C), 137.5 (CH), 138.3 (C), 148.8 (CH), 150.1 (CH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2918 (w), 1613 (w), 1591 (w), 1568 (w), 1539 (w), 1539 (w), 1489 (m), 1463 (s), 1415 (w), 1372 (s), 1342 (m), 1299 (s), 1254 (s), 1189 (m), 1166 (m), 1134 (m), 1126 (m), 1104 (m), 1093 (m), 1026 (s), 937 (m), 900 (m), 806 (m), 777 (m), 756 (s), 742 (s), 710 (s), 661 (m), 640 (m), 623 (m), 602 (m), 555 (w). MS (EI, 70 eV): m/z (%) = 254 (M^+, 17), 253 (M, 100), 236 (18), 223 (18), 207 (12), 206 (14), 205 (16), 195 (15), 192 (22), 191 (12), 182 (15), 179 (12), 167 (22), 166 (48), 165 (13), 164 (25), 154 (11), 152 (14), 140 (14), 139 (20), 138 (12), 87 (10), 63 (13), 30 (10). HRMS (EI, 70 eV): Calcd. for $C_{14}H_{11}O_2N_3$: 253.08458; found: 253.08417.

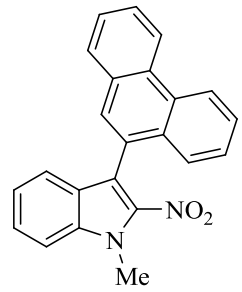
1-Methyl-3-(1-naphtyl)-2-nitroindole (2j):



According to the general procedure compound **2j** was isolated as a yellow solid (72 mg, 42%), mp = 115 – 116 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.21 (s, 3H, CH_3), 7.20 – 7.21 (m, 2H, Ar), 7.40 – 7.46 (m, 1H, Ar), 7.50 – 7.63 (m, 4H, Ar), 7.65 – 7.70 (m, 1H, Ar), 7.86 (d, $^{3}J_{H-H}$ = 8.61, 1H, Ar), 8.06 – 8.10 (m, 2H, Ar). ^{13}C NMR (63 MHz, DMSO-d_6): δ = 32.9 (CH_3), 111.8 (CH), 117.0 (C), 121.8 (CH), 122.3 (CH), 124.9 (C), 125.0 (CH), 125.5 (CH), 126.0 (CH), 126.4 (CH), 127.88 (CH), 127.91 (CH), 128.4 (2CH), 129.4 (C), 131.6 (C), 133.2 (C), 136.3 (C), 139.2 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3054 (w), 2923 (w), 1540 (w), 1506 (w), 1485 (w), 1464 (s), 1362 (s), 1296 (s), 1242 (m), 1217 (s), 1178 (m), 1109 (w), 1065 (w), 1015 (w), 926 (w), 912 (m), 894 (m), 798 (m), 780 (s), 773 (s), 752 (s), 741 (s), 647 (w), 622 (w), 604 (m), 552 (m), 538 (m). MS (EI, 70 eV): m/z (%) = 303 (M+, 16), 302 (M, 74), 272 (10), 271 (12), 257 (26), 256 (100), 255 (50), 254 (16), 242 (22), 241 (74), 240 (54), 238 (11), 215 (13), 214 (11), 213 (18), 128 (18), 127 (14), 120 (15), 106 (12). HRMS (EI, 70 eV): Calcd. for $C_{19}H_{14}O_2N_2$: 302.10498; found: 302.10485.

1-Methyl-2-nitro-3-(9-phenanthryl)-indole (2k):



According to the general procedure compound **2k** was isolated as a yellow solid (96 mg, 48%), mp = 226 – 227 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.24 (s, 3H, CH_3), 7.18 – 7.23 (m, 1H, Ar), 7.27 (d, $^{3}J_{H-H}$ = 8.0 Hz, 1H, Ar), 7.52 – 7.64 (m, 3H, Ar), 7.70 – 7.92 (m, 5H, Ar), 8.02 (d, $^{3}J_{H-H}$ = 7.6 Hz, 1H, Ar), 8.94 (pt, $^{3}J_{H-H}$ = 8.4 Hz, 2H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 32.9 (CH_3), 111.9 (CH), 117.1 (C), 121.9 (CH), 122.3 (CH), 122.9 (CH), 123.3 (CH), 125.0 (C), 125.8 (CH), 126.9 (CH), 126.97 (CH), 127.05 (CH), 127.4 (CH), 128.0 (CH), 128.3 (C), 128.4 (CH), 128.7 (CH), 129.8 (C), 129.9 (C), 130.6 (C), 131.0 (C), 136.5 (C), 139.3 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922 (w), 1601 (w), 1546 (w), 1526 (w), 1496 (m), 1463 (s), 1378 (m), 1362 (s), 1307 (s), 1215 (m), 1199 (m), 1169 (w), 1156 (w), 1150 (w), 1126 (m), 1031 (w), 952 (w), 914 (m), 860 (w), 802 (w), 777 (w), 767 (w), 736 (s), 722 (s), 616 (m), 596 (w), 574 (w), 538 (w). MS (EI, 70 eV): m/z (%) = 353 (M^+, 28), 352 (M, 100), 335 (30), 323 (15), 322 (14), 321 (21), 320 (13), 308 (12), 307 (32), 306 (84), 305 37), 305 (14), 294 (14), 292 (35), 291 (67), 290 (52), 289 (10), 288 (19), 265 (11), 263 (17), 153 (29), 152 (23), 151 (12), 145 (30), 131 (25). HRMS (EI, 70 eV): Calcd. for $C_{23}H_{16}O_2N_2$: 352.12063; found: 352.12085.

1.2.2 Supplement to chapter 3

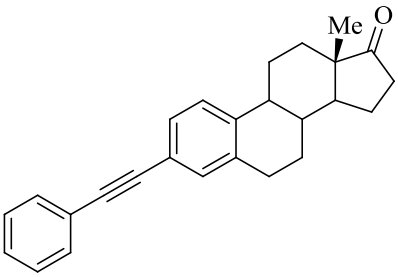
Synthesis of the starting material – estronyl triflate (10):

Estrone (**3**) (1g, 3.7 mmol), NEt_3 (0.62 ml, 1.2 equiv.) and DCM (20 ml) were added in a round-bottom 50 ml flask and cooled at an ice bath to 0°C. Then TfCl (0.47 ml, 1.2 equiv.) was slowly added with a syringe while stirring, whereas reaction color became red-orange. The reaction mixture was left to warm to 20 °C and to stay overnight. At the next day the mixture was quenched with a solution of $NaHCO_3$ (20 ml) and extracted with DCM. The product was purified by column chromatography (EA : Heptane = 1:5, spots of the starting material and of the product are seen at TLC only after treatment of vanillin/sulfuric acid visualization reagent). Yield 1.35 g, 91%.

General procedure for the synthesis of compounds 11a-i:

Estronyl triflate (**10**) (100 mg, 0.25 mmol), $Pd(PPh_3)_4$ (29 mg, 0.1 equiv.), CuI (4.8 mg, 0.1 equiv.), $NH(i\text{-}Pr)_2$ (76 mg, 3.0 equiv.) and DMF (3 ml) were added in a Schlenk flask under argon atmosphere. The mixture was degassed by changing vacuum and argon and appropriate acetylene (1.2 equiv.) was added with a syringe. The mixture was degassed three times and stirred at 100 °C overnight. The solvent was evaporated in vacuo. The residue was purified by column chromatography (EA : Heptane = 1:10).

3-Phenylethynyl-estra-1,3,5(10)-trien-17-one (11a):

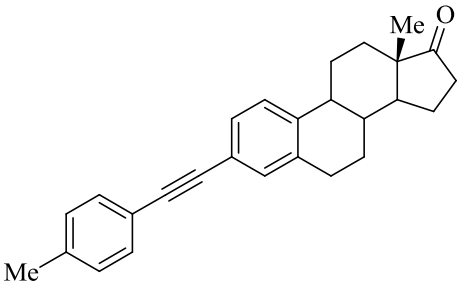


According to the general procedure compound **11a** was isolated as a yellow solid (77 mg, 87%), mp = 216 – 217 °C (lit.[74] 224 – 225 °C), $[\alpha]_D$ = +78.5° (c 2.18, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 3H, CH_3), 1.34 – 1.60 (m, 6H, aliphatic), 1.89 – 2.14 (m, 4H, aliphatic), 2.20 – 2.29 (m, 1H, aliphatic), 2.33 – 2.49 (m, 2H, aliphatic), 2.82 – 2.86 (m, 2H aliphatic), 7.19 – 7.27 (m, 6H, Ar + $CDCl_3$), 7.43 – 7.46 (m, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 25.6 (CH_2), 26.3 (CH_2), 29.1 (CH_2), 31.5 (CH_2), 35.8 (CH_2), 38.0 (CH), 44.5 (CH), 48.0 (C), 50.5 (CH), 88.7 (C_{alkyne}), 89.5 (C_{alkyne}), 120.6 (C), 123.4 (C), 125.4 (CH), 128.1 (CH), 128.3 (2CH), 128.9 (CH), 131.5 (2CH), 132.0 (CH), 136.6 (C), 140.3 (C), 220.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3056 (w), 2926 (m), 2867 (m), 1731 (s), 1595 (w), 1500 (m), 1442 (m), 1371 (w), 1261 (w), 1216 (w), 1083 (m), 1053 (m), 1008 (m), 964 (w),

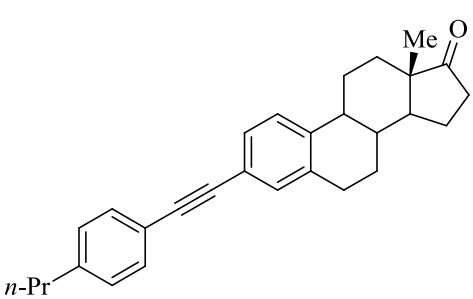
912 (m), 823 (m), 794 (w), 756 (s), 691 (s), 620 (w), 577 (m), 529 (m). MS (EI, 70 eV): m/z (%) = 354 (100) [M+], 355 (30), 241 (12), 230 (12), 229 (14), 228 (17), 215 (17), 202 (10). HRMS (EI): calcd. for $C_{26}H_{26}O$ [M+] 354.19782; found 354.19799.

3-(p-Tolylethynyl)-estra-1,3,5(10)-trien-17-one (11b):



According to the general procedure compound **11b** was isolated as a yellow solid (71 mg, 77%), mp = 186 – 187 °C, $[\alpha]_D$ = +120.2° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3H, CH_3), 1.37 – 1.60 (m, 6H, aliphatic), 1.88 – 2.13 (m, 4H, aliphatic), 2.19 – 2.48 (m, 6H, aliphatic + CH_3), 2.81 – 2.85 (m, 2H, aliphatic), 7.07 (d, $^3J_{H-H}$ = 7.93 Hz, 2H, Ar), 7.16 – 7.24 (m, 3H, Ar + $CDCl_3$), 7.33 (d, $^3J_{H-H}$ =8.12 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.5 (CH_3), 21.6(CH_2), 25.6 (CH_2), 26.4 (CH_2), 29.2 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 38.0 (CH), 44.5 (CH), 48.0 (C), 50.6 (CH), 88.8 (C_{alkyne}), 89.0 (C_{alkyne}), 120.4 (C), 120.8 (C), 125.4 (CH), 128.9 (CH), 129.1 (2CH), 131.5 (2CH), 132.0, (CH) 136.6 (C), 138.2 (C), 140.0 (C), 220.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3029 (w), 2932 (m), 2872 (w), 1731 (m), 1601 (w), 1511 (m), 1451 (w), 1425 (w), 1372 (w), 1338 (w), 1256 (w), 1178 (w), 1082 (m), 1050 (w), 1005 (m), 911 (m), 816 (s), 692 (m), 637 (w), 575 (m), 538 (m). MS (EI, 70 eV): m/z (%) = 368 (100) [M^+], 369 (30), 215 (10). HRMS (EI): calcd. for $C_{27}H_{28}O$ [M^+] 368.21347; found 368.21387.

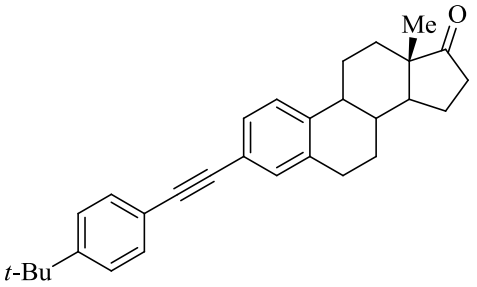
3-(*p*-*n*-Propylphenylethynyl)-estra-1,3,5(10)-trien-17-one (11c):



According to the general procedure compound **11c** was isolated as a yellow solid (93 mg, 94%), mp = 153 – 154 °C, $[\alpha]_D$ = +106.0° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 – 0.89 (m, 6H, $2CH_3$), 1.37 – 1.60 (m, 8H, aliphatic), 1.88 – 2.13 (m, 4H, aliphatic), 2.19 – 2.27 (m, 1H, aliphatic), 2.32 – 2.45 (m, 2H, aliphatic), 2.49 – 2.54 (m, 2H, aliphatic), 2.81 – 2.85 (m, 2H, aliphatic), 7.07 (d, $^3J_{H-H}$ = 8.31 Hz, 2H, Ar), 7.16 – 7.24 (m, 3H, Ar + $CDCl_3$), 7.35 (d, $^3J_{H-H}$ =8.12 Hz, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.7 (CH_3), 13.8 (CH_3), 21.6 (CH_2), 24.3 (CH_2), 25.6 (CH_2), 26.4 (CH_2), 29.1 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.9 (CH_2), 38.0 (CH), 44.5 (CH), 47.9 (C), 50.5 (CH), 88.8 (C_{alkyne}), 89.0 (C_{alkyne}), 120.6 (C), 120.8 (C), 125.3 (CH), 128.5 (2CH), 128.9

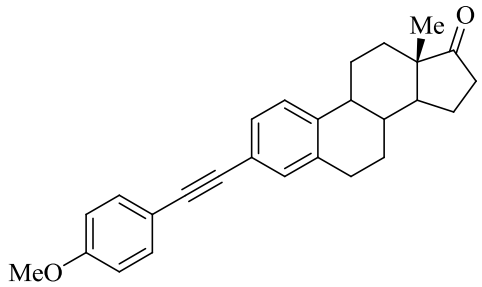
(CH), 131.4 (2CH), 132.0 (CH), 136.6 (C), 140.0 (C), 143.0 (C), 220.7 (C=O). IR (cm^{-1}): $\tilde{\nu}$ = 3026 (w), 2929 (s), 2859 (m), 1736 (s), 1601 (w), 1510 (m), 1451 (m), 1404 (m), 1371 (m), 1337 (m), 1254 (m), 1214 (s), 1179 (w), 1081 (m), 1005 (m), 912 (m), 901 (m), 888 (m), 819 (s), 575 (m). MS (EI, 70 eV): m/z (%) = 396 (100) [M+], 397 (31), 367 (18). HRMS (EI) calcd. for $C_{29}H_{32}O$ [M+] 396.24477; found 396.24435.

3-(*p-tert*-Butylphenylethynyl)-estra-1,3,5(10)-trien-17-one (11d):



According to the general procedure compound **11d** was isolated as a yellow solid (93 mg, 91%), mp = 205 – 206 °C, $[\alpha]_D$ = +111.5° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3H, CH_3), 1.25 (s, 9H, $C(CH_3)_3$), 1.37 – 1.55 (m, 6H, aliphatic), 1.88 – 2.10 (m, 4H, aliphatic), 2.20 – 2.27 (m, 1H), 2.36 – 2.47 (m, 2H, aliphatic), 2.82 – 2.85 (m, 2H, aliphatic), 7.16 – 7.24 (m, 3H, Ar + $CDCl_3$), 7.28 (d, $^3J_{H-H}$ = 8,3 Hz, 2H, Ar), 7.37 (d, $^3J_{H-H}$ = 8,3 Hz, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 25.6 (CH_2), 26.4 (CH_2), 29.1 (CH_2), 31.2 ($C(CH_3)_3$), 31.6 (CH_2), 34.8 ($C(CH_3)_3$), 35.8 (CH_2), 38.0 (CH), 44.4 (CH), 47.9 (C), 50.5 (CH), 88.8 (C_{alkyne}), 88.9 (C_{alkyne}), 120.4 (C), 120.8 (C), 125.3 (2CH), 125.4 (CH), 128.9 (CH), 131.3 (2CH), 132.0 (CH), 136.6 (C), 140.0 (C), 151.3 (C), 220.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 708 (w), 796 (m), 822 (m), 844 (m), 889 (m), 1006 (m), 1055 (m), 1082 (m), 1105 (m), 1204 (m), 1260 (m), 1294 (w), 1337 (w), 1363 (m), 1455 (m), 1464 (m), 1509 (m), 1552 (w), 1737 (s), 2861 (w), 2937 (m). MS (EI, 70 eV): m/z (%) = 410 (100) [M+], 411 (30), 396 (29), 395 (96). HRMS (EI): calcd. for $C_{30}H_{34}O$ [M+] 410.26042; found 410.26012.

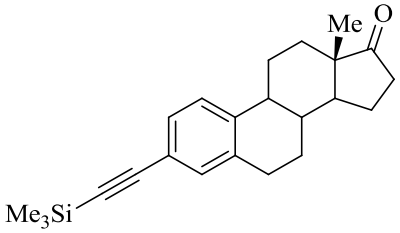
3-(*p*-Methoxyphenylethynyl)-estra-1,3,5(10)-trien-17-one (11e):



According to the general procedure compound **11e** was isolated as a yellow solid (95 mg, 99%), mp = 206 – 207 °C, $[\alpha]_D$ = +95.9° (c 0.66, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3H, CH_3), 1.37 – 1.59 (m, 6H, aliphatic), 1.88 – 2.12 (m, 4H, aliphatic), 2.19 – 2.27 (m, 1H, aliphatic), 2.32 – 2.47 (m, 2H, aliphatic), 2.80 – 2.85 (m, 2H, aliphatic), 3.74 (s, 3H, OCH_3), 6.79 (d, $^3J_{H-H}$ = 8.85 Hz, 2H, Ar), 7.15 – 7.23 (m, 3H, Ar + $CDCl_3$), 7.37 (d, $^3J_{H-H}$ = 8.84 Hz, 2H, Ar). ^{13}C NMR

(63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 25.6 (CH_2), 26.4 (CH_2), 29.1 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 38.0 (CH), 44.4 (CH), 47.9 (C), 50.5 (CH), 55.3 (OCH_3), 88.1 (C_{alkyne}), 88.7 (C_{alkyne}), 114.0 (2CH), 115.6 (C), 120.9 (C), 125.3 (CH), 128.8 (CH), 131.9 (CH), 133.0 (2CH), 136.5 (C), 139.9 (C), 159.5 (C), 220.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922 (m), 2871 (w), 2848 (w), 1729 (s), 1598 (w), 1568 (w), 1512 (s), 1461 (m), 1451 (m), 1443 (m), 1402 (w), 1373 (w), 1338 (w), 1286 (m), 1243 (s), 1183 (w), 1171 (m), 1106 (m), 1083 (m), 1052 (w), 1026 (s), 1007 (m), 967 (w), 912 (m), 881 (m), 836 (s), 812 (s), 783 (m), 744 (w), 709 (m), 670 (w), 638 (w), 577 (m), 535 (s). MS (EI, 70 eV): m/z (%) = 384 (100) [M^+], 385 (26), 215 (12), 202 (12). HRMS (EI): calcd. for $C_{27}H_{28}O_2$ [M^+] 384.20828; found 384.20794.

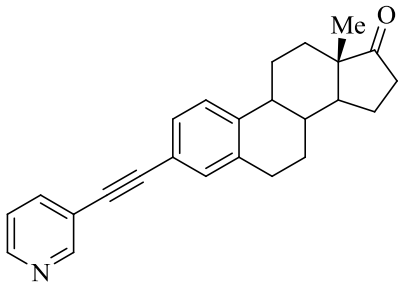
3-(Trimethylsilylethynyl)-estra-1,3,5(10)-trien-17-one (11f):



According to the general procedure compound **11f** was isolated as a brown solid (100 mg, 94%), mp = 140 – 141 °C, $[\alpha]_D$ = +95.3° (c 0.60, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.17 (s, 9H, TMS), 0.84 (s, 3H, CH_3), 1.36 – 1.59 (m, 6H, aliphatic), 1.87 – 2.13 (m, 4H, aliphatic), 2.17 – 2.26 (m, 1H, aliphatic), 2.30 – 2.48 (m, 2H, aliphatic), 2.78 – 2.82 (m, 2H, aliphatic), 7.15 – 7.19 (m, 3H, Ar + $CDCl_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 0.0 ($(CH_3)_3Si$), 13.8 (CH_3), 21.5 (CH_2), 25.5 (CH_2), 26.3 (CH_2), 29.0 (CH_2), 31.5 (CH_2), 35.8 (CH_2), 37.9 (CH), 44.4 (CH), 47.9 (C), 50.5 (CH), 93.3 (C_{alkyne}), 105.2 (C_{alkyne}), 120.4 (C), 125.2 (CH), 129.2 (CH), 132.4 (CH), 136.4 (C), 140.4 (C), 220.6 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938 (m), 2861 (w), 2154 (w), 1738 (s), 1493 (m), 1448 (m), 1404 (w), 1251 (m), 1086 (m), 1053 (m), 1005 (m), 912 (m), 885 (m), 832 (s), 763 (m), 700 (m), 658 (m), 579 (m), 540 (w). MS (EI, 70 eV): m/z (%) = 350 (45) [M+], 351 (14), 336 (29), 335 (100). HRMS (EI): calcd. for $C_{23}H_{30}OSi$ [M+] 350.20604; found 350.20587.

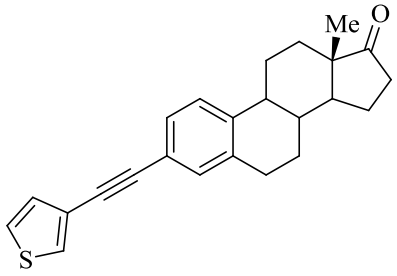
3-(2-(Pyridin-3-yl)ethynyl)-estra-1,3,5(10)-trien-17-one (11g):



According to the general procedure compound **11g** was isolated as a yellow solid (62 mg, 70%), mp = 197 – 198 °C, $[\alpha]_D$ = +140.1° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 3H, CH_3), 1.34 – 1.60 (m, 6H, aliphatic), 1.89 – 2.14 (m, 4H, aliphatic), 2.21 – 2.29 (m, 1H, aliphatic), 2.33 – 2.49 (m, 2H, aliphatic), 2.83 – 2.87 (m, 2H, aliphatic), 7.19 – 7.28 (m, 4H, Ar + $CDCl_3$), 7.71 – 7.75 (m, 1H, Ar), 8.46 (br.s, 1H, Ar), 8.68 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 25.6 (CH_2), 26.3 (CH_2), 29.1 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 38.0 (CH), 44.5 (CH), 48.0 (C), 50.5 (CH), 85.3 (C_{alkyne}), 93.1 (C_{alkyne}), 119.8 (C), 120.8 (C), 123.2 (CH), 125.6 (CH), 129.1 (CH), 132.2 (CH), 136.8 (C), 138.6 (CH), 141.0 (C), 148.1 (CH), 152.0 (CH), 220.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3062 (w), 2931 (m), 2873 (m), 1730 (s), 1564 (w), 1497 (m), 1452 (m), 1404 (w), 1372 (w), 1337 (w), 1258 (w), 1190 (w), 1082 (m), 1051 (w), 1022 (m), 1005 (m), 911 (m), 836 (m), 825 (m), 812 (s), 774 (m), 707 (s), 630 (m), 575 (m), 529 (m). MS (EI, 70 eV): m/z (%) = 355 (100) [M+], 356 (29), 298 (12), 245 (10), 244 (11), 243 (11), 231 (11), 230 (16), 229 (11), 217 (12), 216 (12). HRMS (EI): calcd. for $C_{25}H_{25}ON$ [M+] 355.19307; found 355.19293.

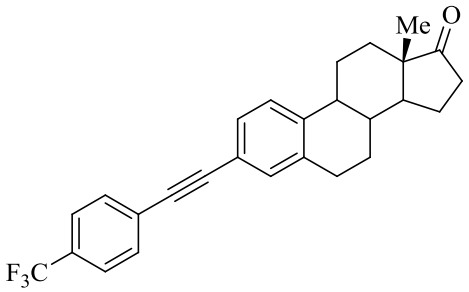
3-(2-(Thiophen-3-yl)ethynyl)-estra-1,3,5(10)-trien-17-one (11h):



According to the general procedure compound **11h** was isolated as a yellow solid (81 mg, 90%), mp = 192 – 193 °C, $[\alpha]_D$ = +145.3° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 3H, CH_3), 1.38 – 1.60 (m, 6H, aliphatic), 1.88 – 2.13 (m, 4H, aliphatic), 2.20 – 2.28 (m, 1H, aliphatic), 2.32 – 2.48 (m, 2H, aliphatic) 2.81 – 2.85 (m, 2H, aliphatic), 7.10 – 7.12 (m, 1H, Ar)), 7.17 – 7.24 (m, 4H, Ar + $CDCl_3$), 7.41 – 7.42 (m, 1H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 25.6 (CH_2), 26.3 (CH_2), 29.1 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 38.0 (CH), 44.5 (CH), 47.9 (C), 50.5 (CH), 83.9 (C_{alkyne}), 88.9 (C_{alkyne}), 120.5 (C), 122.5 (C), 125.3 (CH), 125.4 (CH), 128.3 (CH), 128.8 (CH), 139.9, 131.9 (CH), 136.6 (C), 140.2 (C), 220.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3100 (w), 2922 (w), 2867 (w), 1731 (s), 1491 (w), 1451 (w), 1371 (w), 1353 (w), 1257 (m), 1083 (m), 1054 (m), 1005 (m), 952 (m), 891 (m), 862 (m), 819 (m), 786 (s), 701

(m), 625 (s), 577 (m). MS (EI, 70 eV): m/z (%) = 360 (100) [M+], 361 (30), 234 (12), 221 (13). HRMS (EI): calcd. for $C_{24}H_{24}OS$ [M+] 360.15424; found 360.15413.



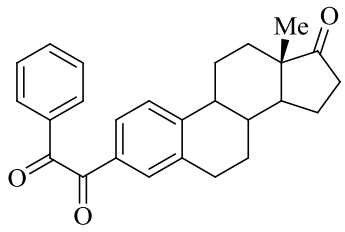
3-(*p*-Trifluorophenylethynyl)-estra-1,3,5(10)-trien-17-one (11i):

According to the general procedure compound **11i** was isolated as a yellow solid (58 mg, 55%), mp = 183 – 184 °C, $[\alpha]_D$ = +85.0° (c 0.53, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (s, 3H, CH_3), 1.42 – 1.56 (m, 6H, aliphatic), 1.88 – 2.11 (m, 4H, aliphatic), 2.21 – 2.27 (m, 1H, aliphatic), 2.32 – 2.49 (m, 2H, aliphatic), 2.82 – 2.87 (m, 2H, aliphatic), 7.22 – 7.27 (m, 3H, Ar), 7.52 (m, 4H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 25.6 (CH_2), 26.3 (CH_2), 29.1 (CH_2), 31.5 (CH_2), 35.8 (CH_2), 37.9 (CH), 44.5 (CH), 47.9 (C), 50.5 (CH), 87.4 (C_{alkyne}), 92.0 (C_{alkyne}), 119.8 (C), 124.0 (q, $^1J_{C\text{-}F}$ = 272.0 Hz, CF_3), 125.2 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2*C*H-C-CF_3), 125.5 (CH), 127.3 (C), 129.1 (CH), 129.7 (q, $^2J_{C\text{-}F}$ = 32.6 Hz, C-CF_3), 131.7 (2CH), 132.2 (CH), 136.8 (C), 140.9 (C), 220.6 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.7 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930 (m), 2858 (w), 1737 (s), 1613 (w), 1516 (w), 1492 (w), 1453 (w), 1432 (w), 1405 (m), 1380 (w), 1320 (s), 1261 (m), 1216 (w), 1165 (s), 1121 (s), 1105 (s), 1084 (m), 1064 (s), 1014 (m), 1006 (m), 914 (w), 901 (w), 889 (m), 847 (m), 838 (m), 823 (m), 800 (m), 780 (m), 750 (m), 709 (m), 694 (w), 643 (w), 627 (w), 599 (m), 576 (m), 535 (w). MS (EI, 70 eV): m/z (%) = 422 (100) [M^+], 423 (29), 365 (14), 324 (12), 312 (12), 311 (10), 310 (11), 309 (13), 298 (12), 297 (10), 296 (12), 283 (10), 215 (11). HRMS (EI, 70 eV): calcd. for $C_{27}H_{25}OF_3$ [M^+] 422.18520; found 422.18516.

General procedure for the synthesis of compounds 12a-d:

Alkyn **(11)** (0.28 mmol), palladium acetate (6.3 mg, 0.1 equiv.), $CuBr_2$ (6.2 mg, 0.1 equiv.) and DMSO (3 ml) were stirred in a flask with an access of air at 120 °C overnight. The solvent was evaporated in vacuo. The residue was purified by column chromatography (EA : Heptane = 1:5).

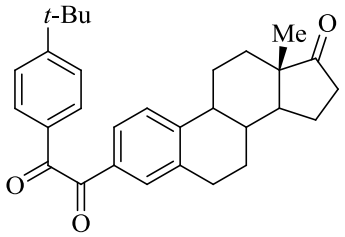
(Estra-1,3,5(10)-trien-17-on-3-yl)-2-(phenylethane)-1,2-dione (12a):



According to the general procedure compound **12a** was isolated as a yellow solid (63 mg, 58%), mp = 80 – 81 °C, $[\alpha]_D$ = +51.0° (c 1.38, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3H, CH_3), 1.39 – 1.60 (m, 6H, aliphatic), 1.89 – 2.14 (m, 4H, aliphatic), 2.24 – 2.32 (m, 1H, aliphatic), 2.34 – 2.48 (m, 2H, aliphatic), 2.85 – 2.90 (m, 2H, aliphatic), 7.34 – 7.45 (m, 3H, Ar), 7.55 – 7.68 (m, 3H, Ar), 7.87 – 7.90 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 35.8 (CH_2), 37.7 (CH), 44.9 (CH), 47.8 (C), 50.5 (CH), 126.1 (CH), 127.3 (CH), 129.0 (2CH), 129.9 (2CH), 130.4 (CH), 130.7 (C), 133.1 (C), 134.8 (CH), 137.6 (C), 147.8 (C), 194.5 (C=O), 194.8 (C=O), 220.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926 (w), 2860 (w), 1734 (s), 1663 (s), 1597 (s), 1564 (w), 1450 (m), 1374 (w), 1320 (w), 1220 (s), 1160 (m), 1140 (w), 1084 (w), 1008 (w), 911 (w), 821 (w), 792 (w), 746 (m), 715 (s), 686 (m), 653 (s), 581 (w), 547 (w). MS (EI, 70 eV): m/z (%) = 386 (0.2) [M^+], 282 (20), 281 (100), 105 (11). HRMS (EI): calcd. for $C_{26}H_{26}O_3$ [M^+] 386.18765; found 386.18699.

(Estra-1,3,5(10)-trien-17-on-3-yl)-2-(*p-tert*-butylphenylethane)-1,2-dione (12b):

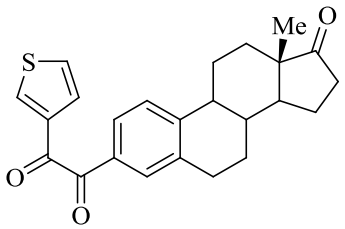


According to the general procedure compound **12b** was isolated as a yellow solid (81 mg, 65%), mp = 80 – 81 °C, $[\alpha]_D$ = +46.1° (c 8.45, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3H, CH_3), 1.27 (s, 9H, $C(CH_3)_3$), 1.40 – 1.56 (m, 6H, aliphatic), 1.90 – 2.14 (m, 4H, aliphatic), 2.24 – 2.49 (m, 3H, aliphatic), 2.85 – 2.90 (m, 2H, aliphatic), 7.35 (d, $^3J_{H\text{-}H}$ = 8.12 Hz, 1H, Ar), 7.43 – 7.46 (m, 2H, Ar), 7.63 – 7.68 (m, 2H, Ar), 7.81 – 7.84 (m, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 29.2 (CH_2), 31.0 ($C(CH_3)_3$), 31.5 (CH_2), 35.4 (C), 35.8 (CH_2), 37.7 (CH), 44.9 (CH), 47.8 (C), 50.5 (CH), 125.98 (2CH), 126.04 (CH), 127.3 (CH), 129.9 (2CH), 130.4 (CH), 130.6 (C), 130.8 (C), 137.5 (C), 147.6 (C), 158.9 (C), 194.4 (C=O), 194.7 (C=O), 220.3 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925 (m), 1734 (s), 1667(s), 1601 (s), 1565 (m), 1408 (m), 1225 (s), 1184 (s), 1108 (m), 1008 (s), 949 (m), 920 (m), 854 (m), 820 (m), 774 (m), 701 (s), 672 (m), 584

(m), 545 (s). MS (EI, 70 eV): m/z (%) = 442 (1) [M^+], 282 (23), 281 (100), 161 (46). HRMS (EI): calcd. for $C_{30}H_{34}O_3$ [M^+] 442.25025; found 442.25021.

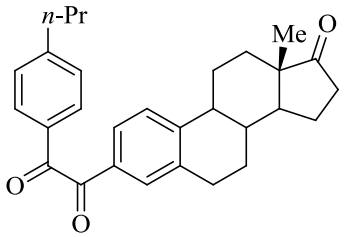
(Estra-1,3,5(10)-trien-17-on-3-yl)-2-(3-thiophenylethane)-1,2-dione (12c):



According to the general procedure compound **12c** was isolated as a yellow solid (65 mg, 59%), mp = 89 – 90 °C, $[\alpha]_D$ = +117.6° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3H, CH_3), 1.46 – 1.60 (m, 6H, aliphatic), 1.90 – 2.14 (m, 4H, aliphatic), 2.24 – 2.49 (m, 3H, aliphatic), 2.86 – 2.91 (m, 2H, aliphatic), 7.31 – 7.37 (m, 2H, Ar), 7.58 – 7.60 (m, 3H, Ar), 8.11 – 8.13 (m, 1H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 35.8 (CH_2), 37.7 (CH), 44.9 (CH), 47.8 (C), 50.5 (CH), 126.0 (CH), 127.1 (2CH), 127.5 (CH), 130.4 (C), 130.7 (CH), 136.9 (CH), 137.5 (C), 138.2 (C), 147.7 (C), 187.5 (C=O), 193.2 (C=O), 220.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3102 (w), 2926 (m), 2858 (w), 1733 (s), 1653 (s), 1600 (m), 1562 (m), 1505 (m), 1452 (m), 1408 (m), 1374 (w), 1337 (w), 1295 (w), 1256 (w), 1227 (s), 1156 (m), 1138 (m), 1080 (m), 1007 (m), 944 (w), 870 (m), 818 (m), 773 (w), 728 (s), 712 (s), 670 (m), 621 (m), 582 (m), 547 (w). MS (EI, 70 eV): m/z (%) = 392 (0.1) [M^+], 282 (20), 281 (100), 111 (11). HRMS: calcd. for $C_{24}H_{24}O_3S$ [M^+] 393.15189; found 393.15188.

(Estra-1,3,5(10)-trien-17-on-3-yl)-2-(*p*-*n*-propylphenylethane)-1,2-dione (12d):



According to the general procedure compound **12d** was isolated as a yellow solid (95 mg, 79%), mp = 81 – 82 °C, $[\alpha]_D$ = +19.1° (c 3.41, $CHCl_3$).

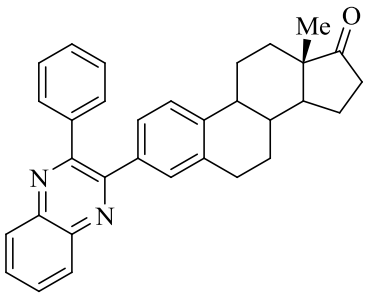
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 – 0.90 (m, 6H, aliphatic), 1.39 – 1.63 (m, 8H, aliphatic), 1.90 – 2.14 (m, 4H, aliphatic), 2.24 – 2.49 (m, 3H, aliphatic), 2.56 – 2.61 (m, 2H, aliphatic), 2.87 – 2.90 (m, 2H, aliphatic), 7.22 (d, $^3J_{H\text{-}H}$ = 8.12 Hz, 2H), 7.36 ($^3J_{H\text{-}H}$ =8.31 Hz, 1H), 7.63 – 7.68 (m, 2H, Ar), 7.80 (d, $^3J_{H\text{-}H}$ =8.31 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.75 (CH_3), 13.81 (CH_3), 21.6 (CH_2), 24.1 (CH_2), 25.5 (CH_2), 26.2 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 35.8 (CH_2), 37.7 (CH), 38.3 (CH_2), 44.9 (CH), 47.9 (C), 50.6 (CH), 126.1, 127.3 (2CH), 129.2 (2CH), 130.1 (2CH), 130.5 (CH), 130.9 (C), 131.0 (C), 137.6 (C), 147.6 (C), 150.7 (C), 194.5 (C=O), 194.8 (C=O), 220.3 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930 (m), 2870 (w), 2252 (w), 1733 (m), 1665

(s), 1602 (s), 1566 (m), 1454 (m), 1415 (m), 1221 (s), 1165 (m), 1007(m), 910 (m), 843 (m), 728 (s), 646 (m), 581 (m), 547 (m). MS (EI, 70 eV): m/z (%) = 428 (3) [M^+], 283 (14), 282 (80), 281 (100), 148 (12), 147 (86), 91 (12). HRMS (EI): calcd. for $C_{29}H_{32}O_3$ [M^+] 428.23460; found 428.23465.

General procedure for the synthesis of compounds 13a-d:

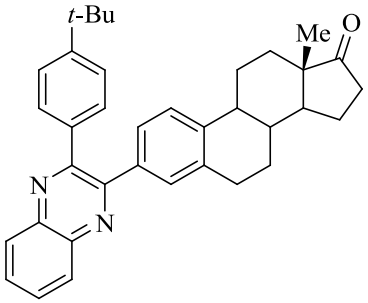
Dione **(12)** (0.26 mmol) and *o*-phenylenediamine (36.4 mg, 1.3 equiv.) were dissolved in ethanol (4 ml) and stirred at 50 °C 1 h. The solvent was evaporated in vacuo. The residue was purified by column chromatography (EA : Heptane = 1:4).

2-(Estra-1,3,5(10)-trien-17-on-3-yl)-3-phenyl-quinoxaline (13a):



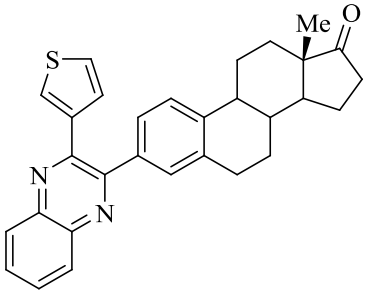
According to the general procedure compound **13a** was isolated as a yellow solid (109 mg, 92%), mp = 102 – 103 °C, $[\alpha]_D$ = +85.4° (c 0.85, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3H, CH_3), 1.39 – 1.55 (m, 6H, aliphatic), 1.86 – 2.12 (m, 4H, aliphatic), 2.24 – 2.47 (m, 3H, aliphatic), 2.78 – 2.80 (m, 2H, aliphatic), 7.10 (br.s, 2H, Ar), 7.27 – 7.29 (m, 4H, Ar), 7.46 – 7.49 (m, 2H, Ar), 7.65 – 7.68 (m, 2H, Ar), 8.07 – 8.10 (m, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 25.6 (CH_2), 26.4 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 38.0 (CH), 44.4 (CH), 47.9 (C), 50.6 (CH), 125.0 (CH), 127.3 (CH), 128.2 (2CH), 128.7 (CH), 129.1 (CH), 129.2 (CH), 129.7 (CH), 129.80 (2CH), 129.84 (CH), 130.3 (CH), 136.4 (C), 136.6 (C), 139.3 (C), 140.6 (C), 141.1 (C), 141.3 (C), 153.3 (C), 153.4 (C), 220.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2921 (m), 2854 (w), 1734 (s), 1608 (w), 1556 (w), 1538 (w), 1497 (w), 1476 (w), 1452 (w), 1404 (w), 1373 (w), 1342 (m), 1256 (m), 1220 (w), 1172 (w), 1136 (w), 1083 (m), 1067 (w), 1051 (m), 1003 (m), 988 (w), 906 (w), 844 (w), 826 (w), 811 (w), 794 (w), 760 (s), 696 (s), 641 (w), 609 (m), 589 (m), 566 (m). MS (EI, 70 eV): m/z (%) = 458 (100) [M^+], 459 (38), 443 (12), 414 (16), 402 (12), 401 (10), 387 (17), 361 (10), 348 (12), 347 (18), 346 (11), 319 (10), 206 (13), 205 (11), 178 (23), 173 (14), 172 (17), 166 (16), 155 (10), 152 (10), 150 (11), 115 (11), 76 (13), 67 (18), 66 (14), 52 (10), 41 (13), 40 (14). HRMS (EI, 70 eV): calcd. for $C_{32}H_{30}ON_2$ [M^+] 458.23527; found 458.23613.

2-(Estra-1,3,5(10)-trien-17-on-3-yl)-3-(*p-tert*-butylphenyl)-quinoxaline (13b):



According to the general procedure compound **13b** was isolated as a yellow solid (118 mg, 88%), mp = 121 – 122 °C, $[\alpha]_D$ = +104.5° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 3H, CH_3), 1.26 (s, 9H, $C(CH_3)_3$), 1.45 – 1.56 (m, 6H, aliphatic), 1.88 – 2.13 (m, 4H, aliphatic), 2.23 – 2.48 (m, 3H, aliphatic), 2.77 – 2.80 (m, 2H, aliphatic), 7.10 – 7.15 (m, 2H, Ar), 7.30 (d, $^3J_{H-H}$ = 8.5 Hz, 3H, Ar), 7.42 (d, $^3J_{H-H}$ = 8.4 Hz, 2H, Ar), 7.66 (dd, $^3J_{H-H}$ = 6.4 Hz, $^4J_{H-H}$ = 3.4 Hz, 2H, Ar), 8.08 (dd, $^3J_{H-H}$ = 6.4 Hz, $^4J_{H-H}$ = 3.5 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 25.6 (CH_2), 26.4 (CH_2), 29.3 (CH_2), 31.3 ($C(CH_3)_3$), 31.6 (CH_2), 34.7 ($C(CH_3)_3$), 35.9 (CH_2), 38.0, 44.5 (2CH), 48.0 (C), 50.6 (CH), 125.0 (CH), 125.2 (2CH), 127.3 (CH), 129.1 (CH), 129.1 (CH), 129.5 (2CH), 129.7 (2CH), 130.3 (CH), 136.3 (C), 136.5 (C), 136.5 (C), 140.6 (C), 141.10 (C), 141.13 (C), 152.0 (C), 153.3 (C), 153.5 (C), 220.8 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926 (w), 2865 (w), 1738 (s), 1609 (w), 1556 (w), 1540 (w), 1500 (w), 1475 (w), 1454 (w), 1404 (w), 1393 (w), 1362 (w), 1341 (m), 1255 (m), 1221 (w), 1172 (2), 1110 (m), 1084 (w), 1051 (m), 907 (w), 891 (w), 839 (m), 824 (m), 761 (s), 737 (w), 710 (w), 605 (s), 558 (m). MS (EI, 70 eV): m/z (%) = 514 (100) [M^+], 515 (39), 499 (22), 458 (10), 457 (24), 57 (10). HRMS (EI, 70 eV): calcd. for $C_{36}H_{38}N_2O$ [M^+] 514.29787; found 514.29693.

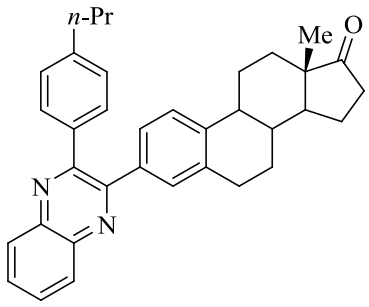
2-(Estra-1,3,5(10)-trien-17-on-3-yl)-3-(thiophen-3-yl)-quinoxaline (13c):



According to the general procedure compound **13c** was isolated as a yellow solid (99 mg, 82%), mp = 111 – 112 °C, $[\alpha]_D$ = +90.2° (c 1.08, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 3H, CH_3), 1.44 – 1.55 (m, 6H, aliphatic), 1.89 – 2.10 (m, 4H, aliphatic), 2.28 – 2.48 (m, 3H, aliphatic), 2.83 – 2.85 (m, 2H, aliphatic), 7.19 – 7.28 (m, 5H, Ar + $CDCl_3$), 7.40 (s, 1H, Ar), 7.64 – 7.66 (m, 2H, Ar), 8.03 – 8.05 (m, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 25.7 (CH_2), 26.4 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 38.0 (CH), 44.4 (CH), 47.9 (C), 50.6 (CH), 125.1 (CH), 125.3 (CH), 126.8 (CH), 127.5 (CH), 128.85 (CH), 128.98 (CH), 129.1 (CH), 129.7 (CH), 129.77 (CH), 129.82 (CH), 136.75 (C), 136.79 (C), 140.3 (C), 140.8 (C), 140.9 (C), 141.1 (C), 148.5 (C), 153.4 (C), 220.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920 (m), 2854 (w), 1734 (s), 1608 (w), 1559

(w), 1524 (w), 1500 (w), 1476 (w), 1452 (w), 1423 (m), 1374 (w), 1330 (m), 1254 (m), 1222 (w), 1182 (w), 1136 (w), 1084 (m), 1052 (m), 1006 (m), 907 (w), 867 (m), 843 (m), 817 (m), 787 (s), 760 (s), 712 (m), 655 (m), 622 (w). MS (EI, 70 eV): m/z (%) = 464 (100) [M^+], 465 (27), 463 (29), 431 (14), 353 (12), 339 (11), 327 (16), 325 (10), 314 (13), 313 (50), 301 (25), 300 (54), 299 (13), 287 (10), 185 (11), 170 (43), 161 (13), 153 (13), 149 (15), 140 (15). HRMS (EI, 70 eV): calcd. for $C_{30}H_{28}ON_2S$ [M^+] 464.19169; found 464.19139.

2-(Estra-1,3,5(10)-trien-17-on-3-yl)-3-(*p*-*n*-propylphenyl)-quinoxaline (13d):



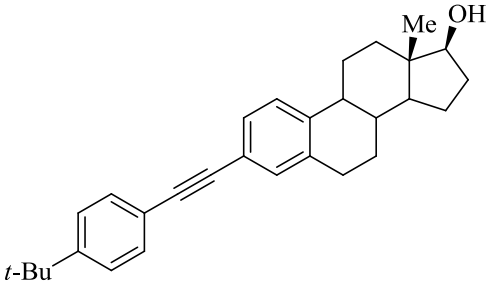
According to the general procedure compound **13d** was isolated as a yellow solid (125 mg, 96%), mp = 114 – 115 °C, $[\alpha]_D$ = +66.0° (c 2.55, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 – 0.95 (m, 6H, $2CH_3$), 1.44 – 1.55 (m, 4H, aliphatic), 1.59 – 1.66 (m, 4H, aliphatic), 1.94 – 2.17 (m, 4H, aliphatic), 2.31 – 2.55 (m, 3H, aliphatic), 2.58 – 2.63 (m, 2H, $CH_2CH_2CH_3$), 2.84 – 2.89 (m, 2H, aliphatic), 7.14 – 7.18 (m, 4H, Ar), 7.37 (s, 1H, Ar), 7.46 (d, $^3J_{H-H}$ = 8.1 Hz, 2H, Ar), 7.72 – 7.75 (m, 2H, Ar), 8.15 – 8.18 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_3), 13.9 (CH_3), 21.6 (CH_2), 24.4 (CH_2), 25.6 (CH_2), 26.4 (CH_2), 29.3 (CH_2), 31.6 (CH_2) 35.8 (CH_2), 37.8 (CH_2), 38.0 (CH), 44.4 (CH), 48.0 (C), 50.6 (CH), 125.0 (CH), 127.3 (CH), 128.4 (2CH), 129.0 (CH), 129.1 (CH), 129.7 (2CH), 129.8 (2CH), 130.3 (CH), 136.4 (C), 136.5 (C), 136.6 (C), 140.7 (C), 141.0 (2C), 143.6 (C), 153.3 (C), 153.5 (C), 220.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954 (m), 2926 (s), 2857 (s), 1736 (s), 1609 (w), 1556 (w), 1537 (w), 1500 (w), 1475 (m), 1453 (m), 1407 (m), 1392 (m), 1374 (w), 1340 (s), 1276 (m), 1255 (m), 1220 (m), 1184 (w), 1172 (w), 1136 (m), 1117 (m), 1084 (m), 1067 (m), 1051 (m), 1010 (m), 989 (m), 962 (w), 926 (w), 906 (w), 891 (w), 841 (m), 824 (m), 801 (m), 761 (s), 731 (m), 711 (m), 638 (w), 608 (m), 551 (m). MS (EI, 70 eV): m/z (%) = 500 (100) [M^+], 501 (37), 457 (17). HRMS (EI, 70 eV): calcd. for $C_{35}H_{36}ON_2$ [M^+] 500.28222; found 500.28273.

General procedure for the synthesis of compounds 14 and 15:

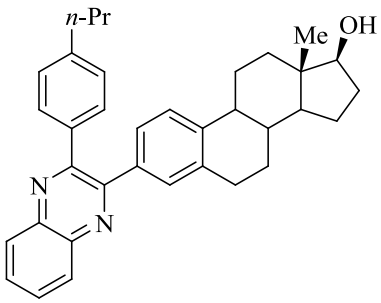
Alkyn **(11d)** or quinoxaline **(13d)** (0.24 mmol) was dissolved in a mixture DCM-MeOH 1:1 (4 ml) and $NaBH_4$ (24.5 mg, 2.7 equiv.) was added in one portion. After stirring 1 h at 25 °C 1 ml of water was added and the mixture was evaporated in vacuo to dryness. The residue was purified by column chromatography (EA : Heptane = 1:3).

3-(*p-tert*-Butylphenylethynyl)-estra-1,3,5(10)-trien-17β-ol (14):



According to the general procedure compound **14** was isolated as a white solid (60 mg, 59%), mp = 200 – 201 °C, $[\alpha]_D$ = +41.2° (c 1.30, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (s, 3H, CH_3), 1.33 – 1.40 (m, 12H, aliphatic + $C(CH_3)_3$), 1.46 – 1.55 (m, 4H, aliphatic), 1.69 – 1.75 (m, 1H, aliphatic), 1.88 – 1.93 (m, 1H, aliphatic), 1.96 – 2.00 (m, 1H, aliphatic), 2.10 – 2.17 (m, 1H, aliphatic), 2.23 – 2.28 (m, 1H, aliphatic), 2.33 – 2.27 (m, 1H, aliphatic), 2.85 – 2.88 (m, 2H, aliphatic), 3.73 – 3.76 (m, 1H, C*H*OH), 7.25 – 7.27 (m, 2H, Ar + $CDCl_3$), 7.29 – 7.31 (m, 1H, Ar), 7.35 – 7.37 (m, 2H, Ar), 7.45 – 7.46 (m, 2H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.1 (CH_3), 23.1 (CH_2), 26.0 (CH_2), 27.1 (CH_2), 29.3 (CH_2), 30.6 (CH_2), 31.2 (C(*C*H_3)$_3$), 34.8 (*C*(CH_3)$_3$), 36.7 (CH_2), 38.5 (CH), 43.2 (C), 44.5 (CH), 50.2 (CH), 81.9 (CHOH), 88.8 (C_{alkyne}), 89.0 (C_{alkyne}), 120.5 (C), 120.6 (C), 125.3 (2CH), 125.4 (CH), 128.8 (CH), 131.3 (2CH), 132.0 (CH), 136.8 (C), 140.7 (C), 151.3 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3625 (w), 3605 (w), 2922 (s), 2861 (m), 1506 (m), 1453 (m), 1435 (m), 1393 (m), 1376 (m), 1362 (m), 1336 (w), 1265 (m), 1246 (m), 1203 (m), 1175 (w), 1136 (m), 1114 (w), 1105 (w), 1069 (m), 1045 (s), 1014 (m), 963 (w), 892 (m), 831 (s), 796 (m), 774 (m), 737 (w), 712 (w), 639 (w), 577 (m), 565 (s). MS (EI, 70 eV): m/z (%) = 412 (100) [M^+], 413 (32), 398 (20), 397 (66). HRMS (EI, 70 eV): calcd. for $C_{30}H_{36}O$ [M^+] 412.27607; found 412.27613.

2-(Estra-1,3,5(10)-trien-17β-ol-3-yl)-3-(*p-n*-propylphenyl)-quinoxaline (15):



According to the general procedure compound **15** was isolated as a white solid (93 mg, 92%), mp = 121 – 122 °C, $[\alpha]_D$ = +14.7° (c 1.42, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.79 (s, 3H, CH_3), 0.93 (t, $^3J_{H\text{-}H}$ = 7.3 Hz, 3H, $CH_2CH_2CH_3$), 1.43 – 1.54 (m, 6H, aliphatic), 1.61 – 1.70 (m, 4H, aliphatic), 1.86 – 1.98 (m, 2H, aliphatic), 2.09 – 2.35 (m, 3H, aliphatic), 2.59 – 2.65 (m, 2H, $CH_2CH_2CH_3$), 2.80 – 2.83 (m, 2H, aliphatic), 3.70 – 3.76 (m, 1H, C*H*OH), 7.14 – 7.19 (m, 4H, Ar), 7.34 (s, 1H, Ar), 7.45 – 7.48 (m, 2H, Ar), 7.74 (dd, $^3J_{H\text{-}H}$ = 6.4 Hz, $^4J_{H\text{-}H}$ = 3.4 Hz, 2H, Ar), 8.16 (dd, $^3J_{H\text{-}H}$ = 6.4 Hz, $^4J_{H\text{-}H}$ = 3.4 Hz, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 11.1 (CH_3),

13.7 (CH_3), 23.1 (CH_2), 24.4 (CH_2), 26.0 (CH_2), 27.1 (CH_2), 29.4 (CH_2), 30.6 (CH_2), 36.7 (CH_2), 37.8 (CH_2), 38.5 (CH), 43.2 (C), 44.4 (CH), 50.2 (CH), 81.8 (CHOH), 125.0 (CH), 127.1 (CH), 128.4 (2CH), 129.0 (2CH), 129.7 (4CH), 130.2 (CH), 136.1 (C), 136.5 (C), 136.8 (C), 140.97 (C), 141.01 (C), 141.3 (C), 143.5 (C), 153.4 (C), 153.5 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3372 (w), 2925 (m), 2866 (m), 1708 (w), 1630 (w), 1610 (w), 1589 (w), 1556 (w), 1537 (w), 1511 (m), 1454 (m), 1411 (w), 1391 (m), 1341 (s), 1249 (m), 1221 (m), 1184 (w), 1168 (w), 1137 (m), 1076 (m), 1054 (s), 1021 (m), 1009 (m), 988 (m), 960 (w), 907 (w), 893 (w), 843 (m), 825 (m), 801 (m), 760 (s), 731 (m), 645 (m), 608 (s), 552 (m). MS (EI, 70 eV): m/z (%) = 502 (100) [M^+], 503 (36), 459 (12). HRMS (EI, 70 eV): calcd. for $C_{35}H_{38}ON_2$ [M^+] 502.29787; found 502.29819.

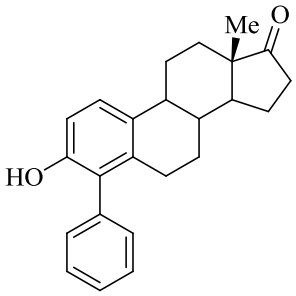
1.2.3 Supplement to chapter 4

All starting materials, 2-, 4-bromoestrone and 2,4-dibromoestrone, were received from the University of Szeged, Hungary.

General procedure for the synthesis of compounds 17a-m:

4-Bromoestrone (**16a**) (100 mg, 0.286 mmol), boronic acid (1.5 equiv.), $Pd(PPh_3)_4$ (17.0 mg, 0.05 equiv.), K_3PO_4 (121.5 mg, 2.0 equiv.) and dioxane (4 ml) were added in a pressure tube under argon atmosphere. The mixture was stirred at 101 °C overnight. The solvent was evaporated in vacuo. The residue was purified by column chromatography (EA : Heptane = 1:5).

4-Phenyl-estrone (17a):

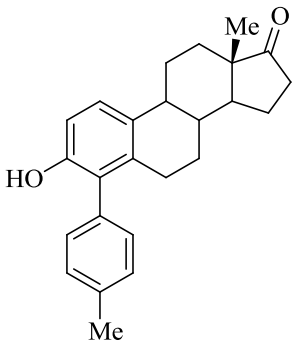


According to the general procedure compound **17a** was isolated as a light yellow solid (87 mg, 88%), mp = 89 – 90 °C, $[\alpha]_D$ = +86.4° (c 1.00, $CHCl_3$) (lit.[105] $[\alpha]_D^{20}$ = +83.1° (c 1.77, EtOH)).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.31 – 1.39 (m, 1H, aliphatic), 1.45 – 1.65 (m, 5H, aliphatic), 1.87 – 2.16 (m, 4H, aliphatic), 2.26 – 2.33 (m, 1H, aliphatic), 2.42 – 2.58 (m, 4H, aliphatic), 4.62 (br.s, 1H, OH), 6.86 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 1H, Ar), 7.24 – 7.30 (m, 3H, Ar + $CDCl_3$), 7.40 – 7.45 (m, 1H, Ar), 7.48 – 7.455 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$):

δ = 13.9 (CH_3), 21.6 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.5 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.8 (CH), 44.4 (CH), 48.0 (C), 50.4 (CH), 112.6 (CH), 125.9 (CH), 127.5 (C), 128.2 (CH), 129.5 (2CH), 130.1 (CH), 130.5 (CH), 132.0 (C), 135.41 (C), 135.45 (C), 150.9 (C), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3543 (w), 3363 (w), 2924 (m), 2857 (w), 1733 (s), 1587 (w), 1472 (m), 1453 (m), 1437 (m), 1422 (m), 1404 (w), 1372 (w), 1343 (w), 1286 (m), 1272 (m), 1258 (m), 1206 (m), 1166 (m), 1083 (w), 1055 (m), 1029 (w), 1009 (m), 947 (w), 915 (w), 899 (2), 821 (m), 804 (m), 762 (m), 701 (s), 642 (m), 581 (m). MS (EI, 70 eV): m/z (%) = 346 (100) [M^+], 347 (27), 261 (28), 248 (14), 235 (10), 222 (28), 221 (12), 207 (10), 202 (14), 189 (10), 181 (14), 178 (10), 165 (15), 55 (11), 41 (15). HRMS (EI, 70 eV): calcd. for $C_{24}H_{26}O_2$ [M^+] 346.19273; found 346.19267.

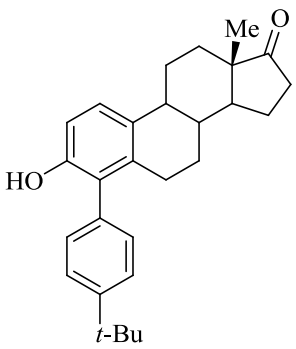
4-(*p*-Tolyl)-estrone (17b):



According to the general procedure compound **17b** was isolated as a light yellow solid (102 mg, 99%), mp = 104 – 105 °C, $[\alpha]_D$ = +78.4° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.28 – 1.39 (m, 1H, aliphatic), 1.49 – 1.63 (m, 5H, aliphatic), 1.86 – 2.18 (m, 4H, aliphatic), 2.26 – 2.34 (m, 1H, aliphatic), 2.49 (s, 3H, CH_3), 2.49 – 2.53 (m, 4H, aliphatic), 4.68 (br.s, 1H, OH), 6.84 (d, $^3J_{H\text{-}H}$ = 8.54 Hz, 1H, Ar), 7.13-7.19 (m, 2H, Ar), 7.23 – 7.26 – (m, 1H, Ar + $CDCl_3$), 7.30 – 7.34 (m, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.3 (CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 28.5 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 112.5 (CH), 125.8 (CH), 127.4 (C), 129.9 (CH), 130.23 (CH), 130.26 (CH), 130.3 (CH), 131.9 (C), 132.1 (C), 135.5 (C), 137.9 (C), 151.0 (C), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3539 (w), 3370 (w), 2923 (m), 2861 (w), 1734 (s), 1588 (w), 1514 (w), 1473 (s), 1453 (m), 1438 (m), 1403 (w), 1373 (w), 1342 (w), 1283 (m), 1272 (m), 1258 (m), 1207 (m), 1180 (m), 1165 (m), 1108 (w), 1082 (w), 1054 (m), 1008 (m), 949 (w), 922 (w), 901 (w), 816 (s), 789 (m), 725 (w), 674 (w), 646 (w), 581 (m). MS (EI, 70 eV): m/z (%) = 360 (100) [M^+], 361 (27), 275 (30), 262 (12), 236 (22), 195 (13). HRMS (EI, 70 eV): calcd. for $C_{25}H_{28}O_2$ [M^+] 360.20838; found 360.20841.

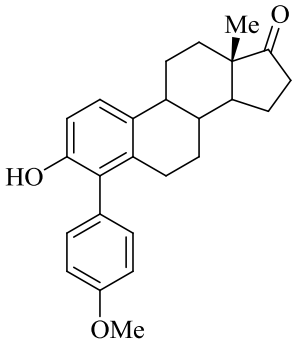
4-(*p*-*tert*-Butyl)-phenyl-estrone (17c):



According to the general procedure compound **17c** was isolated as a light yellow solid (104 mg, 90%), mp = 150 – 151 °C, $[\alpha]_D$ = +71.5° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.32 – 1.38 (m, 1H, aliphatic), 1.38 (s, 9H, $C(CH_3)_3$), 1.49 – 1.61 (m, 5H, aliphatic), 1.87 – 2.16 (m, 4H, aliphatic), 2.27 – 2.33 (m, 1H, aliphatic), 2.42 – 2.53 (m, 4H, aliphatic), 4.67 (br.s, 1H, OH), 6.86 (d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, Ar), 7.18 – 7.26 (m, 3H, Ar + $CDCl_3$), 7.50 – 7.53 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.6 (CH_2), 31.4 ($C(CH_3)_3$), 31.6 (CH_2), 34.7 ($C(CH_3)_3$), 35.9 (CH_2), 37.9 (CH), 44.4 (CH), 48.0 (C), 50.4 (CH), 112.5 (CH), 125.7 (CH), 126.42 (CH), 126.47 (CH), 127.4 (C), 129.6 (CH), 130.1 (CH), 131.9 (C), 132.1 (C), 135.7 (C), 151.05 (C), 151.10 (C), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3544 (w), 3306 (w), 2954 (m), 2919 (m), 2863 (m), 1718 (s), 1585 (w), 1515 (w), 1472 (m), 1436 (m), 1402 (w), 1372 (m), 1342 (m), 1321 (w), 1288 (s), 1259 (m), 1201 (m), 1166 (m), 1115 (w), 1056 (m), 1024 (w), 1009 (m), 952 (w), 923 (w), 902 (w), 831 (m), 819 (s), 802 (m), 761(w), 717 (w), 667 (m), 598 (s), 563 (m). MS (EI, 70 eV): m/z (%) = 402 (100) [M^+], 403 (31), 387 (26), 317 (15), 278 (10), 57 (20), 55 (10), 41 (17). HRMS (EI, 70 eV): calcd. for $C_{28}H_{34}O_2$ [M^+] 402.25533; found 402.25473.

4-(*p*-Methoxyphenyl)-estrone (17d):

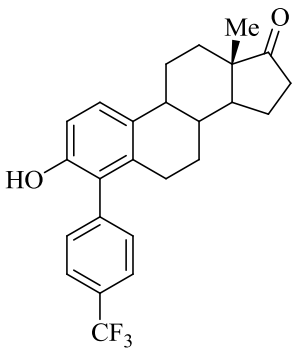


According to the general procedure compound **17d** was isolated as a yellow solid (107 mg, 99%), mp = 97 – 98 °C, $[\alpha]_D$ = +60.0° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.31 – 1.39 (m, 1H, aliphatic), 1.49 – 1.62 (m, 5H, aliphatic), 1.87 – 2.16 (m, 4H, aliphatic), 2.25 – 2.32 (m, 1H, aliphatic), 2.42 – 2.53 (m, 4H, aliphatic), 3.87 (s, 3H, OCH_3), 4.69 (br.s, 1H, OH), 6.85 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 1H, Ar), 7.01 – 7.06 (m, 2H, Ar), 7.16 – 7.26 (m, 3H, Ar + $CDCl_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.6 (CH_2), 28.5 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 55.3 (OCH_3), 112.4 (CH), 114.9 (CH), 115.0 (CH), 125.8 (CH), 127.1 (2C), 131.2 (CH), 131.6 (CH), 131.9 (C), 135.8 (C), 151.2 (C), 159.4 (C), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3534 (w), 3391 (w),

2924 (m), 2856 (w), 1733 (s), 1608 (w), 1587 (w), 1512 (s), 1472 (s), 1454 (m), 1424 (m), 1405 (w), 1373 (w), 1282 (m), 1242 (s), 1174 (s), 1105 (m), 1083 (w), 1031 (s), 1006 (m), 948 (w), 922 (w), 901 (w), 930 (s), 809 (s), 789 (m), 750 (w), 715 (w), 674 (w), 646 (w), 608 (m), 581 (m), 550 (m). MS (EI, 70 eV): m/z (%) = 376 (100) [M^+], 377 (27), 291 (17), 252 (18). HRMS (EI, 70 eV): calcd. for $C_{25}H_{28}O_3$ [M^+] 376.20330; found 376.20304.

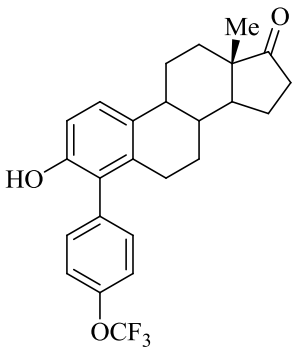
4-(*p*-Trifluoromethylphenyl)-estrone (17e):



According to the general procedure compound **17e** was isolated as a light brown solid (108 mg, 91%), mp = 104 – 105 °C, $[\alpha]_D$ = +85.3° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.33 – 1.40 (m, 1H, aliphatic), 1.53 – 1.59 (m, 5H, aliphatic), 1.89 – 2.16 (m, 4H, aliphatic), 2.26 – 2.37 (m, 1H, aliphatic), 2.44 – 2.54 (m, 4H, aliphatic), 4.59 (br.s, 1H, OH), 6.84 (d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, Ar), 7.26 – 7.29 (m, 1H, Ar + $CDCl_3$), 7.39 – 7.44 (m, 2H, Ar), 7.75 – 7.78 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.4 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 113.1 (CH), 124.1 (q, $^1J_{C\text{-}F}$ = 271.7 Hz, CF_3), 126.2 (m, ^3J not given, 2CH), 126.40 (C), 126.44 (CH), 130.2 (q, $^2J_{C\text{-}F}$ = 32.5 Hz, *C*-CF_3), 130.6 (CH), 130.9 (CH), 132.4 (C), 135.3 (C), 140.0 (C), 150.6 (C), 220.9 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = 62.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3318 (w), 2926 (m), 2861 (w), 1716 (m), 1616 (w), 1587 (w), 1474 (w), 1439 (w), 1403 (w), 1321 (s), 1293 (m), 1208 (w), 1159 (s), 1177 (s), 1104 (s), 1065 (s), 1019 (m), 957 (w), 924 (w), 902 (w), 835 (m), 822 (m), 807 (m), 780 (w), 748 (w), 693 (m), 656 (m), 608 (m). MS (EI, 70 eV): m/z (%) = 414 (100) [M^+], 415 (27), 357 (12), 330 (12), 329 (25), 316 (18), 304 (12), 303 (13), 301 (10), 291 (10), 290 (27), 289 (10), 55 (12), 41 (14). HRMS (EI, 70 eV): calcd. for $C_{25}H_{25}O_2F_3$ [M^+] 414.18012; found 414.17903.

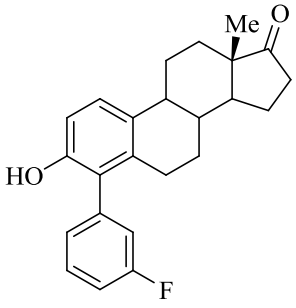
4-(*p*-Trifluoromethoxyphenyl)-estrone (17f):



According to the general procedure compound **17f** was isolated as a light yellow solid (118 mg, 96%), mp = 94 – 95 °C, $[\alpha]_D$ = +83.3° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.33 – 1.39 (m, 1H, aliphatic), 1.49 – 1.63 (m, 5H, aliphatic), 1.88 – 2.16 (m, 4H, aliphatic), 2.25 – 2.33 (m, 1H, aliphatic), 2.42 – 2.54 (m, 4H, aliphatic), 4.57 (br.s, 1H, OH), 6.85 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 1H, Ar), 7.25 – 7.38 (m, 5H, Ar + $CDCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 28.9 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 112.9 (CH), 120.5 (q, $^1J_{C\text{-}F}$ = 257.1 Hz, CF_3), 121.8 (2CH), 126.2 (C), 126.3 (CH), 131.7 (CH), 132.0 (CH), 132.3 (C), 134.4 (C), 135.5 (C), 149.0 (q, $^3J_{C\text{-}F}$ = 1.9 Hz, *C*-OCF_3), 150.8 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = 57.7 (CF_3), 220.9 (C=O). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3556 (w), 3350 (w), 2928 (w), 2861 (w), 1723 (m), 1587 (w), 1509 (w), 1488 (w), 1475 (m), 1454 (w), 1440 (w), 1405 (w), 1374 (w), 1251 (s), 1201 (s), 1154 (s), 1100 (m), 1055 (m), 1009 (m), 950 (w), 923 (m), 902 (w), 812 (m), 693 (w), 675 (w), 642 (m), 581 (m). MS (EI, 70 eV): m/z (%) = 430 (100) [M^+], 431 (26), 346 (12), 345 (30), 332 (15), 320 (10), 319 (11), 306 (23), 69 (15), 55 (10), 41 (11). HRMS (EI, 70 eV): calcd. for $C_{25}H_{25}O_3F_3$ [M^+] 430.17503; found 430.17490.

4-(*m*-Fluorophenyl)-estrone (17g):

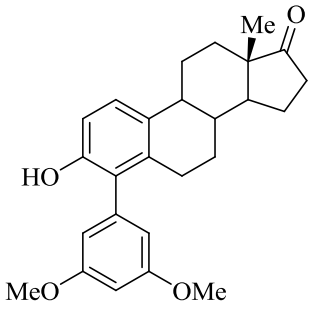


According to the general procedure compound **17g** was isolated as a light yellow solid (96 mg, 92%), mp = 98 – 99 °C, $[\alpha]_D$ = +112.5° (c 1.00, $CHCl_3$). A mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 and 0.93 (s, 3H, CH_3), 1.33 – 1.40 (m, 1H, aliphatic), 1.45 – 1.64 (m, 5H, aliphatic), 1.88 – 2.16 (m, 4H, aliphatic), 2.25 – 2.33 (m, 1H, aliphatic), 2.41 – 2.54 (m, 4H, aliphatic), 4.63 (br.s, 1H, OH), 6.85 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 1H, Ar), 6.97 – 7.16 (m, 3H, Ar), 7.18 (d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, Ar), 7.43 – 7.53 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.13 and 26.15 (CH_2), 26.5 (CH_2), 28.4 and 28.5 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.78 and 37.80 (CH), 44.28 and 44.34 (CH), 48.0 (C), 50.4 (CH), 112.9 (CH), 115.0 and 115.3 (CH), 117.24 (d, $^2J_{C\text{-}F}$ = 26.6 Hz) and 117.52 (d, $^2J_{C\text{-}F}$ = 26.6 Hz) (CH), 125.90 (d, $^2J_{C\text{-}F}$ = 30.4 Hz) and 125.94 (d, $^2J_{C\text{-}F}$ = 30.6 Hz) (CH), 126.25 and 126.29 (CH), 126.41 (C), 131.03 (d, $^3J_{C\text{-}F}$ = 8.5 Hz) and 131.05 (d, $^3J_{C\text{-}F}$ = 8.7 Hz) (CH),

132.17 (C), 135.30 and 135.33 (C), 137.95 (d, $^{3}J_{C\text{-}F}$ = 7.4 Hz) and 137.97 (d, $^{3}J_{C\text{-}F}$ = 7.5 Hz) (C), 150.7 (C), 163.33 (d, $^{1}J_{C\text{-}F}$ = 248.3 Hz) and 163.40 (d, $^{1}J_{C\text{-}F}$ = 248.1 Hz) (C-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.45 and -111.53 (CF), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3550 (w), 3340 (w), 2925 (m), 2859 (w), 1723 (s), 1614 (m), 1580 (s), 1472 (s), 1453 (m), 1437 (m), 1421 (m), 1373 (w), 1343 (w), 1323 (w), 1290 (m), 1274 (m), 1261 (m), 1266 (m), 1199 (m), 1184 (m), 1152 (m), 1097 (w), 1084 (w), 1073 (w), 1055 (m), 1013 (m), 949 (w), 925 (w), 884 (m), 819 (m), 785 (s), 748 (m), 703 (s), 647 (m), 581 (m), 542 (m). MS (EI, 70 eV): m/z (%) = 364 (100) [M^+], 365 (27), 307 (10), 280 (10), 279 (27), 266 (16), 253 (11), 240 (26), 239 (11), 220 (14), 199 (11), 183 (12), 55 (10), 41 (14). HRMS (EI, 70 eV): calcd. for $C_{24}H_{25}O_2F$ [M^+] 364.18331; found 364.18327.

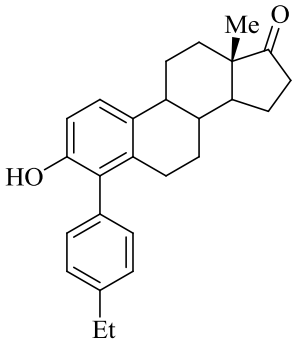
4-(3,5-Dimethoxyphenyl)-estrone (17h):



According to the general procedure compound **17h** was isolated as a light yellow solid (102 mg, 88%), mp = 95 – 96 °C, $[\alpha]_D$ = +90.9° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.33 – 1.40 (m, 1H, aliphatic), 1.49 – 1.65 (m, 5H, aliphatic), 1.88 – 2.16 (m, 4H, aliphatic), 2.25 – 2.34 (m, 1H, aliphatic), 2.41 – 2.60 (m, 4H, aliphatic), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.78 (br.s, 1H, OH), 6.40 – 6.43 (m, 2H, Ar), 6.50 – 6.52 (m, 1H, Ar), 6.85 (d, $^{3}J_{H\text{-}H}$ = 8.6 Hz, 1H, Ar), 7.23 – 7.26 (m, 1H, Ar + $CDCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 28.2 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.9 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 55.4 ($2OCH_3$), 100.3 (CH), 107.5 (CH), 108.0 (CH), 112.6 (CH), 126.0 (CH), 127.5 (C), 131.9 (C), 135.2 (C), 137.3 (C), 150.7 (C), 161.7 (C), 161.8 (C), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3400 (w), 2927 (w), 2858 (w), 1733 (m), 1587 (s), 1452 (m), 1417 (m), 1343 (m), 1278 (m), 1251 (w), 1202 (s), 1150 (s), 1060 (m), 1024 (m), 1014 (m), 945 (w), 924 (m), 817 (m), 787 (m), 704 (m), 581 (m). MS (EI, 70 eV): m/z (%) = 406 (100) [M^+], 407 (27), 321 (17), 282 (12), 281 (10), 55 (11), 41 (12). HRMS (ESI, 70 eV): calcd. for $C_{26}H_{30}O_4$ [M^+] 406.21386; found 406.21368.

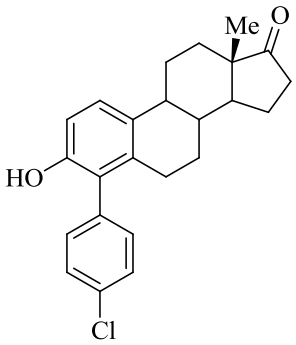
4-(*p*-Ethylphenyl)-estrone (17i):



According to the general procedure compound **17i** was isolated as a yellow solid (106 mg, 99%), mp = 110 – 111 °C, $[\alpha]_D$ = +78.5° (c 1.02, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.31 (t, $^3J_{H\text{-}H}$ = 7.6 Hz, 3H, CH_2CH_3), 1.28 – 1.35 (m, 1H, aliphatic), 1.49 – 1.61 (m, 5H, aliphatic), 1.87 – 2.16 (m, 4H, aliphatic), 2.26 – 2.34 (m, 1H, aliphatic), 2.42 – 2.53 (m, 4H, aliphatic), 2.73 (q, $^3J_{H\text{-}H}$ = 7.6 Hz, 2H, CH_2CH_3), 4.59 (br.s, 1H, OH), 6.85 (d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, Ar), 7.16 – 7.21 (m, 2H, Ar), 7.23 – 7.26 (m, 1H, Ar + $CDCl_3$), 7.32 – 7.36 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 15.4 (CH_2CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 28.5 (CH_2), 28.6 (CH_2CH_3), 31.6 (CH_2), 35.9 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 112.5 (CH), 125.7 (CH), 127.5 (C), 129.0 (CH), 129.03 (CH), 129.9 (CH), 130.4 (CH), 131.9 (C), 132.4 (C), 135.6 (C), 144.2 (C), 151.0 (C), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3540 (w), 3369 (w), 2926 (m), 2857 (m), 1734 (s), 1587 (m), 1513 (w), 1472 (s), 1453 (m), 1438 (m), 1404 (m), 1372 (m), 1342 (w), 1322 (w), 1271 (s), 1259 (s), 1112 (w), 1083 (m), 1054 (m), 1008 (m), 950 (w), 923 (m), 901 (w), 830 (s), 821 (s), 806 (s), 733 (m), 673 (m), 646 (m), 581 (m). MS (EI, 70 eV): m/z (%) = 374 (100) [M^+], 375 (30), 289 (22), 276 (11), 250 (20). HRMS (EI, 70 eV): calcd. for $C_{26}H_{30}O_2$ [M^+] 374.22403; found 374.22323.

4-(*p*-Chlorophenyl)-estrone (17j):

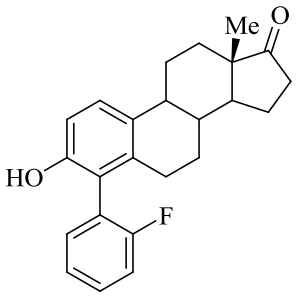


According to the general procedure compound **17j** was isolated as a light yellow solid (95 mg, 87%), mp = 109 – 110 °C, $[\alpha]_D$ = +71.8° (c 1.01, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.31 – 1.39 (m, 1H, aliphatic), 1.49 – 1.61 (m, 5H, aliphatic), 1.87 – 2.16 (m, 4H, aliphatic), 2.25 – 2.31 (m, 1H, aliphatic), 2.41 – 2.54 (m, 4H, aliphatic), 4.57 (br.s, 1H, OH), 6.84 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 1H, Ar), 7.18 – 7.27 (m, 3H, Ar + $CDCl_3$), 7.46 – 7.51 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.8 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 112.8 (CH), 126.2 (CH), 126.4 (C), 129.7 (2CH), 131.5 (CH), 131.9 (CH), 132.2 (C), 134.1 (C), 134.2 (C), 135.4 (C), 150.8 (C), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3543 (w), 3344 (w), 2926 (m), 2858 (w), 1723 (s), 1586 (m), 1473 (s), 1453 (m), 1438 (m),

1424 (w), 1392 (w), 1373 (w), 1344 (w), 1285 (m), 1259 (m), 1207 (m), 1166 (m), 1088 (s), 1055 (m), 1014 (m), 949 (w), 923 (w), 901 (w), 820 (s), 803 (s), 769 (w), 758 (w), 716 (m), 660 (w), 576 (m). MS (EI, 70 eV): m/z (%) = 380 (100) [M^+], 382 (37), 381 (26), 297 (11), 296 (10), 295 (28), 282 (18), 270 (10), 269 (12), 256 (26), 215 (13), 202 (13), 189 (11), 178 (10), 165 (11), 67 (10), 55 (16), 41 (17), 39 (10), 29 (10). HRMS (EI, 70 eV): calcd. for $C_{24}H_{25}O_2Cl$[M^+] 380.15376; found 380.15281; calcd. for $C_{24}H_{25}O_2{}^{37}Cl$[M^+] 382.15081; found 382.15141.

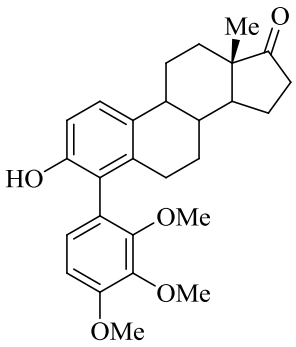
4-(*o*-Fluorophenyl)-estrone (17k):



According to the general procedure compound **17k** was isolated as a brown solid (98 mg, 94%), mp = 95 – 96 °C, $[\alpha]_D$ = +82.1° (c 1.44, $CHCl_3$). A mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 and 0.93 (2s, 3H, CH_3), 1.33 – 1.42 (m, 1H, aliphatic), 1.50 – 1.66 (m, 5H, aliphatic), 1.88 – 2.28 (m, 4H, aliphatic), 2.25 – 2.35 (m, 1H, aliphatic), 2.40 – 2.63 (m, 4H, aliphatic), 4.60 (br.s, 1H, OH), 6.85 (d, $^3J_{H-H}$ = 8.6 Hz, 1H, Ar), 7.19 – 7.29 (m, 4H, Ar + $CDCl_3$), 7.40 – 7.47 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 and 13.9 (CH_3), 21.6 (CH_2), 26.0 and 26.1 (CH_2), 26.5 (CH_2), 27.62 and 28.2 (CH_2), 31.64 and 31.66 (CH_2), 35.9 (CH_2), 37.73 and 37.83 (CH), 44.21 and 44.35 (CH), 48.00 and 48.03 (C), 50.44 and 50.48 (CH), 112.85 and 112.87 (CH), 116.48 (d, $^2J_{C-F}$ = 22.2) and 116.57 (d, $^2J_{C-F}$ = 22.3) (CH), 121.24 and 121.31 (C), 122.95 (d, $^2J_{C-F}$ = 17.8 Hz) and 122.98 (d, $^2J_{C-F}$ = 17.6 Hz) (C), 124.95 – 125.02 (several signals, CH, C), 126.6 (CH), 130.39 (d, $^3J_{C-F}$ = 8.0 Hz) and 130.41 (d, $^3J_{C-F}$ = 8.1 Hz) (CH), 132.1 – 132.4 (several signals, CH), 136.21 and 136.37 (C), 151.06 and 151.16 (C), 160.1 (d, $^1J_{C-F}$ = 246.6 Hz) and 160.4 (2d, $^1J_{C-F}$ = 246.9 Hz) (C-F), 220.97 and 221.01 (C=O). ^{19}F NMR (75 MHz, $CDCl_3$): δ = -112.8 and -112.5 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3342 (w), 2925 (m), 2858 (w), 1721 (s), 1588 (w), 1474 (m), 1451 (m), 1345 (w), 1277 (m), 1256 (m), 1214 (m), 1168 (m), 1110 (w), 1083 (w), 1056 (m), 1032 (w), 1009 (m), 948 (w), 923 (w), 902 (w), 818 (s), 798 (w), 755 (s), 684 (w), 637 (m), 582 (m), 556 (m). MS (EI, 70 eV): m/z (%) = 364 (100) [M^+], 365 (29), 280 (11), 279 (30), 266 (16), 254 (10), 253 (14), 240 (32), 239 (14), 55 (10), 41 (11). HRMS (EI, 70 eV): calcd. for $C_{24}H_{25}O_2F$ [M^+] 364.18331; found 364.18433.

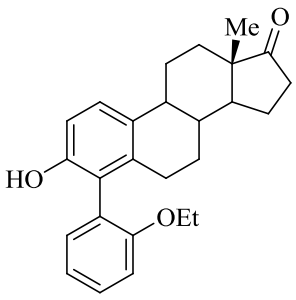
4-(2,3,4-Trimethoxyphenyl)-estrone (17l):



According to the general procedure compound **17l** was isolated as a light yellow solid (84 mg, 67%), mp = 121 – 122 °C, $[\alpha]_D$ = +82.5° (c 1.00, $CHCl_3$). A mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 and 0.89 (2s, 3H, CH_3), 1.39 – 1.69 (m, 6H, aliphatic), 1.81 – 1.99 (m, 3H, aliphatic), 2.05 – 2.13 (m, 1H, aliphatic), 2.24 – 2.29 (m, 1H, aliphatic), 2.34 – 2.52 (m, 4H, aliphatic), 3.58 and 3.60 (2s, 3H, OCH_3), 3.81 and 3.82 (2s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.68 – 6.76 (m, 2H, Ar), 6.83 – 6.88 (m, 1H, Ar), 7.14 (d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, Ar), 8.800 and 8.803 (2s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 and 13.9 (CH_3), 21.5 (CH_2), 25.9 and 26.1 (CH_2), 26.5 and 26.6 (CH_2), 27.5 and 28.4 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.8 and 37.9 (CH), 44.3 (CH), 48.0 (C), 50.45 and 50.53 (CH), 56.0 (OCH_3), 61.1 (OCH_3), 61.2 (OCH_3), 108.1 and 108.2 (CH), 112.3 and 112.6 (CH), 121.25 and 121.33 (C), 123.8 and 123.9 (C), 125.6 and 125.9 (CH), 125.90 and 125.93 (CH), 131.9 and 132.1 (C), 136.3 and 136.6 (C), 142.9 and 143.1 (C), 151.1 and 151.2 (C), 152.0 (C), 154.0 (C), C=O not given. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3415 (w), 2923 (m), 2854 (w), 1725 (s), 1588 (w), 1461 (s), 1408 (m), 1375 (w), 1271 (s), 1232 (m), 1209 (m), 1164 (m), 1119 (m), 1093 (s), 1071 (s), 1045 (m), 1008 (s), 949 (w), 922 (m), 878 (w), 819 (m), 795 (m), 743 (m), 692 (w), 649 (w), 581 (w). MS (EI, 70 eV): m/z (%) = 436 (100) [M^+], 437 (27). HRMS (EI, 70 eV): calcd. for $C_{27}H_{32}O_5$[M^+] 436.22443; found 436.22402.

4-(*o*-Ethoxyphenyl)-estrone (17m):



According to the general procedure compound **17m** was isolated as a light yellow solid (88 mg, 79%), mp = 144 – 145 °C, $[\alpha]_D$ = +77.7° (c 2.31, $CHCl_3$). A mixture of diastereomers.

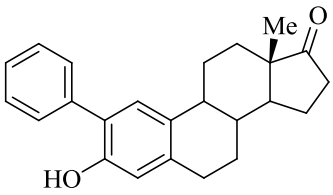
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 and 0.93 (2s, 3H, CH_3), 1.26 and 1.27 (2t, $^3J_{H\text{-}H}$ = 7.0 Hz, 3H, $2CH_2CH_3$), 1.32 – 1.40 (m, 1H, aliphatic), 1.47 – 1.61 (m, 5H, aliphatic), 1.86 – 2.16 (m, 4H, aliphatic), 2.25 – 2.37 (m, 1H, aliphatic), 2.42 – 2.53 (m, 4H, aliphatic), 4.05 (q, $^3J_{H\text{-}H}$ = 7.0 Hz, 3H, $2CH_2CH_3$), 4.67 and 4.72 (2br.s, 1H, OH), 6.84 and 6.85 (2d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, Ar), 7.00 – 7.09 (m, 2H, Ar), 7.14 – 7.18 (m, 1H, Ar), 7.22 – 7.26 (m, 1H, Ar + $CDCl_3$), 7.36 – 7.42 (m, 1H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.84 and 13.87 (CH_3), 14.6 and 14.7 (CH_3), 21.55 and 21.57 (CH_2), 25.9 and 26.1 (CH_2), 26.5 and 26.6 (CH_2),

27.2 and 28.3 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 37.8 and 37.9 (CH), 44.2 and 44.4 (CH), 47.99 and 48.01 (C), 50.5 and 50.6 (CH), 63.8 and 64.0 (CH_2CH_3), 112.3 and 112.6 (CH), 112.99 and 113.07 (CH), 121.3 and 121.4 (CH), 124.1 and 124.2 (C), 124.2 and 124.4 (C), 125.5 and 125.7 (CH), 129.78 and 129.83 (CH), 131.6 and 131.8 (C), 132.0 and 132.3 (CH), 136.0 and 136.3 (C), 150.9 and 151.1 (C), 156.3 and 156.9 (C), 220.6 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3397 (w), 2925 (w), 2861 (w), 1733 (s), 1590 (w), 1472 (m), 1447 (s), 1390 (w), 1372 (w), 1341 (m), 1278 (m), 1257 (m), 1228 (s), 1160 (m), 1123 (m), 1083 (m), 1040 (s), 1008 (m), 947 (w), 922 (m), 900 (w), 808 (m), 753 (s), 714 (w), 685 (m), 641 (m), 602 (w), 581 (m). MS (EI, 70 eV): m/z (%) = 390 (100) [M^+], 391 (28), 305 (17), 266 (12), 29 (25). HRMS (ESI, 70 eV): calcd. for $C_{26}H_{30}O_3$ [M^+] 390.21895; found 390.21851.

General procedure for the synthesis of compounds 18a-h:

2-Bromoestrone (**16b**) (100 mg, 0.286 mmol), boronic acid (1.5 equiv.), $Pd(PPh_3)_4$ (17.0 mg, 0.05 equiv.), RuPhos (6.7 mg, 0.05 equiv.), K_2CO_3 (79.1 mg, 2.0 equiv.) and dioxane (4 ml) were added in a pressure tube under argon atmosphere. The mixture was stirred 16 h at 101°C. The solvent was evaporated in vacuo. The residue was purified by column chromatography (EA : Heptane = 1:5).

2-Phenyl-estrone (18a):

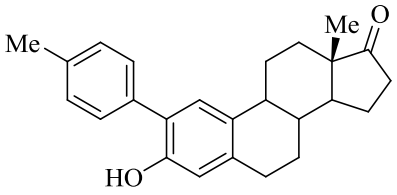


According to the general procedure compound **18a** was isolated as a white solid (74 mg, 75%), mp = 197 – 198 °C (lit.[99] 169 °C), $[\alpha]_D$ = +161.1° (c 1.00, $CHCl_3$) (lit.[99] $[\alpha]_D$ = +112.0° (c 1.00, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.42 – 1.70 (m, 6H, aliphatic), 1.93 – 2.20 (m, 4H, aliphatic), 2.25 – 2.35 (m, 1H, aliphatic), 2.37 – 2.57 (m, 2H, aliphatic), 2.91 – 2.96 (m, 2H, aliphatic), 5.17 (br.s, 1H, OH), 6.75 (s, 1H, Ar), 7.17 (s, 1H, Ar), 7.34 – 7.41 (m, 1H, Ar), 7.46 – 7.48 (m, 4H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 38.4 (CH), 44.0 (CH), 48.0 (C), 50.4 (CH), 115.7 (CH), 125.8 (C), 127.2 (CH), 127.6 (CH), 129.1 (2CH), 129.2 (2CH), 132.2 (C), 137.4 (C), 137.7 (C), 150.4 (C), 221.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3329 (w), 2928 (m), 2859 (w), 1723 (s), 1614 (w), 1513 (w), 1485 (m), 1451 (m), 1409 (s), 1372 (w), 1341

(w), 1293 (m), 1256 (m), 1237 (m), 1200 (m), 1157 (m), 1082 (w), 1054 (m), 1033 (w), 986 (w), 970 (w), 948 (w), 922 (w), 893 (m), 875 (w), 827 (w), 769 (s), 723 (w), 698 (s), 651 (m), 589 (m), 564 (m). MS (EI, 70 eV): m/z (%) = 346 (100) [M^+], 347 (23), 261 (25), 248 (13), 222 (23), 221 (11), 202 (13), 178 (11), 165 (12), 55 (10), 41 (12). HRMS (ESI, 70 eV): calcd. for $C_{24}H_{26}O_2$ [M^+] 346.19273; found 346.19267.

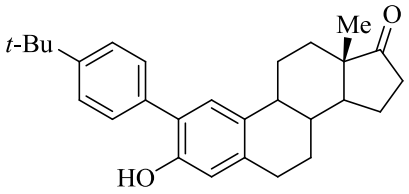
2-(*p*-Tolyl)-estrone (18b):



According to the general procedure compound **18b** was isolated as a white solid (77 mg, 75%), mp = 201 – 202 °C, $[\alpha]_D$ = +160.5° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.47 – 1.65 (m, 6H, aliphatic), 1.93 – 2.19 (m, 4H, aliphatic), 2.25 – 2.33 (m, 1H, aliphatic), 2.38 – 2.56 (m, 2H, aliphatic), 2.41 (s, 3H, CH_3), 2.91 – 2.95 (m, 2H, aliphatic), 5.26 (br.s, 1H, OH), 6.74 (s, 1H, Ar), 7.16 (s, 1H, Ar), 7.26 – 7.30 (m, 2H, Ar + $CDCl_3$), 7.36 (d, $^3J_{H\text{-}H}$ = 7.9 Hz, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.2 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.6 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 38.4 (CH), 44.0 (C), 48.0 (CH), 50.4 (CH), 115.6 (CH), 125.8 (C), 127.2 (CH), 128.9 (2CH), 129.9 (2CH), 132.1 (C), 134.4 (C), 137.4 (C), 137.5 (C), 150.5 (C), 221.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3342 (w), 2925 (m), 2854 (w), 1723 (s), 1620 (w), 1571 (w), 1558 (w), 1518 (w), 1491 (s), 1454 (m), 1402 (m), 1374 (w), 1338 (m), 1293 (m), 1277 (m), 1237 (s), 1172 (m), 1138 (m), 1110 (w), 1082 (w), 1051 (m), 1024 (m), 1011 (m), 969 (w), 948 (w), 923 (w), 891 (m), 870 (m), 853 (m), 822 (m), 793 (m), 731 (m), 568 (m). MS (EI, 70 eV): m/z (%) = 360 (100) [M^+], 361 (26), 275 (19), 236 (18). HRMS (ESI, 70 eV): calcd. for $C_{25}H_{28}O_2$ [M^+] 360.20838; found 360.20759.

2-(*p-tert*-Butylphenyl)-estrone (18c):

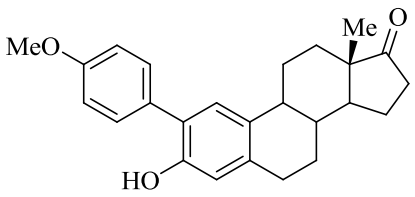


According to the general procedure compound **18c** was isolated as a white solid (94 mg, 82%), mp = 229 – 230 °C, $[\alpha]_D$ = +129.6° (c 1.00, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.37 (s, 9H, $C(CH_3)_3$), 1.47 – 1.66 (m, 6H, aliphatic), 1.92 – 2.19 (m, 4H, aliphatic), 2.24 – 2.34 (m, 1H, aliphatic), 2.34 – 2.57 (m, 2H, aliphatic), 2.90 – 2.95 (m, 2H, aliphatic), 5.17 (br.s, 1H, OH), 6.74 (s, 1H, Ar), 7.17 (s, 1H, Ar), 7.37 – 7.41 (m, 2H, Ar), 7.48 – 7.52 (m, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.0 (CH_2),

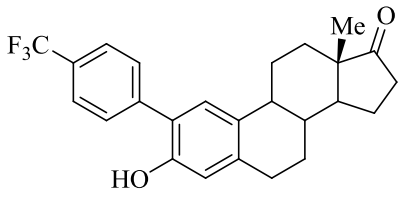
26.6 (CH_2), 29.3 (CH_2), 31.3 ($C(CH_3)_3$), 31.6 (CH_2), 34.6 ($C(CH_3)_3$), 35.9 (CH_2), 38.4 (CH), 44.0 (CH), 48.0 (C), 50.4 (CH), 115.6 (CH), 125.7 (C), 126.2 (2CH), 127.2 (CH), 128.7 (2CH), 132.1 (C), 134.3 (C), 137.5 (C), 150.5 (C), 150.7 (C), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3347 (w), 2960 (m), 2920 (m), 2864 (w), 1723 (s), 1613 (w), 1584 (w), 1519 (w), 1500 (m), 1465 (w), 1453 (w), 1423 (m), 1395 (m), 1361 (m), 1342 (m), 1293 (m), 1257 (m), 1193 (s), 1157 (m), 1121 (w), 1084 (w), 1055 (m), 1024 (w), 1014 (w), 986 (w), 970 (w), 949 (w), 922 (w), 896 (m), 876 (m), 838 (s), 828 (s), 801 (w), 752 (s), 715 (m), 665 (m), 623 (m), 605 (m), 585 (m), 598 (s). MS (EI, 70 eV): m/z (%) = 402 (100) [M^+], 403 (32), 388 (26), 287 (86), 57 (14), 41 (14). HRMS (ESI, 70 eV): calcd. for $C_{28}H_{34}O_2$ [M^+] 402.25533; found 402.25513.

2-(*p*-Methoxyphenyl)-estrone (18d):



According to the general procedure compound **18d** was isolated as a light yellow solid (86 mg, 80%), mp = 183 – 184 °C, $[\alpha]_D$ = +137.0° (c 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.47 – 1.64 (m, 6H, aliphatic), 1.92 – 2.19 (m, 4H, aliphatic), 2.22 – 2.32 (m, 1H, aliphatic), 2.37 – 2.57 (m, 2H, aliphatic), 2.89 – 2.94 (m, 2H, aliphatic), 3.85 (s, 3H, OCH_3), 5.15 (br.s, 1H, OH), 6.73 (s, 1H, Ar), 6.97 – 7.03 (m, 2H, Ar), 7.14 (s, 1H, Ar), 7.35 – 7.41 (m, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.2 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 38.4 (CH), 44.0 (CH), 48.0 (C), 50.4 (CH), 55.4 (OCH_3), 114.6 (2CH), 115.6 (CH), 125.5 (C), 127.2 (CH), 129.5 (C), 130.2 (2CH), 132.1 (C), 137.3 (C), 150.5 (C), 159.2 (C), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3350 (w), 2925 (m), 2861 (w), 1720 (s), 1609 (m), 1571 (w), 1519 (w), 1501 (s), 1465 (w), 1453 (m), 1428 (m), 1400 (m), 1374 (w), 1341 (w), 1295 (m), 1242 (s), 1177 (s), 1110 (w), 1085 (w), 1054 (w), 1033 (s), 988 (w), 970 (w), 949 (w), 922 (w), 895 (w), 874 (w), 828 (s), 805 (m), 793 (w), 744 (w), 716 (w), 627 (m), 567 (m). MS (EI, 70 eV): m/z (%) = 376 (100) [M^+], 377 (28), 291 (11), 252 (11). HRMS (ESI, 70 eV): calcd. for $C_{25}H_{28}O_3$ [M^+] 376.20330; found 376.20276.

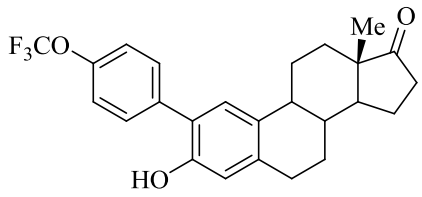
2-(*p*-Trifluoromethylphenyl)-estrone (18e):



According to the general procedure compound **18e** was isolated as a white solid (85 mg, 72%), mp = 250 – 251 °C, $[\alpha]_D$ = +123.6° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.48 – 1.65 (m, 6H, aliphatic), 1.94 – 2.19 (m, 4H, aliphatic), 2.27 – 2.34 (m, 1H, aliphatic), 2.39 – 2.57 (m, 2H, aliphatic), 2.91 – 2.94 (m, 2H, aliphatic), 5.18 (br.s, 1H, OH), 6.73 (s, 1H, Ar), 7.18 (s, 1H, Ar), 7.62 (d, $^3J_{H-H}$ = 8.1 Hz, 2H, Ar), 7.70 (d, $^3J_{H-H}$ = 8.1 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 35.9 (CH_2), 38.3 (CH), 43.9 (CH), 48.0 (C), 50.4 (CH), 116.2 (CH), 124.6 (C), 124.2 (q, $^1J_{C-F}$ = 272.0 Hz, CF_3), 125.7 (q, $^3J_{C-F}$ = 3.7 Hz, 2CH), 127.4 (CH), 129.41 (q, $^2J_{C-F}$ = 32.6 Hz, *C*-CF3), 129.48 (2CH), 132.7 (C), 138.5 (C), 141.6 (C), 150.4 (C), 221.2 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.5 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3365 (w), 2937 (w), 2877 (w), 1722 (s), 1612 (m), 1524 (w), 1505 (w), 1469 (w), 1429 (m), 1396 (m), 1371 (w), 1324 (s), 1289 (m), 1259 (m), 1200 (m), 1158 (s), 1117 (s), 1109 (s), 1069 (s), 1013 (m), 986 (w), 965 (w), 948 (w), 923 (w), 902 (m), 881 (m), 840 (s), 739 (m), 724 (m), 704 (m), 654 (s), 599 (m), 587 (m), 570 (m). MS (EI, 70 eV): m/z (%) = 414 (100) [M^+], 415 (28), 357 (12), 330 (10), 329 (23), 316 (17), 304 (11), 303 (14), 301 (12), 290 (22), 289 (12), 55 (12), 41 (13). HRMS (ESI, 70 eV): calcd. for $C_{25}H_{25}O_2F_3$ [M^+] 414.18012; found 414.17980.

2-(*p*-Trifluoromethoxyphenyl)-estrone (18f):

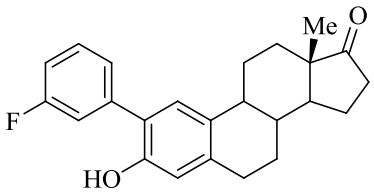


According to the general procedure compound **18f** was isolated as a white solid (95 mg, 77%), mp = 109 – 110 °C, $[\alpha]_D$ = +122.2° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.47 – 1.64 (m, 6H, aliphatic), 1.93 – 2.19 (m, 4H, aliphatic), 2.25 – 2.33 (m, 1H, aliphatic), 2.38 – 2.56 (m, 2H, aliphatic), 2.90 – 2.94 (m, 2H, aliphatic), 5.06 (br.s, 1H, OH), 6.72 (s, 1H, Ar), 7.15 (s, 1H, Ar), 7.30 (d, $^3J_{H-H}$ = 8.1 Hz, 2H, Ar), 7.48 – 7.53 (m, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 35.9 (CH_2), 38.3 (CH), 43.9 (CH), 48.0 (C), 50.4 (CH), 116.0 (CH), 120.5 (q, $^1J_{C-F}$ = 257.5 Hz, CF_3), 121.4 (2CH), 124.6 (C), 127.4 (CH), 130.6 (2CH), 132.5 (C), 136.4 (C), 138.1 (C), 148.5 (q, $^3J_{C-F}$ = 2.3 Hz, *C*-OCF_3), 150.3 (C), 220.9 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -57.8 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3334 (w), 2924 (m), 2860 (w), 1721

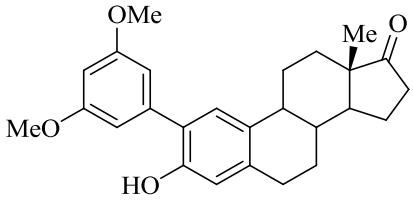
(s), 1615 (w), 1499 (m), 1453 (w), 1430 (m), 1398 (m), 1375 (w), 1341 (w), 1295 (m), 1249 (s), 1202 (s), 1155 (s), 1106 (m), 1085 (m), 1054 (m), 1018 (m), 921 (m), 896 (m), 870 (m), 851 (m), 829 (m), 810 (m), 650 (m), 577 (m). MS (EI, 70 eV): m/z (%) = 430 (100) [M^+], 431 (24), 346 (10), 345 (21), 332 (14), 319 (10), 306 (19), 69 (19), 55 (10). HRMS (ESI, 70 eV): calcd. for $C_{25}H_{25}O_3F_3$ [M^+] 430.17503; found 430.17478.

2-(*m*-Fluorophenyl)-estrone (18g):



According to the general procedure compound **18g** was isolated as a light yellow solid (82 mg, 79%), mp = 132 – 133 °C, $[\alpha]_D$ = +129.8° (c 1.00, $CHCl_3$).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.48 – 1.64 (m, 6H, aliphatic), 1.94 – 2.19 (m, 4H, aliphatic), 2.25 – 2.39 (m, 1H, aliphatic), 2.39 – 2.56 (m, 2H, aliphatic), 2.90 – 2.94 (m, 2H, aliphatic), 5.20 (br.s, 1H, OH), 6.73 (s, 1H, Ar), 7.03 – 7.09 (m, 1H, Ar), 7.16 – 7.27 (m, 3H, Ar + $CDCl_3$), 7.38 – 7.46 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 35.9 (CH_2), 38.3 (CH), 43.9 (CH), 48.0 (C), 50.4 (CH), 114.4 (d, $^2J_{C\text{-}F}$ = 21.0 Hz, CH), 116.0 (CH), 116.2 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, CH), 124.65 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, CH), 124.7 (d, $^4J_{C\text{-}F}$ = 2.0 Hz, C), 127.2 (CH), 130.5 (d, $^3J_{C\text{-}F}$ = 8.5 Hz, CH), 132.4 (C), 138.2 (C), 139.9 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, C), 150.3 (C), 163.1 (d, $^1J_{C\text{-}F}$ = 247.0 Hz, C-F), 221.2 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -112.1 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3348 (w), 2921 (m), 2858 (w), 1721 (s), 1612 (m), 1579 (m), 1511 (w), 1482 (m), 1453 (m), 1402 (s), 1375 (m), 1339 (m), 1297 (m), 1276 (m), 1254 (s), 1211 (m), 1154 (m), 1133 (w), 1084 (w), 1054 (w), 1012 (m), 960 (w), 924 (w), 899 (w), 874 (s), 824 (w), 782 (s), 730 (m), 692 (s), 654 (m), 579 (m). MS (EI, 70 eV): m/z (%) = 364 (100) [M^+], 365 (25), 279 (22), 266 (17), 253 (12), 251 (12), 240 (19), 239 (11), 220 (10), 55 (11), 41 (14). HRMS (ESI, 70 eV): calcd. for $C_{24}H_{25}O_2F$ [M^+] 364.18331; found 364.18303.

2-(3,5-Dimethoxyphenyl)-estrone (18h):



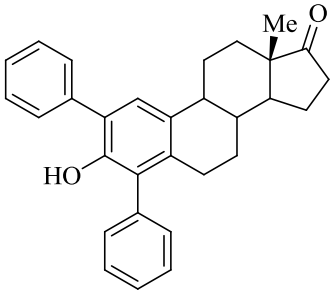
According to the general procedure compound **18h** was isolated as a light yellow solid (116 mg, 84%), mp = 115 – 116 °C, $[\alpha]_D$ = +161.6° (c 1.00, $CHCl_3$).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.47

– 1.64 (m, 6H, aliphatic), 1.93 – 2.18 (m, 4H, aliphatic), 2.25 – 2.33 (m, 1H, aliphatic), 2.37 – 2.56 (m, 2H, aliphatic), 2.90 – 2.94 (m, 2H, aliphatic), 3.82 (s, 6H, $2OCH_3$), 5.32 (br.s, 1H, OH), 6.48 (pt, $^4J_{H\text{-}H}$ = 2.3 Hz, 1H, Ar), 6.57 (d, $^4J_{H\text{-}H}$ = 2.3 Hz, 2H, Ar), 6.74 (s, 1H, Ar), 7.17 (s, 1H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.6 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 29.3 (CH_2), 31.5 (CH_2), 35.9 (CH_2), 38.4 (CH), 43.9 (CH), 48.0 (C), 50.4 (CH), 55.4 ($2OCH_3$), 99.7 (CH), 106.9 (2CH), 115.6 (CH), 125.6 (C), 126.8 (CH), 132.1 (C), 137.9 (C), 139.3 (C), 150.3 (C), 161.5 (2C), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3369 (w), 2924 (m), 2856 (w), 1720 (s), 1591 (s), 1504 (w), 1453 (m), 1399 (s), 1372 (w), 1341 (m), 1255 (m), 1202 (s), 1192 (s), 1149 (s), 1057 (s), 1007 (m), 959 (w), 925 (w), 895 (w), 872 (m), 833 (s), 791 (m), 721 (w), 696 (m), 582 (m). MS (EI, 70 eV): m/z (%) = 406 (100) [M^+], 407 (28), 321 (11), 282 (10). HRMS (ESI, 70 eV): calcd. for $C_{26}H_{30}O_4$ [M^+] 406.21386; found 406.21387.

General procedure for the synthesis of compounds 19a-n:

2,4-Dibromoestrone (**16c**) (100 mg, 0.234 mmol), boronic acid (3 equiv.), $Pd(PPh_3)_4$ (13.5 mg, 0.05 equiv.), RuPhos (5.5 mg, 0.05 equiv.), K_2CO_3 (129.4 mg, 4.0 equiv.) and dioxane (4 ml) were added in a pressure tube under argon atmosphere. The mixture was stirred 40 h (or 72 h) at 101 °C. The solvent was evaporated in vacuo. The residue was purified by column chromatography (EA : Heptane = 1:4).

2,4-Diphenyl-estrone (19a):

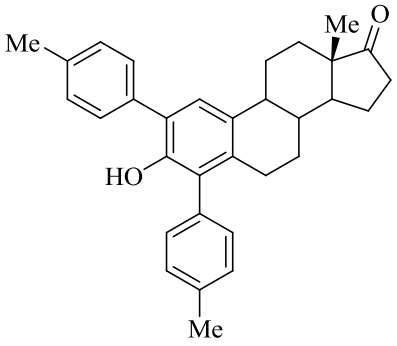


According to the general procedure compound **19a** was isolated as a light yellow solid (98 mg, 99%), mp = 110 – 111 °C (lit.[105] 118 °C), $[\alpha]_D$ = +81.3° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3), 1.38 – 1.67 (m, 6H, aliphatic), 1.91 – 2.20 (m, 4H, aliphatic), 2.33 – 2.41 (m, 1H, aliphatic), 2.46 – 2.57 (m, 4H, aliphatic), 4.84 (s, 1H, OH), 7.31 – 7.37 (m, 4H, Ar), 7.42 – 7.47 (m, 3H, Ar), 7.50 – 7.60 (m, 4H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.9 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 125.8 (C), 127.0 (CH), 127.2 (CH), 128.1 (CH), 128.2 (C), 128.5 (2CH), 129.3 (2CH), 129.4 (2CH), 130.1 (CH), 130.4 (CH), 132.1 (C), 135.1 (C), 135.9 (C), 138.2 (C), 147.7 (C), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3530 (w), 2922

(m), 2856 (w), 1734 (s), 1601 (w), 1496 (w), 1461 m), 1438 (m), 1410 (m), 1372 (w), 1339 (w), 1310 (w), 1257 (m), 1230 (m), 1145 (m), 1083 (w), 1056 (w), 1031 (m), 1009 (w), 952 (w), 920 (w), 890 (w), 821 (w), 778 (m), 755 (m), 699 (s), 641 (w), 620 (w), 587 (m), 562 (w). MS (EI, 70 eV): m/z (%) = 422 (100) [M^+], 423 (40), 337 (14), 298 (13), 265 (13), 41 (12). HRMS (ESI, 70 eV): calcd. for $C_{30}H_{30}O_2$ [M^+] 422.22403; found 422.22350.

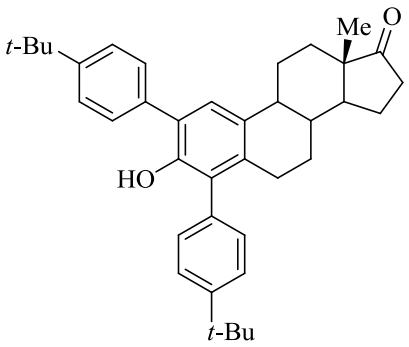
2,4-Di-(*p*-tolyl)-estrone (19b):



According to the general procedure compound **19b** was isolated as a light yellow solid (96 mg, 91%), mp = 134 – 135 °C, $[\alpha]_D$ = +72.2° (c 1.02, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.46 – 1.64 (m, 5H, aliphatic), 1.91 – 2.17 (m, 4H, aliphatic), 2.40 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.27 – 2.57 (m, 6H, aliphatic), 4.87 (s, 1H, OH), 7.19 – 7.34 (m, 7H, Ar + $CDCl_3$), 7.47 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 21.6 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.9 (CH), 44.4 (CH), 48.0 (C), 50.4 (CH), 125.6 (C), 126.8 (CH), 128.0 (C), 129.1 (2CH), 129.2 (2CH), 129.9 (CH), 130.09 (CH), 130.10 (CH), 130.2 (CH), 131.9 (C), 132.7 (C), 135.0 (C), 135.3 (C), 136.8 (C), 137.7 (C), 147.9 (C), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3526 (w), 2921 (m), 2860 (m), 1737 (s), 1605 (w), 1512 (m), 1454 (s), 1426 (m), 1397 (m), 1373 (m), 1339 (m), 1308 (w), 1256 (m), 1232 (m), 1208 (m), 1145 (m), 1110 (m), 1083 (m), 1055 (m), 1041 (m), 1022 (m), 1009 (m), 969 (w), 952 (w), 925 (w), 891 (w), 818 (s), 805 (s), 767 (m), 722 (m), 666 (m), 581 (w), 546 (m), 530 (m). MS (EI, 70 eV): m/z (%) = 450 (100) [M^+], 451 (38), 365 (9), 326 (9), 285 (8). HRMS (ESI, 70 eV): calcd. for $C_{32}H_{34}O_2$ [M^+] 450.25533; found 450.25665.

2,4-Di-(*p*-*tert*-butylphenyl)-estrone (19c):

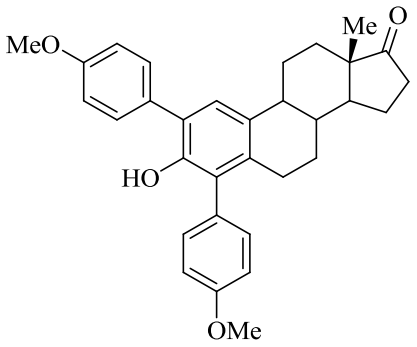


According to the general procedure compound **19c** was isolated as a yellow solid (106 mg, 85%), mp = 141 – 142 °C, $[\alpha]_D$ = +66.1° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.36 (s, 9H, $C(CH_3)_3$), 1.40 (s, 9H, $C(CH_3)_3$), 1.50 – 1.64 (m, 6H, aliphatic), 1.95 – 2.16 (m, 4H, aliphatic), 2.33 – 2.39

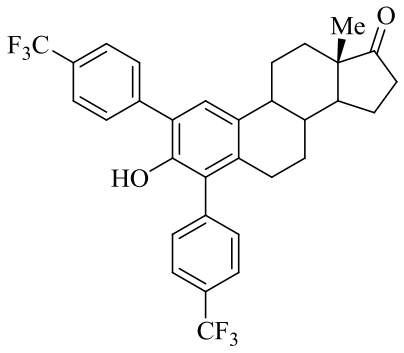
(m, 1H, aliphatic), 2.45 – 2.54 (m, 4H, aliphatic), 4.91 (s, 1H, OH), 7.23 – 7.25 (m, 2H, Ar + $CDCl_3$), 7.31 (s, 1H, Ar), 7.43 – 7.53 (m, 6H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.6 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.6 (CH_2), 31.4 (2C(CH_3)$_3$), 31.6 (CH_2), 34.5 (C(CH_3)$_3$), 34.7 (C(CH_3)$_3$), 35.9 (CH_2), 37.9 (CH), 44.4 (CH), 48.0 (C), 50,4 (CH), 114.7 (CH), 125.4 (CH), 125.5 (C), 126.25 (CH), 126.30 (CH), 126.35 (CH), 126.8 (CH), 128.0 (C), 128.9 (CH), 129.6 (CH), 130.0 (CH), 131.9 (C), 132.6 (C), 135.0 (C), 135.3 (C), 148.0 (C), 149.9 (C), 150.9 (C), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3530 (w), 2953 (m), 2684 (w), 1738 (s), 1610 (w), 1515 (w), 1456 (s), 1428 (m), 1393 (m), 1362 (m), 1339 (w), 1311 (w), 1259 (s), 1230 (m), 1202 (m), 1179 (w), 1149 (m), 1083 (w), 1055 (w), 1017 (m), 1008 (m), 952 (w), 924 (w), 892 (w), 830 (s), 716 (w), 658 (m), 568 (s). MS (EI, 70 eV): m/z (%) = 534 (100) [M$^+$], 535 (43), 520 (15), 519 (38), 57 (31), 41 (11). HRMS (ESI, 70 eV): calcd. for $C_{38}H_{46}O_2$ [M$^+$] 534.34923; found 534.34874.

2,4-Di-(*p*-methoxyphenyl)-estrone (19d):



According to the general procedure compound **19d** was isolated as a light yellow solid (112 mg, 99%), mp = 117 – 118 °C, $[\alpha]_D$ = +84.2° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.46 – 1.64 (m, 6H, aliphatic), 1.91 – 2.17 (m, 4H, aliphatic), 2.32 – 2.39 (m, 1H, aliphatic), 2.46 – 2.54 (m, 4H, aliphatic), 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.87 (s, 1H, OH), 6.97 (d, $^3J_{H\text{-}H}$ = 8.7 Hz, 2H, Ar), 7.05 (d, $^3J_{H\text{-}H}$ = 8.2 Hz, 2H, Ar), 7.21 – 7.28 (m, 3H, Ar), 7.51 (d, $^3J_{H\text{-}H}$ = 8.7 Hz, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.9 (CH), 44.4 (CH), 48.0 (C), 50.4 (CH), 55.29 (OCH_3), 55.30 (OCH_3), 113.9 (2CH), 114.8 (CH), 114.9 (CH), 125.3 (C), 126.7 (CH), 127.6 (C), 127.7 (C), 130.3 (2CH), 130.6 (C), 131.2 (CH), 131.6 (CH), 131.9 (C), 135.0 (C), 148.1 (C), 158.8 (C), 159.3 (C), 220.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3521 (w), 2924 (m), 2857 (w), 2834 (w), 1734 (s), 1607 (m), 1573 (w), 1510 (s), 1456 (s), 1400 (m), 1373 (w), 1339 (w), 1286 (m), 1241 (s), 1174 (s), 1146 (w), 1107 (m), 1084 (w), 1031 (s), 953 (w), 924 (w), 902 (w), 891 (w), 829 (s), 808 (m), 763 (m), 742 (w), 694 (w), 666 (w), 647 (w), 621 (w), 560 (m), 538 (m). MS (EI, 70 eV): m/z (%) = 482 (100) [M$^+$], 483 (33), 397 (3), 358 (5), 317 (5). HRMS (ESI, 70 eV): calcd. for $C_{32}H_{34}O_4$ [M$^+$] 482.24516; found 482.24510.

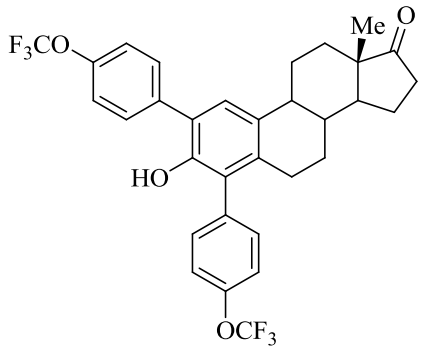
2,4-Di-(*p*-trifluoromethylphenyl)-estrone (19e):



According to the general procedure compound **19e** was isolated as a yellow solid (116 mg, 89%), mp = 127 – 128 °C, $[\alpha]_D$ = +52.1° (c 1.55, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.37 – 1.64 (m, 6H, aliphatic), 1.97 – 2.17 (m, 4H, aliphatic), 2.36 – 2.48 (m, 5H, aliphatic), 4.73 (s, 1H, OH), 7.33 (s, 1H, Ar), 7.45 – 7.49 (m, 2H, Ar), 7.69 (m, 4H, Ar), 7.79 – 7.81 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.2 (CH), 47.9 (C), 50.4 (CH), 124.3 (q, $^1J_{C\text{-}F}$ = 272.2 Hz, C-F), 124.8 (C), 125.4 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, 2CH), 125.6 (q, $^1J_{C\text{-}F}$ = 272.4 Hz, C-F), 126.36 (CH), 126.39 (CH), 127.2 (C), 127.5 (CH), 129.3 (q, $^2J_{C\text{-}F}$ = 32.4 Hz, C), 129.6 (2CH), 130.5 (q, $^2J_{C\text{-}F}$ = 32.6 Hz, C), 130.7 (CH), 130.9 (CH), 132.9 (C), 135.8 (C), 139.8 (C), 141.7 (C), 147.5 (C), 220.6 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.6 (CF_3), -62.5 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3556 (w), 3275 (w), 2928 (w), 2862 (w), 1725 (m), 1615 (m), 1461 (m), 1433 (w), 1398 (m), 1376 (w), 1319 (s), 1260 (m), 1160 (s), 1105 (s), 1064 (s), 1016 (s), 957 (m), 926 (w), 904 (w), 838 (m), 760 (m), 699 (m), 673 (m), 600 (m). MS (EI, 70 eV): m/z (%) = 558 (100) [M^+], 559 (34), 539 (11), 473 (15), 460 (12), 434 (17), 12 (55). HRMS (ESI, 70 eV): calcd. for $C_{32}H_{28}O_2F_6$ [M^+] 558.19880; found 558.19935.

2,4-Di-(*p*-trifluormethoxyphenyl)-estrone (19f):

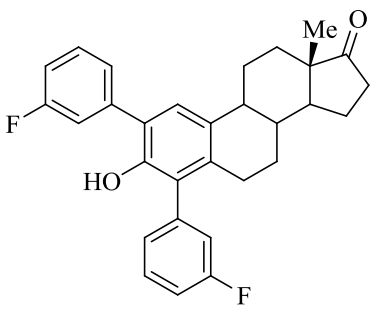


According to the general procedure compound **19f** was isolated as a light yellow solid (109 mg, 79%), mp = 97 – 98 °C, $[\alpha]_D$ = +73.1° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.39 – 1.64 (m, 6H, aliphatic), 1.97 – 2.17 (m, 4H, aliphatic), 2.32 – 2.39 (m, 1H, aliphatic), 2.46 – 2.55 (m, 4H, aliphatic), 4.69 (s, 1H, OH), 7.26 – 7.29 (m, 3H, Ar + $CDCl_3$), 7.36 – 7.37 (m, 4H, Ar), 7.58 (d, $^3J_{H\text{-}H}$ = 8.6 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.3 (CH), 47.9 (C), 50.4 (CH), 120.49 (q, $^1J_{C\text{-}F}$ = 257.7 Hz, OCF_3), 120.52 (q, $^1J_{C\text{-}F}$ = 257.0 Hz, OCF_3), 120.9 (2CH), 121.8 (2CH), 124.6 (C), 127.0 (C), 127.3 (CH), 130.7 (2CH), 131.7 (CH), 132.0 (CH), 132.6 (C), 134.3 (C), 135.6

(C), 136.7 (C), 147.6 (C), 148.4 (C), 149.1 (C), 220.7 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = 57.8 (CF_3), -57.7 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3545 (w), 2928 (w), 2861 (w), 1732 (m), 1507 (m), 1460 (m), 1431 (w), 1398 (w), 1375 (w), 1340 (w), 1250 (s), 1203 (s), 1153 (s), 1017 (m), 922 (m), 831 (m), 674 (m), 643 (w), 609 (w), 581 (w), 541 (m). MS (EI, 70 eV): m/z (%) = 590 (100) [M^+], 591 (33), 505 (19), 466 (14), 69 (18), 55 (12). HRMS (ESI, 70 eV): calcd. for $C_{32}H_{28}O_4F_6$ [M^+] 590.18863; found 590.18736.

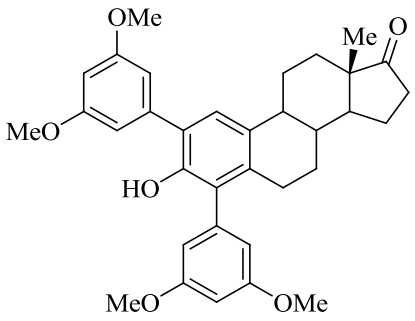
2,4-Di-(*m*-fluorophenyl)-estrone (19g):



According to the general procedure compound **19g** was isolated as a light yellow solid (91 mg, 85%), mp = 111 – 112 °C, $[\alpha]_D$ = +108.0° (c 1.00, $CHCl_3$). A mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.939 and 0.943 (2s, 3H, CH_3), 1.37 – 1.65 (m, 6H, aliphatic), 1.92 – 2.20 (m, 4H, aliphatic), 2.31 – 2.39 (m, 1H, aliphatic), 2.46 – 2.55 (m, 4H, aliphatic), 4.80 and 4.81 (s, 1H, OH), 7.00 – 7.17 (m, 4H, Ar), 7.27 – 7.43 (m, 4H, Ar), 7.46 – 7.54 (m, 1H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.4 and 28.5 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.2 and 44.3 (CH), 47.9 (C), 50.4 (CH), 114.1 (d, $^2J_{C\text{-}F}$ = 21.1 Hz, CH), 115.2 (d, $^2J_{C\text{-}F}$ = 21.0 Hz, CH), 116.1 and 116.5 (CH), 117.2 (d, $^2J_{C\text{-}F}$ = 20.9 Hz) and 117.5 (d, $^2J_{C\text{-}F}$ = 21.0 Hz) (CH), 124.66 – 124.72 (several signals, C), 124.8 (d, $^4J_{C\text{-}F}$ = 2.8 Hz, CH), 125.85 (d, $^2J_{C\text{-}F}$ = 20.5 Hz) and 125.90 (d, $^2J_{C\text{-}F}$ = 20.4 Hz) (CH), 127.16 (C), 127.18 (d, $^4J_{C\text{-}F}$ = 2.8 Hz, CH), 129.9 (d, $^3J_{C\text{-}F}$ = 8.5 Hz, CH), 131.0 (d, $^3J_{C\text{-}F}$ = 8.4 Hz) and 131.1 (d, $^3J_{C\text{-}F}$ = 8.6 Hz) (CH), 132.5 (C), 135.47 and 135.50 (C), 137.9 and 138.0 (C), 140.2 and 140.3 (C), 147.5 (C), 162.8 (d, $^1J_{C\text{-}F}$ = 245.8 Hz, C-F), 163.3 (d, $^1J_{C\text{-}F}$ = 248.3 Hz) and 163.4 (d, $^1J_{C\text{-}F}$ = 248.3 Hz) (C-F), 220.7 (C=O). ^{19}F NMR (235 MHz, $CDCl_3$): δ = -113.10 and -113.07 (CF), -111.45 and -111.40 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3539 (w), 3070 (w), 2924 (m), 2858 (w), 1733 (s), 1612 (m), 1581 (s), 1469 (w), 1458 (m), 1425 (m), 1403 (m), 1373 (w), 1339 (w), 1310 (w), 1295 (w), 1260 (s), 1194 (s), 1156 (m), 1133 (m), 1120 (m), 1084 (w), 1072 (w), 1056 (w), 1027 (w), 1014 (w), 1004 (w), 958 (w), 936 (m), 920 (w), 873 (m), 842 (w), 829 (w), 785 (s), 762 (m), 716 (m), 697 (m), 670 (m), 642 (w), 582 (w), 549 (w). MS (EI, 70 eV): m/z (%) = 458 (100) [M^+], 459 (28), 373 (17), 360 (11), 334 (12), 55 (15), 41 (12). HRMS (ESI, 70 eV): calcd. for $C_{30}H_{28}O_2F_2$ [M^+] 458.20519; found 458.20528.

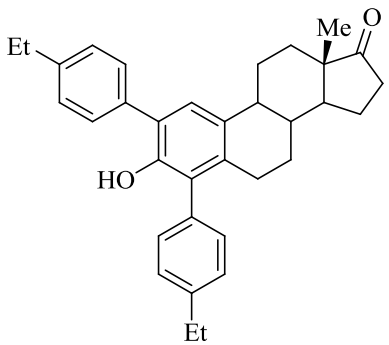
2,4-Di-(3,5-dimethoxyphenyl)-estrone (19h):



According to the general procedure compound **19h** was isolated as a light yellow solid (89 mg, 70%), mp = 114 – 115 °C, $[\alpha]_D$ = +52.4° (c 1.00, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.32 – 1.41 (m, 1H, aliphatic), 1.51–1.63 (m, 5H, aliphatic), 1.92 – 2.17 (m, 4H, aliphatic), 2.31 – 2.39 (m, 1H, aliphatic), 2.45 – 2.61 (m, 4H, aliphatic), 3.81 (br.s, 12H, 4OCH_3), 5.07 (s, 1H, OH), 6.45 – 6.47 (m, 3H, Ar), 6.51 – 6.53 (m, 1H, Ar), 6.71 (d, $^4J_{H\text{-}H}$ = 2.3 Hz, 2H, Ar), 7.31 (br.s, 1H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.2 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.9 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 55.4 (4OCH_3), 99.5 (CH), 100.1 (CH), 107.3 (2CH), 107.5 (CH), 108.0 (CH), 125.6 (C), 126.7 (CH), 128.2 (C), 132.0 (C), 135.2 (C), 137.8 (C), 140.1 (C), 147.6 (C), 160.8 (2C), 161.55 (C) 161.58 (C), 220.8 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3508 (w), 2926 (m), 2853 (w), 2837 (w), 1733 (s), 1589 (s), 1453 (m), 1417 (m), 1402 (m), 1366 (m), 1336 (m), 1296 (m), 1252 (m), 1201 (s), 1150 (s), 1058 (s), 992 (m), 961 (m), 940 (m), 927 (m), 901(m), 830 (s), 784 (m), 728 (m), 699 (m), 615 (m), 581 (m), 538 (m). MS (EI, 70 eV): m/z (%) = 542 (100), 544 (9), 543 (49), 271 (18). HRMS (EI, 70 eV): calcd. for $C_{34}H_{38}O_6$ [M^+] 542.26629; found 542.26555.

2,4-Di-(*p*-ethylphenyl)-estrone (19i):

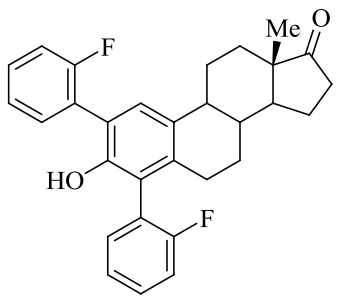


According to the general procedure compound **19i** was isolated as a light yellow solid (111 mg, 99%), mp = 113 – 114 °C, $[\alpha]_D$ = +74.0° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H, CH_3), 1.25 – 1.33 (m, 7 H, 2CH_2CH_3 + aliphatic), 1.50–1.63 (m, 5H, aliphatic), 1.89 – 2.19 (m, 4H, aliphatic), 2.31 – 2.39 (m, 1H, aliphatic), 2.45 – 2.57 (m, 4H, aliphatic), 2.65 – 2.77 (m, 4H, 2CH_2CH_3), 4.88 (s, 1H, OH), 7.21 – 7.29 (m, 5H, Ar + $CDCl_3$), 7.33 – 7.35 (m, 2H, Ar), 7.47 – 7.50 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 15.3 (CH_3), 15.5 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.54 (CH_2), 28.56 (CH_2), 28.61 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.9 (CH), 44.3 (CH), 48.0 (C), 50.4 (CH), 125.6 (C), 126.8 (CH), 128.0 (2CH), 128.1 (C), 128.82 (CH), 128.84 (CH), 129.2 (2CH), 129.9 (CH), 130.3 (CH), 131.9 (C), 132.9 (C), 135.0

(C), 135.5 (C), 143.1 (C), 144.0 (C), 147.9 (C), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3527 (w), 2961 (m), 2927 (m), 2869 (m), 1737 (s), 1650 (w), 1645 (w), 1605 (w), 1511 (m), 1455 (s), 1429 (m), 1399 (m), 1372 (m), 1337 (m), 1257 (m), 1232 (m), 1145 (m), 1126 (m), 1115 (m), 1083 (m), 1054 (m), 1020 (m), 1008 (m), 967 (m), 953 (m), 924 (m), 902 (m), 891(m), 828 (s), 718 (m), 665 (m), 648 (m), 638 (m), 623 (m), 566 (m), 533 (m). MS (EI, 70 eV): m/z (%) = 478 (100) [M^+], 479 (55), 152 (12), 151 (13), 133 (19), 57 (10), 55 (12), 41 (12), 36 (10). HRMS (ESI, 70 eV): calcd. for $C_{34}H_{38}O_2$ [M+H] 479.29446; found 479.29408.

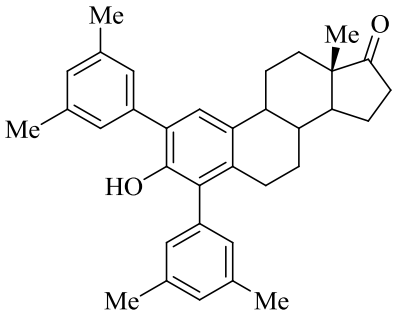
2,4-Di-(*o*-fluorophenyl)-estrone (19j):



According to the general procedure compound **19j** was isolated as a light yellow solid (104 mg, 97%), mp = 118 – 119 °C, $[\alpha]_D$ = +92.2° (c 1.00, $CHCl_3$). A mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 and 0.94 (2s, 3H, CH_3), 1.34 – 1.42 (m, 1H, aliphatic), 1.50 – 1.64 (m, 5H, aliphatic), 1.95 – 2.17 (m, 4H, aliphatic), 2.36 – 2.54 (m, 5H, aliphatic), 4.69 and 4.71 (2s, 1H, OH), 7.14 – 7.36 (m, 7H, Ar + $CDCl_3$), 7.39 – 7.46 (m, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 and 13.9 (CH_3), 21.5 (CH_2), 26.0 and 26.1 (CH_2), 26.4 (CH_2), 27.6 and 28.3 (CH_2), 31.55 and 31.58 (CH_2), 35.8 (CH_2), 37.71 and 37.77 (CH), 44.1 and 44.2 (CH), 47.9 and 48.0 (C), 50.39 and 50.43 (CH), 115.72 and 115.76 (CH), 116.1 – 116.2 (several signals, CH), 116.5 and 116.6 (CH), 120.1 (C), 121.9 and 122.0 (C), 123.19 (d, $^2J_{C\text{-}F}$ = 17.7 Hz) and 123.28 (d, $^2J_{C\text{-}F}$ = 17.4 Hz) (C), 124.2 – 124.3 (several signals, CH), 124.8 – 124.9 (several signals, CH), 125.29 (d, $^2J_{C\text{-}F}$ = 15.8 Hz) and 125.39 (d, $^2J_{C\text{-}F}$ = 16.0 Hz) (C), 128.2 (CH), 129.4 (d, $^3J_{C\text{-}F}$ = 8.2 Hz) and 129.5 (d, $^3J_{C\text{-}F}$ = 7.9 Hz) (CH), 130.20 (d, $^3J_{C\text{-}F}$ = 7.9 Hz) and 130.24 (d, $^3J_{C\text{-}F}$ = 8.1 Hz) (CH), 131.9 – 132.3 (several signals, 2CH + 2C), 136.6 and 136.7 (C), 148.3 and 148.4 (C), 160.0 (d, $^1J_{C\text{-}F}$ = 246.8 Hz, 2C-F), 220.9 (C=O). ^{19}F NMR (235 MHz, $CDCl_3$): δ = -112.7 and -112.9 (CF), -114.016 and -114.024 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3550 (w), 2925 (w), 2857 (w), 1731 (m), 1576 (w), 1491 (m), 1444 (m), 1414 (m), 1373 (w), 1340 (w), 1255 (m), 1206 (m), 1144 (m), 1097 (m), 1083 (w), 1032 (m), 1008 (w), 944 (w), 925 (w), 903 (w), 847 (w), 820 (w), 806 (w), 755 (s), 665 (w), 634 (w), 597 (w), 581 (w), 542(m). MS (EI, 70 eV): m/z (%) = 458 (100) [M^+], 459 (31), 373 (20), 360 (11), 334 (24), 55(11). HRMS (EI, 70 eV): calcd. for $C_{30}H_{28}O_2F_2$: 458.20519; found 458.20501.

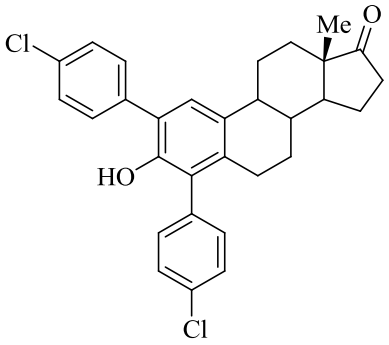
2,4-Di-(3,5-dimethylphenyl)-estrone (19k):



According to the general procedure compound **19k** was isolated as a light yellow solid (111 mg, 99%), mp = 111 – 112 °C, $[\alpha]_D$ = +104.1° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 3H, CH_3), 1.36 – 1.64 (m, 6H, aliphatic), 1.90 – 2.17 (m, 4H, aliphatic), 2.36 – 2.37 (m, 13H, $4CH_3$ + aliphatic), 2.46 – 2.59 (m, 4H, aliphatic), 4.94 (br.s, 1H, OH), 6.92 (s, 1H, Ar), 6.94 (s, 1H, Ar), 6.98 (s, 1H, Ar), 7.05 (s, 1H, Ar), 7.17 (m, 2H, Ar), 7.26 (s, 1H, Ar + $CDCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.39 ($2CH_3$), 21.41 ($2CH_3$), 21.6 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.5 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 38.0 (CH), 44.4 (CH), 48.0 (C), 50.5 (CH), 125.8 (C), 126.6 (CH), 127.0 (2CH), 127.6 (CH), 128.0 (CH), 128.3 (C), 128.9 (CH), 129.6 (CH), 131.8 (C), 134.8 (C), 135.9 (C), 138.0 (2C), 138.2 (C), 138.86 (C), 138.88 (C), 147.7 (C), 221.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3525 (w), 2917 (s), 2857 (m), 1737 (s), 1599 (s), 1453 (s), 1402 (m), 1373 (m), 1335 (w), 1318 (m), 1259 (m), 1203 (m), 1165 (w), 1143 (m), 1085 (w), 1057 (m), 1035 (m), 1002 (m), 957 (w), 934 (w), 888 (w), 847 (s), 833 (m), 785 (w), 728 (w), 706 (s), 680 (w), 665 (w), 646 (w), 626 (w), 582 (w), 542 (w). MS (EI, 70 eV): m/z (%) = 478 (100) [M^+], 479 (38). HRMS (ESI, 70 eV): calcd. for $C_{34}H_{38}O_2$ [M^+] 478.28663; found 478.28554.

2,4-Di-(*p*-chlorophenyl)-estrone (19l):

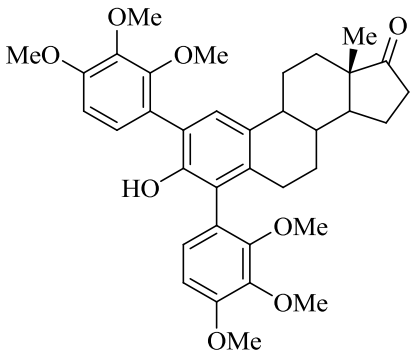


According to the general procedure compound **19l** was isolated as a dark yellow solid (28 mg, 24%), mp = 119 – 120 °C, $[\alpha]_D$ = +58.2° (c 0.65, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (m, 3H, CH_3), 1.32 – 1.36 (m, 1H, ailiphatic), 1.55–1.62 (m, 5H, aliphatic), 1.96 – 2.17 (m, 4H, aliphatic), 2.29 – 2.37 (m, 1H, aliphatic), 2.44 – 2.55 (m, 4H, aliphatic), 4.71 (s, 1H, OH), 7.25 – 7.30 (m, 3H, Ar + $CDCl_3$), 7.38 – 7.41 (m, 2H, Ar), 7.46 – 7.54 (m, 4H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.6 (CH_2), 31.6 (CH_2), 35.8 (CH_2), 37.8 (CH), 44.2 (CH), 47.9 (C), 50.4 (CH), 124.7 (C), 127.1 (CH), 128.6 (2CH), 129.7 (2CH), 130.6 (2CH), 130.59 (C), 131.5 (CH), 131.8 (CH), 132.5 (C), 133.2 (C), 134.1 (C), 134.3 (C), 135.4 (C), 136.5 (C), 147.54 (C), 220.8 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3533 (w), 2921 (m), 2853 (m), 1731 (s), 1650 (w), 1590 (w), 1490 (s), 1455 (s), 1427 (m), 1389 (m), 1339 (m), 1258 (m), 1230

(m), 1144 (m), 1126 (m), 1087 (s), 1056 (m), 1014 (s), 967 (m), 925 (m), 902 (m), 893 (m), 819 (s), 802 (s), 732 (m), 720 (m), 693 (m), 665 (m), 640 (m), 581 (m). MS (EI, 70 eV): m/z (%) = 490 (100) [M^+], 494 (14), 493 (21), 492 (69), 491 (34). HRMS (EI, 70 eV): calcd. for $C_{30}H_{28}O_2Cl_2$ [M+] 490.14609; found 490.14496; calcd. for $C_{30}H_{28}O_2Cl^{37}Cl$ [M+] 492.14314; found 492.14362.

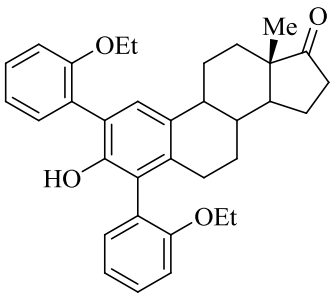
2,4-Di-(2,3,4-trimethoxyphenyl)-estrone (19m):



According to the general procedure compound **19m** was isolated as a light yellow solid (52 mg, 37%), mp = 105 – 106 °C, $[\alpha]_D$ = +43.4° (c 1.00, $CHCl_3$). A mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 and 0.95 (2s, 3H, CH_3), 1.54 – 1.62 (m, 6H, aliphatic), 1.91 – 2.17 (m, 4H, aliphatic), 2.30 – 2.37 (m, 1H, aliphatic), 2.45 – 2.54 (m, 4H, aliphatic), 3.68 – 3.75 (m, 6H, 2OCH_3), 3.89 – 3.93 (m, 12H, 4OCH_3), 6.40 and 6.42 (2s, 1H, OH), 6.76 – 6.89 (m, 3H, Ar), 7.06 – 7.09 (m, 1H, Ar), 7.22 – 7.26 (d, $^3J_{H-H}$ = 4.5 Hz, 1H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.86 and 13.93 (CH_3), 21.5 (CH_2), 26.0 and 26.2 (CH_2), 26.6 and 27.4 (CH_2), 28.3 and 29.7 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.7 and 37.9 (CH), 44.3 (CH), 48.0 (C), 50.5 and 50.6 (CH), 55.9 and 56.1 (2OCH_3), 60.8 – 61.1 (several signals, 3OCH_3), 61.50 and 61.53 (OCH_3), 107.54 and 107.59 (CH), 108.5 (CH), 122.8 and 123.0 (C), 124.0 (C), 125.30 and 125.33 (CH), 125.52 and 125.56 (C), 126.06 and 126.12 (C), 126.2 (CH), 127.2 and 127.4 (CH), 131.9 and 132.1 (C), 136.3 and 136.5 (C), 142.2 (C), 148.9 and 149.0 (C), 150.34 and 150.36 (C), 151.5 (C), 152.0 (C), 153.05 and 153.14 (C), 153.2 (C), C=O not given. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924 (w), 1734 (m), 1596 (w), 1494 (m), 1455 (s), 1405 (s), 1338 (w), 1289 (s), 1231 (m), 1212 (m), 1093 (s), 1058 (m), 1034 (s), 1006 (s), 917 (w), 891 (m), 797 (m), 701 (w), 681 (w), 582 (w). MS (EI, 70 eV): m/z (%) = 602 (100) [M^+], 604 (12), 603 (56), 43 (13). HRMS (EI, 70 eV): calcd. for $C_{36}H_{42}O_8$ [M+] 602.28742; found 602.28714.

2,4-Di-(*o*-ethoxyphenyl)-estrone (19n):

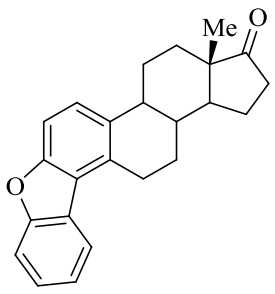


According to the general procedure compound **19n** was isolated as a dark yellow solid (86 mg, 72%), mp = 94 – 95 °C, $[\alpha]_D$ = +52.4° (c 1.00, $CHCl_3$). A mixture of diastereomers. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.94 and 0.95 (2s, 3H, CH_3), 1.21 – 1.28 (m, 4H, CH_2CH_3 + aliphatic), 1.31 – 1.38 (m, 3H, CH_2CH_3), 1.49 – 1.64 (m, 5H, aliphatic), 1.89 – 2.17 (m, 4H, aliphatic), 2.31 – 2.59 (m, 5H, aliphatic), 4.00 – 4.14 (m, 4H, $2CH_2CH_3$), 6.06 and 6.07 (2s, 1H, OH), 6.99 – 7.20 (m, 5H, Ar), 7.24 – 7.26 (m, 1H, Ar + $CDCl_3$), 7.29 – 7.44 (m, 3H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.87 and 13.92 (CH_3), 14.7 (CH_2CH_3), 14.8 and 14.9 (CH_2CH_3), 21.6 (CH_2), 25.95 and 26.09 (CH_2), 26.6 and 26.7 (CH_2), 27.1 and 28.0 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 37.9 (CH), 44.4 (CH), 48.0 (C), 50.58 and 50.62 (CH), 64.04 and 64.2 (CH_2CH_3), 64.98 (CH_2CH_3), 113.12 (CH), 113.2 and 113.4 (CH), 120.92 and 120.96 (CH), 121.93 and 121.96 (CH), 123.50 and 123.56 (C), 126.45 and 126.48 (C), 127.2 and 127.33 (C), 127.34 and 127.43 (CH), 128.63 – 128.72 (several signals, 2CH + C), 131.59 – 131.69 (several signals, CH + C), 132.5 (CH), 136.0 and 136.2 (C), 148.97 and 149.10 (C), 155.01 and 155.05 (C), 156.16 and 156.55 (C), 221.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3536 (w), 3371 (w), 2924 (w), 2857 (w), 1736 (m), 1596 (w), 1579 (w), 1491 (m), 1439 (m), 1389 (w), 1372 (w), 1341 (w), 1277 (m), 1227 (m), 1159 (w), 1116 (m), 1084 (m), 1038 (m), 1008 (m), 952 (w), 922 (m), 901 (w), 865 (w), 830 (w), 750 (s), 693 (w), 638 (w), 581 (m), 540 (w). MS (EI, 70 eV): m/z (%) = 510 (100) [M^+], 511 (36), 317 (9), 271 (7), 107 (8), 29 (9). HRMS (EI, 70 eV): calcd. for $C_{34}H_{38}O_4$: 510.27646; found 510.27613.

General procedure for the synthesis of compounds 20 and 21a:

4-(*o*-Fluorophenyl)-estrone (**17k**) or 2,4-di-(*o*-fluorophenyl)-estrone (**19j**) (0.274 mmol), K_2CO_3 (75.9 mg, 2.0 equiv.) and DMF were added in a round-bottom 50 ml flask and stirred 4 h at 150 °C. The solvent was evaporated in vacuo and the residue was purified by column chromatography (EA : Heptane = 3:1).

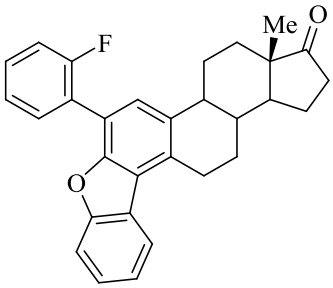
Benzofuro[2',3';3,4]estra-1,3,5(10)-trien-17-on (20):



According to the general procedure compound **20** was isolated as a white solid (65 mg, 69%), mp = 268 – 269 °C, $[\alpha]_D$ = +97.6° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3), 1.58 – 1.73 (m, 6H, aliphatic), 1.99 – 2.04 (m, 1H, aliphatic), 2.12 – 2.29 (m, 3H, aliphatic), 2.44 – 2.58 (m, 3H, aliphatic), 3.25 – 3.37 (m, 1H, aliphatic), 3.46 – 3.55 (m, 1H, aliphatic), 7.32 – 7.48 (m, 4H, Ar), 7.58 (d, $^3J_{H-H}$ = 8.0 Hz, 1H, Ar), 8.01 (d, $^3J_{H-H}$ = 7.7 Hz, 1H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.9 (CH_3), 20.6 (CH_2), 25.3 (CH_2), 25.5 (CH_2), 26.8 (CH_2), 30.7 (CH_2) 34.9 (CH_2), 37.0 (CH), 43.4 (CH), 46.9 (C), 49.4 (CH), 107.7 (CH), 110.5 (CH), 121.3 (C), 121.5 (CH), 121.7 (CH), 123.6 (CH), 123.9 (C), 125.4 (CH), 131.3 (C), 133.0 (C), 153.4 (C), 155.4 (C), C=O not given. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (w), 2920 (w), 2854 (w), 1733 (w), 1472 (w), 1443 (w), 1430 (w), 1382 (w), 1258 (s), 1208 (w), 1166 (w), 1080 (m), 1012 (s), 960 (w), 928 (w), 860 (m), 799 (s), 746 (s), 735 (m), 696 (m), 667 (m), 600 (m), 557 (w). MS (EI, 70 eV): m/z (%) = 344 (100) [M^+], 345 (27), 287 (10), 259 (22), 246 (15), 234 (10), 233 (15), 232 (10), 231 (15), 220 (28), 219 (26), 218 (23), 207 (13), 205 (22), 189 (12), 181 (15). HRMS (EI, 70 eV): calcd. for $C_{24}H_{24}O_2$[M^+] 344.17708; found 344.17727.

2-(o-Fluorophenyl)-benzofuro[2',3';3,4]estra-1,3,5(10)-trien-17-on (21a):



According to the general procedure compound **21a** was isolated as a light yellow solid (74 mg, 77%), mp = 256 – 257 °C, $[\alpha]_D$ = +96.3° (c 1.00, $CHCl_3$).

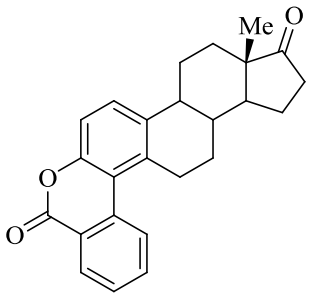
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (s, 3H, CH_3), 1.60 – 1.81 (m, 6H, aliphatic), 2.05 – 2.32 (m, 4H, aliphatic), 2.51 – 2.60 (m, 3H, aliphatic), 3.30 – 3.42 (m, 1H, aliphatic), 3.52 – 3.60 (m, 1H, aliphatic), 7.29 – 7.47 (m, 5H, Ar), 7.53 – 7.58 (m, 2H, Ar), 7.63 – 7.69 (m, 1H, Ar), 8.03 – 8.06 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 21.7 (CH_2), 26.3 (CH_2), 26.6 (CH_2), 27.8 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 38.0 (CH), 44.4 (CH), 47.9 (C), 50.4 (CH), 111.7 (CH), 116.9 (d, $^2J_{C-F}$ = 22.4 Hz, CH), 117.3 (C), 122.60 (CH), 122.64 (C), 122.70 (CH), 124.1 (d, $^4J_{C-F}$ = 3.4 Hz, CH), 124.5 (d, $^2J_{C-F}$ = 15.0 Hz, C), 124.9 (C), 126.0 (d, $^4J_{C-F}$ = 2.5 Hz, CH), 126.5 (CH), 129.5 (d, $^3J_{C-F}$ = 8.3 Hz, CH), 131.8 (d, $^3J_{C-F}$ = 3.3 Hz, CH), 132.2 (C), 134.2 (C), 151.8

(C), 156.4 (C), 156.8 (d, $^{1}J_{C\text{-}F}$ = 245.2 Hz, C-F), 220.9 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -114.6 (CF). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923 (m), 2856 (w), 1730 (s), 1575 (w), 1502 (w), 1445 (m), 1389 (m), 1379 (w), 1254 (m), 1212 (s), 1174 (m), 1099 (w), 1085 (w), 1060 (w), 1010 (m), 927 (w), 896 (w), 865 (w), 829 (m), 799 (m), 761 9s), 749 (s), 672 (m), 648 (m), 598 (m), 583 (m), 565 (m), 536 (m). GC/MS (EI, 70 eV): m/z (%) = 438 (100) [M^+], 439 (28), 353 (12), 327 (9), 314 (21), 313 (16), 312 (11), 299 (15), 275 (22). HRMS (EI, 70 eV): calcd. for $C_{30}H_{27}O_2F$ [M+] 438.19896; found 438.19875.

Procedure for the synthesis of compound 22:

4-Bromoestrone (**16a**) (200 mg, 0.574 mmol), *o*-ethoxycarbonylphenyl boronic acid (340 mg, 3.0 equiv.), $Pd(PPh_3)_4$ (33.2 mg, 0.05 equiv.), RuPhos (13.4 mg, 0.05 equiv.), K_2CO_3 (318.0 mg, 4.0 equiv.) and dioxane (4 ml) were added in a pressure tube under argon atmosphere. The mixture was stirred at 110 °C 72 h. The solvent was evaporated in vacuo. The residue was purified by column chromatography (EA : Heptane = 2:1).

Isocoumarino[3',4';3,4]estra-1,3,5(10)-trien-17-on (22):



According to the general procedure compound **22** was isolated as a pale pink solid (158 mg, 74%), mp = 235 – 236 °C, $[\alpha]_D$ = +131.4° (c 1.00, $CHCl_3$).

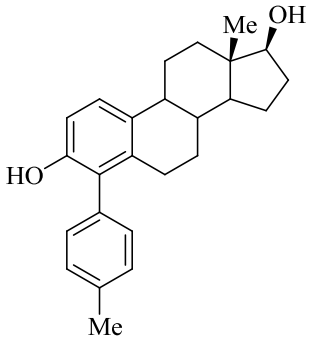
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (s, 3H, CH_3), 1.36 – 1.46 (m, 1H, aliphatic), 1.55 – 1.74 (m, 5H, aliphatic), 1.98 – 2.23 (m, 4H, aliphatic), 2.37 – 2.44 (m, 2H, aliphatic), 2.49 – 2.58 (m, 1H, aliphatic), 3.28 – 3.36 (m, 1H, aliphatic), 3.41 – 3.52 (m, 1H, aliphatic), 7.21 (d, $^{3}J_{H\text{-}H}$ = 8.7 Hz, 1H, Ar), 7.46 (d, $^{3}J_{H\text{-}H}$ = 8.7 Hz, 1H, Ar), 7.53 – 7.59 (m, 1H, Ar), 7.75 – 7.81 (m, 1H, Ar), 8.35 (d, $^{3}J_{H\text{-}H}$ = 8.4 Hz, 1H, Ar), 8.46 (dd, $^{4}J_{H\text{-}H}$ = 1.5 Hz, $^{3}J_{H\text{-}H}$ = 7.8 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 21.5 (CH_2), 26.68 (CH_2), 26.75 (CH_2), 31.8 (CH_2), 32.5 (CH_2), 35.9 (CH_2), 37.6 (CH), 45.6 (CH), 48.0 (C), 50.3 (CH), 115.7 (CH), 117.3 (C), 122.6 (C), 127.2 (CH), 127.92 (CH), 127.95 (CH), 130.8 (CH), 133.8 (CH), 135.7 (C), 135.9 (C), 136.9 (C), 150.3 (C), 161.4 (C), 220.3 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2935 (w), 2922 (w), 2876 (w), 2843 (w), 1737 (s), 1714 (s), 1604 (m), 1586 (m), 1566 (w), 1487 (m), 1457 (w), 1448 (m), 1438 (w), 1401 (w), 1377 (w), 1293 (m), 1273 (m), 1256 (s),

1228 (m), 1210 (w), 1195 (w), 1172 (w), 1108 (m), 1093 (m), 1074 (m), 1064 (m), 1047 (m), 1038 (m), 1002 (m), 958 (m), 928 (w), 837 (w), 823 (w), 804 (s), 782 (s), 761 (w), 739 (s), 714 (m), 691 (s), 681 (s), 652 (w), 607 (m), 593 (w), 584 (w), 549 (w). GC/MS (EI, 70 eV): m/z (%) = 372 (100) [M^+], 373 (28), 248 (14), 202 (12), 189 (12), 165 (10). HRMS (EI, 70 eV): calcd. for $C_{25}H_{24}O_3$ [M+] 372.17200; found 372.17175.

General procedure for the synthesis of compounds 23-25:

An appropriate aryl-estrone **17b**, **18b** or **19b** (0.222 mmol) was dissolved in MeOH (2ml) in a round-bottom 25 ml flask. Then solution of NaOH (26.6 mg, 3.0 equiv.) in MeOH (2ml) was added to the mixture at once. $NaBH_4$ (22.4 mg, 2.7 equiv.) was added and the mixture was stirred 1 h at 20 °C. Water (1 ml) was added, the solvent was evaporated in vacuo and the residue was purified by column chromatography (EA : Heptane = 1:2).

4-(*p*-Tolyl)-17β-estradiol (23):

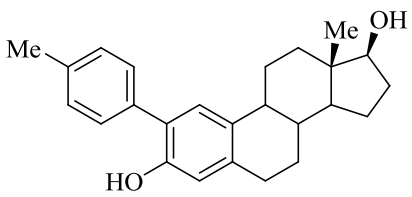


According to the general procedure compound **23** was isolated as a white solid (70 mg, 88%), mp = 210 – 211 °C, $[\alpha]_D$ = +22.0° (c 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (s, 3H, CH_3), 1.27 – 1.58 (m, 7H, aliphatic), 1.64 – 1.67 (m, 1H, aliphatic), 1.75 – 1.80 (m, 1H, aliphatic), 1.94 – 2.00 (m, 1H, aliphatic), 2.06 – 2.15 (m, 1H, aliphatic), 2.19 – 2.28 (m, 1H, aliphatic), 2.34 – 2.44 (m, 6H, CH_3 + aliphatic), 3.59 (t, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, aliphatic), 4.63 (br.s, 1H, OH), 6.70 (d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, Ar), 7.02 (d, $^3J_{H\text{-}H}$ = 6.1 Hz, 2H, Ar), 7.23 – 7.26 (m, 1H, Ar + $CDCl_3$), 7.18 (d, $^3J_{H\text{-}H}$ = 5.9 Hz, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 11.0 (CH_3), 21.3 (CH_3), 23.1 (CH_2), 26.5 (CH_2), 27.2 (CH_2), 28.7 (CH_2), 30.6 (CH_2), 36.8 (CH_2), 38.3 (CH), 43.2 (C), 44.3 (CH), 50.0 (CH), 81.9 (CH), 112.3 (CH), 125.8 (CH), 127.4 (C), 129.9 (CH), 130.16 (CH), 130.22 (CH), 130.4 (CH), 132.3 (C), 132.5 (C), 135.7 (C), 137.8 (C), 150.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3537 (m), 3490 (w), 2921 (s), 2867 (m), 1723 (m), 1589 (w), 1512 (w), 1473 (s), 1379 (w), 1341 (w), 1320 (m), 1280 (s), 1250 (s), 1223 (m), 1174 (s), 1133 (s), 1072 (m), 1050 (s), 1016 (s), 967 (w), 937 (m), 815 (s), 789 (m), 760 (w), 742 (m), 726 (m), 705 (w), 676 (w), 651 (w), 615 (w), 553 (w), 531 (w). MS (EI, 70 eV): m/z (%) = 362 (100) [M^+], 363 (28), 276 (11), 275 (14), 262 (23), 250 (11), 249

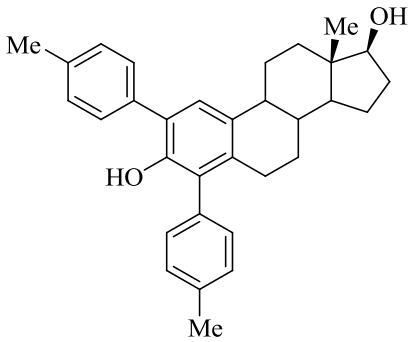
(15), 236 (16), 223 (10), 195 (17). HRMS (ESI, 70 eV): calcd. for $C_{25}H_{30}O_2$ [M^+] 362.22403; found 362.22384.

2-(*p*-Tolyl)-17β-estradiol (24):



According to the general procedure compound **24** was isolated as a white solid (80 mg, 99%), mp = 153 – 154 °C (lit.[106] 154 – 156 °C), $[\alpha]_D$ = +57.4° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (s, 3H, CH_3), 1.32 – 1.55 (m, 6H, aliphatic), 1.67 – 1.76 (m, 2H, aliphatic), 1.88 – 1.96 (m, 2H, aliphatic), 2.07 – 2.34 (m, 3H, aliphatic), 2.41 (s, 3H, CH_3), 2.85 – 2.90 (m, 2H, aliphatic), 3.73 (t, $^3J_{H\text{-}H}$ = 8.4 Hz, 1H, aliphatic), 5.08 (br.s, 1H, OH), 6.72 (s, 1H, Ar), 7.16 (s, 1H, Ar), 7.26 – 7.29 (m, 2H, Ar + $CDCl_3$), 7.35 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 11.1 (CH_3), 21.2 (CH_3), 23.1 (CH_2), 26.4 (CH_2), 27.2 (CH_2), 29.4 (CH_2), 30.6 (CH_2), 36.7 (CH_2), 38.9 (CH), 43.2 (C), 43.9 (CH), 50.1 (CH), 81.9 (CH), 115.6 (CH), 125.6 (C), 127.2 (CH), 128.9 (2CH), 129.9 (2CH), 132.7 (C), 134.5 (C), 137.4 (C), 137.6 (C), 150.2 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3334 (w), 2921 (m), 2862 (m), 1501 (m), 1445 (w), 1420 (m), 1396 (s), 1338 (m), 1294 (m), 1261 (w), 1246 (w), 1205 (m), 1190 (m), 1154 (w), 1127 (m), 1072 (w), 1040 (s), 1010 (s), 969 (w), 945 (w), 892 (w), 867 (w), 817 (s), 727 (m), 634 (m), 613 (m), 554 (m), 539 (m). MS (EI, 70 eV): m/z (%) = 362 (100) [M^+], 363 (29), 262 (15), 249 (12), 236 (13), 197 (11), 195 (12). HRMS (ESI, 70 eV): calcd. for $C_{25}H_{30}O_2$ [M^+] 362.22403; found 362.22349.

2,4-Di-(*p*-tolyl)-17β-estradiol (25):



According to the general procedure compound **25** was isolated as a white solid (90 mg, 90%), mp = 150 – 151 °C, $[\alpha]_D$ = +25.1° (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (s, 3H, CH_3), 1.27 – 1.70 (m, 8H, aliphatic), 1.80 – 1.83 (m, 1H, aliphatic), 1.94 – 2.00 (m, 1H, aliphatic), 2.07 – 2.16 (m, 1H, aliphatic), 2.26 – 2.33 (m, 1H, aliphatic), 2.40 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.46 – 2.52 (m, 3H, aliphatic), 3.74 (t, $^3J_{H\text{-}H}$ = 8.4 Hz, 1H, aliphatic), 4.85 (br.s, 1H, OH), 7.18 – 7.26 (m, 4H, Ar + $CDCl_3$), 7.31 (m, 3H, Ar), 7.47 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 2H, Ar). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 11.1 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 23.1 (CH_2), 26.6

(CH_2), 27.3 (CH_2), 28.7 (CH_2), 30.6 (CH_2), 36.8 (CH_2), 38.4 (CH), 43.2 (C), 44.3 (CH), 50.1 (CH), 81.9 (CH), 125.4 (C), 126.8 (CH), 128.0 (C), 129.2 (4CH), 129.9 (CH), 130.0 (CH), 130.1 (CH), 130.3 (CH), 132.5 (C), 132.8 (C), 135.2 (C), 135.5 (C), 136.7 (C), 137.6 (C), 147.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3526 (m), 3283 (w), 2921 (m), 2868 (m), 1512 (m), 1461 (s), 1427 (m), 1396 (m), 1338 (m), 1313 (m), 1277 (m), 1247 (s), 1229 (m), 1187 (w), 1133 (m), 1077 (m), 1058 (s), 1019 (m), 970 (w), 945 (w), 912 (w), 890 (w), 818 (s), 804 (s), 767 (m), 733 (m), 720 (m), 666 (m), 553 (m), 545 (m), 527 (s). MS (EI, 70 eV): m/z (%) = 452 (100) [M^+], 453 (35), 285 (10). HRMS (ESI, 70 eV): calcd. for $C_{32}H_{36}O_2$ [M^+] 452.27098; found 452.27084.

Supplement 2

Crystallographic data

Crystal data for 1-methyl-2-nitro-3-phenylindole (2a):

Identification code	is_ai92
Empirical formula	$C_{15}H_{12}N_2O_2$
Formula weight	252.27
Temperature	173(2) K
Wavelength	0.71073Å
Crystal system	monoclinic
Space group (H.-M.)	P 21/c
Space group (Hall)	-P 2ybc
Unit cell dimensions	a = 6.1513(4) Å α = 90.00°
	b = 16.5378(10) Å β = 96.129(4)°
	c = 12.0556(9) Å γ = 90.00°
Volume	1219.39(14) $Å^3$
Z	4
Density (calculated)	1.374 Mg/m^3
Absorption coefficient	0.093 mm^{-1}
F(000)	1000
Crystal size	0.60 x 0.32 x 0.18 mm^3
Θ range for data collection	5.986 to 46.711°
Index ranges	$-8\leq h\leq 8$, $-20\leq k\leq 21$, $-15\leq l\leq 15$
Reflections collected	14574
Independent reflections	2940 [R(int) = 0.0600]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9926 and 0.9744
Refinement method	Full-matrix least-squares on F^2
Data/ restraints/ parameters	2940/ 0/ 173
Goodness-of-fit on F^2	1.029
Final R indices [$I>2\sigma(I)$]	R1 = 0.0527, wR2 = 0.1163
R indices (all data)	R1 = 0.0988, wR2 = 0.1428

Crystal data for 1-methyl-2-nitro-3-(*m*-trifluoromethylphenyl)-indole (2c):

Identification code	is_ai100	
Empirical formula	$C_{16}H_{11}N_2O_2$	
Formula weight	320.27	
Temperature	173(2) K	
Wavelength	0.71073Å	
Crystal system	triclinic	
Space group (H.-M.)	P -1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 8.1522(2) Å	α = 74.4980(10)°
	b = 8.4118(2) Å	β = 78.8120(10)°
	c = 10.9415(3) Å	γ = 73.5340(10)°
Volume	687.66(3)Å^3	
Z	2	
Density (calculated)	1.547 Mg/m^3	
Absorption coefficient	0.131 mm^{-1}	
F(000)	328	
Crystal size	0.48 x 0.34 x 0.11 mm^3	
Θ range for data collection	5.254 to 65.032°	
Index ranges	-11≤h≤11, -12≤k≤12, -15≤l≤15	
Reflections collected	21981	
Independent reflections	4371 [R(int) = 0.0162]	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9858 and 0.9399	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	4371/ 0/ 209	
Goodness-of-fit on F^2	1.028	
Final R indices [I>2σ(I)]	R1 = 0.0466, wR2 = 0.1258	
R indices (all data)	R1 = 0.0548, wR2 = 0.1343	

Crystal data for 3-(*p*-*n*-propylphenylethynyl)-estra-1,3,5(10)-trien-17-one (11c):

Identification code	av_sb22	
Empirical formula	$C_{29}H_{30}O$	
Formula weight	394.53	
Temperature	173(2) K	
Wavelength	0.71073Å	
Crystal system	monoclinic	
Space group (H.-M.)	P 21	
Space group (Hall)	P 2yb	
Unit cell dimensions	a = 6.9542(5) Å	α = 90.00°
	b = 7.8665(6) Å	β = 95.599(4)°
	c = 21.0214(15) Å	γ = 90.00°
Volume	1144.49(15) $Å^3$	
Z	2	
Density (calculated)	1.145 Mg/m^3	
Absorption coefficient	0.067 mm^{-1}	
F(000)	424	
Crystal size	0.35 x 0.29 x 0.09 mm^3	
Θ range for data collection	2.77 to 26.70°	
Index ranges	$-9\leq h\leq 9$, $-11\leq k\leq 11$, $-27\leq l\leq 29$	
Reflections collected	16543	
Independent reflections	6282 [R(int) = 0.0585]	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7460 and 0.6831	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	6282/ 110/ 353	
Goodness-of-fit on F^2	1.016	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0531, wR2 = 0.1184	
R indices (all data)	R1 = 0.0913, wR2 = 0.1369	

Crystal data for 4-*p*-*tert*-butylphenyl-estrone (17c):

Identification code	is_ai255	
Empirical formula	$C_{28}H_{34}O_2$, 0.5 (CH_2Cl_2)	
Formula weight	445.01	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group (H.-M.)	P 21 21 21	
Space group (Hall)	P 2ac 2ab	
Unit cell dimensions	a = 8.1311(3) Å	α = 90.00°
	b = 14.5769(5) Å	β = 90.00°
	c = 20.3923(7) Å	γ = 90.00°
Volume	2417.02(15) $Å^3$	
Z	4	
Density (calculated)	1.223 Mg/m^3	
Absorption coefficient	0.181 mm^{-1}	
F(000)	956	
Crystal size	0.34 x 0.25 x 0.12 mm^3	
Θ range for data collection	2.438 to 29.998°	
Index ranges	-9≤h≤11, -20≤k≤20, -28≤l≤28	
Reflections collected	34506	
Independent reflections	7034 [R(int) = 0.0450]	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7460 and 0.6965	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	7034/ 0/ 277	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2σ(I)]	R1 = 0.0514, wR2 = 0.1179	
R indices (all data)	R1 = 0.0696, wR2 = 0.1253	

Crystal data for 2-*p*-*tert*-butylphenyl-estrone (18c):

Identification code	is_ai272	
Empirical formula	$C_{28}H_{34}O_2$, 0.33 (CH_4O)	
Formula weight	413.23	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	trigonal	
Space group (H.-M.)	R 3 :H	
Space group (Hall)	R 3	
Unit cell dimensions	a = 30.1858(8) Å	α = 90.00°
	b = 30.1858(8) Å	β = 90.00°
	c = 6.5281(2) Å	γ = 120.00°
Volume	5151.4(3) $Å^3$	
Z	9	
Density (calculated)	1.199 Mg/m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	2016	
Crystal size	0.35 x 0.09 x 0.08 mm^3	
Θ range for data collection	2.337 to 25.242°	
Index ranges	$-42 \leq h \leq 42$, $-42 \leq k \leq 42$, $-8 \leq l \leq 9$	
Reflections collected	23934	
Independent reflections	6517 [R(int) = 0.0647]	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.994 and 0.975	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	6517/ 2/ 293	
Goodness-of-fit on F^2	0.906	
Final R indices [I>2σ(I)]	R1 = 0.0478, wR2 = 0.0735	
R indices (all data)	R1 = 0.0885, wR2 = 0.0844	

Crystal data for 2-*p*-trifluoromethylphenyl-estrone (18e):

Identification code	is_ai275	
Empirical formula	$C_{25}H_{25}F_3O_2$	
Formula weight	414.45	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group (H.-M.)	P 21 21 21	
Space group (Hall)	P 2ac 2ab	
Unit cell dimensions	a = 11.7734(4) Å	α = 90.00°
	b = 13.0921(4) Å	β = 90.00°
	c = 13.3581(4) Å	γ = 90.00°
Volume	2059.00(11) $Å^3$	
Z	4	
Density (calculated)	1.337 Mg/m^3	
Absorption coefficient	0.102 mm^{-1}	
F(000)	872	
Crystal size	0.23 x 0.18 x 0.12 mm^3	
Θ range for data collection	2.178 to 29.998°	
Index ranges	-15≤h≤16, -18≤k≤18, -18≤l≤18	
Reflections collected	30084	
Independent reflections	6000 [R(int) = 0.0592]	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7460 and 0.7034	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	6000/ 19/ 280	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2σ(I)]	R1 = 0.0550, wR2 = 0.1180	
R indices (all data)	R1 = 0.0825, wR2 = 0.1341	

Crystal data for isocoumarino[3',4';3,4]estra-1,3,5(10)-trien-17-on (22):

Identification code	is_ta13	
Empirical formula	$C_{25}H_{24}O_3$	
Formula weight	372.44	
Temperature	123(2) K	
Wavelength	0.71073Å	
Crystal system	monoclinic	
Space group (H.-M.)	P 21	
Space group (Hall)	P 2yb	
Unit cell dimensions	a = 8.2304(9) Å	α = 90.00°
	b = 6.9042(7) Å	β = 97.574(5)°
	c = 16.1273(17) Å	γ = 90.00°
Volume	908.43(17) $Å^3$	
Z	2	
Density (calculated)	1.362 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	396	
Crystal size	0.18 x 0.12 x 0.03 mm^3	
Θ range for data collection	2.95 to 24.32°	
Index ranges	$-10 \leq h \leq 10$, $0 \leq k \leq 9$, $0 \leq l \leq 21$	
Reflections collected	18736	
Independent reflections	2375 [R(int) = 0.0791]	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.745638 and 0.682721	
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	2375/ 1/ 254	
Goodness-of-fit on F^2	1.078	
Final R indices [I>2σ(I)]	R1 = 0.0488, wR2 = 0.1005	
R indices (all data)	R1 = 0.0739, wR2 = 0.1105	

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