Total Synthesis of Viniferifuran and Dehydroampelopsin B Analogues

Adrian Krzyzanowski

Adrian Krzyzanowski
Master Thesis 60 ECTS
Report passed: 30th May 2018
Supervisors: Mikael Elofsson, Michael Saleeb
Examiner: Bertil Eliasson
Abstract

Evolution of antimicrobial resistance has been observed against most of the antibiotics developed to date, and the danger of the post-antibiotic era is slowly emerging on the horizon. The antimicrobial resistance poses a serious threat to human health and the current clinical care, generating high excess medical expenses. Thus, it is evident that an alternative to the classical antibiotic therapies is needed. Treatments based on targeting bacterial virulence without affecting the in vitro viability of the microbes could be a potential solution, possibly generating a weaker selection for resistance. Herein we present the synthesis of natural-products-inspired molecules based on heterocyclic cores of indole, benzo[b]thiophene and benzo[b]selenophene, that are expected to exhibit inhibitory activity against bacterial virulence. The key transformations in the synthesis of the indole-based molecules included Sonogashira coupling, palladium-catalysed Cacchi cyclisation and Horner-Wadsworth-Emmons reaction. The syntheses of the benzo[b]thiophene- and benzo[b]selenophene-based compounds were achieved through the utilisation of Sonogashira coupling, alkyne electrophilic cyclisation as well as two consecutive Suzuki-Miyaura coupling reactions.
List of Abbreviations

AMR  Antimicrobial resistance
aq.  Aqueous
Boc  tert-Butyloxycarbonyl
n-BuLi  n-Butyllithium
calcd.  Calculated
Cbz  Carboxybenzyl
dba  trans,trans-Dibenzylideneacetone
DCM  Dichloromethane
DIBAL  Diisobutylaluminium hydride
DIPEA  N,N-Diisopropylethylamine
DMAP  4-Dimethylaminopyridine
DMF  Dimethylformamide
DMSO  Dimethyl sulfoxide
dppf  1,1’-Bis(diphenylphosphino)ferrocene
Et,O  Diethyl ether
EtOAc  Ethyl acetate
EtOH  Ethanol
eq.  Equivalent(s)
ESI  Electrospray ionisation
GDP  Gross domestic product
HBpin  Pinacolborane
HPLC  High-performance liquid chromatography
HRMS  High resolution mass spectrometry
HWE  Horner–Wadsworth–Emmons
LC-MS  Liquid chromatography–mass spectrometry
m/z  Mass-to-charge ratio
Me  Methyl
MeCN  Acetonitrile
MeOH  Methanol
MWI  Microwave Irradiation
OAc  Acetate
OTf  Triflate
P(o-tol)_3  Tri(o-tolyl)phosphine
PG  Protective group
Ph  Phenyl
PhMe  Toluene
rt  Room temperature
sat.  Saturated
SPhos  2-Dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
T3SS  Type III secretion system
TBAF  Tetrabutylammonium fluoride
TBAI  Tetrabutylammonium iodide
TEA  Triethylamine
TFA  Trifluoroacetic acid
TFAA  Trifluoroacetic anhydride
TIPS  Triisopropylsilyl
TIPSCI  Triisopropylsilyl chloride
TLC  Thin layer chromatography
TMG  1,1,3,3-Tetramethylguanidine
TOF  Time-of-flight
XPhos  2-Dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

Author’s Contributions

Design of the synthetic pathways, synthesis and purification of all the intermediates and final products, collection of all of the analytical data and interpretation of the results.
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1. Introduction

1.1 Antimicrobial Resistance

In 1928, due to a serendipitous accident, Alexander Fleming noted that a substance, produced on a Petri dish contaminated with mould, killed bacteria that he had been examining. This fortuitous observation led to a development of the world’s first antibiotic – penicillin. In the following years a number of different antibiotics were deployed, revolutionising healthcare and forming a foundation of the modern medicine. Common bacterial diseases such as pneumonia or tuberculosis could be treated easily with this novel type of medicine, vastly reducing dangers associated with routine surgeries, medical treatments and childbirths.\[1\] However, already in 1940, bacterial strains producing penicillinase, enzyme inactivating penicillin, were discovered, marking a beginning of a struggle with what we know today as antimicrobial resistance (AMR) – ability of microorganisms to resist antimicrobial drug therapies.\[2\] Evolution of AMR has been observed against most of the antibiotics developed to date, and now it is evident that the danger of the post-antibiotic era is slowly emerging on the horizon.\[3,4\]

Bacteria have always been developing resistance towards antimicrobials; however, AMR became a significant medical problem only in the recent years. This is due to the increase in antibiotic use caused by improper antibiotic prescriptions, sales and utilisation outside the healthcare sector, as well as, the decrease of the rate at which novel antibiotics are introduced.\[4\] Between 1940s and 1960s over 20 new classes of antibiotics were deployed. Between 1960s and 2010 only two new classes were introduced to the market, and the main focus appeared to be on the discovery of effective antibiotic analogues. This approach was efficient enough to keep pace with the emergence of AMR until approximately ten years ago. Now, however, it is evident that too few novel antibiotics reach the market to counterbalance the rapid development of AMR, and the problem is exacerbated by the lack of financial incentives for pharmaceutical companies to develop new antibiotics.\[5,6\] It has been estimated that 700,000 deaths annually is caused by antimicrobial-resistant infections, where at least 50,000 lives is claimed every year in Europe and the USA alone. Furthermore, it has been predicted that the continued rise in resistance could lead to approximately 300 million people dying prematurely and a loss of over 7% GDP of the world economy, or 210 trillion USD by year 2050. If not tackled properly, AMR could also lead to a significant decrease in life quality through the effacement of the modern medicine, as the current health care treatments are heavily dependent on antibiotics. Thus, even standard medical procedures such as hip replacement or appendix removal could become too dangerous to perform due to the risk of life-threatening bacterial infections.\[1\] It is evident that the current practices of antibiotic use are no longer sustainable and an alternative to the classical antibiotic therapies is needed.

1.2 Antivirulence Drugs

Classical antibiotics operate by inhibiting essential bacterial functions necessary for in vitro survival or growth.\[11\] However, bacteria can effectively acquire drug resistance through de novo mutations and horizontal gene transfer. In consequence, the mode of action of antibiotics resulting in reduction of viability typically allows resistant strains to grow in competition-free environment, and thus, strongly select for AMR.\[9\] Treatments based on novel modes of action, targeting bacterial virulence without affecting the in vitro viability of the microbes could be a potential solution, possibly generating a weaker selection for resistance.\[11,12\] Virulence is defined as a measure of
pathogenicity of an organism and the ability of the organism to cause disease, where virulence factors, non-essential to in vitro growth agents such as toxins or proteases, allow pathogens to invade the host, cause damage and evade host defences.\textsuperscript{[10]} Antivirulence drugs act in vivo by inhibiting virulence factors or virulence mechanisms without affecting viability of the microorganisms, and thus, theoretically, they allow for clearance of the infection by the host immune system.\textsuperscript{[11]} Moreover, as antivirulence agents do not kill bacteria and are pathogen specific, they could potentially cause significantly less damage to the beneficial gastrointestinal tract microbiota than standard antibiotics, and in consequence, eliminate the post-antibiotic predisposition of the host to secondary infections and minimise the risk of colonisation with drug resistant microbes.\textsuperscript{[13]} These antimicrobials typically target bacterial virulence by inhibiting toxin function or delivery through specialised secretory systems, bacterial adhesion, regulation of organism-specific virulence gene expression or cell-to-cell signalling.\textsuperscript{[11,14-16]}

Antivirulence drugs are not intended to harm bacteria, and they are typically characterised by narrow spectrum and various modes of action. Thus, at the advent of the antivirulence agents, it was believed that the drugs could be ‘evolution-proof’, causing significantly less selective pressure for AMR than antibiotics.\textsuperscript{[11,14-16]} Today, however, it is evident that these drugs are not completely evolution-proof with a number of reports of resistant strains isolated in laboratory and clinical settings.\textsuperscript{[17-20]} Allen et al. proposed that selection for resistant strains against antivirulence drugs could be predicted based on the role and function of the affected virulence factors.\textsuperscript{[21]} Antivirulence drugs were predicted to select against resistant strains when virulence factors are not beneficial to the pathogen, or when they are collectively beneficial to a well-mixed population at a site of the treatment. Although it is arguable whether there are virulence factor that can confer no benefit to a pathogen during infection, theoretically, in such case, targeting virulence should not result in selective pressure for AMR, but could even completely select against virulence due to the increased metabolic costs of the virulence factor expression in drug resistant organisms. Inhibition of virulence resulting in a well-mixed population of resistant individuals, producing collectively beneficial virulence factors, and non-virulent ‘cheat’ bacteria, could lead to a complete exploitation of the resistant organisms by the non-resistant individuals, thus, strongly selecting against AMR. Allen et al. also proposed that antivirulence agents should generate relatively weak selection for AMR by acting on quorum sensing-controlled virulence factors and conditionally beneficial or conditionally expressed virulence factors. Environmental specificity was predicted to weaken a development of resistance through restricting the exposure to selection and mutational supply. Lastly, antivirulence drugs were predicted to select for resistant strains when beneficial virulence factors and collectively beneficial virulence factors in structured populations are targeted. When virulence factors contribute to the fitness of the pathogen in a host, inhibition of the virulence will be detrimental to the pathogen, and thus, it is expected to select for AMR. In appropriately structured populations of pathogens, beneficial virulence factors produced by resistant individuals could benefit colonially related organisms, promote cooperation, and therefore, select for AMR. Currently, however, the exact prediction of the effect of the ativirulence drugs on AMR is a very difficult task due to generally poor understanding of the microbial costs and benefits conferred by bacterial virulence.\textsuperscript{[21]}

Not all antivirulence drugs are ‘evolution-proof’, and inevitably some AMR is expected to be developed against future antivirulence treatments. However, in comparison to traditional antibiotics where AMR is always beneficial to pathogens, the resistance against antivirulence agents, depending on the target, could appear at
significantly lower rate or even, in some cases, not at all. This should result in longer market lifetimes of antivirulence drugs, and therefore, financial incentives to pharmaceutical companies. Although more work should be done in order to fully elucidate and understand bacterial virulence and the effects of its inhibition, it is evident that antivirulence agents offer promising, potentially life-saving solution to the current problem with AMR.

1.3 Stilbenoids – Natural Plant Products with Medicinal Significance

Plants and their natural products have been utilised as medicines for thousands of years.[22,23] First records of the use of plants to treat ailments date already to circa 2600 BC and originate from ancient Mesopotamia.[22] In modern times, however, natural plant products are still significant and crucial element of the medicine as well as a very important source of structures for development of novel pharmaceuticals.[24] We have been interested in one particular group of the natural products, stilbenoids, which has been increasingly gaining popularity in the scientific community due to its wide spectrum of biological activities and intriguing molecular structures.

Stilbenoids, hydroxylated derivatives of stilbene, are a family of plant polyphenols originating in phenylpropanoid pathway, which are often characterised by complex molecular structures.[25-30] They are known for their vast spectrum of diverse biological activities and numerous positive effects on human health, including, among others, antioxidant, anticancer, antidiabetic, antifungal, antiaging and cardioprotective properties.[e.g. 31-45] Resveratrol (1) is one of the most well-known and extensively studied stilbenes, and it is also a very important building block for formation of a vast diversity of more complex stilbenoids.[28] Resveratrol oligomers are believed to be synthesised in plants chiefly as phytoalexins, in order to defend the plants from infections or injuries.[28,46-48] The first characterised resveratrol oligomer was (-)-hopeaphenol (2). This resveratrol tetramer, first isolated in 1951 from a Thai medicinal plant, Hopea odorata, has been recently reported to exhibit micromolar antivirulence activity in Yersinia pseudotuberculosis and Pseudomonas aeruginosa cell-based assays, by acting against type III secretion system (T3SS).[49-53] T3SS is a generally conserved syringe-like protein complex that allows pathogens to inject virulence effectors into host cytosol, typically causing disruption of crucial cellular processes, including cell cycle progression, gene expression, programmed cell death or vesicular trafficking.[11,54] Therefore, T3SS is an attractive target for development of novel antivirulence agents. Moreover, compound 2 was shown not to exert any significant effect on the growth of the assessed panel of Gram-negative and Gram-positive bacteria, and it also reduced cell entry and intracellular growth of Chlamydia trachomatis.[53] Resveratrol dimers: natural products, ɛ-viniferin (3), viniferifuran (4a), ampelopsin B (5) and so far not found in nature dehydroampelopsin B (6a), are characterised by the structures closely related to (-)-hopeaphenol. Compound 3 has been recognised as an important intermediate in a biosynthesis of more complex resveratrol oligomers based on benzofuran cores,[26-28] and it was also hypothesised that 6 could exist in nature as it constitute the core of natural products shoreaketone (7) and malibatol A (8).[55] Interestingly, similarly to 2, compounds 3 and 4a have been found to exhibit inhibitory activity against T3SS in Y. pseudotuberculosis and P. aeruginosa [unpublished data, Vo et al.]. Though, in contrast to (-)-hopeaphenol (2), those stilbenoids were also characterised by considerable cytotoxicity in eukaryotic cell cultures [unpublished data, Vo et al.]. We hypothesised, however, that a synthesis of analogues and derivatives of 3 and 4a, as well as 5 and 6a, could potentially produce potent T3SS inhibitors with no or minimal cytotoxicity, at the same time
fulfilling the requirements of the Lipinski’s rule of five for orally bioavailable drugs.\[56\]

Figure 1. Molecular structures of selected stilbenoids.

Due to a growing interest in stilbenoids over the past decade, numerous synthetic methods employing both biomimetic and de novo strategies have been developed. Biomimetic methods typically utilise enzyme or metal based oxidative dimerisation reactions of stilbenoid monomers.\[28,57-59\] However, as biomimetic strategies typically do not allow for easy modifications of the structures, a multitude of de novo syntheses emerged. De novo synthesis of resveratrol dimers was pioneered by Snyder and colleagues in 2007,\[60\] followed by a large number of innovative syntheses of complex stilbenoids by various research groups.\[61-71\] Following recent and successful total syntheses of compounds 3, 4a, 5 and 6a,\[55,72\] we focused on incorporating indole, benzo[b]thiophene as well as benzo[b]selenophene cores into the scaffolds of those natural products. Herein, we report the total syntheses of indole-, benzo[b]thiophene- and benzo[b]selenophene-based analogues (4b-e and 6b-e) of viniferifuran (4a) and dehydroampelopsin B (6a), as potential antivirulence agents which could inhibit T3SS in Y. pseudotuberculosis and P. aeruginosa.

1.4 Aim and Objectives

The aim of the study is to synthesise novel analogues of viniferifuran and dehydroampelopsin B, based on indole (4b-c and 6b-c), benzo[b]thiophene (4d, 6d) and benzo[b]selenophene (4e, 6e) cores. Total syntheses of the target molecules will be based on de novo approach, where concise and modular synthetic pathways will be designed, starting from reasonably priced and commercial available materials. This should allow for straightforward future structural modifications and potential creation of a compound library, if necessary. The key transformations will be based on
palladium-catalysed coupling reactions, which should result in reliable reactivity, good chemo-selectivity and considerable flexibility in terms of reagent choice. We intend to synthesise the analogues as potential novel antivirulence agents with an intention of future testing against T3SS in *Y. pseudotuberculosis* and *P. aeruginosa*.

### 2. Popular Scientific Summary

Today, we are standing on the verge of the dreadful post-antibiotic era, where microbes are resistant to the known antibiotics. The problem is caused by the short antibiotic life-times, antibiotic misuse and overuse, as well as, high costs of antibiotic development and lack of financial incentives for pharmaceutical companies.\(^4\)\(^-\)\(^6\) If the problem of the antibiotic resistance is not resolved, 300 million people could die prematurely over the next 30 years, generating astronomical medical costs and straining the global economy.\(^1\) Widespread of antibiotic resistance means also that the standard medical procedures could become unavailable, due to a high dependence of the modern medicine on antibiotics, thus, significantly decreasing our quality of life. A promising solution to this problem could be a development of a new type of drugs - antivirulence agents, which in contrast to antibiotics, do not kill bacteria and do not halt their growth, but instead, they disarm the pathogens, preventing them from causing damage to the infected host. Thus, antivirulence drugs are expected to be significantly less affected by microbial resistance than classical antibiotic therapies.\(^11\)\(^,\)\(^12\)

In this study, a synthetic strategy to obtain eight novel, nature-inspired molecules was developed, and subsequently, the desired compounds were produced from simple, commercially available substances, through an application of a multitude of complex chemical reactions. The target molecules were based on structures of natural plant products, where their central atom – oxygen, was replaced by nitrogen, sulphur and selenium atom. The molecules were obtained as potential antivirulence agents, and in the future study, they will be tested against pathogens to examine their antivirulence properties. If any of those novel molecules exhibit antivirulence activity, we will find ourselves one step closer to solving the dire problem of the microbial antibiotic resistance.

### 3. Social and Ethical Aspects

There are no ethical concerns regarding this research project. The target molecules and the synthesised intermediates will not be tested on humans or animals. The project was conducted according to the safety regulations of the Department of Chemistry at the Umeå University.
4. Results and Discussion

4.1 Overview of the Synthetic Strategy

It was decided to undertake a modular approach to the synthesis of the analogues, based strongly on palladium-catalysed coupling reactions, as this could potentially allow for straightforward future modifications of any structural components, and in consequence, for a relatively simple molecular library creation (Scheme 1). Target products 4b-e and 6b-e should be obtained through deprotection of structure 9. Theoretically, it should be possible to induce cyclisation of 9 to obtain seven-membered ring moiety of 6 during the deprotection step, if a Brønsted–Lowry acid is used in the reaction.\(^{73}\) Protected 9 should be afforded either via palladium-catalysed Suzuki-Miyaura\(^{74}\) or Heck reaction,\(^{75}\) or through phosphonate-based Horner-Wadsworth-Emmons (HWE) reaction with 10.\(^{76}\) Both approaches could potentially afford high trans-isomer selectivity. Depending on the reaction choice to reach 9, either halide or aldehyde group should be present at position C-4 in compound 10. Synthesis of intermediate 10, based on the indole moiety, should be achieved through palladium-catalysed Cacchi cyclisation reaction from 11, consisting of indole core formation and concomitant coupling at position C-3.\(^{77}\) Compound 10, based either on benzo[b]thiophene or benzo[b]selenophene scaffold, could potentially be reached through alkyne electrophilic cyclisation with iodine\(^{78,79}\) and subsequent chemoselective Suzuki-Miyaura cross-coupling at position C-3. Intermediates 11 and 13 should be obtained in yet another palladium-catalysed transformation, Sonogashira coupling, from relatively simple molecules 12 and 14, respectively.\(^{80}\) The syntheses will be attempted with methyl protective groups, however, if necessary, alternatives such as cyclopropymethyl or acetyl protective groups could be potentially utilised.

![Scheme 1](image)

Scheme 1. Overview of the synthetic strategy to achieve analogues of viniferifuran and dehydroampelopsin B, based on indole, benzo[b]thiophene and benzo[b]selenophene cores.

4.2 Synthesis of Permethylated Indole-based Analogues

Synthesis of the indole-based targets 4b,c and 6b,c was attempted starting from commercially available 2-bromo-4-methoxy-6-nitrophenol (15) (Scheme 2). Compound 15 was transformed into 16 by reducing the nitro to amino group, using Zn and NH\(_4\)Cl in 91% yield. This was followed by protection/activation of the amino group with trifluoroacetyl group by treatment with TFAA/TEA, which gave 17 in excellent yield. The trifluoroacetyl group had been introduced in a preparation for
Cacchi cyclisation, where the appropriate pKa of the NH moiety seems to be a crucial factor in the reaction, and naked amino group typically fails to give the expected product.[81]

Scheme 2. Attempted synthesis towards indole-based analogues of viniferifuran and dehydroampelopsin
B. Intermediate 11a could not be obtained with the tested reaction conditions.

Compound 17 was then transformed, through triflation of the hydroxyl group, into 12 in 93% yield, by using PhNTf₂ and NaH. Different Sonogashira coupling conditions were tested in order to obtain the key target intermediate 11a (Table 1), which would further allow formation of the indole core, possibly in a one-pot procedure. Unfortunately, no 11a was detected under any of the assessed conditions, but, it appeared that in copper-free reactions with Pd(OAc)₂ or PdCl₂, XPhos and Cs₂CO₃ in DMF, compound 19 and/or 18 were synthesised instead. This observation clearly indicated that the bromo position on 12 was more activated towards the Sonogashira coupling than the OTf position. As in general case aryl triflates are often more reactive towards Sonogashira coupling than aryl bromides, we assumed that the OTf position in compound 12 must have been deactivated through a higher electron density than at the bromo position.[82] The synthetic scheme was revised (Scheme 3), and the Sonogashira coupling with 4-ethynylanisole was decided to be performed on a relatively electron poor substrate. In order to further increase the efficiency of the coupling, it was decided to eliminate the competitive coupling site and replace the bromo group with an aldehyde group.

Table 1. Attempted Sonogashira coupling reactions with compound 12 and 4-ethynylanisole under different reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Components</th>
<th>Temp. (°C)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>11a</td>
</tr>
<tr>
<td>1</td>
<td>Pd(OAc)₂, CuI, dppf, TEA, DMF</td>
<td>70-100</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂, CuI, TBAI, TEA, DMF</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh₃)Cl₂, CuI, TMG, DMF</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂, XPhos, Cs₂CO₃, DMF</td>
<td>50-80</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>PdCl₂, XPhos, Cs₂CO₃, DMF</td>
<td>50-80</td>
<td>0</td>
</tr>
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</table>
The revised synthetic pathway started with a synthesis of relatively electron poor 21 from reasonably priced and commercially available 2-hydroxy-5-methoxy-3-nitrobenzaldehyde (20). Starting compound 20 was treated with Tf₂O and TEA in DCM, in order to introduce the triflate group. Interestingly, 21 could not be obtained with PhNTf₂. Synthesis of 21 was followed by a Sonogashira coupling reaction. A number of different coupling conditions were tested (Table 2), and the best result was achieved with Pd(PPh₃)₄, 2,6-lutidine and CuI in 1,4-dioxane at 60 °C, giving 22 in very good and reproducible yield of 81%. This result is in agreement with the observations of Dakin et al., who found that using 2,6-lutidine as base and 1,4-dioxane as solvent, in comparison to alternative coupling conditions, significantly diminished decomposition of unstable triflate-containing reagent, and in consequence, greatly increased the yield. Surprisingly, when TBAI was used as an additive in our reaction, in contrast to our expectations, the yield decreased almost by half, and the reaction time had to be increased significantly in order to achieve a full substrate conversion (entry 4, Table 2). The synthesis was then further optimised by performing the triflyation and the Sonogashira coupling in one protocol, without chromatographic purification of prone to hydrolysis 21, affording 22 in 64% yield over two steps.

![Scheme 3. Preparation of permethylated indole-based analogues of viniferifuran (9a and 9b).](image)

**Table 2. Attempted Sonogashira coupling reactions between purified 21 and 4-ethynylanisole.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd] Catalyst</th>
<th>Base</th>
<th>Other Components</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time</th>
<th>Isolated Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₂Cl₂</td>
<td>TEA</td>
<td>CuI</td>
<td>MeCN</td>
<td>60</td>
<td>Overnight</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₂Cl₂</td>
<td>TMG</td>
<td>CuI</td>
<td>MeCN</td>
<td>60</td>
<td>Overnight</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>Cs₂CO₃</td>
<td>XPhos</td>
<td>MeCN</td>
<td>60</td>
<td>Overnight</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₄</td>
<td>Lutidine</td>
<td>CuI, TBAI</td>
<td>Dioxane</td>
<td>60</td>
<td>2 days</td>
<td>44</td>
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<tr>
<td>5</td>
<td>Pd(PPh₃)₄</td>
<td>TEA</td>
<td>CuI, TBAI</td>
<td>Dioxane</td>
<td>60</td>
<td>Overnight</td>
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<td>Pd(PPh₃)₂Cl₂</td>
<td>TEA</td>
<td>CuI</td>
<td>DMF</td>
<td>60</td>
<td>60 days</td>
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<tr>
<td>7</td>
<td>Pd₂(dbta)₃CHCl</td>
<td>DIPEA</td>
<td>Ph(o-tol)₃</td>
<td>THF</td>
<td>60</td>
<td>Overnight</td>
<td>65</td>
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<td>Pd(PPh₃)₂Cl₂</td>
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<td>CuI</td>
<td>Dioxane</td>
<td>60</td>
<td>60 days</td>
<td>70</td>
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<td>CuI</td>
<td>Dioxane</td>
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<td>CuI</td>
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</tbody>
</table>
Next, the nitro group in 22 needed to be selectively reduced in presence of a triple bond and aldehyde group directly attached to the aromatic ring. Various methods were tested including protocols based on reduction with SnCl₂, Zn and NH₄Cl, In and HCl, Na₂S₂O₄ and NH₄OH, as well as, Fe and CaCl₂. However, the most optimal result was achieved using Fe with HCl in a mixture of EtOH, THF and H₂O, between 80 °C and 90 °C. Subsequently, intermediate 11b was synthesised from compound 23 using TFAA/TEA, in good yield of 49% over two steps. After some optimisation, synthesis of the key molecule 10a was successfully achieved by Cacchi cyclisation in excellent 94% yield. The transformation was achieved cleanly with iodide 25, Pd(PPh₃)₄ as catalyst and Cs₂CO₃ as base in dry MeCN under microwave irradiation (MWI) at 100 °C. No premature cyclisation and formation of non-substituted at position C-3 indole by-product was detected. It was noted, however, that the Cacchi cyclisation did not occur unless the used reagents, 25 and 11b, were of satisfactorily high purity. Synthesis of the final permethylated scaffold 9a, directly from 10a, was attempted with HWE reaction using phosphonate 27 and NaH in THF under MWI[55], but complex mixtures were formed in the process, with only trace amount of the desired product. To solve this problem, it was decided to incorporate a protective group onto the indole nitrogen. Protection of 10a with TIPS using TIPSCl and NaH failed, possibly due to high sterical hindrance between the reagents. However, protection with Boc, Cbz and allyl groups was possible, allowing to successfully perform HWE reaction. Overall, protection and the HWE reaction were the most efficient when Boc group was used. Boc cleavage from the main product of the HWE reaction was achieved in one pot with TBAF hydrate and MWI at 120 °C, using modified method developed by Routier et al.,[84] affording the target permethylated indole-based analogue 9a in very good yield of 81%. Interestingly, any attempts of cleaving Boc with aq. TFA, heat, or TIPSCl with phenol in DCM were ineffective. The milestone compound 9a was synthesised in a good overall yield of 24% over seven steps. Synthesis of 9b was achieved starting with methylation of 10a, using MeI and NaH, which gave intermediate 10c in quantitative yield. The following HWE reaction, performed under MWI, afforded 9b, the second permethylated indole-based analogue of viniferifuran, in 77% yield, and 23% overall yield over seven steps.

4.3 Synthesis of Permethylated Benzo[b]thiophene- and Benzo[b]selenophene-based Analogues

The synthesis of benzo[b]thiophene- and benzo[b]selenophene-based analogues (4d,e and 6d,e) was started by obtaining a known molecule 14 (Scheme 4). Compound 28 was treated with Br₂ in DCM/MeOH mixture to give dibrominated intermediate 29 in 55% yield.[85] Subsequently, the amino group in 29 was converted into iodide in a Sandmeyer-type reaction, using isoamyl nitrite and I₂ in benzene, resulting in compound 14 in 57% yield.[86] Molecule 30, after some optimisation, was synthesised in good yield of 70% in a sterically challenged Sonogashira coupling reaction, using standard coupling reagents at reflux. Due to a shrewd synthetic design and similarity in reactivity of the following benzo[b]thiophene and benzo[b]selenophene species, 30 could be conveniently used as a common and easy to reach intermediate for synthesis of 9c and 9d.
Compounds 13a and 13b were reached in quantitative yields by two-step procedure, involving selective lithiation of only one of the bromo positions in 30, with one equivalent of n-BuLi at -78 °C, followed by an addition of Me2S2 or Me2Se2. It was planned that this transformation would be followed by electrophilic cyclisation reactions with I2, based on a method developed by Larock and colleagues. The cyclisation was supposed to occur at rt; however, in order to obtain 31 it was needed to apply relatively harsh conditions and heat the reaction mixture to 80 °C in a microwave reactor for at least one hour. Benzo[b]thiophene 31a and benzo[b]selenophene 31b were obtained in excellent yield of 98% and 96%, respectively. The next reaction, Suzuki-Miyaura coupling between 31 and 3,5-dimethoxyphenylboronic acid, proved to be very challenging due to prevalent deiodination of 31 and unwanted double coupling at both iodo and bromo position. Extensive screening of reaction conditions was performed, testing various combinations of numerous catalysts, bases, solvent mixtures, temperatures and concentrations under conventional as well as microwave heating. As a result of our efforts, we managed to successfully synthesise and isolate Suzuki products 10d and 10e, both in satisfactory yield of 49%. The optimal protocol was highly reproducible and involved using Pd(dppf)Cl2·DCM complex, K3PO4, 1,4-dioxane/H2O in 6:1 ratio and heating in a microwave reactor. Lastly, the permethylated analogues, 9c and 9d, were obtained in a second Suzuki-Miyaura reaction, catalysed by Pd2(dba)3·CHCl3 complex aided by SPhos, in presence of K3PO4. It appeared that the volume ratio of 1,4-dioxane/H2O used in the reaction had tremendous impact on the reaction efficiency, and the ratio of 6:1 was found to give satisfactory results. The permethylated analogues, 9c and 9d, were synthesised in five steps from known compound 14 in overall yield of 27% and 28%, respectively.

4.4 Deprotection and Cyclisation

Demethylation of compounds 9a-d was attempted with BBr3 in DCM. Indole based molecules 4b and 4c were afforded in satisfactory 39% and 56% yield, respectively, when compounds 9a and 9b were treated with BBr3 over 24h (entry 1 and 2, Table 1). When the same reaction conditions were applied to 9c and 9d, products 4d and 4e were obtained in 26% and 28% yield, respectively (entry 3 and 5, Table 1). However
in all tested reactions, the deprotection always occurred with partial, concomitant cyclisation to 6, forming internal seven-membered ring. Cyclisation seemed to occur more extensively with benzo[b]thiophene- and benzo[b]selenophene-based molecules than with the indole-based compounds, giving 6d in 23% yield and 6e in 20% yield, when the reaction mixtures were stirred from -78 °C to rt. Decreasing the temperature range and stirring at maximum -30 °C, resulted in slight increase in yields of 4d (28%) and 4e (34%), and decrease in cyclisation (6d, 16% yield; 6e, 14% yield). This tentatively suggested that the cyclisation of the benzo[b]thiophene- and benzo[b]selenophene-based molecules was, to some extent, controlled kinetically (entry 4 and 6, Table 1). Decreasing the temperature also resulted in significantly lower reaction rate, increasing the reaction time from 1 day to 3 days.

When an old bottle of BBr₃ was used for deprotection of indole 9a in a pilot reaction, a 1:1 mixture of uncyclised/cyclised products was obtained. This suggested that the possible moisture content in the bottle, translated into HBr presence in the BBr₃ mixture, resulted in the significant amount of cyclisation. This hypothesis was tested by treating 9a-d with fresh BBr₃ and 47% aq. HBr. This resulted in formation of the demethylated and cyclised target structures 6b-e as the main products (entries 8-11, Table 3). Although the indoles 6b and 6c were obtained in rather modest yields, the cyclised benzo[b]thiophene- and benzo[b]selenophene-based molecules were afforded in respectable yields of 49% and 45%, respectively, with only trace amounts of the uncyclised products.

**Table 3. Demethylation and cyclisation of compounds 9a-d.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>BBr₃ used (eq.)</th>
<th>Temp. (°C)</th>
<th>aq. HBr added</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH</td>
<td>6</td>
<td>-78 to rt</td>
<td>No</td>
<td>24h</td>
<td>39% (4b) 5% (6b)</td>
</tr>
<tr>
<td>2</td>
<td>NMe</td>
<td>6</td>
<td>-78 to rt</td>
<td>No</td>
<td>24h</td>
<td>56% (4c) 9% (6c)</td>
</tr>
<tr>
<td>3</td>
<td>S</td>
<td>6</td>
<td>-78 to rt</td>
<td>No</td>
<td>24h</td>
<td>26% (4d) 23% (6d)</td>
</tr>
<tr>
<td>4</td>
<td>S</td>
<td>6</td>
<td>-80 to -30</td>
<td>No</td>
<td>3 days</td>
<td>28% (4d) 16% (6d)</td>
</tr>
<tr>
<td>5</td>
<td>Se</td>
<td>6</td>
<td>-78 to rt</td>
<td>No</td>
<td>24h</td>
<td>28% (4e) 20% (6e)</td>
</tr>
<tr>
<td>6</td>
<td>Se</td>
<td>6</td>
<td>-80 to -30</td>
<td>No</td>
<td>3 days</td>
<td>34% (4e) 14% (6e)</td>
</tr>
<tr>
<td>7</td>
<td>NH</td>
<td>15 + 15ᵃ</td>
<td>0 to rt</td>
<td>Yes</td>
<td>3 days</td>
<td>Decomposition</td>
</tr>
<tr>
<td>8</td>
<td>NH</td>
<td>15</td>
<td>-78 to rt</td>
<td>Yesᵇ</td>
<td>24h</td>
<td>10% (4b) 19% (6b)</td>
</tr>
<tr>
<td>9</td>
<td>NMe</td>
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<td>Overnight</td>
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</tr>
<tr>
<td>10</td>
<td>S</td>
<td>15</td>
<td>0 to rt</td>
<td>Yes</td>
<td>Overnight</td>
<td>1.5% (4d) 49% (6d)</td>
</tr>
<tr>
<td>11</td>
<td>Se</td>
<td>15</td>
<td>0 to rt</td>
<td>Yes</td>
<td>Overnight</td>
<td>1.5% (4e) 45% (6e)</td>
</tr>
</tbody>
</table>

ᵃ The reaction was started with 15 eq. of BBr₃, and due to incomplete demethylation another 15 eq. of BBr₃ were added after 1.5 days.ᵇ Aq. HBr was added after demethylation was complete.
5. Conclusions and Outlook

In conclusion, successful strategies for the synthesis of a number of analogues (4b-e, 6b-e) of viniferifuran (4a) and dehydroampelopsin B (6a) have been reported. To our knowledge, those are the first examples of resveratrol oligomers based on heteroatom different than oxygen. The indole-based analogues (4b,c and 6b,c) were synthesised over eight steps from commercially available 2-hydroxy-5-methoxy-3-nitrobenzaldehyde (20). The benzo[b]thiophene- and benzo[b]selenophene-based analogues were obtained in six steps from known compound 1,3-dibromo-2-iodo-5-methoxybenzene (14) or in eight steps from commercially available 4-methoxyaniline (28). Due to a modular design of the synthetic pathways, potential modification to the structures could be easily applied, thus, theoretically allowing to create a library of related molecules. Moreover, the strategies presented herein have a potential to be applied for synthesis of a variety of other stilbenoid-inspired structures and natural product analogues. The synthesised permethylated viniferifuran analogues (9a-d), as well as, the demethylated cyclised and uncyclised products (4b-e, 6b-e) will be tested in biological assays against T3SS in P. aeruginosa and Y. pseudotuberculosis, as part of the further study towards novel antivirulence agents.
6. Experimental

6.1 General Methods

All air and moisture sensitive reactions were performed under an inert atmosphere of N₂ gas, and the moisture sensitive reactions were carried out in oven- or flame-dried glassware. If not stated otherwise, all reagents and solvents were purchased from commercial suppliers: Sigma-Aldrich, Alfa-Aesar, Acros, Cobi-Blocks, Fluorochem, Fisher or VWR. Organic solvents for moisture sensitive reactions were obtained from a dry solvent system (Glass Contour Solvent Systems, SG Water USA), except MeCN, which was dried by distillation from CaH₂ and stored over activated 3Å molecular sieves. Microwave reactions were carried out in Biotage Initiator EXP EU and Biotage Initiator+ EU (Biotage Sweden AB, Sweden). TLC analyses were performed on aluminium sheets coated with silica gel 60 F₂₅₄ from Merck, and visualisation was achieved by UV light at 254 or 366 nm or a solution of vanilline in EtOH and H₂SO₄. LC-MS analyses were performed using Agilent 1260 Infinity with 6130 Quadrupole (Agilent Technologies, USA) equipped with Agilent Prosholl 120 EC-C18 2.7 μm 3 x 50 mm column and H₂O/CH₃CN (0.1% HCOOH) as the eluent system, and detection at 210 and 254 nm. Purification by flash chromatography was performed either manually on 70-230 mesh silica gel (Merck) or automatically on Biotage Isolera One system with Biotage SNAP KP-SIL 50 μm or Biotage SNAP Ultra 25 μm silica gel cartridges. HPLC purification was done on a Agilent 1260 Infinity HPLC system equipped with Macherey-Nagel Nucleodur C18 HTEc 5 μm 21 x 250 mm column (Macherey-Nagel GmbH & Co. KG, Germany), with a flow rate 20 ml/min, detection at 210 and 254 nm and the eluent system: 25% → 95% MeOH in H₂O over 30 min. HRMS analyses were performed using Agilent 6230 Accurate-Mass TOF LC-MS with electrospray ionisation. The NMR spectral data were recorded at 298 or 299K on a Bruker DRX 400 MHz, 600 MHz or Bruker Acend 850 MHz spectrometer (Bruker Corporation, USA). The δ values were referenced to the residual solvent signals of CDCl₃ (7.26 ppm), DMSO-d₆ (2.50 ppm) or acetone-d₆ (2.05 ppm) as an internal standard for ¹H, and CDCl₃ (77.16 ppm), DMSO-d₆ (39.52 ppm) or acetone-d₆ (29.84 ppm) as an internal standard for ¹³C.¹³⁷

6.2 Synthesis of Indole-based Analouges

1-Iodo-3,5-dimethoxybenzene (25) was prepared following the previously reported procedure.¹⁸⁸ To a mixture of 3,5-dimethoxyaniline (675 mg, 4.41 mmol), H₂O (8 ml) and 12M aq. HCl (2.70 ml, 32.9 mmol), cooled down to 0 °C, was added NaNO₂ (366 mg, 5.31 mmol) portion-wise. KI (7.325 g, 44.13 mmol) was added portion-wise at 0 °C, and the reaction mixture was stirred at 0 °C for 1h. The mixture was slowly warmed up to rt and was further stirred for 21h. To the mixture was added aq. Na₂SO₃, and the product was extracted with Et₂O (5x), the combined organic layers were washed with water, sat. brine, dried (Na₂SO₄), and the solvent was evaporated in vacuo affording oily crude product. The crude was purified by flash chromatography (silica gel, 2% → 20% EtOAc in heptane) yielding the title compound 25 as white crystals (727 mg, 2.75 mmol, 63%): ¹H NMR (727 mg, 2.75 mmol, 63%): ¹H NMR (400 MHz, CDCl₃): δ [ppm] 6.86 (d, J = 2.2 Hz, 2H), 6.40 (t, J = 2.2 Hz, 1H), 3.76 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] 161.2, 115.9, 100.8, 94.2, 55.6. The spectral data agreed with the previously reported results.
Diethyl 4-methoxybenzylphosphonate (27) was synthesised following a modification of the previously reported protocol. A mixture of 4-methoxybenzyl chloride (2.00 ml, 14.7 mmol) and triethyl phosphite (2.53 ml, 14.8 mmol) was heated at 130 °C for 3 days in a sealed vial. The reaction mixture was diluted with EtOAc and washed with water, sat. brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to afford compound 27 as light yellow oil (quant., approx. 90% purity based on NMR, residual triethyl phosphate detected): $^1$H NMR (400 MHz, CDCl$_3$): δ [ppm] 7.20 (m, 2H), 6.84 (m, 2H), 4.05 – 3.93 (m, 4H), 3.78 (s, 3H), 3.08 (d, $J$ = 21.1 Hz, 2H), 1.23 (t, $J$ = 7.1 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ [ppm] 158.7 (d, $J_{P-C}$ = 3 Hz), 130.8 (d, $J_{P-C}$ = 7 Hz), 123.5 (d, $J_{P-C}$ = 9 Hz), 114.1 (d, $J_{P-C}$ = 3 Hz), 62.2 (d, $J_{P-C}$ = 7 Hz), 55.3, 32.9 ($J_{P-C}$ = 139 Hz), 16.5 (d, $J_{P-C}$ = 6 Hz); $^{31}$P NMR (162 MHz, CDCl$_3$): δ [ppm] 26.8. The spectral data were found to be in accordance with the previously reported results. The product was used without further purification, except for synthesis of 9a, where prior to the reaction 27 was purified by distillation at reduced pressure.

5-Methoxy-2-((4-methoxyphenyl)ethynyl)-3-nitrobenzaldehyde (22).

5-Methoxy-2-((4-methoxyphenyl)ethynyl)-3-nitrobenzaldehyde (22).

5-Methoxy-2-((4-methoxyphenyl)ethynyl)-3-nitrobenzaldehyde (22).
was removed in vacuo, and the remaining mixture was diluted with EtOAc, washed with diluted aq. NaCl solution, back-extracted with EtOAc (3x), washed with sat. brine and dried (Na₂SO₄). The solvent was evaporated in vacuo, affording crude brown oil containing 3-amino-5-methoxy-2-((4-methoxyphenyl)ethynyl)benzaldehyde (23). The oil was dissolved in dry THF (60 ml), and dry TEA (940 μl, 6.7 mmol) was added. The solution was cooled to 0 °C, and TFAA (540 μl, 3.9 mmol) was added drop-wise. The reaction mixture was stirred overnight at rt under N₂. The reaction mixture was quenched with water, sat. brine was added, and the mixture was diluted with EtOAc. The organic phase was separated and the aq. phase was back-extracted with EtOAc (3x). All organic phases were combined, washed with brine, dried (Na₂SO₄) and evaporated in vacuo. The afforded crude product was purified by flash chromatography (silica gel, 10% → 38% DCM in heptane; heptane contained 2% TEA) yielding 11b as yellow solid (598 mg, 1.59 mmol, 49%): ¹H NMR (600 MHz, DMSO- d₆): δ [ppm] 11.41 (s, 1H), 10.48 (s, 1H), 7.50 (m, 2H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 2.7 Hz, 1H), 7.03 (m, 2H), 3.89 (s, 3H), 3.80 (s, 3H); ¹³C NMR (151 MHz, DMSO-d₆): δ [ppm] 190.8, 160.0, 159.1, 155.2 (q, J_F-C = 37 Hz), 138.4, 137.1, 132.9, 119.0, 116.0 (q, J_F-C = 288 Hz), 115.7, 114.5, 113.7, 110.5, 99.7, 80.1, 56.0, 55.3.

3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-1H-indole-4-carbaldehyde (10a).

A mixture of 11b (414 mg, 1.10 mmol), 25 (406 mg, 1.54 mmol), Pd(PPh₃)₄ (63.4 mg, 0.055 mmol) and Cs₂CO₃ (1.08 g, 3.32 mmol) was flushed with N₂. Degassed, dry MeCN (19.5 ml) was added, and N₂ was bubbled through the mixture. The reaction mixture was stirred at 100 °C for 40 min in a microwave reactor. The reaction mixture was diluted with EtOAc, washed with water, sat. brine, dried (Na₂SO₄), and the solvent was evaporated in vacuo. Purification with flash chromatography (silica gel, 5% to 32% EtOAc in toluene; toluene contained 1% TEA; the impure fractions were further purified with chromatography: silica gel, 5% → 44% EtOAc in heptane; heptane contained 1% TEA) yielded 10a as orange solid (428 mg, 1.03 mmol, 94%): ¹H NMR (600 MHz, DMSO-d₆): δ [ppm] 11.74 (s, 1H), 9.75 (s, 1H), 7.38 (m, 2H), 7.24 (d, J = 2.5 Hz, 1H), 7.17 (d, J = 2.5 Hz, 1H), 6.93 (m, 2H), 6.55 (t, J = 2.2 Hz, 1H), 6.54 (d, J = 2.2 Hz, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 3.72 (s, 6H); ¹³C NMR (151 MHz, DMSO-d₆): δ [ppm] 189.9, 161.0, 158.8, 154.9, 139.4, 138.0, 135.8, 130.7, 128.7, 128.1, 124.6, 124.1, 114.0, 111.9, 108.7, 106.1, 101.7, 99.3, 55.6, 55.2, 55.1.

tert-Butyl 3-(3,5-dimethoxyphenyl)-4-formyl-6-methoxy-2-(4-methoxyphenyl)-1H-indole-1-carboxylate (10b).

To a mixture of 10a (60 mg, 0.14 mmol) and DMAP (2 mg, 0.02 mmol) in dry MeCN (2.6 ml) was added a solution of Boc anhydride (39 mg, 0.18 mmol) in dry MeCN (400 μl). The reaction mixture was stirred for 5h at rt under N₂, then, it was quenched with aq. NH₄Cl, extracted with EtOAc (3x), washed with sat. aq. NaHCO₃, brine, dried (Na₂SO₄) and solvent was evaporated in vacuo, affording 10b as orange solid (quant.): ¹H NMR (600 MHz, DMSO-d₆): δ [ppm] 9.61 (s, 1H), 8.06 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.24 (m, 2H), 6.89 (m, 2H), 6.47 (d, J = 2.2 Hz, 2H), 6.44 (t, J = 2.2 Hz, 1H), 3.89 (s, 3H), 3.73 (s, 3H), 3.66 (s, 6H), 1.23 (s, 9H); ¹³C NMR (151 MHz, DMSO): δ [ppm] 189.4, 160.4, 158.9, 156.8, 149.4, 137.5, 137.5, 136.9, 131.1, 128.7, 124.8, 124.5, 120.1, 113.1, 108.6, 108.2, 105.6, 99.4, 83.9, 55.8, 55.2, 55.1, 27.0.
(E)-3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-(4-methoxystyryl)-1H-indole (9a).

To a mixture of NaH (60% in oil, 87 mg, 2.2 mmol) and compound 10a (350 mg, 0.676 mmol) was added a solution of 27 (524 mg, 2.03 mmol, purified by distillation under reduced pressure) in dry THF (10 ml). The reaction mixture was stirred for 1h at 70 °C in a microwave reactor under N₂, then more NaH (60% in oil, 111 mg, 0.676 mmol) was added, and the mixture was stirred for another 1h 15 min at 70 °C with a microwave assistance under N₂, before quenching with water (2.3 ml). TBAF hydrate (1.89 g, 6.76 mmol) was added, and the mixture was stirred for 2h at 120 °C in a microwave reactor, then diluted with EtOAc, washed with water, back-extracted with EtOAc (3x), and the combined organic layers were washed with sat. brine. Drying over Na₂SO₄, evaporation under reduced pressure, followed by purification with flash chromatography (silica gel, 15% → 45% EtOAc in heptane) yielded product 9a as yellow solid (285 mg, 0.547 mmol, 81%): ¹H NMR (600 MHz, DMSO-d₆): δ [ppm] 11.28 (s, 1H), 7.37 (m, 2H), 7.00 – 6.94 (m, 4H), 6.91 – 6.87 (m, 3H), 6.84 – 6.81 (m, 3H), 6.65 (t, J = 2.3 Hz, 1H), 6.50 (d, J = 2.3 Hz, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.70 (s, 6H); ¹³C NMR (151 MHz, DMSO-d₆): δ [ppm] 160.6, 158.6, 158.2, 155.8, 139.9, 137.1, 132.8, 130.3, 130.1, 128.3, 127.1, 126.7, 125.0, 123.9, 121.2, 113.9, 113.9, 113.2, 109.6, 104.3, 98.6, 93.9, 55.3, 55.2, 55.1, 55.1.

3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-1-methyl-1H-indole-4-carbaldehyde (10c).

NaH (60% in oil, 48 mg, 1.2 mmol), washed with hexane (4x), was suspended in dry THF (1 ml), and a solution of 10a (200 mg, 0.479 mmol) in dry THF (5 ml) was added drop-wise at 0 °C. The suspension was stirred at 0 °C for 15 min and then at rt for another 15 min. MeI (88.4 mg, 0.642 mmol) in dry THF (2 ml) was added at 0 °C, and the mixture was stirred at rt for 1h under N₂. The reaction mixture was quenched with diluted aq. solution of NaCl, extracted with EtOAc (3x), washed with sat. brine, dried (Na₂SO₄), and the solvent was evaporated in vacuo, yielding 10c as orange solid (quant.): ¹H NMR (400 MHz, DMSO-d₆): δ [ppm] 9.89 (s, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.30 (m, 2H), 7.22 (d, J = 2.3 Hz, 1H), 6.96 (m, 2H), 6.43 (d, J = 2.2 Hz, 2H), 6.41 (t, J = 2.2 Hz, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 3.65 (s, 6H), 3.63 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ [ppm] 189.9, 160.3, 159.1, 155.1, 139.7, 138.7, 138.7, 131.9, 128.1, 122.6, 122.5, 113.7, 113.4, 108.9, 106.7, 101.1, 98.7, 55.9, 55.1, 55.1, 31.2.

(E)-3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-(4-methoxystyryl)-1-methyl-1H-indole (9b).

To a suspension of NaH (60% in oil, 56 mg, 1.4 mmol) in dry THF (0.5 ml) was added a solution of 27 (338 mg, 1.31 mmol) in dry THF (2 ml), and stirred at rt for 30 min under N₂. To the suspension was added 10c (207 mg, 0.480 mmol) in dry THF (8.5 ml), and the reaction mixture was stirred in a microwave reactor at 100 °C for 1h 40 min and 120 °C for 20 min. The mixture was quenched with a diluted aq. solution of NaCl, and the product was extracted with EtOAc (3x), washed with sat. brine, dried (Na₂SO₄), and the solvent was evaporated in vacuo. The crude product was then purified by flash chromatography (silica gel, 15% → 40% EtOAc in heptane) affording 9b as light-green solid (199 mg, 0.372 mmol, 77%): ¹H NMR (400 MHz, DMSO-d₆): δ [ppm]
7.26 (m, 2H), 7.07 (d, \( J = 2.2 \text{ Hz}, 1\text{H} \)), 7.05 – 6.97 (m, 5H), 6.94 (m, \( 2\text{H} \)), 6.82 (m, 2H), 6.50 (t, \( J = 2.3 \text{ Hz}, 1\text{H} \)), 6.40 (d, \( J = 2.3 \text{ Hz}, 2\text{H} \)), 3.88 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.62 (s, 6H), 3.56 (s, 3H) ;

\( ^{13}\text{C NMR} (100 \text{ MHz, DMSO-}d_6) \): δ [ppm] 159.9, 158.8, 158.7, 155.9, 139.0, 137.8, 136.8, 132.0, 130.3, 130.0, 127.2, 127.0, 124.1, 123.4, 119.4, 114.6, 113.9, 113.6, 109.9, 104.7, 98.0, 93.2, 55.6, 55.1, 55.1, 55.0, 30.9.

**General Procedure A:** A stirred solution of permethylated indole (1 eq.) in dry DCM (1 ml) was cooled to -78 °C, and a freshly prepared 1M solution of BBr\(_3\) in DCM (6.1 eq.) was added drop-wise under \( \text{N}_2 \). The progress of the reaction was monitored by LC-MS. The mixture was allowed to slowly warm up to rt overnight, and after stirring for a total of 24h in a relative darkness, it was quenched with sat. aq. NaHCO\(_3\) solution, and then, the mixture was immediately neutralised by adding 5% aq. citric acid solution. The mixture was extracted with EtOAc (3x), and the combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), and the solvent was evaporated under reduced pressure. Purification by flash chromatography (silica gel, 0% → 10% MeOH in DCM) gave green solid, which was further purified by HPLC.

\((E)-5-(6\text{-Hydroxy-2-(4-hydroxyphenyl)-4-(4-hydroxystyryl)}-1H\text{-indol-3-yl})\text{-benzene-1,3-diol (4b)}\).

Demethylatin of \(9a\) (30 mg, 0.057 mmol), as described in the General Procedure A, afforded \(4b\) (10.2 mg, 0.023 mmol, 39%) as light-green solid, as well as, cyclised by-product \(6b\) (1.3 mg, 0.003 mmol, 5%).

\(4b\): \( ^{1}H \text{NMR} (600 \text{ MHz, acetone-}d_6) \): δ [ppm] 10.12 (s, 1H), 8.47 – 8.14 (m, 4H, integrated as 2.6H), 7.90 (s, 1H), 7.35 (m, 2H), 7.23 (d, \( J = 16.3 \text{ Hz}, 1\text{H} \)), 7.06 (m, 2H), 6.98 (d, \( J = 2.1 \text{ Hz}, 1\text{H} \)), 6.87 (d, \( J = 16.3 \text{ Hz}, 1\text{H} \)), 6.81 (d, \( J = 2.1 \text{ Hz}, 1\text{H} \)), 6.77 – 6.69 (m, 4H), 6.49 (t, \( J = 2.2 \text{ Hz}, 1\text{H} \)), 6.44 (d, \( J = 2.2 \text{ Hz}, 2\text{H} \));

\( ^{13}\text{C NMR} (151 \text{ MHz, acetone-}d_6) \): δ [ppm] 159.7, 157.6, 157.3, 154.4, 141.5, 138.7, 133.6, 132.0, 130.8, 129.3, 128.5, 127.4, 125.7, 125.1, 122.4, 116.2, 116.0, 114.9, 111.2, 105.6, 102.1, 96.6; HRMS (ESI): m/z calcd. for C\(_{28}\)H\(_{21}\)NO\(_5\) [M-H] - 450.1346; found 450.1348.

\((E)-5-(6\text{-Hydroxy-2-(4-hydroxyphenyl)-4-(4-hydroxystyryl)}-1\text{-methyl-1H-indol-3-yl})\text{-benzene-1,3-diol (4c)}\).

Following the General Procedure A, \(4c\) (14.6 mg, 0.031 mmol, 56%) was obtained as light-green solid from \(9b\) (30 mg, 0.056 mmol). Cyclised compound \(6c\) (2.3 mg, 0.005 mmol, 9%) was also isolated.

\(4c\): \( ^{1}H \text{NMR} (600 \text{ MHz, acetone-}d_6) \): δ [ppm] 8.56 – 7.83 (m, 5H, integrated as 3.7H), 7.26 (d, \( J = 16.3 \text{ Hz}, 1\text{H} \)), 7.19 (m, 2H), 7.06 (m, 2H), 7.04 (d, \( J = 2.1 \text{ Hz}, 1\text{H} \)), 6.90 (d, \( J = 16.3 \text{ Hz}, 1\text{H} \)), 6.82 (m, 2H), 6.76 (d, \( J = 2.1 \text{ Hz}, 1\text{H} \)), 6.71 (m, 2H), 6.36 (t, \( J = 2.2 \text{ Hz}, 1\text{H} \)), 6.34 (d, \( J = 2.2 \text{ Hz}, 2\text{H} \)), 3.55 (s, 3H);

\( ^{13}\text{C NMR} (151 \text{ MHz, acetone-}d_6) \): δ [ppm] 159.0, 157.8, 157.6, 154.4, 140.8, 139.6, 137.7, 132.9, 132.0, 130.7, 128.5, 127.6, 125.2, 124.1, 120.7, 116.4, 116.2, 115.8, 111.6, 105.6, 101.7, 95.3, 31.2; HRMS (ESI): m/z calcd. for C\(_{29}\)H\(_{23}\)NO\(_5\) [M-H] - 464.1503; found 464.1497.
5,11-Bis(4-hydroxyphenyl)-10,11-dihydro-6H-benzo[6,7]cyclohepta[1,2,3-cd]-indole-1,3,8-triol (6b).

A stirred solution of permethylated indole 9a (30 mg, 0.057 mmol) in dry DCM (1 ml) was cooled to -78 °C, and a freshly prepared 1M solution of BBr₃ in DCM (860 μl, 0.86 mmol) was added drop-wise under N₂. The reaction mixture was allowed to slowly warm up to rt overnight, and after stirring for a total of 24h in a relative darkness and confirming the deprotection by LC-MS analysis, 47% aq. HBr (30 μl) was slowly added. The mixture was stirred overnight at rt, before quenching with sat. aq. NaHCO₃. The mixture was immediately neutralised with 5% aq. citric acid solution, then extracted with EtOAc (3x), washed with brine, dried (Na₂SO₄), and the solvent was removed in vacuo. The obtained crude was purified by flash chromatography (silica gel, 0% → 10% MeOH in DCM) and then further by HPLC, affording the title compound 6b (4.9 mg, 0.011 mmol, 19%) as pale yellow solid, as well as, the uncyclised indole 4b (2.6 mg, 0.006 mmol, 10%).

6b: ¹H NMR (600 MHz, acetone-d₆): δ [ppm] 9.65 (s, 1H), 8.48 (s, 1H), 8.08 (s, 1H), 7.77 (s, 1H), 7.69 – 7.59 (m, 2H), 7.37 (m, 2H), 7.04 (m, 2H), 6.86 (m, 2H), 6.52 – 6.43 (m, 5H), 6.30 (d, J = 2.3 Hz, 1H), 5.43 (d, J = 5.8 Hz, 1H), 3.65 (dd, J₁ = 15.8, 6.0 Hz, 1H), 3.42 (d, J₂ = 16.0 Hz, 1H); ¹³C NMR (151 MHz, acetone-d₆): δ [ppm] 157.7, 156.5, 156.2, 155.2, 153.8, 138.9, 137.5, 135.1, 134.9, 134.4, 131.1, 129.3, 127.1, 121.7, 116.3, 114.9, 113.8, 111.5, 110.8, 100.4, 94.7, 39.1, 38.2; HRMS (ESI): m/z calcd. for C₂₈H₂₁NO₅ [M-H]- 450.1346; found 450.1334.

5,11-Bis(4-hydroxyphenyl)-6-methyl-10,11-dihydro-6H-benzo[6,7]cyclohepta[1,2,3-cd]indole-1,3,8-triol (6c).

To a solution of the permethylated indole 9b (30 mg, 0.056 mmol) in DCM (1 ml) at 0 °C was added 47% aq. HBr (10 μl), followed by 1M solution of BBr₃ in DCM (840 μl, 0.84 mmol). The reaction mixture was stirred overnight at rt in a relative darkness, then, more 47% aq. HBr (20 μl) was added, and the mixture was stirred for 3h at rt. The reaction was quenched with sat. aq. NaHCO₃, the mixture was immediately neutralised with 5% aq. citric acid solution, extracted with EtOAc (3x), washed with brine, dried over Na₂SO₄, and the solvent was removed under reduced pressure. The obtained crude was purified by flash chromatography (silica gel, 0% → 10% MeOH in DCM) and then further by HPLC, affording the title compound 6c (3.7 mg, 0.008 mmol, 14%) as off-white solid, as well as, the uncyclised indole 4c (2.7 mg, 0.006 mmol, 10%).

6c: ¹H NMR (400 MHz, acetone-d₆): δ [ppm] 8.59 (s, 1H), 8.02 (s, 1H), 7.77 (s, 1H), 7.67 (s, 1H), 7.66 (s, 1H), 7.19 (broad s, 2H), 7.02 – 6.92 (m, 4H), 6.55 – 6.40 (m, 4H), 6.24 (d, J = 2.5 Hz, 1H), 6.19 (d, J = 2.5 Hz, 1H), 5.42 (d, J = 5.2 Hz, 1H), 3.66 (dd, J = 15.9, 6.2 Hz, 1H), 3.43 (d, J = 15.9 Hz, 1H), 3.32 (s, 3H); ¹³C NMR (214 MHz, acetone-d₆): δ [ppm] 158.2, 156.2, 156.1, 155.2, 153.9, 138.9, 138.5, 136.8, 135.2, 135.1, 129.3, 125.8, 121.5, 120.2, 116.5, 115.0, 111.6, 110.7, 100.2, 93.3, 39.3, 38.3, 30.8; HRMS (ESI): m/z calcd. for C₂₉H₂₃NO₅ [M-H]- 464.1503; found 464.1500.
6.3 Synthesis of Benzo[b]thiophane- and Benzo[b]selenophene-based Analogues

(E)-2-(4-methoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (32) was synthesised following a modification of a previously reported procedure. To a solution of 4-ethynylanisole (349 mg, 2.64 mmol) in dry toluene (9 ml) was added DIBAL (1M in toluene, 2.90 ml, 2.90 mmol) and HBpin (neat, 460 μl, 3.2 mmol). The reaction mixture was stirred at 110 °C for 4h 30 min under N₂. After cooling to rt, the mixture was diluted with EtOAc and filtered through a short silica plug. The solvent was evaporated under reduced pressure, and the crude oil was purified by flash chromatography (silica gel, 0% to 5% EtOAc in Heptane) to afford compound 32 as colourless oil which slowly crystallised upon standing at -20 °C, giving white waxy crystals (550 mg, 2.11 mmol, 80%): ¹H NMR (400 MHz, CDCl₃): δ [ppm] 7.44 (m, 2H), 7.35 (d, J = 18.4 Hz, 1H), 6.87 (m, 2H), 6.01 (d, J = 18.4 Hz, 1H), 3.82 (s, 3H), 1.31 (s, 12H). ¹³C NMR (100 MHz, CDCl₃): δ [ppm] 160.4, 149.2, 130.5, 128.6, 114.1, 83.4, 55.4, 25.0. NMR data were in accordance to those reported in the literature.

1,3-Dibromo-2-iodo-5-methoxybenzene (14) was prepared from 4-methoxyaniline (28) following modified, previously described procedures:

To a solution of 4-methoxyaniline (28) (5.007 g, 40.66 mmol) in DCM (39 ml) and MeOH (31 ml), cooled to 0 °C, was added drop-wise Br₂ (neat, 4.26 ml, 83.1 mmol). The reaction mixture was stirred at 0 °C for 1h and at rt for 3h. Additional portion of Br₂ (neat, 1.00 ml, 19.5 mmol) was added, and the mixture was stirred for another 2 h at rt. The reaction was quenched by adding aq. NaHSO₃ solution, and basified with 1M aq. NaOH and sat. aq. NaHCO₃. The product was extracted with DCM (3x) and the combined organic layers were washed with water, sat. brine, dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The resulting crude product was purified by flash chromatography (silica gel, 20% → 40% DCM in heptane) yielding 2,6-dibromo-4-methoxyaniline (29) as off-white solid (7.190 g, 25.59 mmol, 63%): ¹H NMR (400 MHz, CDCl₃): δ [ppm] 7.02 (s, 2H), 4.04 (s, 2H), 3.72 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] 152.2, 136.3, 118.2, 109.3, 56.3. Spectral data agreed with those in the previously published report.

I₂ (7.169 g, 28.24 mmol) and isoamylnitrite (910 μl, 6.8 mmol) were added to a solution of 29 (1.587 g, 5.649 mmol) in benzene (37 ml), and the reaction mixture was stirred at reflux for 23 h before cooling down to rt, diluting with CHCl₃ and quenching with aq. Na₂S₂O₃ solution. The product was extracted with CHCl₃ (3x), washed with water and sat. brine, dried over Na₂SO₄, and the solvent was evaporated in vacuo. The afforded purple crude was purified by flash chromatography (silica gel, 8% → 20% DCM in heptane) yielding the title compound 14 as white crystals (1.253 g, 3.198 mmol, 57%): ¹H NMR (400 MHz, CDCl₃): δ [ppm] 7.16 (s, 2H), 3.78 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ [ppm] 160.4, 131.2, 117.9, 98.0, 56.0. The spectral data were found to be in accordance with the previously reported results.
1,3-Dibromo-5-methoxy-2-((4-methoxyphenyl)ethynyl)benzene (30).
To a mixture of 14 (5.151 g, 13.15 mmol), Pd(PPh$_3$)$_4$ (760 mg, 0.658 mmol) and CuI (125 mg, 0.656 mmol), flushed with N$_2$, was added dry and degassed Et$_3$N (30 ml). N$_2$ was bubbled through the mixture, and a degassed solution of 4-ethynylanisole (1.824 g, 13.80 mmol) in dry Et$_3$N (30 ml) was added. N$_2$ was bubbled again through the mixture, and then, it was stirred at reflux for 25h under N$_2$. The reaction mixture was diluted with EtOAc, filtered through Celite, washed with sat. aq. solution of NH$_4$Cl and back-extracted with EtOAc (3x). The combined organic layers were washed with sat. brine, dried (Na$_2$SO$_4$), and the organic solvent was evaporated in vacuo. Purification by flash chromatography (silica gel, 2% → 5% EtOAc in heptane) afforded the target product 30 as white solid (off-white solid when evaporated from DCM; 3.627 g, 9.157 mmol, 70%): $^1$H NMR (600 MHz, CDCl$_3$): δ [ppm] 7.53 (m, 2H), 7.13 (s, 2H), 6.89 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ [ppm] 160.1, 159.3, 133.2, 126.5, 120.1, 117.7, 115.2, 114.2, 96.9, 86.3, 56.0, 55.5.

(3-Bromo-5-methoxy-2-((4-methoxyphenyl)ethynyl)phenyl)(methyl)sulfane (13a).
A solution of 30 (465 mg, 1.17 mmol) in dry THF (11.6 ml) was cooled under N$_2$ in a dry-ice/acetone bath at -78 °C for 30 min. To the solution was added n-BuLi (2.5M solution in hexanes, 470 μl, 1.2 mmol), and the reaction mixture was stirred at -78 °C for 1h 30 min. A solution of Me$_2$S$_2$ (133 mg, 1.41 mmol) in dry THF (2.2 ml) was added slowly, and the reaction mixture was stirred for another 2h 30 min at -78 °C under N$_2$. The mixture was slowly warmed up to rt and stirred for another 30 min, diluted with EtOAc, washed with water, brine, dried (Na$_2$SO$_4$), and evaporated in vacuo. The target product 13a was obtained as orange solid (quant.): $^1$H NMR (600 MHz, CDCl$_3$): δ [ppm] 7.53 (m, 2H), 6.93 (d, $J = 2.4$ Hz, 1H), 6.88 (m, 2H), 6.63 (d, $J = 2.4$ Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.47 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ [ppm] 159.9, 159.5, 145.1, 133.2, 126.8, 115.7, 115.5, 114.1, 113.2, 109.9, 99.2, 84.6, 55.8, 55.5, 15.6.

4-(4-bromo-3-iodo-6-methoxybenzo[b]thiophen-2-yl)phenol (31a).
A solution of 13a (873 mg, 2.40 mmol) and I$_2$ (732 mg, 2.88 mmol) in DCM (20 ml) was stirred for 1h 15 min at 80 °C in a microwave reactor. The reaction mixture was quenched with aq. Na$_2$S$_2$O$_3$, extracted with EtOAc (3x), washed with sat. brine and dried with Na$_2$SO$_4$. Evaporation in vacuo yielded the target compound 31a as off-white solid (1.122 g, 2.362 mmol, 98%): $^1$H NMR (600 MHz, CDCl$_3$): δ [ppm] 7.47 (m, 2H), 7.33 (d, $J = 2.4$ Hz, 1H), 7.29 (d, $J = 2.4$ Hz, 1H), 6.99 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ [ppm] 160.2, 156.9, 142.3, 142.2, 131.9, 129.4, 128.1, 121.2, 118.3, 113.9, 105.0, 75.6, 56.0, 55.5.

4-Bromo-3-(3,5-dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (10d).
To a mixture of 31a (278 mg, 0.585 mmol), 3,5-dimethoxyphenylboronic acid (117 mg, 0.643 mmol), Pd(dppf)Cl$_2$·DCM complex (49 mg, 0.060 mmol) and K$_3$PO$_4$ (248 mg, 1.17 mmol), flushed with N$_2$, was added degassed 1,4-dioxane (2.4 ml) and degassed H$_2$O (0.4 ml). N$_2$ was bubbled through the mixture for several minutes, and the reaction mixture was stirred for 1h 30 min at 100 °C in a microwave reactor. After dilution with DCM, the solvents were evaporated in vacuo and the crude mixture was purified by
flash chromatography (silica gel, 0% → 19% EtOAc in heptane) affording the title compound 10d as off-white solid (138 mg, 0.284 mmol, 49%): 1H NMR (400 MHz, CDCl3): δ [ppm] 7.30 (d, J = 2.3 Hz, 1H), 7.23 (m, 2H), 7.20 (d, J = 2.3 Hz, 1H), 6.76 (m, 2H), 6.47 (appeared as s, 3H), 3.87 (s, 3H), 3.77 (s, 3H), 3.75 (s, 6H); 13C NMR (100 MHz, CDCl3): δ [ppm] 160.3, 159.3, 157.0, 141.6, 138.8, 138.5, 132.6, 131.6, 130.6, 126.6, 120.0, 117.4, 113.9, 110.4, 104.6, 100.3, 56.0, 55.6, 55.4.

(E)-3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-(4-methoxy-styryl)benzo[b]thiophene (9c).

A mixture of 10d (128 mg, 0.264 mmol), 32 (100 mg, 0.384 mmol), Pd2(dbach)3 CHCl3 complex (11 mg, 0.011 mmol), SPhos (11 mg, 0.027 mmol) and K3PO4 (142 mg, 0.669 mmol) was flushed with N2. To the mixture was added degassed 1,4-dioxane (2.4 ml) and degassed H2O (0.4 ml), and N2 was bubbled through for several minutes. The reaction mixture was stirred for 1h 30 min at 100 °C in a microwave reactor, diluted with EtOAc, filtered through Celite, washed with diluted aq. NaCl solution, sat. brine and dried over Na2SO4. After evaporating the solvent under reduced pressure, the crude mixture was purified by flash chromatography (silica gel, 0% → 23% EtOAc in heptane) yielding the target product 9c as off-white solid (115 mg, 0.213 mmol, 81%): 1H NMR (400 MHz, CDCl3): δ [ppm] 7.27 (d, J = 2.4 Hz, 1H), 7.24 (m, 2H), 7.15 (d, J = 2.4 Hz, 1H), 6.96 (m, 2H), 6.81 – 6.69 (m, 6H), 6.52 – 6.48 (m, 3H), 3.92 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.63 (s, 6H); 13C NMR (100 MHz, CDCl3): δ [ppm] 161.0, 159.2, 159.0, 157.2, 140.9, 140.3, 137.3, 136.0, 132.8, 132.1, 130.5, 130.4, 128.9, 127.8, 127.1, 125.6, 113.9, 113.8, 111.9, 109.4, 104.0, 100.2, 55.8, 55.5, 55.4, 55.4.

(3-Bromo-5-methoxy-2-((4-methoxyphenyl)ethynyl)phenyl)(methyl)selane (13b). A solution of 30 (600 mg, 1.52 mmol) in dry THF (15 ml) was cooled under N2 in a dry-ice/acetone bath at -78 °C for 30 min. To the solution was added n-BuLi (2.5M solution in hexanes, 600 μl, 1.5 mmol), and the reaction mixture was stirred at -78 °C for 1h 30 min. Me2Se2 (neat, 600 μl, 1.8 mmol) was added drop-wise, and the reaction mixture was stirred for another 2h 30 min at -78 °C under N2. The mixture was slowly warmed up to rt and stirred for another 30 min, diluted with EtOAc, washed with water, sat. brine and dried over Na2SO4. After evaporation in vacuo, the target product 13b was obtained as orange solid (quant.): 1H NMR (400 MHz, CDCl3): δ [ppm] 7.53 (m, 2H), 6.97 (d, J = 2.4 Hz, 1H), 6.89 (m, 2H), 6.74 (d, J = 2.4 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.34 (s, 3H); 13C NMR (151 MHz, CDCl3): δ [ppm] 160.0, 159.5, 139.6, 133.2, 126.5, 117.8, 115.4, 114.2, 114.1, 112.9, 98.2, 85.5, 55.8, 55.5, 55.4, 6.9.

4-Bromo-3-iodo-6-methoxy-2-(4-methoxyphenyl)benzo[b]selenophene (31b). A solution of 13b (585 mg, 1.43 mmol) and I2 (434 mg, 1.71 mmol) in DCM (15.5 ml) was stirred at 80 °C for 1h 15 min in a microwave reactor before quenching with aq. Na2S2O3 solution. The product was extracted with EtOAc (3x), washed with sat. brine, dried (Na2SO4), and the solvent was evaporated under reduced pressure. The title compound 31b was obtained as brown/off-white solid (711 mg, 1.36 mmol, 96%, approx. 90% purity as determined based on NMR results): 1H NMR (400 MHz, CDCl3): δ [ppm] 7.41 (m, 2H), 7.38 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 2.4 Hz, 1H), 6.97 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H); 13C NMR (100 MHz, CDCl3): δ [ppm] 160.0, 156.7, 144.5, 143.8, 131.7, 130.8, 130.7, 121.0, 120.0, 113.9, 108.8, 78.0, 56.0, 55.5.
4-Bromo-3-(3,5-dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)benzo[b]-selenophene (10e).

To a mixture of 31b (25 mg, 0.048 mmol), 3,5-dimethoxyphenylboronic acid (9.1 mg, 0.050 mmol), Pd(dppf)Cl$_2$·DCM complex (3.9 mg, 0.0047 mmol) and K$_3$PO$_4$ (21.6 mg, 0.102 mmol), flushed with N$_2$, was added degassed 1,4-dioxane (600 μl) and degassed H$_2$O (100 μl). N$_2$ was bubbled through for several minutes, and the reaction mixture was stirred at 100 °C for 1h 30 min and at 120 °C for 30 min before diluting with DCM and evaporating in vacuo. Purification by flash chromatography (silica gel, 5% → 17% EtOAc in heptane) afforded 10e as light-yellow solid (12.6 mg, 0.024 mmol, 49%):

$^1$H NMR (600 MHz, CDCl$_3$): δ [ppm] 7.39 (d, $J = 2.4$ Hz, 1H), 7.21 (d, $J = 2.4$ Hz, 1H), 7.17 (m, 2H), 6.73 (m, 2H), 6.45 (t, $J = 2.3$ Hz, 1H), 6.43 (d, $J = 2.3$ Hz, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 3.73 (s, 6H);

$^{13}$C NMR (151 MHz, CDCl$_3$): δ [ppm] 160.2, 159.1, 156.8, 143.5, 142.3, 139.9, 135.5, 133.5, 130.9, 128.5, 120.0, 119.3, 113.7, 110.4, 108.4, 100.3, 56.0, 55.6, 55.3.

(E)-3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-(4-methoxy-styryl)benzo[b]selenophene (9d).

To a mixture of 10e (196 mg, 0.368 mmol), 32 (140 mg, 0.538 mmol), Pd$_2$(dba)$_3$·CHCl$_3$ complex (15 mg, 0.015 mmol), SPhos (15 mg, 0.037 mmol) and K$_3$PO$_4$ (199 mg, 0.935 mmol), flushed with N$_2$, was added degassed 1,4-dioxane (3.35 ml) and degassed H$_2$O (560 μl). N$_2$ was bubbled through the mixture for several minutes, and the reaction mixture was stirred at 100 °C for 1h 30 min in a microwave reactor. The mixture was diluted with EtOAc, filtered through Celite, washed with diluted aq. NaCl solution, sat. brine, dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure. Purification by flash chromatography (silica gel, 0% → 23% EtOAc in heptane) gave 9d as light-yellow solid (180 mg, 0.307 mmol, 84%): $^1$H NMR (400 MHz, CDCl$_3$): δ [ppm] 7.36 (d, $J = 2.5$ Hz, 1H), 7.17 (m, 2H), 7.11 (d, $J = 2.5$ Hz, 1H), 6.94 (m, 2H), 6.78 – 6.67 (m, 5H), 6.64 (d, $J = 16.0$ Hz, 1H), 6.47 (d, $J = 2.3$ Hz, 2H), 6.44 (t, $J = 2.3$ Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.60 (s, 6H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ [ppm] 160.9, 159.2, 158.9, 157.1, 142.8, 141.4, 140.6, 138.0, 135.9, 134.0, 130.8, 130.4, 129.0, 128.8, 127.8, 126.4, 113.8, 113.7, 112.4, 109.4, 107.8, 100.2, 55.8, 55.5, 55.4, 55.3.

**General Procedure B:** A solution of a permethylated compound (1 eq.) in dry DCM (1 ml) was cooled to -80 °C, and a freshly prepared 1M solution of BBr$_3$ in DCM (6.1 eq.) was added drop-wise under N$_2$. The reaction mixture was allowed to slowly warm up to -30 °C, and it was stirred at that temperature for 3 days in a relative darkness. The progress of the reaction was monitored by LC-MS. The mixture was quenched with sat. aq. NaHCO$_3$ and immediately after neutralised with 5% aq. citric acid and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and the solvent was removed in vacuo. The obtained crude was purified by flash chromatography (silica gel, 0% → 10% MeOH in DCM) and then further by HPLC.
\( (E)-5-(6\text{-}\text{Hydroxy-2-(4\text{-}Hydroxyphenyl)\text{-}4\text{-}(4\text{-}Hydroxy\text{Styryl})\text{Benzo}[b]\text{Thiophen-3-yl})\text{Benzene-1,3-diol (4d).} \)

Following the General Procedure B, product 4d (7.3 mg, 0.016 mmol, 28%) was obtained as grey solid, starting from 9c (30 mg, 0.056 mmol). Cyclised by-product 6d (4.2 mg, 0.009 mmol, 16%) was also isolated. 4d: \(^1\)H NMR (400 MHz, acetone-\( \text{d}_6 \)) \( \delta \) [ppm] 8.60 – 8.30 (m, 5H, integrated as 3.1H), 7.28 – 7.18 (m, 4H), 7.08 – 6.98 (m, 3H), 6.82 (d, \( J = 16.1 \) Hz, 1H), 6.77 – 6.69 (m, 4H), 6.50 (t, \( J = 2.2 \) Hz, 1H), 6.35 (d, \( J = 2.2 \) Hz, 2H); \(^{13}\)C NMR (214 MHz, acetone-\( \text{d}_6 \)) \( \delta \) [ppm] 159.9, 157.9, 157.9, 155.7, 141.7, 141.6, 136.8, 136.5, 133.7, 132.2, 131.2, 129.4, 128.8, 126.9, 124.7, 116.1, 116.0, 111.9, 110.4, 107.2, 102.9; HRMS (ESI): m/z calcd. for C\(_{28}\)H\(_{20}\)O\(_5\)S \([M-\text{H}]^{-}\) 467.0958; found 467.0964.

\( (E)-5-(6\text{-}\text{Hydroxy-2-(4\text{-}Hydroxyphenyl)\text{-}4\text{-}(4\text{-}Hydroxy\text{Styryl})\text{Benzo}[b]\text{Selenophen-3-yl})\text{Benzene-1,3-diol (4e).} \)

Demethylation of 9d (32.6 mg, 0.056 mmol), as described in the General Procedure B, afforded target product 4e (9.7 mg, 0.019 mmol, 34%) as grey solid, as well as, the cyclised by-product 6e (3.9 mg, 0.008 mmol, 14%). 4e: \(^1\)H NMR (400 MHz, acetone-\( \text{d}_6 \)) \( \delta \) [ppm] 8.56 – 8.24 (m, 5H), 7.37 (d, \( J = 2.4 \) Hz, 1H), 7.20 – 7.12 (m, 3H), 7.03 – 6.95 (m, 3H), 6.79 – 6.66 (m, 5H), 6.45 (t, \( J = 2.2 \) Hz, 1H), 6.32 (d, \( J = 2.2 \) Hz, 2H); \(^{13}\)C NMR (214 MHz, acetone-\( \text{d}_6 \)) \( \delta \) [ppm] 159.8, 157.8, 157.7, 155.6, 143.5, 142.9, 139.9, 138.4, 136.7, 134.1, 131.5, 130.3, 129.3, 128.9, 128.8, 125.4, 116.0, 115.9, 112.5, 111.0, 110.4, 102.8; HRMS (ESI): m/z calcd. for C\(_{28}\)H\(_{20}\)O\(_5\)Se \([M-\text{H}]^{-}\) 515.0402; found 515.0402.

**General Procedure C:** To a solution of a permethylated compound (1 eq.) in DCM (18 ml/mmole), cooled to 0 °C, was added 47% aq. HBr, followed by 1M BBr\(_3\) solution in DCM (15 eq.). The reaction mixture was stirred overnight at rt in a relative darkness, and completion of the reaction was determined by LC-MS. The reaction was quenched with sat. aq. NaHCO\(_3\), and then, immediately neutralised with 5% aq. citric acid. The mixture was extracted with EtOAc (3x), the combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0% → 10% MeOH in DCM) and then further using HPLC.

5,10-Bis(4-hydroxyphenyl)-4,5-dihydro-11-thiadibenzo[cd,h]azulene-2,6,8-triol (6d).

The target product 6d (6.4 mg, 0.014 mmol, 49%) was obtained as pale yellow solid, following the General Procedure C, starting from permethylated benzo[b]thiophene 9c (15 mg, 0.028 mmol), and using 5 μl of 47% aq. HBr. Compound 4d (0.2 mg, 0.4 μmol, 1.5%) was also isolated. 6d: \(^1\)H NMR (400 MHz, acetone-\( \text{d}_6 \)) \( \delta \) [ppm] 8.78 – 7.51 (m, 5H, integrated as 3.2H), 7.21 (m, 2H), 7.00 (m, 2H), 6.96 (d, \( J = 2.2 \) Hz, 1H), 6.86 – 6.75 (m, 3H), 6.48 (m, 2H), 6.41 (d, \( J = 2.5 \) Hz, 1H), 6.28 (d, \( J = 2.5 \) Hz, 1H), 5.33 (d, \( J = 5.8 \) Hz, 1H), 3.73 (dd, \( J = 16.4, 6.2 \) Hz, 1H), 3.47 (d, \( J = 16.4 \) Hz, 1H); \(^{13}\)C NMR (151 MHz, acetone-\( \text{d}_6 \)) \( \delta \) [ppm] 157.8, 156.2, 156.0, 155.4, 155.0, 140.2, 138.2, 137.9, 137.2, 134.2, 132.3, 132.1, 131.7, 129.2, 128.7, 123.2, 117.2, 116.4, 115.1, 114.2, 105.3, 102.3, 39.8, 37.6; HRMS (ESI): m/z calcd. for C\(_{28}\)H\(_{20}\)O\(_5\)S \([M-\text{H}]^{-}\) 467.0958; found 467.0953.
5,10-Bis(4-hydroxyphenyl)-4,5-dihydro-11-selenadibenzo[cd,h]azulene-2,6,8-triol (6e).

The title compound **6e** (9.0 mg, 0.018 mmol, 45%) was afforded as pale yellow solid, using the General Procedure C, starting from **9d** (22.6 mg, 0.039 mmol) and adding 7 μl of 47% aq. HBr. Compound **4e** (0.3 mg, 6 μmol, 1.5%) was also obtained. **6e**: $^1$H NMR (400 MHz, acetone-$d_6$): δ [ppm] 8.85 – 7.47 (m, 5H), 7.13 (m, 2H), 7.09 (d, $J = 2.3$ Hz, 1H), 7.00 (m, 2H), 6.82 (s, 1H), 6.77 (m, 2H), 6.49 (m, 2H), 6.40 (d, $J = 2.4$ Hz, 1H), 6.23 (d, $J = 2.4$ Hz, 1H), 5.26 (d, $J = 5.6$ Hz, 1H), 3.69 (dd, $J = 16.6$, 6.0 Hz, 1H), 3.47 (d, $J = 16.6$ Hz, 1H); $^{13}$C NMR (214 MHz, acetone-$d_6$): δ [ppm] 157.5, 156.1, 155.7, 155.4, 154.9, 141.6, 141.0, 139.5, 139.0, 134.9, 134.5, 134.2, 131.7, 130.9, 129.3, 123.5, 117.4, 116.2, 115.2, 115.1, 109.2, 102.3, 40.0, 37.5; HRMS (ESI): m/z calcd. for C$_{28}$H$_{20}$O$_5$Se [M-H] $^- 515.0403$; found 515.0409.
Acknowledgement

Firstly, and most importantly, I would like to sincerely thank my supervisor Prof. Mikael Elofsson for his great support and accepting me into his wonderful group as a Master’s degree student, thus, giving me this great opportunity to work on the project that allowed me to greatly improve my skills in organic synthetic chemistry. My sincere thanks go to Michael Saleeb, my laboratory supervisor, for his day-to-day support, motivation and sharing his vast experience and knowledge, as well as, his insightful comments. Discussions with Michael were truly enlightening, and, without a doubt, helped me to better myself as a chemist. At the same time, I would also like to thank Rémi Caraballo, Arvind Kumar and Emil Johansson for their immense patience and helpful guidance through every-day laboratory reality. Furthermore, I would like to thank Christian Pett for his help with the HPLC instrument and Marcus Carlsson for the help with HRMS analyses. Naturally, my thanks go to Tobias Sparrman and Mattias Hedenström for solving any of my NMR related issues during the project, and always keeping the instruments operational. Of course, I need to sincerely thank my mentor, Lindon Moodie, for teaching me the ways of synthetic chemistry, for his constant mental support, countless chemistry discussions, sharing his chemistry passion with me and helping me to solve various laboratory and carrier related problems, as well as, his limitless and highly contagious enthusiasm and optimism. Next, I would like to express my enormous gratitude to Prof. Christian Hedberg for introducing me to the art of advanced organic chemistry, his truly invaluable guidance, all his time that he devoted to me, his faith in me, and the indispensible help in making important carrier choices. Finally, I would like to thank my family, especially my beloved mom and dad, for their immense love, support and sacrifice. Without them I would not be able to realise my dream of becoming a chemist and study here, in Umeå.
References


Appendix

Spectral Data for Compounds 12, 16-19

2-Amino-6-bromo-4-methoxyphenol (16). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) [ppm] 8.12 (s, 1H), 6.25 – 6.20 (m, 2H), 4.96 (s, 2H), 3.60 (s, 3H). The spectral data were found to be in agreement with the previously reported results.\(^{[A1]}\)

N-(3-Bromo-2-hydroxy-5-methoxyphenyl)-2,2,2-trifluoroacetamide (17). \(^1\)H NMR (600 MHz, DMSO-d\(_6\)): \(\delta\) [ppm] 10.69 (broad, s, 1H), 9.36 (broad, s, 1H), 7.11 (d, \(J = 3.0\) Hz, 1H), 6.92 (d, \(J = 3.0\) Hz, 1H), 3.70 (s, 3H); \(^13\)C NMR (151 MHz, DMSO-d\(_6\)): \(\delta\) [ppm] 155.5 (q, \(^2\)J\(_{F-C}\) = 37 Hz), 152.3, 142.7, 124.6, 116.8, 115.9 (q, \(^1\)J\(_{F-C}\) = 288 Hz), 112.5, 111.9, 55.9.

2-Bromo-4-methoxy-6-(2,2,2-trifluoroacetamido)phenyl trifluoromethanesulfonate (12). \(^1\)H NMR (600 MHz, DMSO-d\(_6\)): \(\delta\) [ppm] 11.76 (s, 1H), 7.46 (d, \(J = 2.9\) Hz, 1H), 7.16 (d, \(J = 2.9\) Hz, 1H), 3.84 (s, 3H); \(^13\)C NMR (151 MHz, DMSO-d\(_6\)): \(\delta\) [ppm] 159.0, 155.4 (q, \(^2\)J\(_{F-C}\) = 38 Hz), 135.0, 130.1, 118.1, 117.9 (q, \(^1\)J\(_{F-C}\) = 320 Hz), 116.8, 115.6 (q, \(^1\)J\(_{F-C}\) = 288 Hz), 113.7, 56.5.

4-Methoxy-2-((4-methoxyphenyl)ethynyl)-6-(2,2,2-trifluoroacetamido)phenyl trifluoromethanesulfonate (18). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) [ppm] 8.20 (s, 1H), 7.71 (d, \(J = 3.1\) Hz, 1H), 7.51 (m, 2H), 7.00 (d, \(J = 3.1\) Hz, 1H), 6.90 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) [ppm] 160.6, 159.0, 133.6, 132.8, 129.1, 120.9, 116.0, 114.3, 113.9, 109.4, 97.4, 81.1, 56.2, 55.5. Signals for CF\(_3\)CO, CF\(_3\)CO and CF\(_3\)SO\(_2\) were not detected due to low amount of the sample. \(^19\)F NMR (376 MHz, CDCl\(_3\)): \(\delta\) [ppm] -73.1, -76.0.

2,2,2-Trifluoro-N-(5-methoxy-2-(4-methoxyphenyl)benzofuran-7-yl)acetamide (19). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) [ppm] 8.31 (s, 1H), 7.78 – 7.72 (m, 3H), 7.00 (m, 2H), 6.89 (d, \(J = 2.4\) Hz, 1H), 6.85 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) [ppm] 160.5, 157.3, 156.5, 154.7 (q, appeared as \(\delta\) due to low sample concentration, \(^2\)J\(_{F-C}\) = 38 Hz), 139.7, 130.4, 126.6, 122.6, 120.2, 114.5, 104.2, 101.6, 100.7, 56.3, 55.6. Signal for CF\(_3\) was not detected due to low amount of the sample. \(^19\)F NMR (376 MHz, CDCl\(_3\)): \(\delta\) [ppm] -75.5.

NMR Spectra

$^1$H NMR Spectrum of 17:

$^{13}$C NMR Spectrum of 17:
$^1$H NMR Spectrum 12:

$^{13}$C NMR Spectrum of 12:
$^1$H NMR Spectrum of 18:

$^{13}$C NMR Spectrum of 18:
$^1$H NMR Spectrum of 19:

$^{13}$C NMR Spectrum of 19:
$^1$H NMR Spectrum of 22:

$^{13}$C NMR Spectrum of 22:
$^1$H NMR Spectrum of 11b:

$^{13}$C NMR Spectrum of 11b:
$^1$H NMR Spectrum of 10a:

$^{13}$C NMR Spectrum of 10a:
$^1$H NMR Spectrum of 10b:

$^{13}$C NMR Spectrum of 10b:
$^{1}H$ NMR Spectrum of 9a:

$^{13}C$ NMR Spectrum of 9a:
$^1$H NMR Spectrum of 10c:

$^{13}$C NMR Spectrum of 10c:
$^1$H NMR Spectrum of 9b:

$^{13}$C NMR Spectrum of 9b:
$^1$H NMR Spectrum of 4b:

$^{13}$C NMR Spectrum of 4b:
$^1$H NMR Spectrum of 4c:

$^{13}$C NMR Spectrum of 4c:
$^1$H NMR Spectrum of 6b:

$^{13}$C NMR Spectrum of 6b:
$^1$H NMR Spectrum of $6c$:

$^{13}$C NMR Spectrum of $6c$:
$^1$H NMR Spectrum of 30:

$^{13}$C NMR Spectrum of 30:
$^1$H NMR Spectrum of 13a:

$^{13}$C NMR Spectrum of 13a:
1H NMR Spectrum of 31a:

13C NMR Spectrum of 31a:
$^1$H NMR Spectrum of 10d:

$^{13}$C NMR Spectrum of 10d:
$^1$H NMR Spectrum of 9c:

$^{13}$C NMR Spectrum of 9c:
$^1$H NMR Spectrum of 13b:

$^{13}$C NMR Spectrum of 13b:
$^1$H NMR Spectrum of 31b:

$^{13}$C NMR Spectrum of 31b:
$^{1}H$ NMR Spectrum of $10e$:

$^{13}C$ NMR Spectrum of $10e$: 

![NMR Spectra](image.png)
$^1$H NMR Spectrum of 9d:

$^{13}$C NMR Spectrum of 9d:
\(^1\)H NMR Spectrum of 4d:

\(^{13}\)C NMR Spectrum of 4d:
$^1$H NMR Spectrum of 6d:

$^{13}$C NMR Spectrum of 6d:
$^1$H NMR Spectrum of 6e:

$^{13}$C NMR Spectrum of 6e: