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Synthesis of polycyclic heteroaromatic hydrocarbons by Pd-catalyzed cross-coupling reactions, alkyne carbonyl metathesis and acid mediated cycloisomerization

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Acknowledgements

Abstract

The present work deals with the synthesis of polycyclic heteroaromatic hydrocarbons based on functionalization of halogenated pyridine derivatives. Various pyrrolo[1,2-*a*][1,6]naphthyridines, (benzo-)thieno[3,2-*f*]quinoline , (benzo-)thieno[3,2-*f*]isoquinoline and 5- and 6-azaindoles were successfully developed based on sequential site- and regioselective Pd-catalyzed C–C and C–N coupling reactions, alkyne carbonyl metathesis reactions and Brønsted acid mediated cycloisomerization. In all the cases, alkynes containing electron-donating as well as electron-withdrawing aromatic substituents and aliphatic moieties could be used. All compounds were obtained with moderate to very good yields. Selected synthesized final products were studied using UV and fluorescence spectroscopy to determine the optical properties.

Zusammenfassung

Die vorliegende Arbeit beschäftigt sich mit der Synthese von polyzyklischen heteroaromatischen Kohlenwasserstoffen durch Funktionalisierung von halogenierten Pyridinderivaten. Verschiedene Pyrrolo[1,2-*a*][1,6]naphthyridine, (Benzo-)thieno[3,2-*f*]chinolin, (Benzo-)thieno[3,2-*f*]isochinolin und 5- und 6-Azaindole wurden erfolgreich durch regioselektive Pd-katalysierte C–C und C–N Kopplungsreaktionen, Alkin-Carbonyl-Metathese-Reaktionen und Brønsted-Säure-vermittelte Cycloisomerisierungen entwickelt. In allen Fällen konnten Alkine verwendet werden, welche sowohl elektronenreiche, als auch elektronenarme aromatische Substituenten sowie aliphatische Reste enthalten. Alle Verbindungen wurden mit mäßigen bis sehr guten Ausbeuten isoliert. Ausgewählte Syntheseprodukte wurden mittels UV- und Fluoreszenzspektroskopie untersucht, um die optischen Eigenschaften zu bestimmen.

Contents

List of abbreviations

ACM	Alkyne carbonyl metathesis
BF_3*Et_2O	Boron trifluoride etherate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
calcd	Calculated
CB_2	Cannabinoid receptor type 2
CD4 receptor	Cluster of differentiation 4
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
DEPT	Distortionless Enhancement by Polarisation Transfer
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dppf	1,1'-Bis(diphenylphosphino)ferrocene
ε	Molar extinction coefficient
EI	Electrospray Ionization
EML	Emitting layer
Equiv.	Equivalent
ESI	Electrospray Ionization
Et	Ethyl
Et_3N	Triethylamine
ETL	Electron-transporting layer
ϕ	Fluorescence quantum yield
FDA	United States Food and Drug Administration
FPD	Flat panel displays
GC	Gas chromatography
h	Hour
Hetar	Heteroaryl
HIV gp-120	Glycoprotein on the HIV envelope
HNiPr$_2$	Diisopropylamine
HRMS	High Resolution Mass Spectroscopy

Hz	Hertz
*i*Pr	Isopropyl
IR	Infrared spectroscopy
J	Coupling constant
Me	Methyl
mp	Melting point
MS	Mass Spectrometry
NMR	Nuclear magnetic resonance
OA	Oxidative addition
OCM	Olefin carbonyl metathesis
OFET	Organic field-effect transistor
OLED	Organic light-emitting diodes
OMe	Methoxy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
[Pd]	Palladium complex
PAH	Polycyclic aromatic hydrocarbons
PCy_3	Tricyclohexylphosphine
Ph	Phenyl
PHA	Polycyclic Heteroaromatic Structure
PKs	Protein kinases
PPh_3	Triphenylphosphine
ppm	Parts per million
R	Organic moiety
r.t.	Room temperature
RE	Reductive elimination
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
UV/Vis	Ultraviolet and visible absorption spectroscopy
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
λ	Wavelength

1   General introduction

Since ancient times, humans have been interested in understanding, explaining and using natural processes and nature itself for their own benefit. The development of the science has been closely associated with the development of humankind.

With the discovery of fire, more than 1.5 million years ago, the first chemical reaction controlled by the first humans appeared.[1,2] After this phenomenon, humanity started a new era in the development of chemistry, passing through different stages. The first of these is marked by Early metallurgy, with his two stages: Bronze Age, Iron Age, passing through the creation of new materials such as ceramics and glass. Then until the 15th century, Medieval alchemy was practiced and gave way to modern chemistry with the experiments of Robert Boyle (1627-1691).[3,4]

The beginning of modern organic chemistry dates back to 1828, when the German chemist Friedrich Wöhler developed the synthesis of urea, from that moment a new bright stage of science would begin.[5,6] After the birth of carbon chemistry, different processes occurring in living organisms began to be understood and interest in the isolation, origin, structure and properties of natural products increased.

In this regard heterocycles are chemical compounds widespread in nature, such as nucleic acid and alkaloids as caffeine. Additionally, synthetic heterocycles and polyheteroaromatic hydrocarbons have a large number of application due their properties as fungicide, herbicide, antibacterial agents. In pharmaceutical field are well known antibiotic products such as amoxicillin or ciprofloxacin (figure 1).
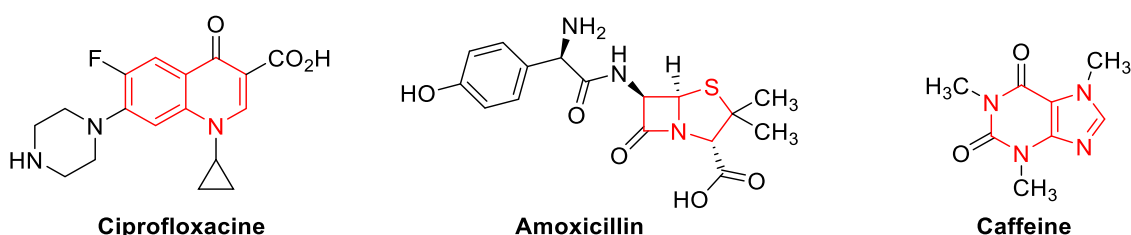
Figure 1. Heterocycles forming part of antibiotics and alkaloids structures.

Heterocycles are characterized as cyclic compounds that contain, at least, one heteroatom in the ring core.[7] Condensed nitrogen compounds have a wide range of applications due to their manifold biological activities. Hence the importance of organic heterocyclic chemistry for drug design and pharmaceutical development on the treatment of human

immunodeficiency virus (HIV) is showcases in the following. Saquinavir was the first antiretroviral protease inhibitor that was used in the therapy and prevention of human immunodeficiency virus (HIV) infections and the acquired immunodeficiency syndrome (AIDS).[8] On the other hand, Fostemsavir is a novel HIV-1 attachment inhibitor and is the first of its kind to receive FDA approval, granted in July 2020.[9] Fostemsavir binds to the HIV gp-120 protein and blocks its adhesion to CD4 receptors, thus preventing HIV infection of the cell. Alternatively, Elvitegravir is also used for the treatment of HIV-1 infection in antiretroviral treatment, as it interferes with HIV-1 replication by inhibiting the insertion of proviral DNA into the host cell genome.[10] In 2019, Badell *et. al.* reported the use of Elvitegravir in suppressing HIV levels during pregnancy and, consequently, significantly reducing perinatal HIV transmission[11] (figure 2).
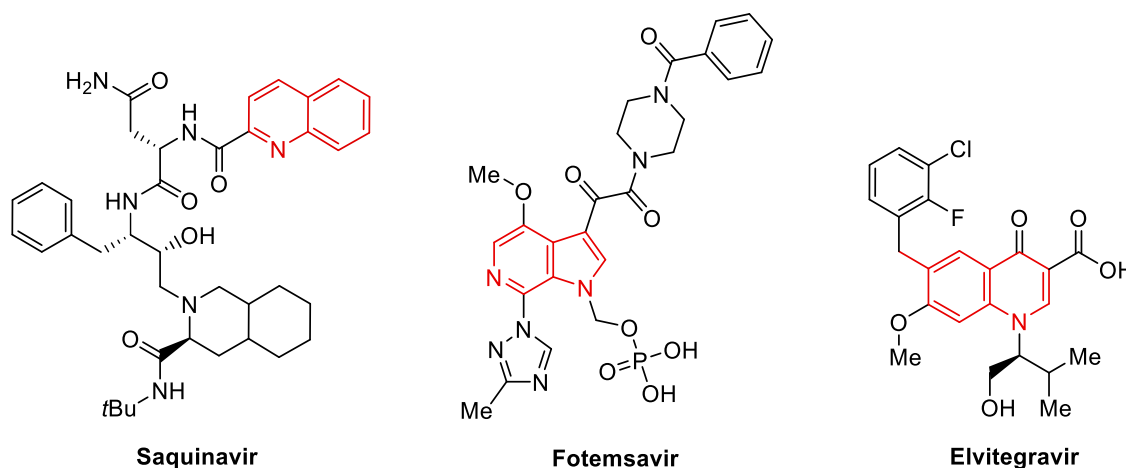
Figure 2. Heterocycles as drugs for treatment of HIV-1.

Saquinavir and Elvitegravir consist of a quinoline core which can be found in a number of antimalaria drugs such as the classical quinine and chloroquine and the relatively new Tafenoquine, which was approved by FDA in 2018 as a single-dose for the radical cure of *Plasmodium vivax* (*P. vivax*) malaria[12,13] (figure 3).

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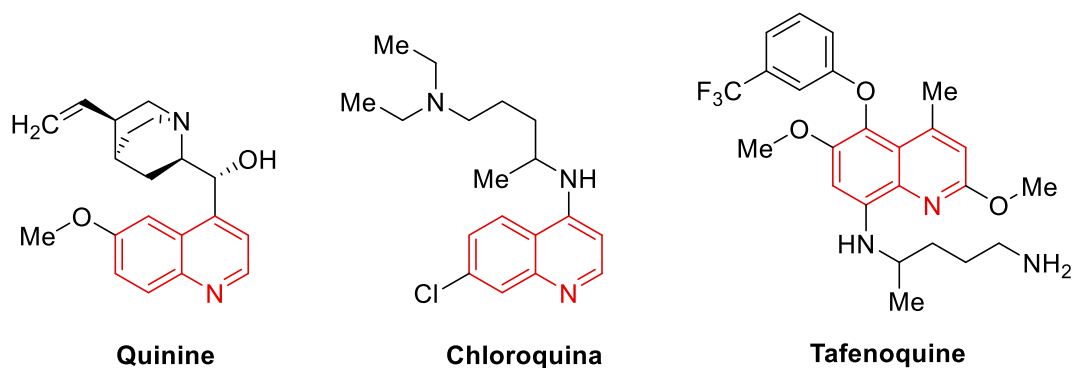
Figure 3. Quinolines derivates with antimalaria activity.

In the field of materials science as organic electronics, these aromatic polyheterocyclic compounds have been essential in the development of semiconductors that show promise in the construction of solar cells, sensors, organic light-emitting diodes (OLEDs) and organic transistors (OFETs).[14] Their optical and electronic properties can be explained by taking into consideration the unsaturated scaffold system, due to the sp^2 hybrid orbitals of the carbon atoms involved in the π-bonding overlap with their neighbours to form a continuous system through which the electrons can move.[15]

The introduction of heteroatoms into polycyclic aromatic hydrocarbons (PAHs) changes the electronic structure and may contribute to improved stability, charge mobility and molecular packing with respect to the corresponding PAH.[16,17] For instance, pentacene, formed by five fused benzene rings, is a PAH known as an organic semiconductor with high charge mobility, but is vulnerable to oxidation and degrades slowly under exposure to environmental conditions, which limits its applications.[18] However, with the introduction of heteroatoms into pentacene scaffold, the stability and solubility of the obtained derivatives are improved and the electronic, photophysical and optical properties are enhanced.[14] The first emissive technology that showed promise involved organic light-emitting diodes (OLEDs), uses aluminium chelate tris(8-hydroxyquinoline) aluminium, (Alq3), as the emitting layer (EML) and electron-transporting layer (ETL) material in flat panel displays (FPDs).[19–21]
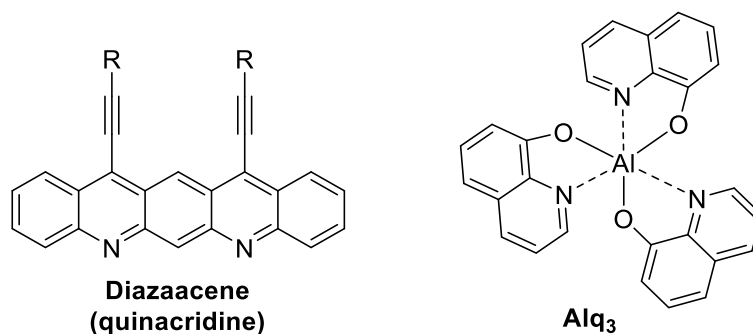
Figure 4. Aromatic heterocycles applied in organic materials.

One of the most essential aspects in the modern organic chemistry is to use advanced and selective catalysts to increase the rate reaction and at the same time it can be regenerated at the end of the chemical process. These catalysts can increase the chemo- (functional group differentiation), regio- (orientational control of two reacting partners) and stereoselectivity (control over stereochemistry) during the reactions, resulting in the desired structure.[22][23]

Preparative organic chemistry is always working on the constant development of new and improved active substances and adapted functional materials. It is the way to contribute to the development of human society.

1.1 Cross-coupling reactions

Organic synthesis is largely motivated to the existence and development of the pharmaceutical industry, goods, biotechnology, food industry, electronic technologies and many others. Therefore, the improvement of organic synthesis processes is an essential tool to obtain new products with unique properties that facilitate the continuous development in all these sectors.[24]

Especially catalysis, has become a powerful tool to obtain novel synthetic compounds with distinctive properties. The employment of highly active catalysts allows the development of more economic and sustainable processes compared to classical and stoichiometric methodologies.[25][26–28] Particularly, Palladium catalyzed cross-coupling reactions have been transferred from academical basic research to the industrial production of fine chemicals such as pharmaceuticals based on their efficiency, good selectivity, easy handling and wide applicability.[29]

In the following different Palladium catalyzed cross-coupling reactions, which have been employed in the experimental part of this thesis, will be discussed more detailed.

1.1.1 Reaction Suzuki

Suzuki reaction is a cross-coupling reaction, based on the reaction of a boronic acid and an organohalide catalyzed by a palladium (0) complex and a general reaction outline is shown in scheme 1. This reaction has become one of the most used in the formation of simple C_{sp2}-C_{sp2} bonds.

In 1979, Norio Miyaura and Akira Suzuki made the first report on this reaction, which inspired a new path in the progress of synthesis strategies. Then, in 2010, Akira Suzuki received, along with Ei-ichi Negishi and Richard F. Heck, the Nobel Prize in Chemistry for their contribution and development of organic synthesis based on palladium-catalyzed cross-couplings reaction.[30–32][33,34][35,36] This reaction is named Suzuki-Miyaura or Suzuki coupling reaction.

Suzuki cross-coupling is one of the most frequently used Pd catalyzed cross coupling reaction in the industry due to mild reaction condition requirements, widely availability of its reagents, high regio- and stereo-selectivity, leading to high reaction performances. It should be noted that the reaction accepts a large number of functional groups, and tolerates moisture or even water as co-solvent. The latter fact allows Suzuki reactions to be performed under more environmentally friendly conditions. It is, more economical and permits its use with a large number of water-soluble reagents. Additionally, the employed boronic acids, are stable towards air and moisture, widely accessible containing various functional groups and are less toxic than organometallic reagents such as organostannane or organozinc derivatives.[24][37][38,39]

$$R_1-X \quad + \quad R_2-BY_2 \quad \xrightarrow[\text{Base}]{\text{Pd(0)}} \quad R_1-R_2 \quad + \quad X-BY_2$$
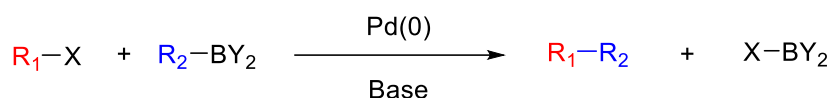
R_1: Aryl

R_2: Aryl or vinyl

X: I, Br, Cl, OTf

Scheme 1. General scheme of the Suzuki- Miyaura reaction.

The mechanism has been intensively studied, and involves three parts (scheme 2). The first step is the oxidative addition (OA) of Pd(0) to the halide, which yields the organopalladium complex (**A**). Consequently, palladium changes its oxidation number from Pd(0) to Pd(II), and acts as an electrophile, now. This part determines usually the rate of the reaction. At first, the oxidative addition forms the *cis*-palladium complex and

is quickly transformed to the more stable *trans*-palladium complex, as long as no bidentate ligands are employed. In the presence of aryl or vinyl halide (pseudohalide), it is accepted that the mechanism of oxidative addition to Pd(0) goes through a concerted pathway for nonpolar substrates and substitution via S_N2 for polar substrates.[29,40] During OA, it is essential to control the selectivity of the reaction in order to obtain the desired products. This can be achieved by good management of substituted halogens in the starting material.[41,42]
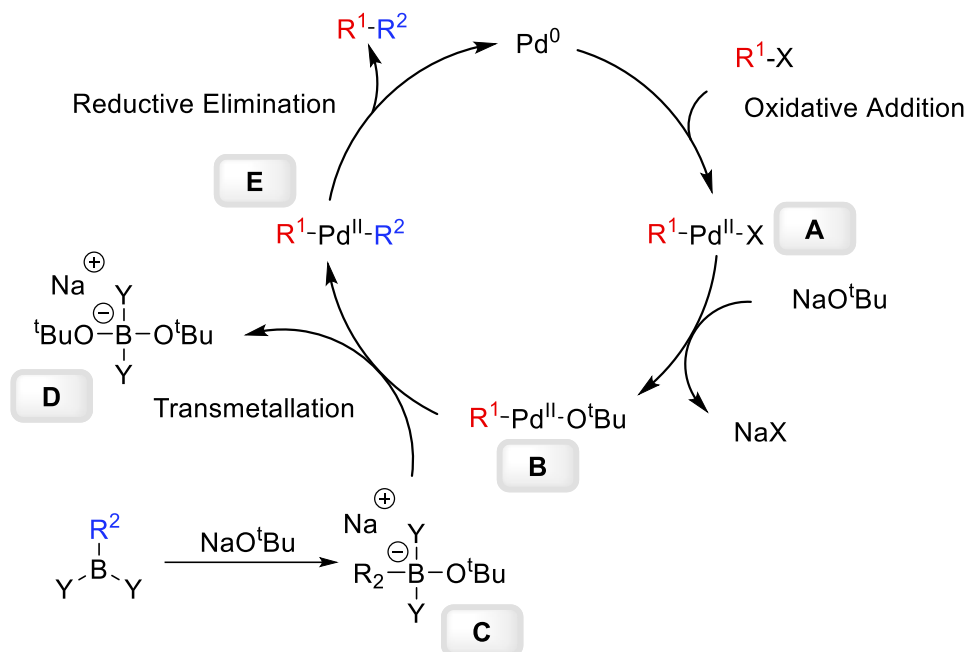
Scheme 2. Mechanism of Suzuki- Miyaura reaction.

The organopalladium complex (**A**) reacts with the base through a metathesis reaction resulting in the corresponding intermediate [R^1-Pd^{II}-O^tBu] (**B**) that subsequently undergoes the transmetallation reaction (TM). Transmetallation involving the transfer of ligands from one metal to another without the latter changing its oxidation number and is an irreversible process. Palladium behaves as an electrophile center, while the other metal acts as a nucleophile. An increase of both the electrophilicity of Pd and the nucleophilicity of the other metal increases the rate of transmetallation. On the other hand, it is essential in this catalytic step that the other metal is less electronegative than the palladium center, so the use of boron (organoborons) is indispensable, particularly in the Suzuki reaction. The formation of the organoboron complex (**C**) required for the transmetallation step, is obtained from the activation of the boron center with the base. Finally, this

transmetallation step yields an organopalladium complex (**E**) that later experiences the reductive elimination.

The third and last step in the catalytic cycle is the reductive elimination (RE) of the desired product and the regeneration of Pd(0) catalyst to start a new catalytic cycle. RE is the reverse of oxidative addition. The RE requires a *cis*-coordination of the respective organic moieties. Therefore, the *trans*-palladium complex undergoes isomerization towards *cis*-palladium complex.

In the Suzuki cross-coupling reaction, the use of an inorganic base is necessary. Some report demonstrated that without the presence of a base in the reaction media, organoboronic compounds do not experience transmetallation. Base is essential in the catalytic cycle in three different steps of the reaction. First, in the formation of the Pd complex $[R^1\text{-}Pd^{II}\text{-}O^tBu]$ (**B**) that undergoes a transmetallation step. Then increasing the nucleophilicity of the boronic acid through the activation of organoboron complex (**C**), by making it more easily available to undergo transmetallation. And finally by supporting the generation of the *cis*-Pd complex (**E**) involved in the formation of the desired product in the reductive elimination step and the regeneration of Pd catalyst.[43]

The fields of application of the Suzuki cross-coupling reaction are diverse, ranging from the preparation of biaryls and biologically active molecules to the development of materials with technological applications.[44][45]

1.1.2   Sonogashira reaction

Sonogashira reaction is a cross-coupling reaction which involves the reaction of a terminal alkyne and an aryl, alkenyl or alkynyl halides. For this coupling, the use of palladium catalyst is essential and usually requires a copper co-catalyst.[46]

Generally, the Sonogashira reaction is employed for the formation of a $C(sp^2)$-$C(sp)$ bond (scheme 3).

$$R_1\text{−}X \quad + \quad H\text{———}R_2 \quad \xrightarrow[\text{Base}]{\text{[Pd(0)], [Cu]}} \quad R_1\text{———}R_2$$

R_1: Aryl

R_2: Aryl or vinyl

X: I, Br, Cl, OTf
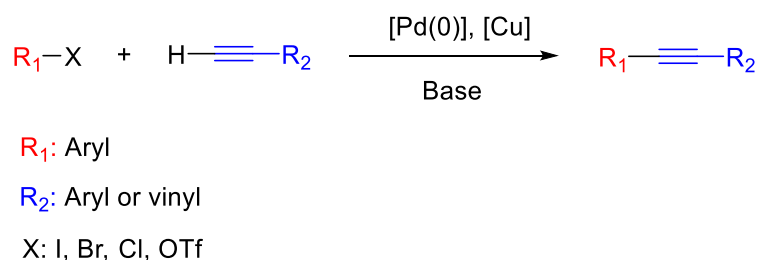
Scheme 3. General scheme of Sonogashira reaction.

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In 1975 the alkynylation reaction of aryl halides using aromatic acetylenes was reported by different authors.[47] It was finally Kenkichi Sonogashira who discovered that the use of copper iodide as co-catalyst together with a Pd catalyst in the presence of an amine as base and solvent allowed the reaction to be performed under milder conditions with improved yields. Continuous development of Pd/Cu system allowed their use in large number of synthetic applications in the following years.

The advantages of this methodology such as mild reaction conditions, high selectivity tolerance to many functional groups makes the Sonogashira coupling become an essential reaction in the development of material science, natural products and pharmaceutical industry containing carbon-carbon triple bonds.[25] The reaction can be performed in the presence of water but oxygen should be excluded from the reaction as it facilitates unwanted Glaser-type side reaction and hence, derived dimerized alkynyl products may sometimes interfere with the isolation of desired Sonogashira coupling products.[43][46,48][49,50]

The general mechanism proposed comprises of three elemental steps - oxidative addition, transmetallation and reductive elimination - analogously to other Pd catalyzed cross coupling reactions (compare previously discussed Suzuki reaction). In contrast to other cross-coupling reactions, the Sonogashira reaction consists of a second catalytic cycle related to copper iodide (Cycle II) (scheme 4).

Firstly, Pd-precatalyst is activated and forms the active Pd(0) catalyst (Cycle I, **A**) (scheme 4). Pd(0) undergoes oxidative addition with an aryl, alkenyl or alkynyl halide and changes the oxidation number to Pd(II) and new palladium complex (**B**) is formed. The newly obtained Pd(II) complex undergoes transmetallation by reacting with an acetylated copper complex originating from the Cu cycle (Cycle II). The oxidative addition is usually considered as a rate-limiting step of the reaction, but in presence of activated aryl halides, the transmetallation step is the rate limiting. Finally reductive elimination yields the desired product and regenerates the active Pd(0) catalyst again.

For reductive elimination to occur, the R^1 and R^2 groups must be in close proximity, so that the Pd complex (**C**) undergoes isomerization to form the *cis*-palladium complex.

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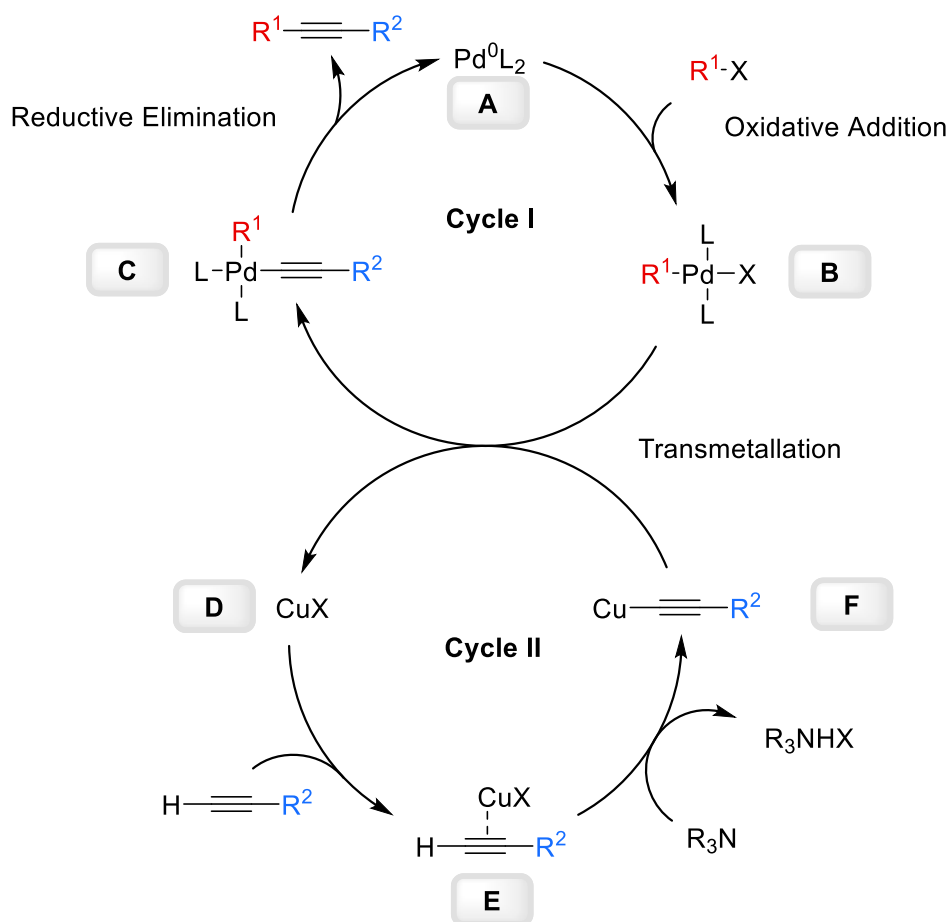
Scheme 4. Mechanism of Sonogashira reaction with Cu.

The Cu cycle mechanism suggests that the base present in the media favours the formation *in situ* of an alkyne π-complex (**E**), with terminal one proton more acidic, resulting from the coordination of the Cu co-catalyst to the triple bond of the acetylene. The organic base promotes the elimination of the terminal proton and consequently leads to the formation of a copper acetylide complex that finally participates in the transmetallation step.

The Sonogashira reaction can also performed under copper-free condition (scheme 5) and its mechanism was detailed examined by Košmrlj *et. al.* in 2018 through experimental and computational studies.[51]
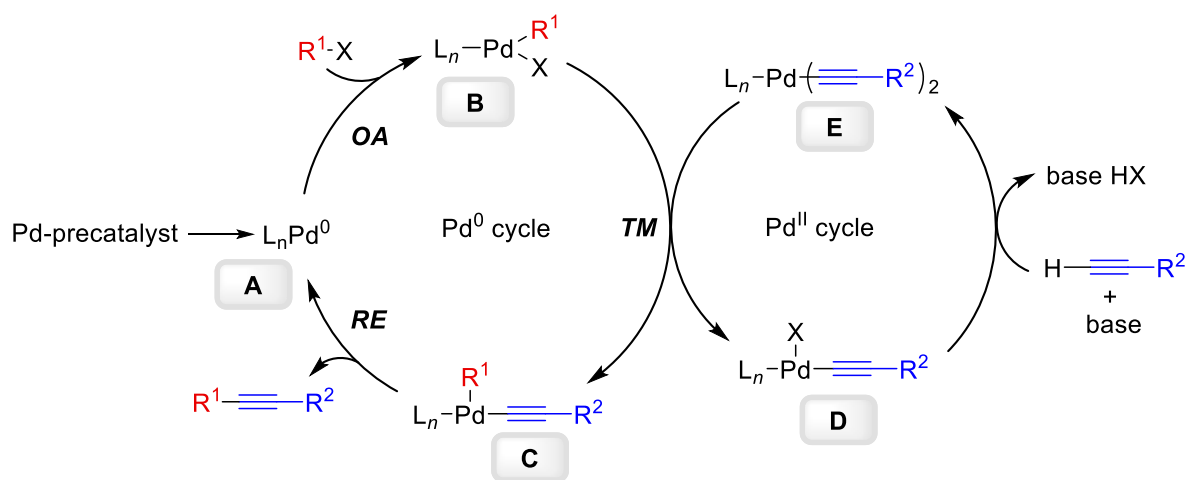
Scheme 5. Mechanism of Sonogashira reaction Cu free.

Similarly to the classical Sonogashira reaction, the catalytic cycle starts with the oxidative addition of the aryl halide to the Pd(0) catalyst affording the Pd complex **B**. The acetylene is metalated forming a Pd(II) acetylide (**D**) in the second cycle. First the monoacetylated palladium complex (**D**) is formed and with support from the base, a second molecule of acetylene is activated to form the diacetylated Pd-complex (**E**). This diacetylated palladium complex and the previously active aryl halide palladium complex (**B**) obtained from the oxidative addition step, participates in the transmetallation step forming complex **C** and regenerating **D**. Finally, the reductive elimination results in the desired disubstituted alkyne product and the regeneration of Pd(0) catalyst (**A**).

1.1.3   Buchwald-Hartwig Amination

Buchwald–Hartwig amination, like Suzuki and Sonogashira reactions, is a cross-coupling reaction, but instead of C-C, carbon–nitrogen bonds are formed. In this case either a primary or secondary amine is used as nucleophile.[52–54]

This reaction was established independently by Stephen L. Buchwald and John F. Hartwig, between 1994 and end of first decade of 2000s.[55,56] Buchwald–Hartwig amination is very important in the synthetic organic chemistry, because it allows the construction of carbon-nitrogen bonds in an easy way, and it's an essential extension of insufficient classical methods to obtain $C(sp^2)$-N bonds. Furthermore, this reaction supplements the limited scope of the substrates and the functional groups, as well as allows mild reaction conditions in comparison to other C–N bonds forming reactions such as Ullmann-Goldberg reactions, Mannich reaction, or reductive amination.[57–59][54]. With

the development of refined phosphine ligands, Buchwald–Hartwig reaction extended its field of application to a large variety of amines and aryl groups.[60][61] The general scheme of the Buchwald-Hartwig reaction shows the formation of a $C(sp^2)$-$N(sp^2)$ bond (scheme 6).

R_1: Aryl

R_2, R_3: Aryl, alkyl or H

X: I, Br, Cl, OTf
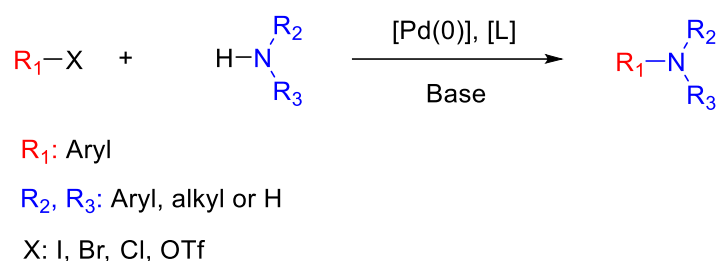
Scheme 6. General scheme of Buchwald-Hartwig amination.

Buchwald–Hartwig reaction undergoes a similar mechanism as typical Palladium catalyzed C-C-cross-coupling reactions (scheme 7). The first step is an oxidative addition of the aryl halide to the Pd(0) complex (**A**) followed by the amine addition to Pd(II) complex (**B**) to yield Pd complex (**C**). This amine addition step is called as ligand exchange. Later complex **C** undergo deprotonation to form complex **D**, that finally go through the reductive elimination to obtain the desired amine product (**E**).[62,63]
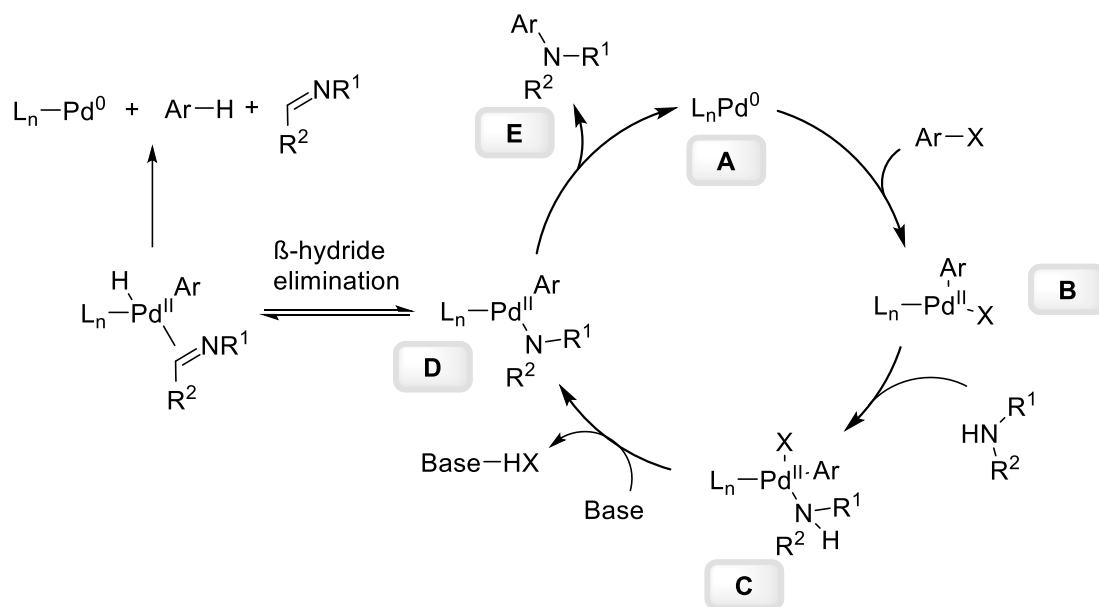
Scheme 7. Mechanism of Buchwald–Hartwig amination.

β-hydride elimination occurs as a competitive side reaction when alkyl or benzylamine is employed. Usually, this side reaction can be suppressed by using bidentate ligands such as Xantphos or BINAP.[61]

1.2   Alkyne carbonyl metathesis

The alkyne carbonyl metathesis reaction is a C-C bond formation discovered in 1956 from a study on [2+2] cycloaddition reactions between alkynes and aromatic aldehydes or ketones by UV radiation.[64] Beyond cross- coupling reaction, metathesis reactions have been of significant interest to synthetic chemists. Olefin metathesis reaction involves the regeneration of new C-C bond through the cut and redistribution of the double bonds of the olefins. This reaction, due to simple mechanism, has the advantage of resulting in fewer undesired by-products, undergoes a high atom economy performance depending on the reaction conditions and the substrates, and at the same time provides an easy way to generate complex structures, that would normally take more time and resources using classical methods.

For the contribution in the elucidation of the mechanism and the discovery of useful catalyst, Yves Chauvin, Robert H. Grubbs y Richard R. Schrock were awarded by the Nobel Prize committee in 2005.[65][66]

Olefin metathesis reaction consists of a [2+2] cycloadditions followed by a [2+2] cycloreversions between the olefin reactants on a metal catalyst. Mechanistically a metal alkylidene catalyst is involved in the formation of the metallacyclobutane intermediate by a formal [2+2] cycloaddition. Subsequently this key intermediate can undergo a [2+2] cycloreversion and yield the desired product or go back towards the starting materials. The metal alkylidine catalyst is regenerated at the end of the process (scheme 8).

The ring-closing metathesis is the most used metathesis process in the synthesis of natural products.[67][68,69] Although olefin metathesis was the first reaction published and developed under this name, other variants of the metathesis reaction have also been reported. Alkyne – alkyne metathesis reaction is analogue to the olefin-olefin metathesis, it involves the reaction of two alkynes, followed by the formation of the four-member ring intermediate and subsequent [2+2] cycloreversions to yield a new pair of alkynes.[70] Therefore, the metathesis reaction between an olefin and an alkyne as reaction partners have been developed, also known as enyne metathesis.[71]

Olefin - Olefin Metathesis
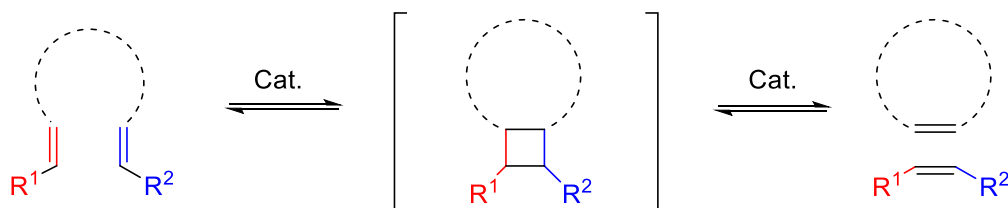
Alkyne - Alkyne Metathesis
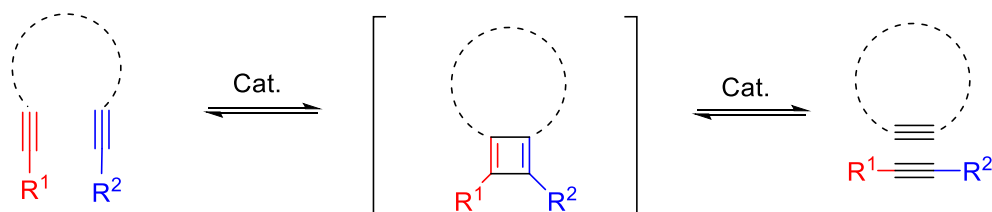
Alkyne - Carbonyl Metathesis
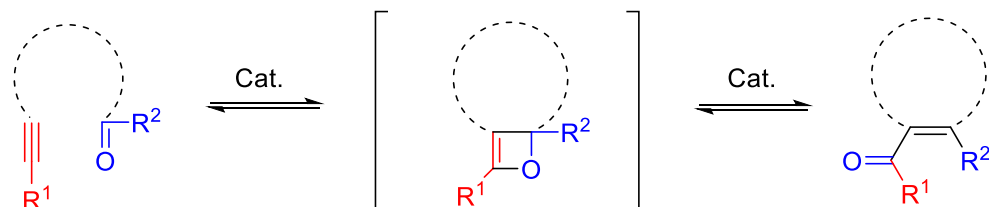
Scheme 8. General scheme of organic metathesis reaction.

The development of different and powerful types of catalysts has extended their use not only in olefin-olefin reactions but also in olefin-alkyne and alkyne-alkyne reactions.

Due to the success and broad applications of metathesis reactions in achieving very interesting structures similar to natural products in an affordable way. These kinds of organic reactions have been extended to other functional groups like carbonyl group, with promising results. The carbonyl group as cross-metathesis reagents together with olefins or alkynes in different reactions yields new carbonyl and olefin or alkyne derivates.[71]

In alkyne carbonyl metathesis, the reaction between alkyne and a carbonyl group has a complete atomic economy. This is because the reaction does not form any by-products, and all the starting material are converted into the desired product. It was reported for the first time by Büchi in 1956.[64] Then in 1959, Vieregge *et. al.*[72] made an important contribution to this type of reaction with the introduction of Lewis-acid catalyst and subsequently with high regio- and stereoselectivity to the reaction of alkynes and aldehydes and ketones.

The mechanism for the alkyne carbonyl metathesis proposed till now starts with the activation of the carbonyl group, followed by a [2+2] cycloaddition between the active carbonyl and an alkyne. Then, an unstable oxetene ring intermediate is generated, followed by the formation of the desired product, an α,β-unsaturated carbonyl. This metathesis mechanism depends to a remarkable extent on the nature of the Lewis acid used. In presence of an oxophilic Lewis acids, such as BF_3, $FeCl_3$ or $InCl_3$, as well as Brønsted acids the carbonyl is activated, followed by a nucleophilic attack of the alkyne and subsequent formation of the oxetane ring by a ring-closing reaction from vinylic cation to carbonyl oxygen. The last step is [2+2] cycloreversion generating the corresponding alkyne–carbonyl metathesis product.[67,71,73]

Unlike, oxophilic Lewis acids and Brønsted acids, the π-electrophilic Lewis acids, such as Ag and Au salts, may initially activate triple bond, forming a vinyl cation intermediate which reacts with carbonyl oxygen followed by formation the four-membered ring intermediate. Analogously, [2+2] cycloreversion affords the desired alkyne–carbonyl metathesis product (scheme 9).[74]
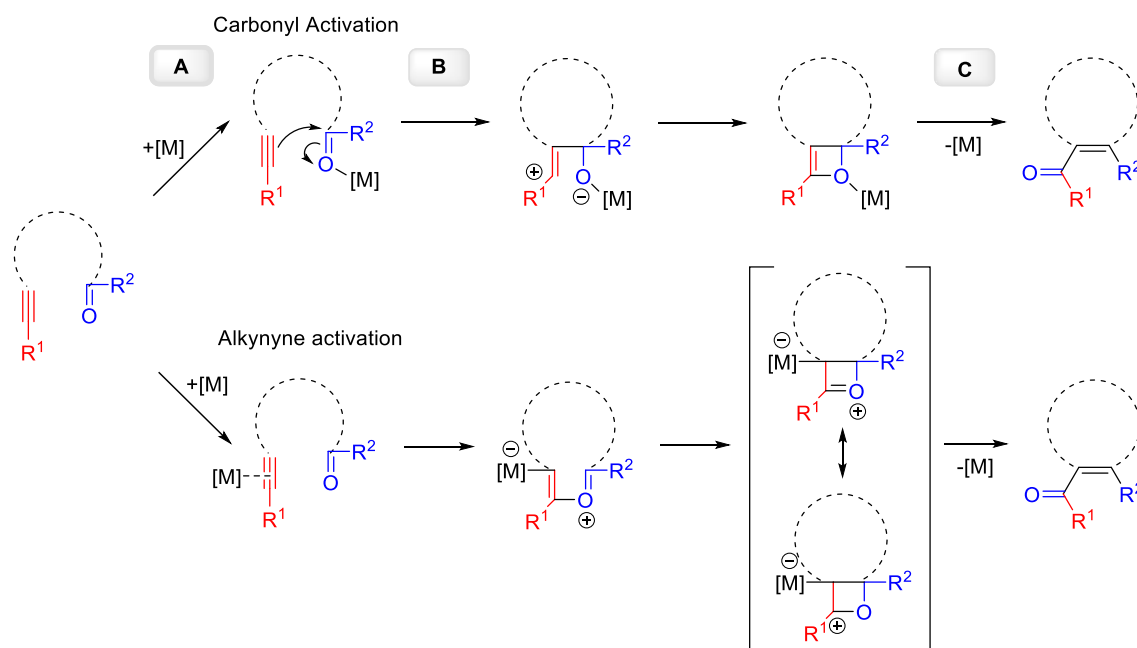
Scheme 9. Mechanism of the intramolecular alkyne carbonyl metathesis reaction. **A** = activation, **B** = [2+2] cycloaddition, **C** = [2+2] cyclorevision. In the carbonyl activation M = B^{III}, Fe^{III}, Ga^{III}, Ti^{IV}, Sb^{V}, Yb^{III}, In^{III}, H^+. In the alkyne activation M = Ag, Au.

Due to its high regio and stereoselectivity, even in presence of versatile functional groups in the chemical environment, the alkyne-carbonyl metathesis has become a useful tool in

the synthesis of large number of polycyclic compounds.[71] This Alkyne-carbonyl metathesis reactions have evolved as powerful methodology in the formation of very complex structures related to natural products or generally in the formation of α,β-unsaturated esters,[75] ketones and amides, as well as five- and six-member ring structures.

Alkyne carbonyl metathesis have been an alternative to classical olefin reaction such as the Horner–Wadsworth–Emmons or Wittig reaction,[76] and have become the main alternative to achieve the desired product in complex structures.[75] This reaction will continue to improve due to the continuous study of new and more efficient catalysts.

1.3   Objective of this thesis

Palladium catalyzed cross-coupling reaction have gained remarkable importance in the development and synthesis in many industries. In addition, the alkyne carbonyl metathesis had become in a useful tool for the selective and versatile cycloisomerization process. Synthesis of polyheteroaromatic hydrocarbon have benefited by the application of these recent process. Besides, the advantages offered by novel C-C bond forming reactions offered for instance by Palladium catalyzed cross-coupling reactions and metathesis reactions, such as mild reaction conditions, high regio- and chemoselectivity and availability of cheaper starting materials, allows to obtain polyheteroaromatic polycycles that are not easily achievable by other methods. Motivated by the relevance of polyheteroaromatic hydrocarbons and the recently developed palladium-catalyzed reactions and metathesis reaction strategies, the aim of this thesis is the extension of the scope of the cross-coupling and the metathesis reactions in the synthesis of polyheterocycle compounds.

In this work, dihalogenated pyridines are used as versatile and easily available starting materials, which undergoes regio- and chemoselective palladium-catalyzed cross-coupling reactions to obtain novel, value added functionalized molecules. These structures will be obtained by Pd catalyzed cross coupling reaction and/or acid mediated alkyne-carbonyl-metathesis reactions. The newly developed synthetic methods will well optimized to obtain high yields of the desired products. Isolated products will be fully characterized by various analytical methods and selected compounds will be studied in more detail with regard to UV/Vis and fluorescence properties.

2   Synthesis of PHAs via alkyne carbonyl metathesis

2.1   Pyrrolo[1,2-*a*][1,6]naphthyridines and thieno[3,2-*f*]isoquinolines

Polycyclic aromatic hydrocarbons (PAH) consist of multiple aromatic rings that only contain carbon and hydrogen in the same scaffold. They occur in petroleum, coal, and tar deposits and as by-products of fuel. The main application of PAHs in the organic electronics field is determined by the semiconducting behaviour of the structures, the solid-state packing, the frontier orbital energies, the reorganization energy and the electronic coupling between molecules. In order to enhance the semiconducting activity, some heteroatoms were introduced in these structures to give multiple polycyclic heteroaromatic molecules (PHAs). It has been demonstrated that PHA structures have higher effective charge transport in organic semiconductors in comparison to their hydrocarbon counterparts.[16][77][78] Polycyclic heteroaromatic structures have found their main application in material science fields.[79] The introduction of N- and S-heterocycles change the electronic properties significantly and have emerged as substance class which in improved results in the field of organic semiconductor development. In particular, nitrogen provides to these structures altered frontier molecular orbital energies, higher stability towards air and moisture, solubility and are often easier synthesized compared to their hydrocarbon counterparts.[77][17] On the other hand, when sulphur is introduced, the stabilization of the structures and a higher charge carrier transport, which are essential for optoelectronic applications, are observed. This is due to the high polarizability of the sulphur in the thiophene structure.[15]

This chapter is focussed on the synthesis of functionalized pyrrolo[1,2-*a*][1,6]naphthyridines and thieno[3,2-*f*]isoquinoline (figure 5). The synthesis of the intermediate products was performed by Suzuki coupling, Sonogashira reaction and acylation reaction in different orders as applicable. The common synthetic characteristic on each scaffold is the last reaction step mediated by ACM reaction to obtain the cyclized final product.

pyrrolo[1,2-*a*][1,6]naphthyridine

thieno[3,2-*f*]isoquinoline

Figure 5. Target scaffolds in this chapter.

2.1.1 Functionalization of pyrrolo[1,2-*a*][1,6]naphthyridines

Pyrrolo[1,2-*a*][1,6]naphthyridine is a polycyclic heteroaromatic hydrocarbon (PHA) combining 1,6-naphtyridine moiety, also known as 1,6-diazanaphthalene, and pyrrole (figure 6). Because of their good application in the pharmacology field, both structures are well document. For example, 1,6-naphtyridine is characterized by its huge application in the medicinal chemistry field due to its activity as anticancer, anti-inflammatory, analgesic, anti-HIV, antimicrobial and anti-oxidant.[80] Similarly, even without been found in natural products, indolizine have a well-documented pharmacological activity as antibacterial, anticancer and antituberculosis.[81,82] Additionally, these scaffolds, due to the presence of nitrogen heteroatoms, have unpaired free electrons, which offers the possibility of acting as electron donors in many chemical processes as ligand.[83–86] Their use in the field of organic electronics have also been reported.[78]

1,6-naphthyridine

1*H*-pyrrole

pyrrolo[1,2-*a*][1,6]naphthyridine
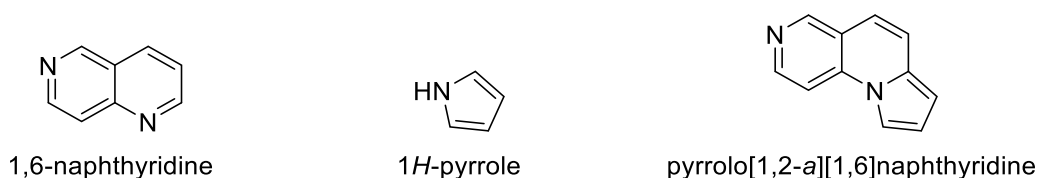
Figure 6. Structure of 1,6-naphthyrydine, 1*H*-pyrrole and pyrrolo[1,2-*a*][1,6-naphthyridine.

The first synthesis of pyrrolo[1,2-*a*][1,6]naphthyridines was published in 2009 by D. I. Chai and M. Lautens.[87] This methodology involved the corresponding *gem-*dibromovinyl substrates in a sequential Suzuki-Miyaura coupling/direct arylation tandem reaction (scheme 1). In this case 3-(2,2-dibromo-vinyl)-4-pyrrol-1-yl-pyridine was subjected to the Suzuki reaction for 12 hours at 100°C, followed by a palladium-catalyzed CH activation reaction to yield the desired product in 63%.

The second report related to the synthesis of this scaffold was made by Li *et. al.* in 2016.[88] The procedure describes a Rhodium-catalyzed double C−H activation/annulation between N-aryl azaindoles and less-reactive electron-rich alkenyl esters, but with low regioselectivity and efficiency, yielding only a 30% (2:1) of the desired product (scheme 1).

A third reaction related to 1,6-naphthyridines was published in 2017 by Pierrat and Co.[89] It started with indium(III)chloride-mediated reaction and microwave-assisted at 160°C for a period of 5 minutes (scheme 10).

In 2017 Prof. Langer's group published an accessible strategy to obtain pyrrolo[1,2-*a*][1,6]naphthyridines.[90] This synthetic route does not demand a special catalyst/ligand-systems and the cycloisomerization is mediated by a simple Lewis acid.
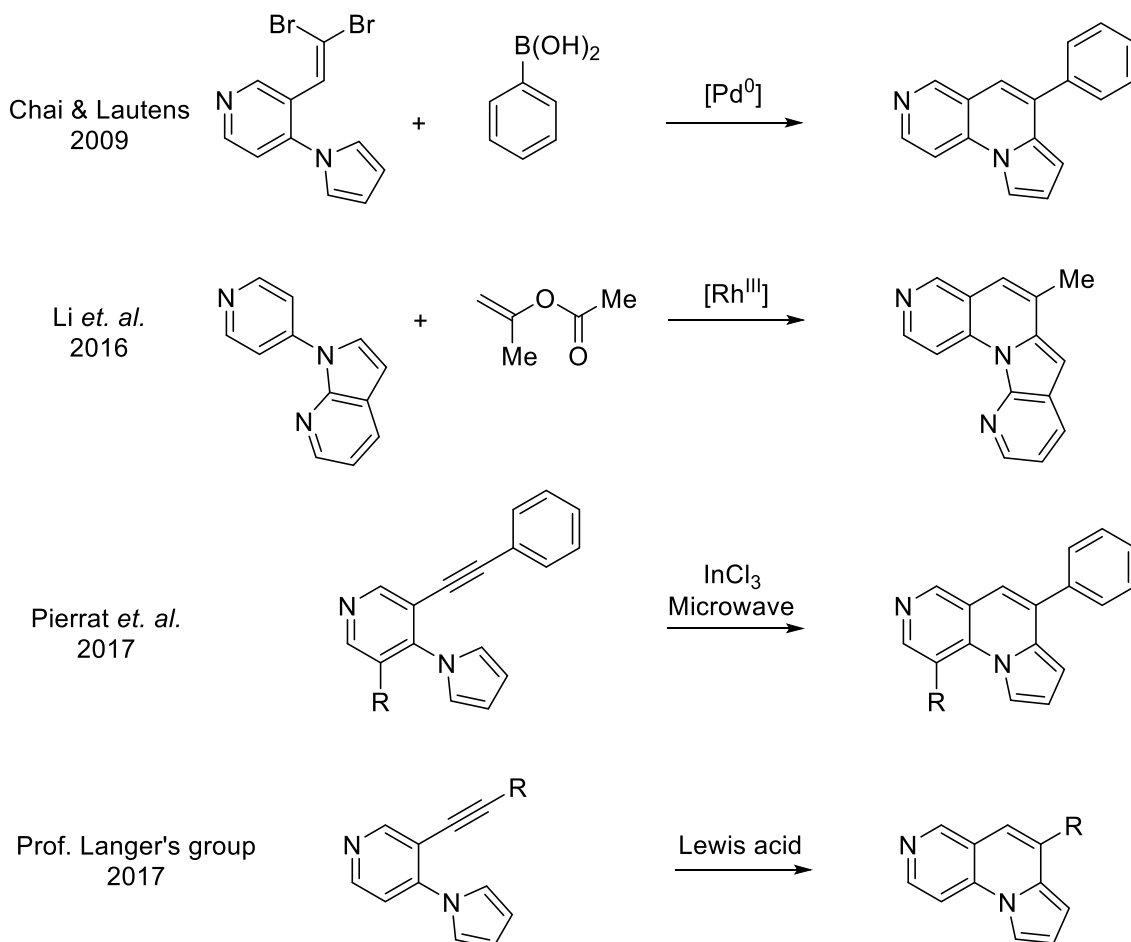
Scheme 10. Synthesis of pyrrolo[1,2-*a*][1,6]naphthyridines reported previously to this work.

In fact, reactions showing the synthetic route of pyrrolo[1,2-*a*][1,6]naphthyridines are not frequent in the literature due to unavailability of starting materials, scope and yields.

According to the publication of Prof. Langer's group, which describes the synthesis of pyrrolo[1,2-*a*]naphthyridines derivatives via Lewis acid-mediated cycloisomerization, *ortho*-alkynyl-N- pyrrolylpyridines can be employed as suitable precursors of the desired compounds. Additionally, this methodology is highly efficient, enables the introduction of several functional groups and allows an easy handling of the experimental part in the laboratory.
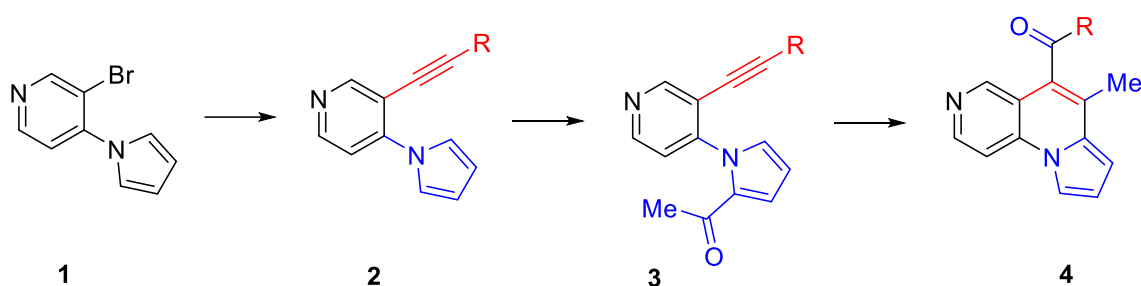
Taking these previous studies and the interesting properties of pyrrolo[1,2-*a*][1,6]naphthyridines into account, this work is directed to the preparation of (6-methylpyrrolo[1,2-*a*][1,6]naphthyridin-5-yl)(phenyl)methanones and (4-methylnaphtho[2,1-*b*]thiophen-5-yl)(phenyl)methanones via alkyne carbonyl metathesis (ACM) reactions (scheme 11).

Scheme 11. General strategy for the synthesis of pyrrolo[1,2-*a*][1,6]naphthyridines in this work.

The motivation to take the challenge of this project were the interesting properties of these scaffolds and the limited number of previous synthetic routes reported for obtaining this kind of structures. This work provides new insights into the field of synthesis of pyridine-based heterocycles via Brønsted-acid-mediated ACM reactions.

In order to achieve a satisfactory synthesis method, a three-step synthesis sequence was developed. It involved the combination of the palladium-catalyzed Sonogashira reaction, followed by an acylation reaction and Brønsted acid-mediated alkyne carbonyl metathesis (ACM) reactions.

To synthesize appropriate starting materials for the ACM reaction, 4-aminopyridine was selectively brominated at the 3-position by an electrophilic aromatic substitution using N-bromosuccinimide (NBS) reaction.[91] The electron density distribution of the pyridine combined to the strongly activating amine substituent in position 4, favoured the regioselective bromination in position 3 due to the *ortho*-effect director of the amine group (scheme 12).

Subsequently, the amino group was transformed into a pyrrole ring by a classical Clauson-Kaas reaction[92][93][94]. 2,5-Dimethoxytetrahydrofuran was added to the stirred mixture of pyridine and acetic acid at 120°C, to produce 3-bromo-4-(1*H*-pyrrol-1-yl)pyridine (**1**) in 79% yield.[90] In this case the acid was used as catalyst and solvent at the same time (scheme 12).
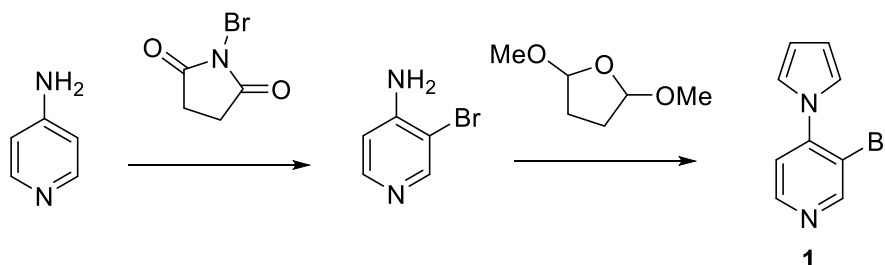
Scheme 12. Preparation of the starting material **1**.

With the introduction of a good leaving group such as bromine in position 3, an active centre in the substituted pyridine is generated. Afterwards, Sonogashira cross coupling reaction using various aryl acetylenes was used to implement required alkynyl moieties to the molecule (table 1).[90]

Table 1. Synthesis of 3-(alkynyl)-4-(1*H*-pyrrol-1-yl)pyridines **2a-d**.
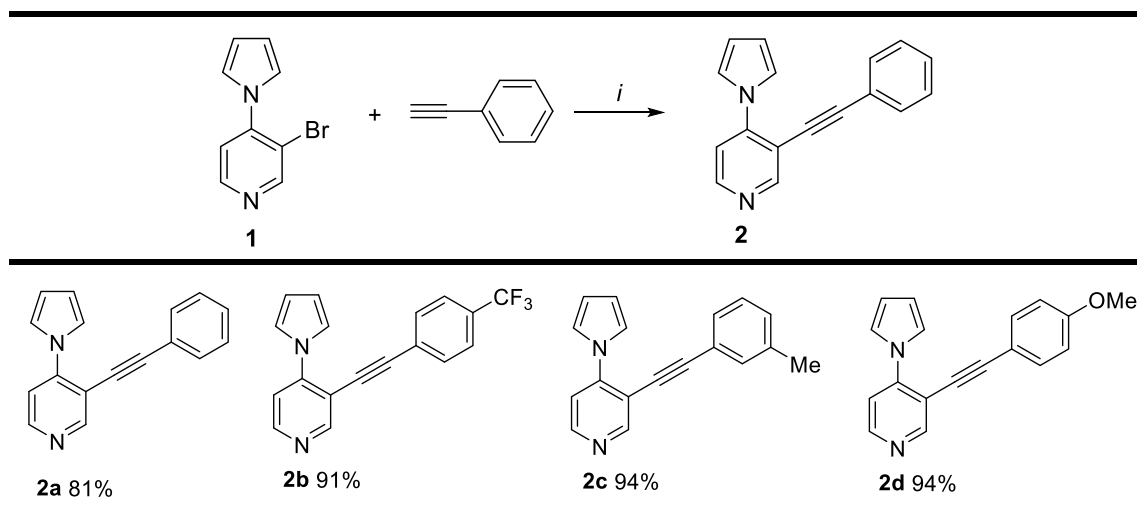
Conditions i: alkyne (1.4 equiv.), PdCl$_2$(CH$_3$CN)$_2$ (5 mol%), XPhos (10 mol%), CuI (5 mol%), Et$_3$N (3.0 equiv.), 1,4-dioxane , r.t., 24 h.

The catalyst system of PdCl$_2$(CH$_3$CN)$_2$/XPhos and CuI gave products **2a-b** in good to excellent yields (81% − 94%). The reaction conditions worked very well for all the used acetylenes independently from the employed substitution pattern and no remarkable effect on the yields introduced by electron-rich or electron-poor functional groups have been observed.

After performing the Sonogashira reaction, the pyrrole ring of compound **2a** was functionalized through an acylation reaction with acetic anhydride as acylating agent. Due the electronic nature of this 5-membered heterocycle ring, the electrophilic aromatic substitution is favoured in pyrrole ring in comparison to the benzene or pyridine ring, respectively and is selectively directed to position 2 of the pyrrole ring.[95] The unshared pair of electrons from the nitrogen atom contained in the pyrrole ring are delocalized on aromatic system and promote two effects, on one hand they considerably stabilizes the cationic intermediate and on the other hand make the carbon atoms electron-rich. This results in the increase of the reactivity towards electrophiles and at the same time facilitate the regioselectivity of the reaction.

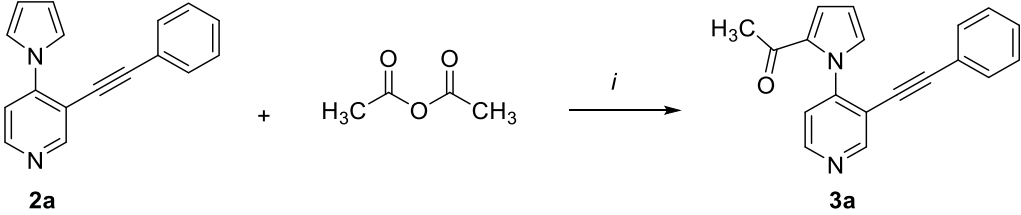In previous works from Prof. Langer's group, the acylated compound was synthesized using trifluoracetic anhydride (TFAA) as the acylating agent. The substitution of the 2,2,2-trifluoroacetyl group on the pyrrole ring gave good results.[96] Trifluoromethyl is an electron-withdrawing group that promotes the electrophilic aromatic substitution reaction in the position 2 of the pyrrole. Parpart and co-workers[96] demonstrated that the replacement of the strong electron-deficient anhydrides (TFAA) by a less electron-deficient anhydrides as acetic anhydride was possible, but with low efficiency and regioselectivity.

Encouraged by the previous results achieved by the Prof. Langer's group, it was necessary to optimize the acylation using acetic anhydride on compound **2a** as a next step (table 2).

Table 2. Optimization of acetylation reaction.

Entry	Acetic anhydride	BF₃*Et₂O	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	1.6 equiv.	10 mol%.	CH_2Cl_2	r.t.	2	20
2	1.0 equiv.	1.0 equiv.	CH_2Cl_2	r.t.	24	50
3	1.0 equiv.	1.0 equiv.	CH_2Cl_2	r.t.	8	71

Parpart *et.al.* in 2018 tested the pyrrole acylation by Friedel-Crafts acylation, using the same strong Lewis acid (BF$_3$), but at 0° C.[96] They got the acetylated product in a moderate yield, but as an inseparable mixture of regioisomers of 2- and 3 acetylated pyrrole derivatives.

The application of BF$_3$*Et$_2$O (1.0 equiv.) in stoichiometric amounts was required to produce good yield in all the cases. Interestingly, longer reactions times resulted in reduced yields of the product, due to some side-reactions observed by TLC analysis. Finally using 1.0 equiv. of the Lewis acid in dichloromethane at r.t. for 8h gave the key precursor for the subsequent ACM reaction in good 71% yield (**3a**).

With these experimental conditions on hand, the synthesis of other acetyl-substituted structures was performed (table 3).

Table 3. Acylation of 3-(alkynyl)-4-(1*H*-pyrrol-1-yl)pyridine **3a-d**.
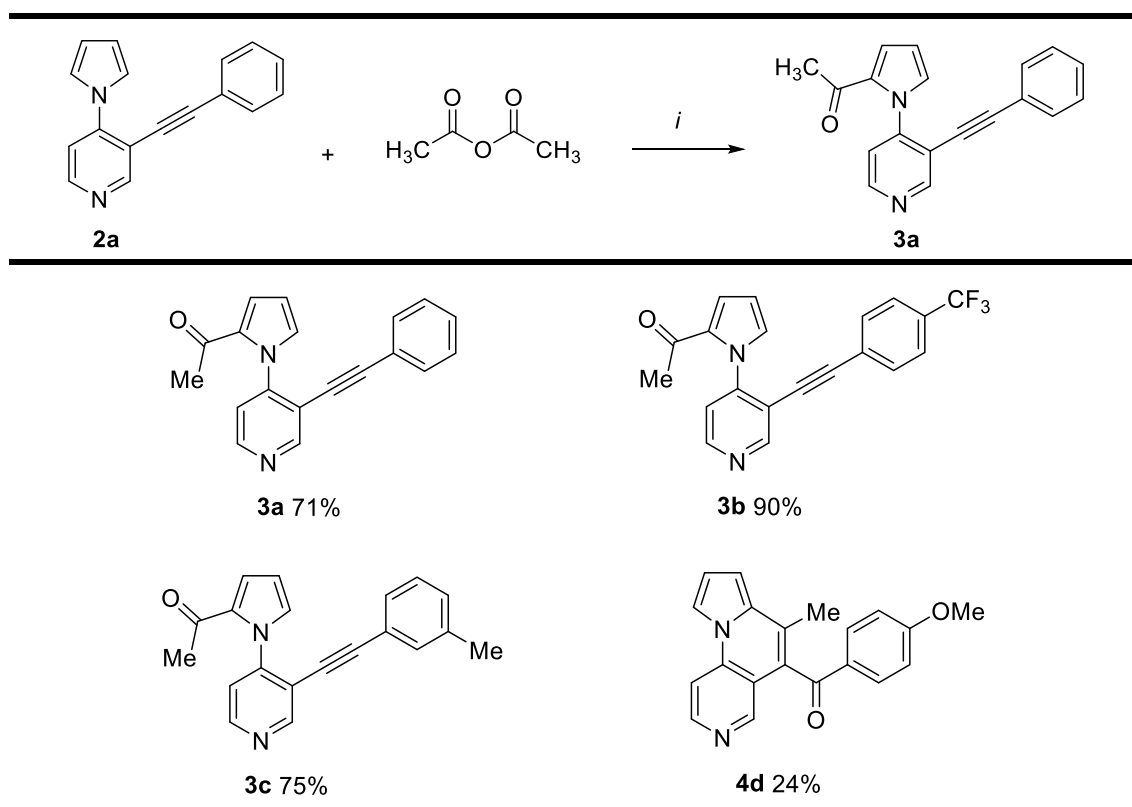
Conditions i: acetic anhydride (1.0 equiv.), BF$_3$*Et$_2$O (1.0 equiv.), CH$_2$Cl$_2$, r.t., 8 h.

Under optimized conditions compound **3a-3c** have been isolated in good to very good yield. Interestingly, starting from compound **2d** the acylated product **3d** could not be isolated. However, already cyclized ACM product was obtained with 24% yield. A possible explanation for this experimental evidence could be found in the strong positive

inductive effect of the methoxy group on the aryl ring of the acetylene. This electron-donating effect causes an increase of the nucleophilicity of the acetylene triple bond, which leads to a better reactivity of the acetylene in the ACM step by improved stabilization of occurring positive charges during the cyclization process. The relative low yield of compound **4d** can be explained by separation issues during column chromatography. TLC analysis reveal two main spots which were hardly separated. The second spot corresponds presumably to non-cyclized product **3d** which could not isolated form the reaction in pure form.

The reaction conditions allow the use of acylation reaction with high regioselectivity and good to excellent product yields between 71% and 90%. In addition, it permitted to obtain the cyclised final product (**4d**) from the methoxy substituent in one-pot reaction.

After ACM precursors were successfully generated through acylation reaction, the final synthesis step, the intramolecular alkyne carbonyl metathesis (ACM), was carried out (scheme 13).
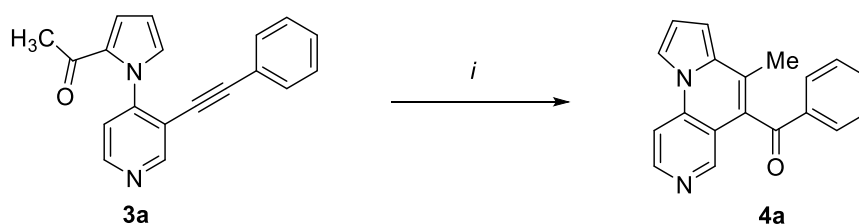
Scheme 13. Cycloisomerization reaction.

Taking into consideration the reaction conditions previously used for related transformations in literature, it was necessary to develop a short optimization to get a better result (table 4). As a first trial the strong Brønsted acid at room temperature was used, which gave no yield of the desired product. Subsequently, the temperature was raised to 40°C and the cyclized ACM product (**4a**) was obtained in excellent 95% yield.

Table 4. Optimization of cyclization reaction of **4a**.
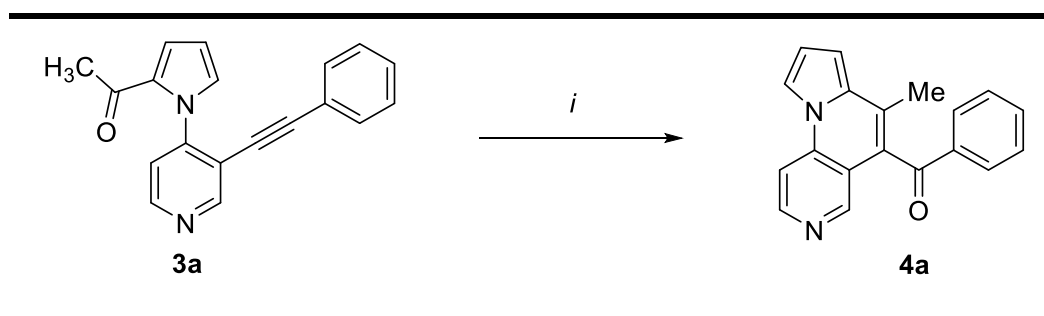
Entry	Catalyst	Solvent	Temp. (°C)	Time	Yield (%)
1	MsOH (50 equiv.)	-	25	1h	-
2	MsOH (50 equiv.)	-	40	4h	95

Considering the results observed during the optimization step, easily it was noticed that the temperature is a sensitive parameter in this kind of reaction. In the same manner, Brønsted acid have an important role in the cyclization process, giving mainly the desired product and avoiding the formation of by-products. Noteworthy MsOH was used as acid and solvent at the same time.

The optimized conditions were applied to the rest of starting materials and very good yields were obtained for all products (table 5).

Table 5. Synthesis of (6-methylpyrrolo[1,2-*a*][1,6]naphthyridin-5-yl)(aryl)methanone derivatives **4a-c**.
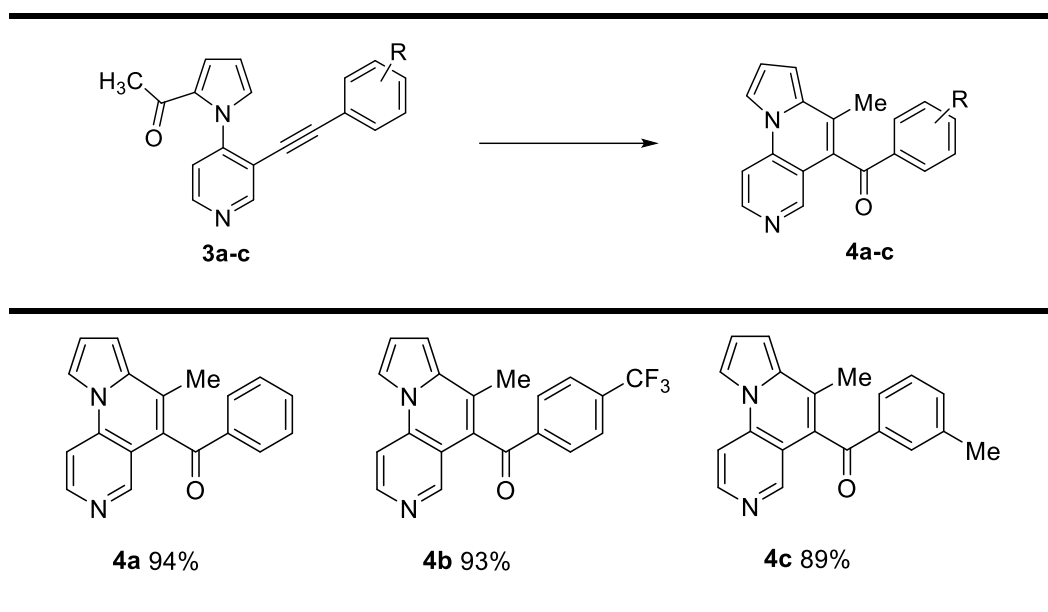
Conditions i: **3a** (0.23 mmol), MsOH (50 equiv.), 40 °C, 4 h.

The effect of the electron rich or poor substituent did not affect the yield. Importantly, the reaction conditions provide very good chemoselectivity as no cycloisomerization product, as a result of direct electrophilic substitution on the pyrrole ring by a potentially occurring vinyl cation during reaction process was detected (scheme 14). The *meta* and *para* substituted positions do not have any effect on the yields in the final product.
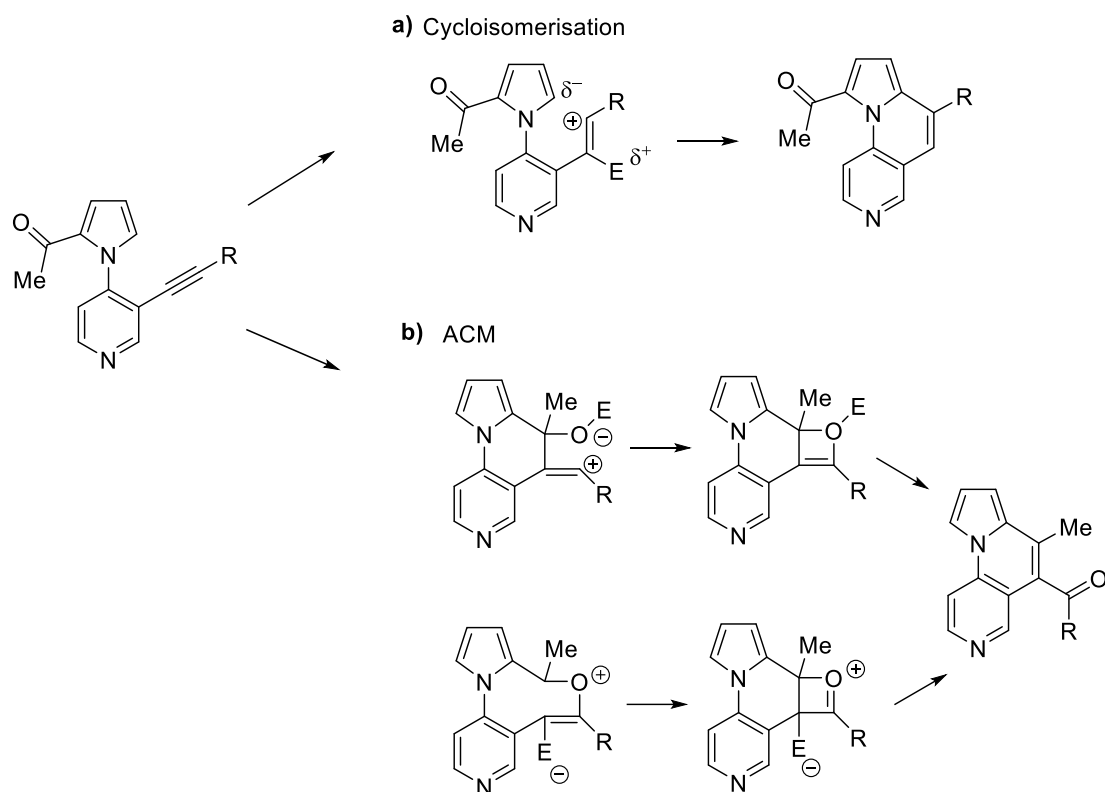
Scheme 14. Possible ACM and cycloisomerization in compounds **3a-c**.

All the structures were confirmed by NMR spectroscopy, IR spectroscopy and mass spectrometry. The structure of the substance **4a** was also confirmed by X-ray crystal structure analysis measurements on single crystals, showing the as prepared benzoyl group orientated nearly orthogonal to the planar pyrrolonaphthyridine scaffold (figure 7).
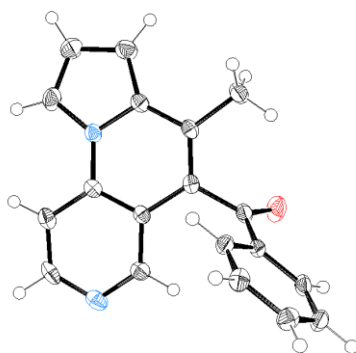
Figure 7. Single crystal structure of **4a**.

The developed methodology allows the synthesis of various pyrrolonaphthyridines in high yields with concomitant introduction of two functional on the ring. Especially the introduced carbonyl group allows for further derivatization. Due to the importance of

carbonyl group in the organic chemistry, its diverse applications in the material science and biology field, the functionalization of the compounds **2a-d** was a good strategy with the aim of enhancing a possible biological or electronic property. The results of this work were published by our group in the journal "Synthesis" in 2021.[97]

2.1.2 Functionalization of thieno[3,2-*f*]isoquinolines

Conjugated polyaromatic hydrocarbons are important due to their activity in the field of medicinal chemistry, organic electronics, and new materials. Most of these organic structures have the presence of heteroatoms which gives the heteroaromatic hydrocarbons unique properties. For example, polyaromatic hydrocarbons isoquinoline derivatives provide several biological activities. These derivatives are used on the therapy against malaria, also in the treatment of colon, lung and pancreatic cancer.[98] Additionally, their anti-inflammatory, antibiotic, antitumoral and anti-HIV activity is well known.[98][99]

In addition, benzo[*b*]thiophene has been widely used in the material science field. Because of its good chemical and physical properties such as conductivity, advantageous orientation of molecules in the solid state, good conjugation and high environmental stability, the thiophene ring is the most widely used ring for the construction of conjugated polymers. Polymers containing thiophene moieties exhibit attractive electronic, optical and redox properties, as well as unique self-assembly capabilities on solid and bulk surfaces.[15][100]

Thieno[3,2-*f*]isoquinolines are polycyclic heteroaromatic hydrocarbons that are a combination of isoquinoline and thiophene. Both core structures have wide applications in both biological and material science, and have been studied for their physical and chemical properties (figure 8).
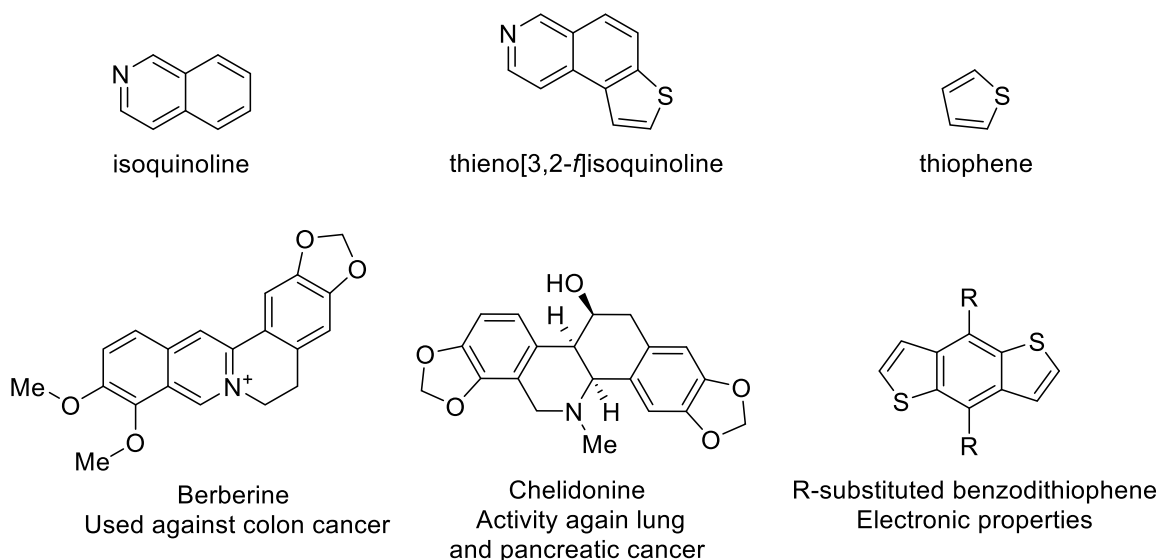
Figure 8. Structures of isoquinoline, thieno[3,2-*f*]isoquinolines and thiophene derivatives.

The aim of this part of my thesis is to extend the application of the methodology previously developed for the ACM using other heterocycles. In this case pyrrole is interchanged with a thiophene ring. The planned reaction steps to achieve the new thieno[3,2-*f*]isoquinolines are shown in the following scheme (scheme 15).
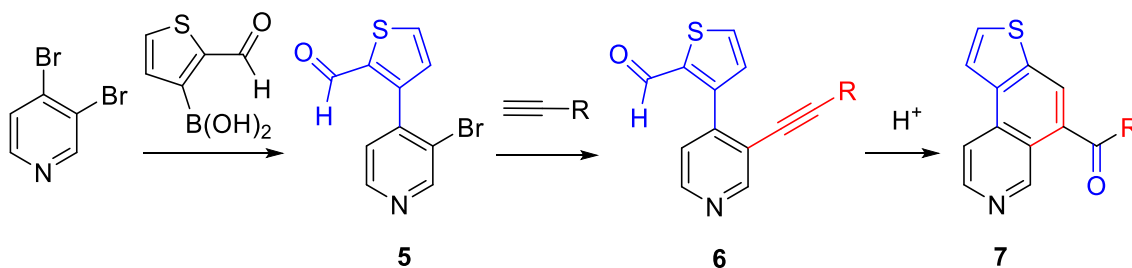
Scheme 15. Synthesis strategy for obtaining thieno[3,2-*f*]isoquinolines derivatives by ACM.

The first step involves a site-selective Suzuki reaction of (2-formylthiophen-3-yl)boronic acid and 3,4-dibromopyridine. In this reaction, the position 4 is favoured due to the reduced electron density at this position induced by the ring nitrogen.

It was necessary to perform an optimization of this Suzuki reaction to obtain acceptable yields (table 6).

Table 6. Optimization of conditions for Suzuki reaction.

Entry	Catalyst	Ligand	Base	Solvent	Temp.(°C)	Time	Yield
1	Pd(OAc)$_2$ 5 mol%	SPhos 10 mol%	K$_3$PO$_4$ 2.0 equiv.	Toluene	100°C	24 h	-
2	Pd(OAc)$_2$ 5 mol%	SPhos 10 mol%	K$_2$CO$_3$ 2.0 equiv.	CH$_3$CN/H$_2$O (1.5:1)	100°C	24 h	-
3	Pd(PPh$_3$)$_4$ 5 mol%		K$_2$CO$_3$ 2.0 equiv.	Dioxane/H$_2$O (6:1)	90°C	24h	45%
4	Pd(PPh$_3$)$_4$ 2.5 mol%		K$_2$CO$_3$ 1.0 equiv.	Dioxane/H$_2$O (6:1)	90°C	18h	28%
5	Pd(PPh$_3$)$_4$ 5 mol%		K$_2$CO$_3$ 2.0 equiv.	Dioxane/H$_2$O (6:1)	90°C	24h	52%

During the optimization process, the effect of the catalyst, base, solvent, temperature and time in the reaction were studied. The final conditions obtained were Pd(PPh$_3$)$_4$, with a solvent mixture of dioxane and H$_2$O stirred at 90 °C for a duration of 24 hours.

With the first intermediary in hand, the second step was the Sonogashira reaction at position 3 of the pyridine ring. Again, a short optimization study was performed for Sonogashira reaction and the results are shown in table 7.

Table 7. Optimization of Sonogashira reaction (**6**).
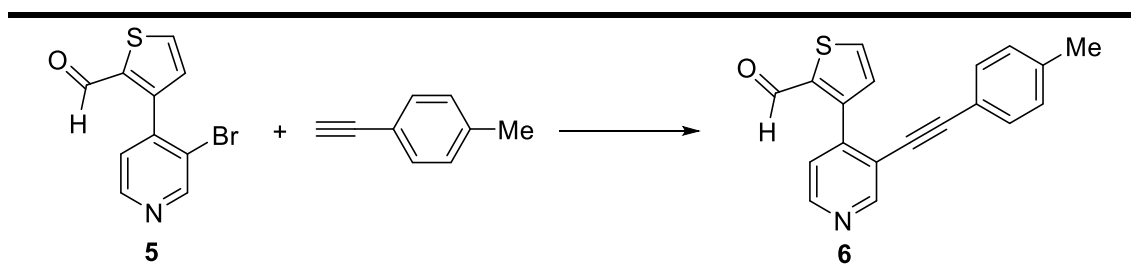
Entry	Catalyst	Ligand	Co-catalyst	Solvent	Temp.(°C)	Time (h)	Yield (%)
1	Pd(PPh₃)₄ 5 mol%		CuI 2 mol%	HN*i*Pr₂	40	1	-
2	Pd(PPh₃)₄ 5 mol%		CuI 2 mol%	HN*i*Pr₂	80	24	55
3	Pd(PPh₃)₄ 5 mol%		CuI 2 mol%	Et₃N	80	20	48
4	PdCl₂(CH₃CN)₂ 5 mol%	XPhos (10 mol%)	CuI 2 mol%	HN*i*Pr₂	80	20	89

The best yield was obtained with 5 mol% of $PdCl_2(CH_3CN)_2$ as catalyst in presence of 10 mol% of XPhos as ligand in diisopropylamine as base and solvent. The reaction was stirred for a duration of 20 hours at 80 °C and the yield was 89% of the desired final product.

With the optimized condition in hand, the scope of the reaction was performed (table 8).

Table 8. Synthesis of 3-(3-(alkynyl)pyridin-4-yl)thiophene-2-carbaldehyde by Sonogashira reaction.

6a 89%   6b 94%   6c 68%

6d 80%   6e 97%
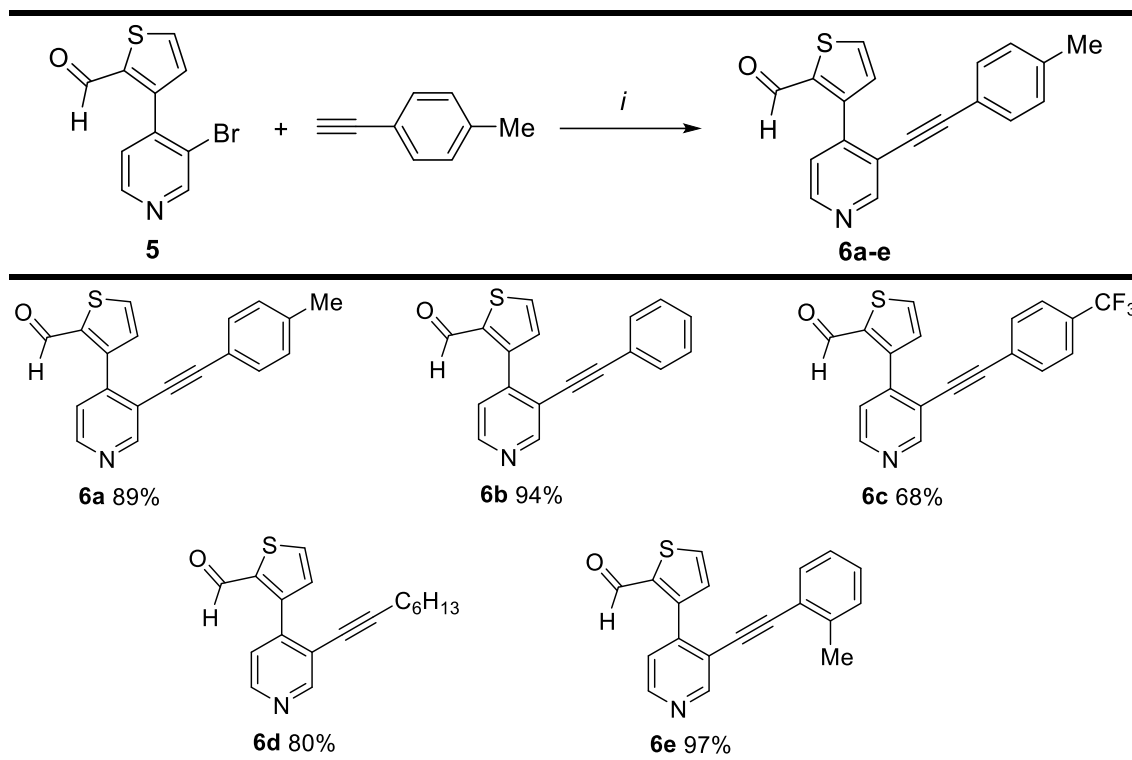
Conditions i: alkyne (1.2 equiv.), $PdCl_2(CH_3CN)_2$ (5 mol%), XPhos (10 mol%), CuI (2 mol%), HN*i*Pr₂, 80 °C, 20 h.

Five intermediates were prepared with optimized conditions in moderate to very good yield. The effect of the substituent on the alkyne had some influence on the progress of the reaction. While alkynes with phenyl- and tolylacetylene as well as 1-octyne gave very good isolated yields, compound **6c**, containing a trifluoromethyl substituent gave reduced 68% yield. The CF$_3$ group is a strong inductively withdrawing group and transmetallation might be hampered.

The cyclization reaction was mediated mechanistically by the alkyne carbonyl metathesis. This [2+2] cycloaddition followed by a reordering of the bonds of the oxetane ring yield the desired phenyl(thieno[3,2-*f*]isoquinolin-5-yl)methanone derivatives (**6a-e**).

After applying the same conditions for the cyclization step as in the previous reaction to obtain (6-methylpyrrolo[1,2-*a*][1,6]naphthyridin-5-yl)(phenyl)methanone (**4a**), the desired compound was not formed. Then, the optimization for the ACM reaction was performed (table 9).

Table 9. Optimization of cyclization reaction.

Entry	Catalyst	Solvent	Temp.	Time	Yield
1	MsOH (50 equiv.)		40 °C	4h	-
2	pTsOH (15 equiv.)	Xylene	120 °C	1h	-
3	MsOH (50 equiv.)		r.t	1h	92%

Regular TLC studies during the reaction progress revealed the fast formation of the product and its decomposition over time. Hence, the reaction was performed at room temperature and only one hour. With these slight changes in the reaction parameters, the desired product was obtained in excellent yield of 92%.

Once the reaction was optimized, the scope for the ACM reaction was studied (table 10).

Table 10. Synthesis of aryl(thieno[3,2-*f*]isoquinolin-5-yl)methanone by ACM reaction.

6a → *i* → **7a**

7a 92%   **7b** 96%   **7c** 85%

7d 80%   **7e** 78%
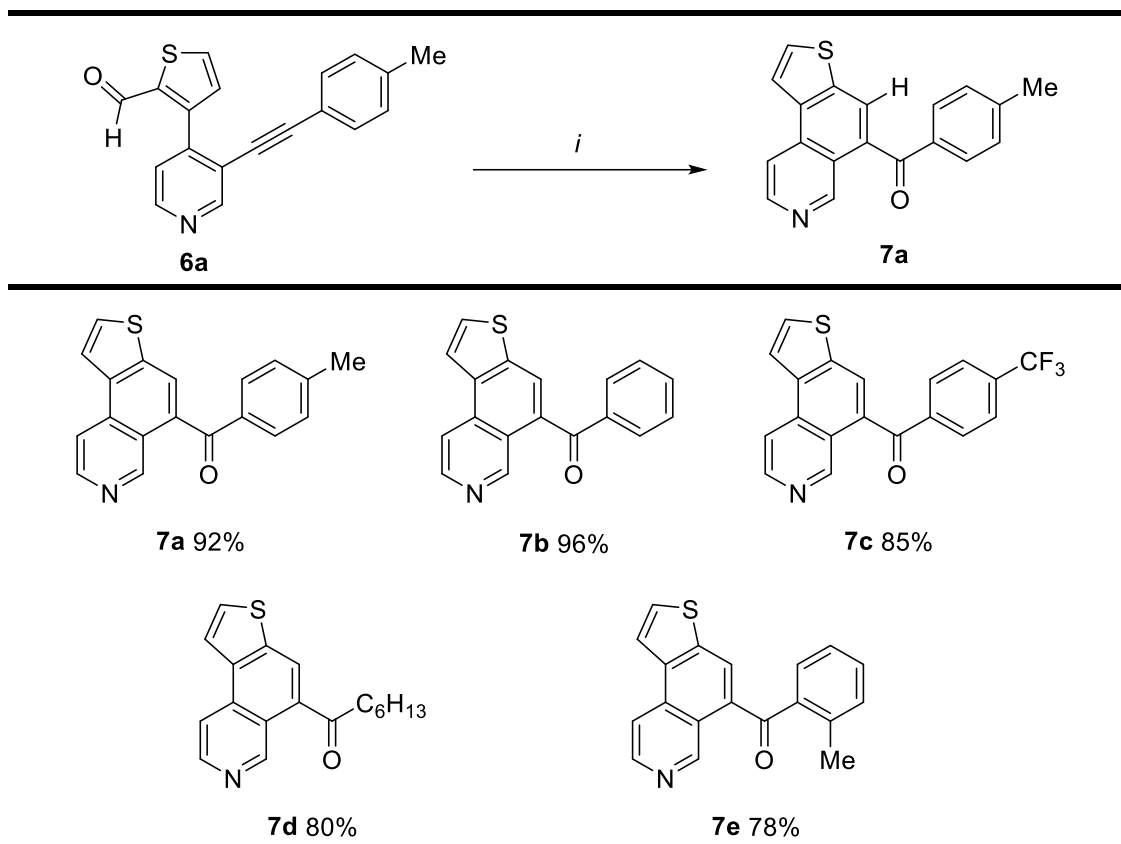
Conditions i: MsOH (50 equiv.), r.t., 1 h.

The five final compounds were obtained in very good yield and the substituents did not have any influence on the yield of the reaction.

All compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry. In addition, the compound **7a** was analysed by X-ray diffraction analysis (figure 9).
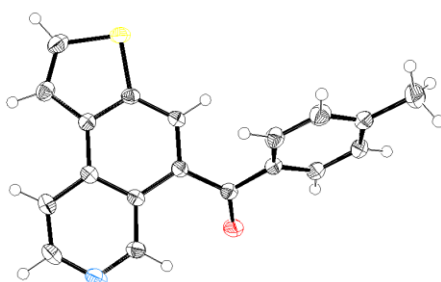
Figure 9. X-ray structure of thieno[3,2-*f*]isoquinolin-5-yl(*p*-tolyl)methanone (**7a**).

2.2 Conclusion

In conclusion, the alkyne carbonyl metathesis (ACM) reaction was successfully applied and high yields of the cyclized final products were obtained. The strong Brønsted acid, methanesulfonic acid (MsOH) turned out to be mandatory for the reaction to proceed. In total, nine final compounds containing pyrrolo[1,2-*a*][1,6]naphthyridines and thieno[3,2-*f*]isoquinoline cores were synthesized. All compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry, and structures of both substance classes were additionally confirmed by single crystal X-ray.

3   Brønsted acid mediated cycloisomerization

3.1   Benzo- and thieno[3,2-*f*]quinoline and acridine derivatives

Quinoline is one of the most widespread heterocycles containing nitrogen atom, it is a versatile molecule that allows the building of large number of compounds that help and contribute to the development of science and society. Quinoline or benzo[*b*]pyridine is a bicyclic ring system consisting of a pyridine- and benzene ring. It's a weak tertiary base, and it can show electrophilic and nucleophilic substitution reactions depending on the reaction conditions on which it is subjected.[101] Quinoline is an essential core of many naturally occurring biologically active compounds,[99,102] and its derivatives have broad applications and are well known for their synthetical[103] and biological activities such as antimalaria, antibiotic, antiseptic, anti-inflammatory, anti-cancer and anticonvulsant.[104] Quinoline can be extracted from coal tar and is often considered as an environmental contaminant caused by petroleum industry.[103]

On the other hand, thiophene is a five-membered heterocycle, easily found in natural state in crude petroleum.[105] The sulphur incorporated in the structure allows the thiophene derivatives to have versatile applications in materials, agrochemicals and pharmacological industry. They are well known for their properties as chemotherapeutic and anti-atherosclerotic agents.[106] For example, 1-[1-(2,5-dimethylthiophen-3-yl)ethyl]-1-hydroxyurea has been probed for their anti-inflammatory activity, whereas 2-butylthiophene has been used as a raw material in the synthesis of anticancer agents.

Nowadays numerous compounds with useful and unique properties contain pyridines and thiophene heterocycles. The combination of quinolines and thiophenes motifs have given very interesting results. Condensation of these structures in one molecule can allow to improve biological or material-like properties.

In the field of medicine, for example, PF-3644022 that contain thieno[3,2-*f*]quinoline motif have the potential to act as MK2 inhibitor in humans[107–109] (figure 10, a). MK2 is a serine-threonine kinase which is involved in the regulation of pro-inflammatory cytokine biosynthesis. The disruption of MK2 signalling leads to a significant reduction of the production of several pro-inflammatory cytokines. Thus, it has therapeutic potential for the inhibition of severe and chronic inflammatory diseases like rheumatoid arthritis, asthma, atherosclerosis, and neuro-inflammation.[110]

In addition, this kind of fused structures are well known to have a huge application in the materials field. For example, benzo- and thieno[3,2-*f*]quinoline scaffolds are used as organic material layers in organic electronic devices[111] (figure 10, **b**). In 2018, Ji *et. al.* reported the use of **c** (figure 10) as a ligand, which coordinated to a metal and works as a dopants for OLED applications.[112] Additionally, compound **d** (figure 10) was demonstrated as a building block of a conjugated polymer, applied solar cells.[100]
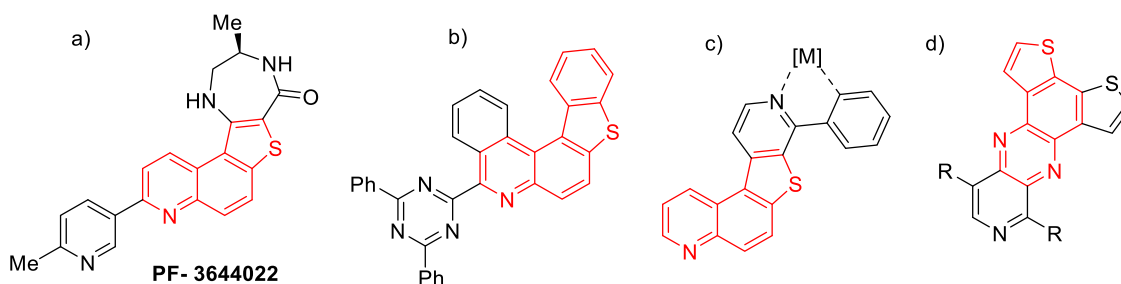
Figure 10. Benzo- and thieno[3,2-*f*]quinolines structures with biological activity (**a**) and uses as organic electronic materials (**b-d**).

The first report in the synthesis of thieno[3,2-*f*]quinoline moiety was made by Fries *et. al.* in 1937. They used 5-aminothionaphthene as starting material and applied a classical Skraup reaction.[113] Later in 1967, Zhiryakov and Abramenko studied the synthesis of 7- and 9-methylthieno[3,2-*f*]quinoline starting from 2-chlorobenzaldehyde following six-step reactions sequence. Chapman *et. al* studied the synthesis of a series of thieno[3,2-*f*]quinolines in 1970.[114]

In the 1990's, the synthesis of thieno[3,2-*f*]quinoline was reported by photocyclization for the first time.[115,116] In 2011, Snick and co-workers reported the synthesis of thieno[3,2-*f*]quinoline derivatives in 40% from an oxidation reaction.[117] In 2020, we proposed an synthetic access to a series of benzo- and thieno[3,2-*f*]quinolines by Brønsted acid mediated cycloisomerization.[118]

The methodology was based on a three-step reaction sequence of which the first two procedures comprised Palladium catalyzed cross coupling reactions followed by acid mediated cyclization (scheme 16).
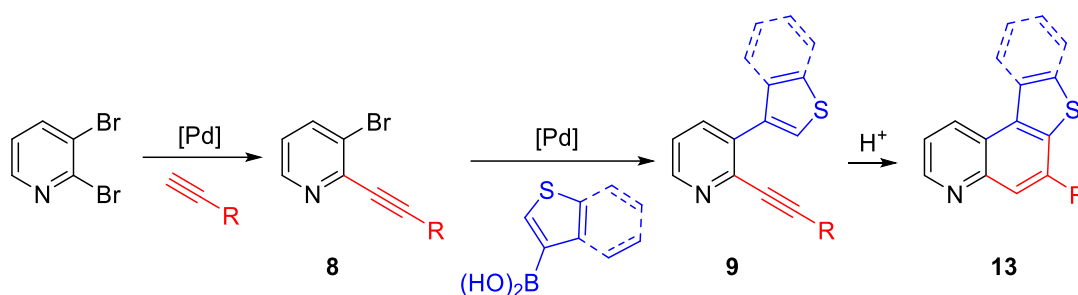
Scheme 16. Synthesis of 4-(alkynyl)thieno[3,2-*f*]quinoline.

The first step involved a Sonogashira coupling employing commercially available 2,3-dibromopyridine and an alkyne as starting materials (table 11). The reaction was performed using Pd(PPh$_3$)$_4$ as a catalyst and CuI as co-catalyst dissolved in Diisopropylamine (HN*i*Pr$_2$) under an argon atmosphere. The best results were obtained by stirring the reaction at 40 °C for a duration of 0.5 hours.

Table 11. Synthesis of 2-(alkynyl)-3-bromopyridines **8a-g**.
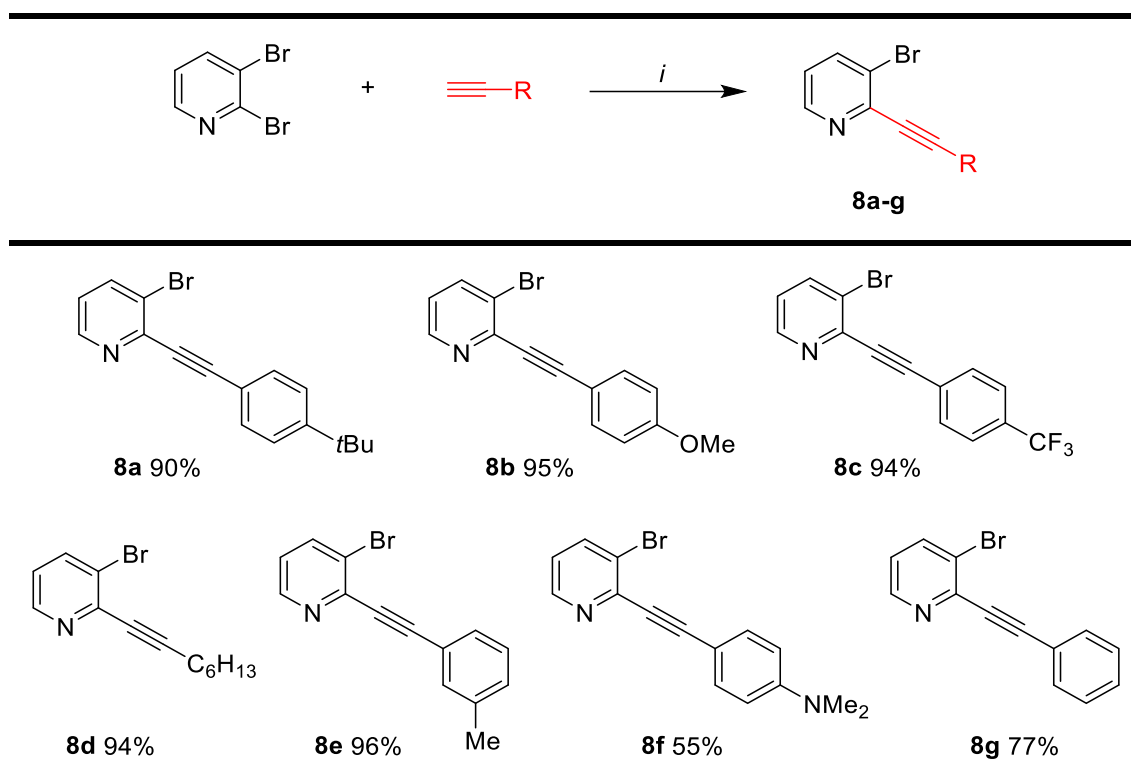
Conditions i: alkyne (1.2 equiv.), Pd(PPh$_3$)$_4$ (5 mol%), CuI (2 mol%), HN*i*Pr$_2$, 40 °C, 0.5 h.

The reaction was directed to position 2 in the pyridine ring, since the adjacent N atom has a negative inductive effect, reducing the electron density in the pyridine ring and

activating the positions 2, 4 and 6 towards a nucleophilic attack. In addition, the bromine substituted in the pyridine ring is a good leaving group.

During the experimental procedure, it was important to work under argon atmosphere, since the catalyst system is sensitive to the atmospheric oxygen because of the copper catalyzed Glaser coupling could otherwise occur as a side-reaction.

In general, the yields for both electro-donor and electro withdrawing aryl groups, were good, between 77% and 96%, except for the compound **8f** which was obtained in 55% yield.

In addition, when electron-rich aliphatic alkynes, such as 1-octyne, are used, good yield of 94% can also be achieved.

Afterwards, Suzuki coupling reactions between the obtained substituted 2-(alkynyl)-3-bromopyridines (**8a-g**) and different thienyl boronic acids were carried out (table 12). Three boronic acids were used: thiophen-3-ylboronic acid, benzo[*b*]thiophen-3-ylboronic acid and (4-bromothiophen-3-yl)boronic acid.

The conditions involved Pd(PPh$_3$)$_4$ as the catalyst, the base K$_2$CO$_3$ and solvents mixture of 1,4-dioxane/H$_2$O under an argon atmosphere at 90 °C. Employment of 1.7 equiv. of the boronic acid ensured a high yield of the desired product.

Table 12. Synthesis of 2-(alkynyl)-3-thiophenpyridines **9a-k.**

9e 80% **9f** 88% **9g** 94% **9h** 93%

9i 78% **9j** 73% **9k** 90%
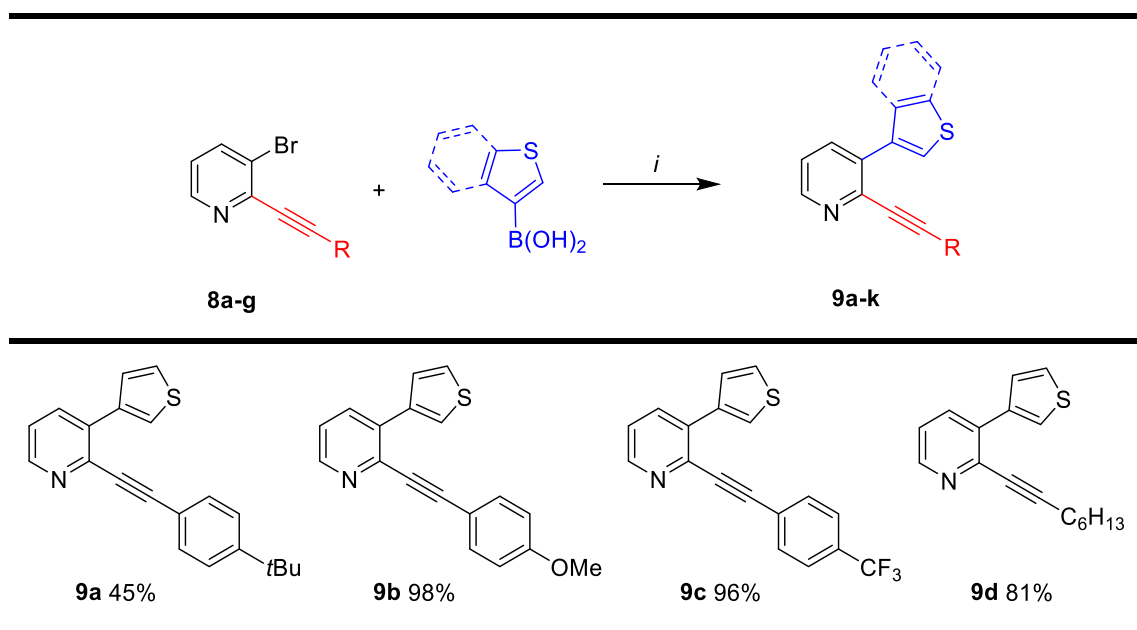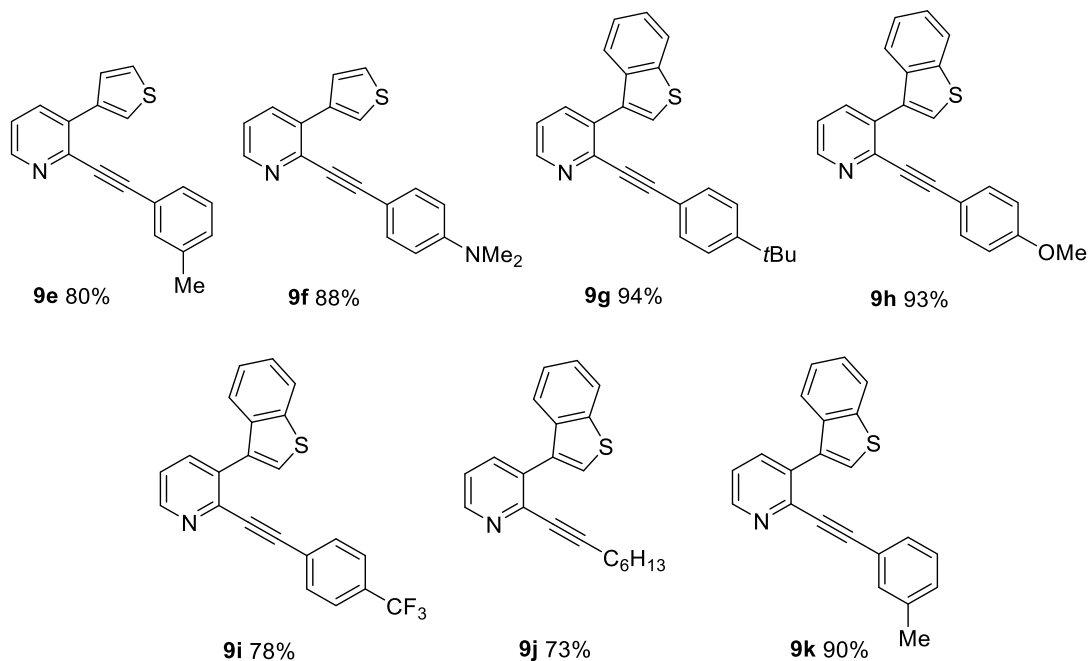
Conditions i: boronic acid (1.7 equiv.), Pd(PPh$_3$)$_4$ (5 mol%), K$_2$CO$_3$ (2.0 equiv.), 1,4-dioxane, 90 °C, 16 h.

Except compound **9a** containing a *tert*-butyl substituent on the alkynyl moiety, all compounds were obtained in very good yields, between 73% and 98%. In general, the conditions used for the Suzuki reaction showed good tolerance towards many functional groups.

In presence of (4-bromothiophen-3-yl)boronic acid, a optimization was required (table 13). In this case it was necessary to change the catalyst system to Pd(OAc)$_2$ /SPhos, and at the same time the solvent mixture to CH$_3$CN/H$_2$O. The reaction was stirred for 24 hours at 100 °C.

Table 13. Optimization for Suzuki reaction using (4-bromothiophen-3-yl)boronic acid.
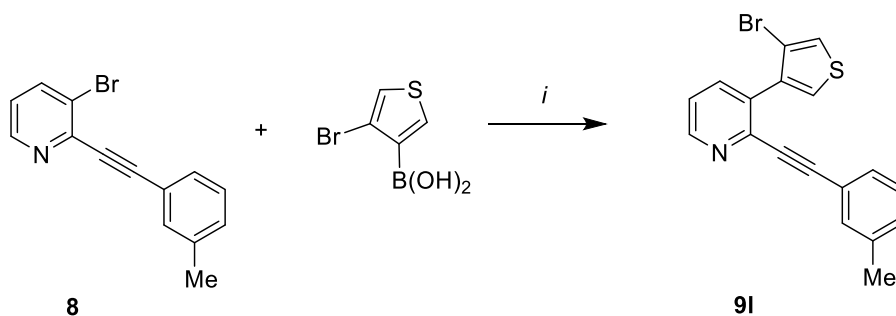
Entry	Catalyst	Ligand	Base	Solvent	Temp.(°C)	Time	Yield
1	Pd(PPh$_3$)$_4$ 5 mol%		K$_2$CO$_3$ 2.0 equiv.	Dioxane/H$_2$O (6:1)	90°C	24 h	-
2	Pd(PPh$_3$)$_4$ 5 mol%		K$_2$CO$_3$ 1.0 equiv.	THF/H$_2$O	60°C	12 h	-
3	Pd(PPh$_3$)$_4$ 5 mol%		K$_3$PO$_4$ 2.0 equiv.	DMF	100°C	22 h	-
4	Pd(PPh$_3$)$_4$ 5 mol%		Na$_2$CO$_3$ 2.0 equiv.	Dioxane	100°C	16 h	-
5	Pd(OAc)$_2$ 5 mol%	P(Cy)$_3$ 10 mol%	K$_2$CO$_3$ 3.0 equiv.	THF	60°C	24 h	-
6	Pd(OAc)$_2$ 5 mol%	SPhos 10 mol%	K$_2$CO$_3$ 2.0 equiv.	Toluene	100°C	24 h	31%
7	Pd(OAc)$_2$ 5 mol%	SPhos 10 mol%	K$_2$CO$_3$ 2.0 equiv.	CH$_3$CN/ H$_2$O	100°C	24 h	57%

Once the conditions for the use a brominated boronic acid were chosen, the scope of the reaction were developed (table 14).

Table 14. Synthesis of 2-(alkynyl)-3-(3-bromothiophen)pyridines **9l-n.**

9l 57%   **9m** 61%   **9n** 59%
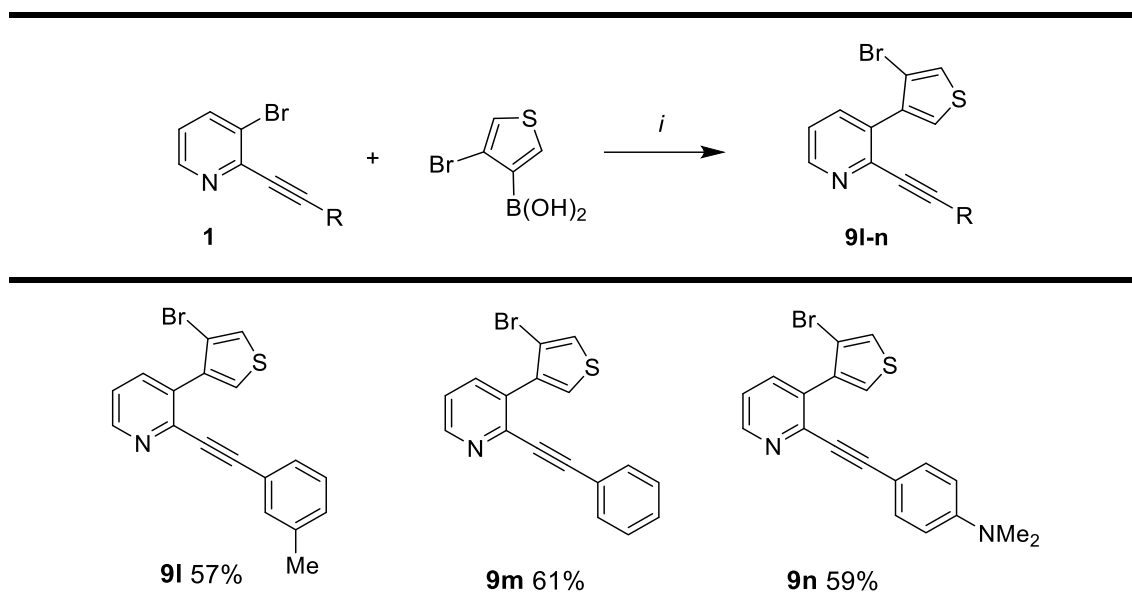
Condition i: boronic acid (1.1 equiv.), Pd(OAc)$_2$ (5 mol%), SPhos (10 mol%), K$_2$CO$_3$ (2.0 equiv.), CH$_3$CN/ H$_2$O, 100 °C, 24 h.

The yields were moderate in all reactions, with a range between 57% and 61%. A possible explanation for this experimental result can be found in a second Suzuki reaction produced in the bromine atom of the (thiophen-3-yl)boronic acid, which leads to the formation of undesired by-product. It could also be associated to steric hindrance effect of this halogen atom.

Encouraged by the previous results, a new synthetic strategy was studied with the aim of synthesizing thieno[2,3-*f*]quinolines. For this purpose, a different starting material, 3-bromo-2-chloroquinoline, was used. The order was reversed to achieve this goal. The Suzuki reaction was performed as a first synthetic step followed by a Sonogashira reaction and finally a cycloisomerization reaction delivers the desired product.

In the structure 3-bromo-2-chloroquinoline (**10**), the chemo-selectivity is reversed in comparison to the previous starting material used (2,3-dibromopyridine). In the case of 3-bromo-2-chloroquinoline, position 3 of the quinoline becomes more reactive than position 2, since the chemo-selective effect (Br > Cl) generally overcomes the electronic effect in palladium-catalyzed cross-coupling reactions. Two intermediate quinoline derivatives **11a-b** have been obtained by this chemoselective Suzuki reactions (table 15).

Table 15. Synthesis of 3-(benzo[*b*]thiophen-3-yl)-2-chloroquinolines and 2-chloro-3-(thiophen-3-yl)quinoline **11a-b**.

10 + **11a-b**

11a 80%

11b 59%
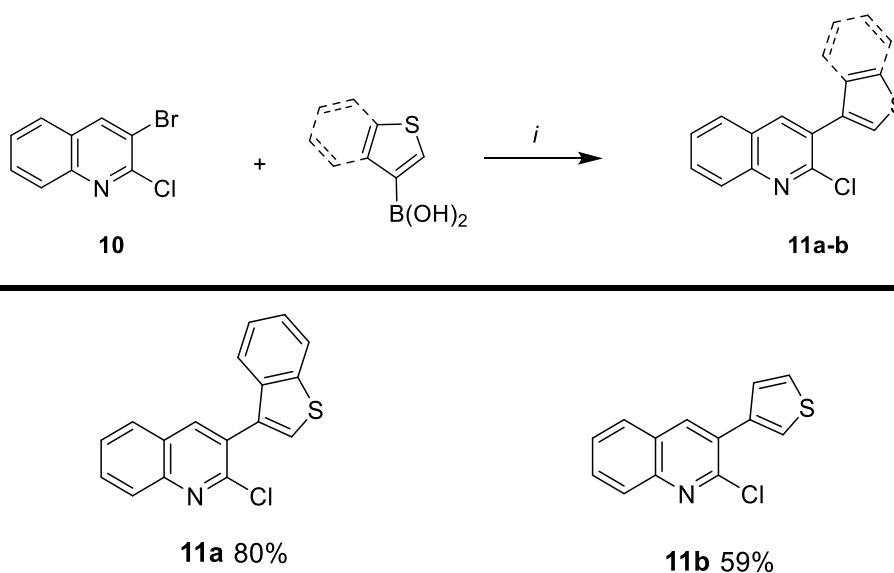
Conditions i: benzo[*b*]-& thiophen-3-ylboronic acid (1.0 equiv.), Pd(dppf)Cl$_2$ (5 mol%), K$_3$PO$_4$ (3.0 equiv.), 1,4-dioxane/H$_2$O (4:1), 100 °C, 3 h.

As it was expected, the reaction of 3-bromo-2-chloroquinoline (**10**) with different boronic acids, under the Suzuki reaction conditions, resulted in corresponding 3-substituted-2-chloroquinoline with good yields. The target compound **11a** and **11b** gave 80% and 59% yield respectively.

The next synthetic procedure involved the Sonogashira coupling between the substituted quinoline and the corresponding phenylacetylene (table 16).

Table 16. Synthesis of 3-(benzo[*b*]thiophen-3-yl)-2-(phenylethynyl)quinolines **12a-b**.
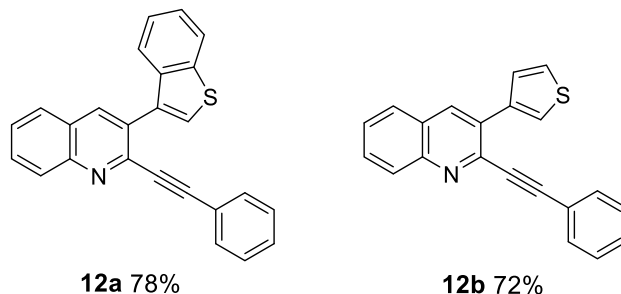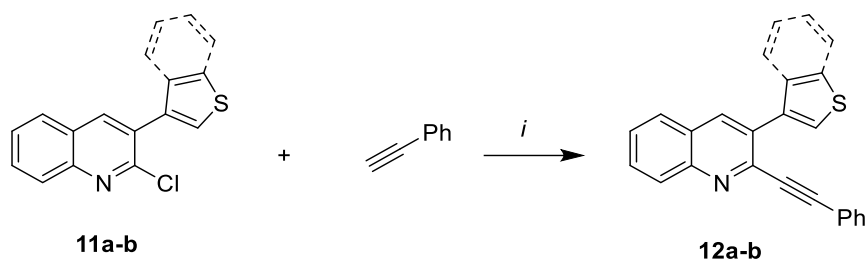
Conditions i: alkyne (1.2 equiv.), Pd(PPh3)4 (5 mol%), CuI (2 mol%), HN*i*Pr2, 70 °C, 20 h.

The reaction showed a good performance with the quinoline moiety instead pyridine, and gave the desired products with 78% and 72% yields.

Finally, as-prepared starting materials **9** and **12** were employed in Brønsted acid mediated cycloisomerization reactions. Mechanistically the triple bonds are activated by Brønsted- or Lewis acids, forming a vinyl cation, which undergoes an electrophilic aromatic substitution on the thiophene ring.

For this reaction methanesulfonic acid (MsOH) was chosen, accompanied with a reaction temperature of 120°C, as these conditions proved appropriate for similar reaction as discussed in the previous chapter. In this reaction, to activate the triple bond, it is necessary to have high temperatures and acidic media. Fortunately, these conditions in

xylene as solvent proved suitable to obtain desired product moderate to good isolated yields. The cycloisomerization reaction and the obtained products are shown below in table 17.

Table 17. Synthesis of benzo- and thieno[3,2-*f*]quinolines and acridine derivatives **13a-p**.

13a 84%   **13b** 92%   **13c** 95%   **13d** 0%

13e 87%   **13f** 66%   **13g** 64%   **13h** 53%

13i 94%   **13j** 71%   **13k** 80%   **13l** 82%

13m 77%   **13n** 83%   **13o** 93%[a]   **13p** 92%[a]
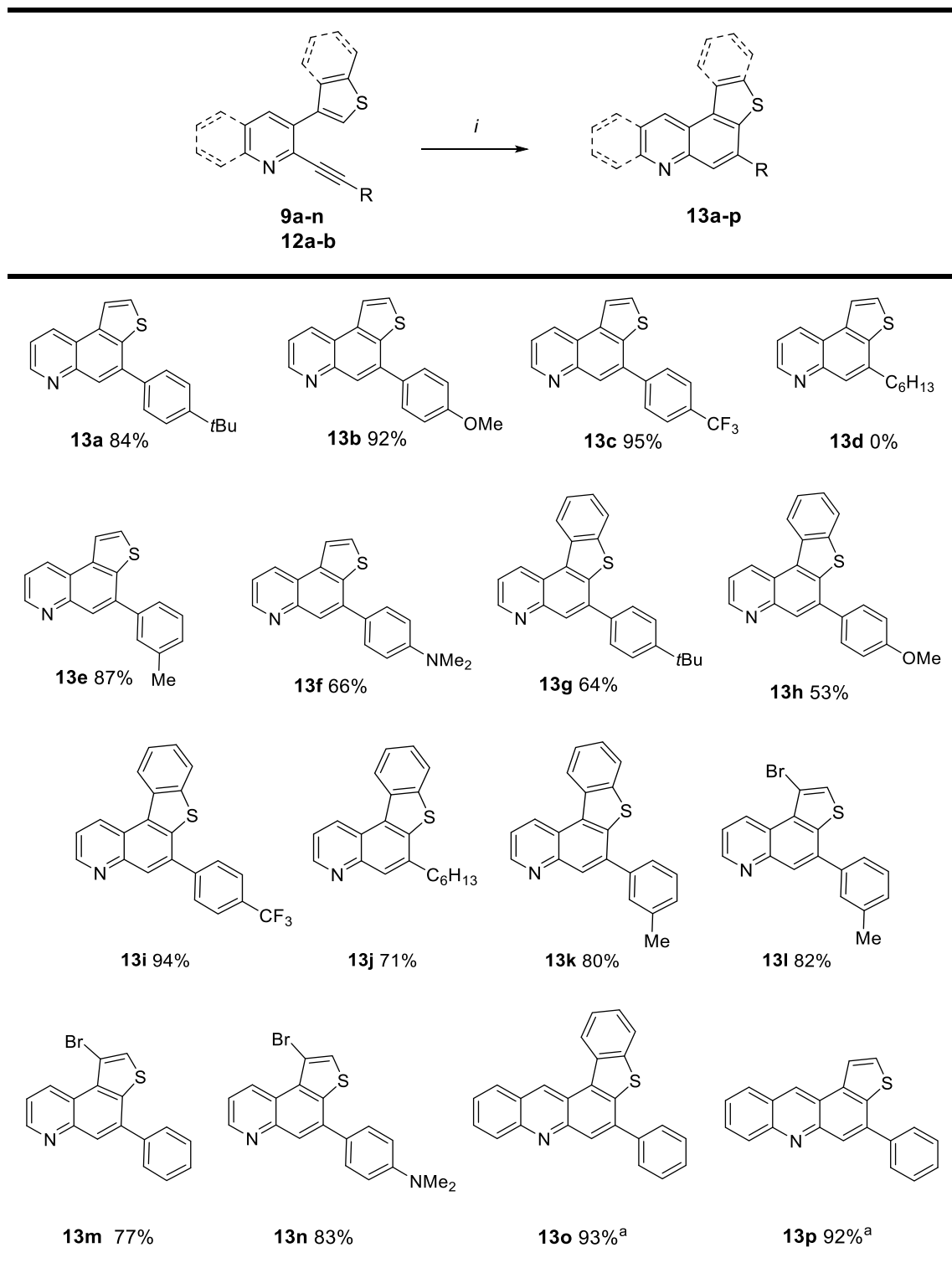
Conditions i: MsOH (50 equiv.), 120 °C, 1 h. [a] Reaction stirred 6 h.

The cycloisomerization of the starting materials allowed the synthesis of benzo[3,2-*f*]- and thieno[3,2-*f*]quinolines (**13a-k**), 1-bromothieno[3,2-*f*]quinolines (**13l-n**) and benzo[4,5]- and thieno[3,2-*a*]acridines (**13o-p**). The reaction proceeded successfully from the reactants **9a-n** and **12o-p** both for electron-rich and electron-poor functional groups.

The electrophilic aromatic substitution by the alkynyl moiety occurred selectively on the 2-position of the thiophene or benzothiophene ring. Substitution on positions 4 of the thiophene ring or on benzothiophene, forming a seven-membered ring system, was not observed in all reactions according to the general reactivity of the heterocycles.

Surprisingly, the highest yields were obtained for the strong electron-withdrawing substituent -CF$_3$ in 4-(4-(trifluoromethyl)phenyl)thieno[3,2-*f*]quinoline **13c** (95%) and 6-(4-(trifluoromethyl)phenyl)benzo[4,5]thieno[3,2-*f*]quinoline **13i** (94%).

A comparison between the derivatives from the same thienylboronic acids showed differences in the yields, thus is somehow a demonstration of the influence of the substituent from the alkyne in the reaction result.

Unfortunately, unlike the homologue **13j** (71%), the product **13d** with the aliphatic hexyl chain was not affordable with this condition. The cyclized product with the electron-rich *tert*-butyl substituent **13a** and **13g**, resulted in a moderate yield of 84% and 68% respectively.

The bromide substituent on the thiophene ring did not affect the yield of the products **13n** (83%) in comparison to **13f** (66%) when the dimethylamine is in *para*-position in the phenyl ring. Methoxy groups attached on the aryl alkyne resulted in a different reaction outcome depending on the thiophene moiety attached to the pyridine ring. While **13b** containing a thiophene ring, gave excellent 92% yield, the respective benzothiophene derivative **13h** gave only moderate 56%.

All the synthesized structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry. The structure **13o** was confirmed also through X-Ray diffraction analysis of a single crystal (figure 11).
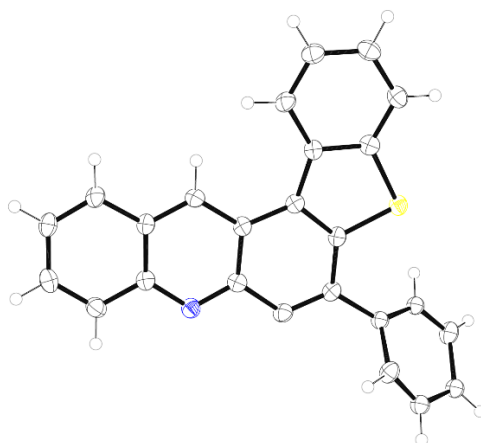
Figure 11. Single crystal structure of **13o**.

3.1.1 Absorption and fluorescence properties

The optical properties of six selected compounds were studied by UV/Vis and fluorescence spectroscopy at 20 °C using ethyl acetate (EtOAc) as solvent. Quantum yields were calculated using quinine hemisulphate monohydrate in H_2SO_4 (0.05 M) as an external standard.[119] All results are summarized and compared in table 18.
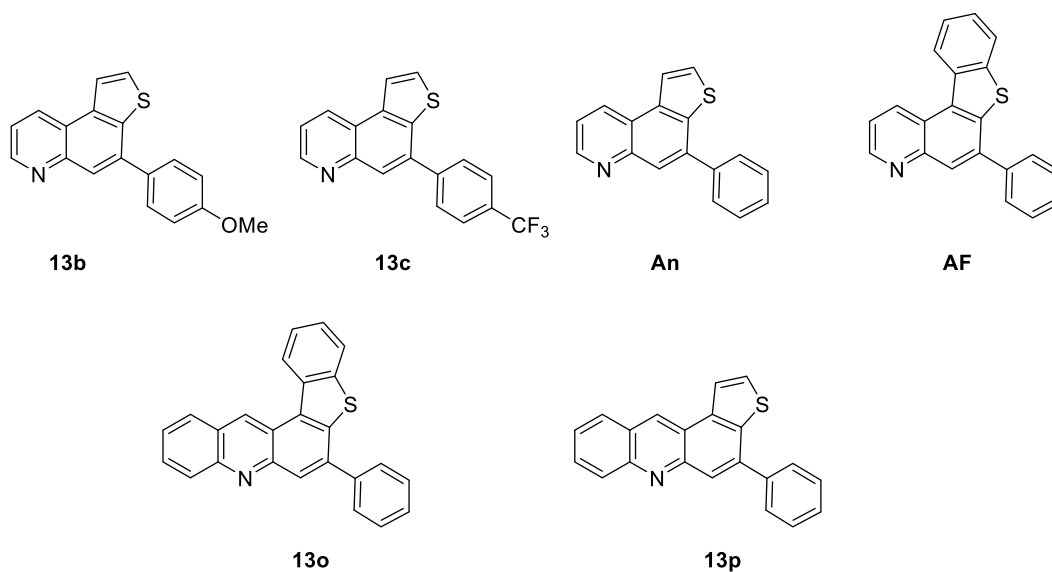
Figure 12. Selected compounds for the determination of optical properties.

Compounds **An** and **AF** were previously synthesized in our research group by Anika Flader in her doctoral thesis.[120]

Table 18. Absorption and emission spectroscopic data of **13b**, **13c**, **An**, **AF**, **13o** and **13p**.

	$\lambda_{1, abs}$ (nm)	log $\varepsilon_{\lambda 1}$	$\lambda_{2, abs}$ (nm)	log $\varepsilon_{\lambda 2}$	$\lambda_{3, abs}$ (nm)	log $\varepsilon_{\lambda 3}$	$\lambda_{4, abs}$ (nm)	log $\varepsilon_{\lambda 4}$	$\lambda_{5, abs}$ (nm)	log $\varepsilon_{\lambda 5}$	ϕ_{fluo} (%)
13b	260	4.44	303	3.96	304	3.96	311	3.96	341	3.94	2
13c	258	4.38	312	3.96	320	3.94	322	3.94	338	3.86	6
An	260	4.50	289	4.17	339	3.86					2
AF	268	4.58	301	3.99	312	4.00	320	3.97	322	3.97	10
13o	265	4.67	291	4.71	387	4.18					2
13p	279	4.77	377	4.15							6

The UV/Vis spectra of the studied structures exhibited an absorption band in the range of 258-341 nm (figure 13 and 14). Spectra from compound **13b**, **13c** and **An**, did not show significant differences. This can be attributed to the fact that the aryl substituents are rotated from the planar thienoquinoline scaffold and hence marginally contribute on the conjugation.
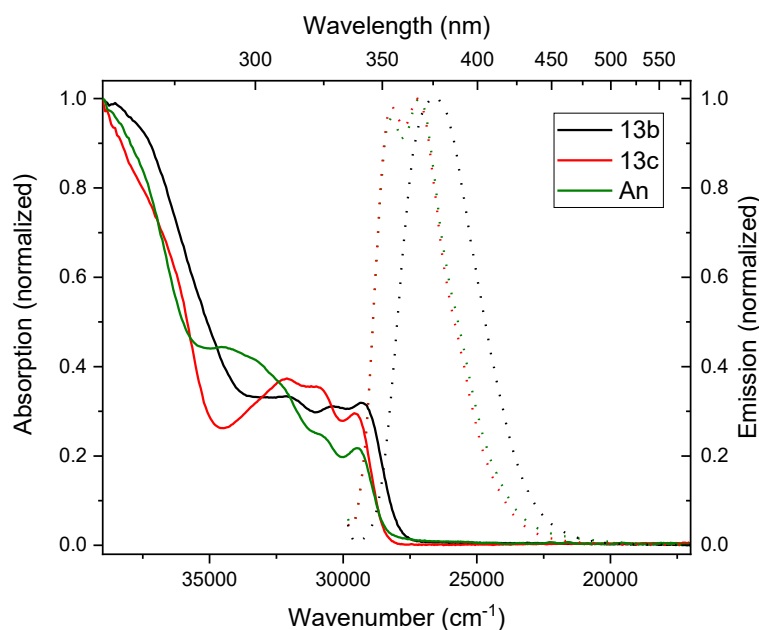
Figure 13. Normalized absorption and emission spectra of compounds **13b**, **13c** and **An**.

The absorption band of the compounds **13o** and **13p** containing the acridine scaffold were red-shifted in comparison to the compounds **An** and **AF** with the quinoline moiety, presumably due to the increased conjugation of π electrons indued by the additional fused benzene ring. The condensation of an additional benzene ring on the thiophene ring results only in minor bathochromic shift of the absorption spectrum (comparison of **13o**

and **13p**). The same effect is observed for compound **AF** with the benzothiophene moiety in comparison with **An**. In general, the behaviour of the UV and absorption spectra showed that the higher the number of conjugated rings in the structure, the more tend the absorption bands towards longer wavelengths.
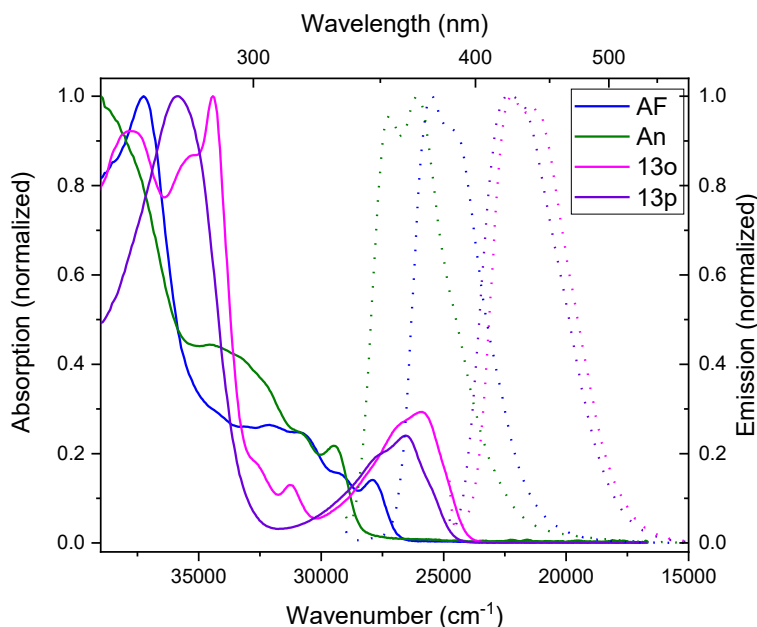
Figure 14. Normalized absorption and emission spectra of compounds **13o**, **13p**, **An** and **AF**.

The emission spectra were measured in EtOAc at 330 nm for compounds **13b**, **13c**, **An** and **AF** and at 380 nm for compounds **13o** and **13p**. The fluorescence quantum yields were determined by comparison to the standard quinine hemisulfate salt monohydrate which exhibits a fluorescence yield of 52%.[119] All the emission spectra showed maxima in the range of 360-400 nm. The emission spectra of compounds **13o** and **13p** were shifted to longer wavelengths, in comparison with **An** and **AF**. The emission spectra showed a similar trend than the absorption measurement. All the studied compounds showed quantum yields in the range of 2-10%.

3.2   Isomeric benzo[4,5]- and thieno[3,2-*f*]isoquinolines

Due to the importance and versatile application of benzo[4,5]- and thieno[3,2-*f*]quinolines derivatives (see chapter 2.1) it was interesting to extend my previous methodology to the synthesis of benzo[4,5]- and thieno[3,2-*f*]isoquinolines.

The key to the strategy is the change in the starting material used. In this case 3,4-dibromopyridine was employed instead of 2,3-dibromopyridine used in the previous chapter 3.1.

Despite having the same composition, both constitutional and conformational isomers can show different chemical, physical and biological properties.

The synthesis strategy for obtaining constitutional isomers consists of three reaction steps. The first one is the Suzuki coupling, followed by the Sonogashira reaction and the cycloisomerization mediated by the Brønsted acid (scheme 17).
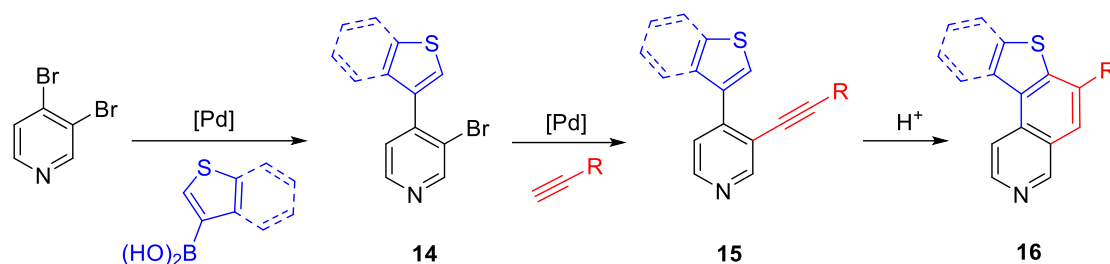
Scheme 17. Strategy for the synthesis of benzo[4,5]- and thieno[3,2-*f*]isoquinolines.

To choose the synthetic route, the reactivity order in the starting material 3,4-dibromopyridine was considered. In this case, position 4 in the pyridine ring was more reactive than position 3 due to the negative inductive effect caused by the nitrogen atom, which reduced the electron density in the pyridine ring and activate the positions 2, 4 and 6 towards a nucleophilic attack. Then, the site-selective Suzuki reaction with 3,4-dibromopyridine and 3-thienylboronic acids allowed the formation of desired products **14a** and **14b** with good yields, 89% and 73% respectively (table 19). The reaction proceeded, as expected, with complete site-selectivity on the 4-position of pyridine ring.

Table 19. Synthesis of 3-(2-bromophenyl)thiophene and 3-(2-bromophenyl)benzo[*b*]thiophene **14a-b**.
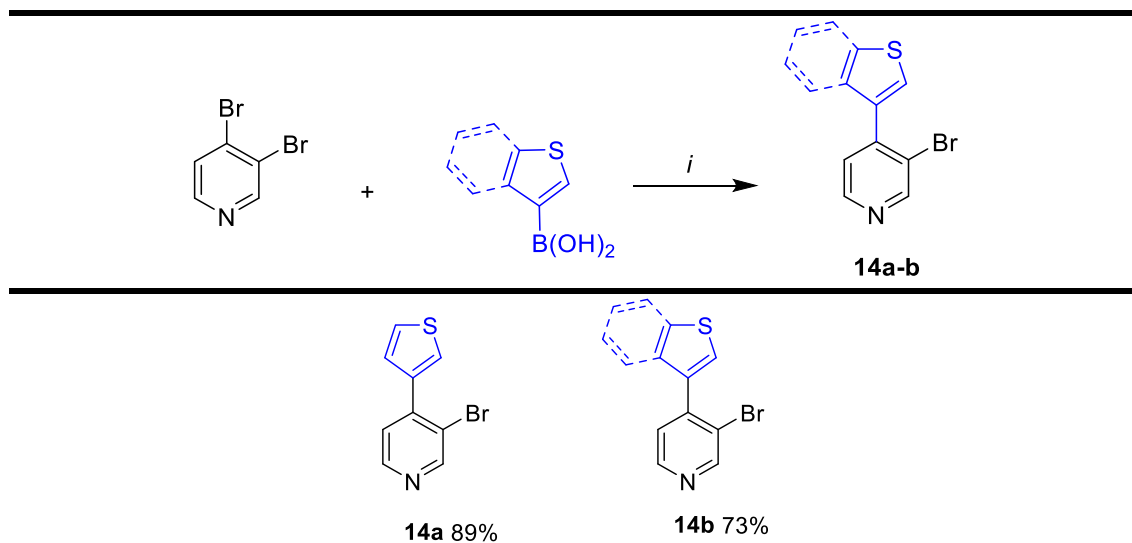
Conditions i: benzo[*b*]-&thiophen-3-ylboronic acid (1.1 equiv.), Pd(PPh$_3$)$_4$ (5 mol%), K$_2$CO$_3$ (2.0 equiv.), 1,4-dioxane/H$_2$O (6:1), 90 °C, 3 h.

With the product from the first step in hands (**14a-b**), the Sonogashira reaction was performed and various alkynyl groups were introduced (table 20).

Table 20. Synthesis of 3-(benzo[*b*]&thieno)-3-(alkynyl)pyridines **15a-w**.

15a 97%	**15b** 95%	**15c** 95%	**15d** 90%
15e 80%	**15f** 84%	**15g** 60%	**15h** 90%
15i 60%	**15j** 51%	**15k** 97%	**15l** 88%
15m 79%	**15n** 89%	**15o** 95%	**15p** 59%
15q 68%	**15r** 79%	**15s** 82%	**15t** 98%

15u 67% **15v** 96% **15w** 97%
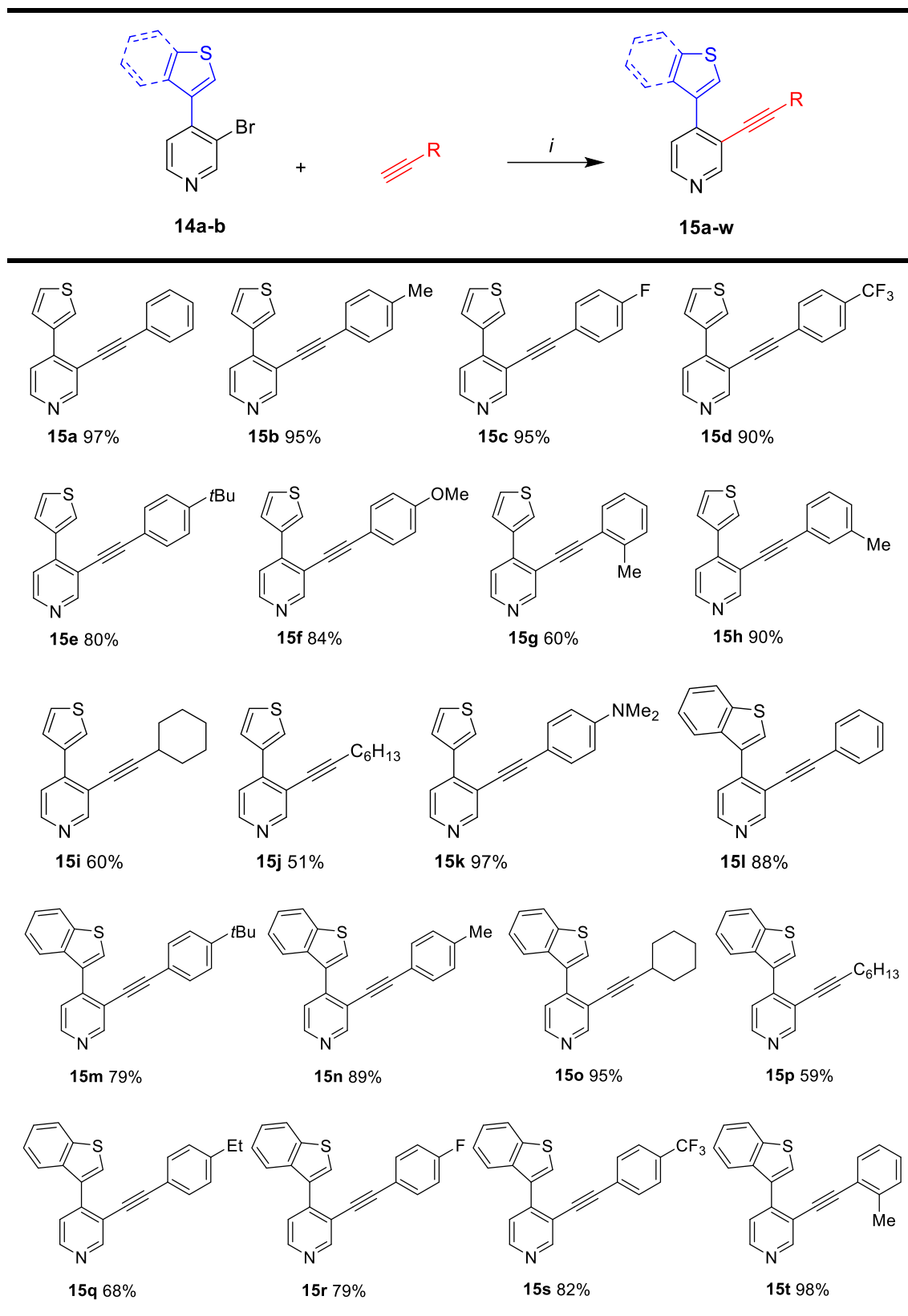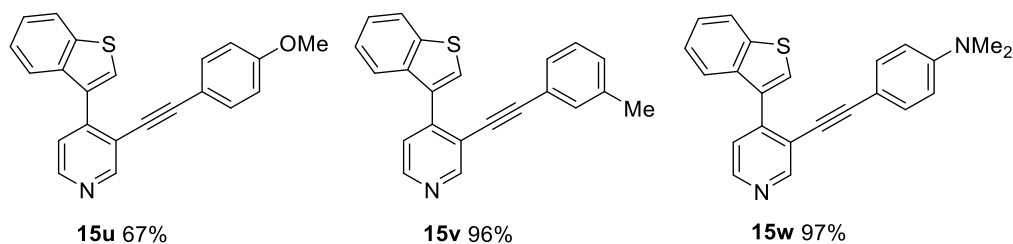
Conditions i: alkyne (1.5 equiv.), Pd(PPh₃)₄ (5 mol%), CuI (2 mol%), Et₃N, 80 °C, 20 h.

In the experiment the catalyst Pd(PPh₃)₄ (5 mol%) and the co-catalyst CuI (2 mol%) dissolved in Et₃N and stirred at 80 °C for 20 h were used as reaction conditions. The compounds **15a-w** were obtained in moderate to predominantly very good yield (51% - 98%). The reaction introduced some aromatic alkynes with electro-donor and electro-withdrawing substituted groups and also aliphatic alkynes.

The highest yields were obtained with the *m*-tolyl substituted alkyne **15t** (98%), 4-ethynyl-N,N-dimethylaniline **15k** and **15w** (97%) and phenylacetylene **15a** (97%). Most of the compounds with electro donor and electro acceptor groups were obtained with good results as well. The lowest values were obtained with the aliphatic derivatives, **15i**, **15j** and **15p**, with 60%, 51% and 59% respectively. In contrast, the analog aliphatic cyclohexyl derivative **15o** was synthesized with a very good yield of 95%.

With the precursor for the final product in hands, the cycloisomerization was performed using MsOH as a Brønsted acid (table 21).

Table 21. Synthesis of benzo[4,5]- and thieno[3,2-*f*]isoquinolines **16a-w**.

15a-w → **16a-w**

16a 53% **16b** 70% **16c** 99% **16d** 87%

16e 94% **16f** 0% **16g** 95% **16h** 98%

16i 85% **16j** 93% **16k** 90% **16l** 80%

16m 72% **16n** 92% **16o** 81% **16p** 47%

16q 88% **16r** 77% **16s** 87% **16t** 70%

16u 73% **16v** 96% **16w** 73%
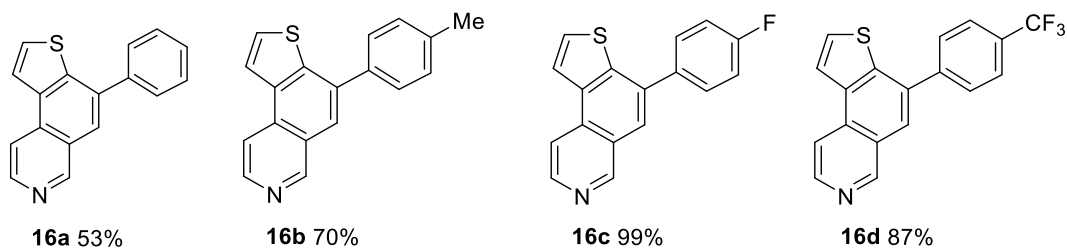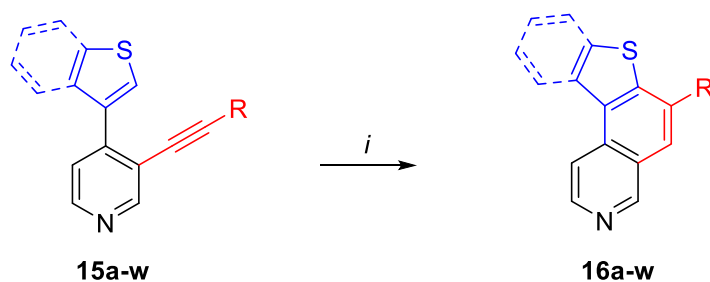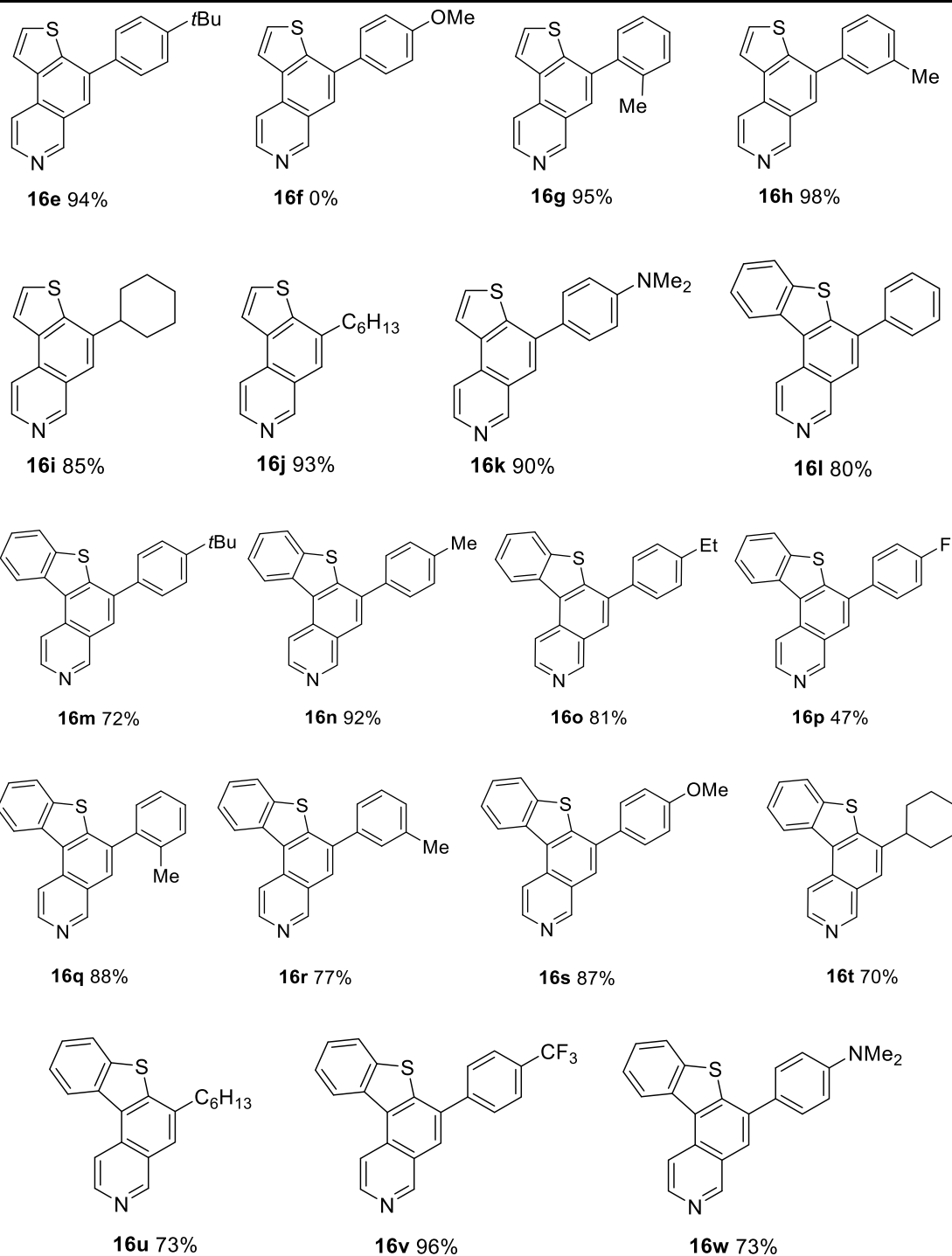
Conditions i: MsOH (30 equiv.), 120 °C, 1 h.

The synthesis of benzo[4,5]- and thieno[3,2-*f*]isoquinolines **16a-w**, resulted in very good yields and high selectivity. The reaction proceeded successfully for both electron-rich and electron-poor functional groups.

Compounds **16a** and **16p** gave moderate yields due to separation problems in the column chromatography. Unfortunately, compounds **16f**, with methoxy substituent and thienyl

ring were not affordable. In contrast compound **16s**, with the methoxy and the benzo[4,5]thienyl substituent gave a good 87% yield. In general, the very good results show the high selectivity of the applied methodology for both thiophene and benzothiophene moiety. Despite the strongly acidic reaction conditions, various functional groups are tolerated such as alkyl, CF_3, OMe, NMe_2 or F.

3.2.1 Absorption and fluorescence properties

The optical properties of three selected compounds were studied by UV/Vis and fluorescence spectroscopy at 20 °C using ethyl acetate (EtOAc) as solvent. Quantum yields were calculated using quinine hemisulphate monohydrate in H_2SO_4 (0.05 M) as an external standard.[119] The main results were shown and compared with each other (table 22).
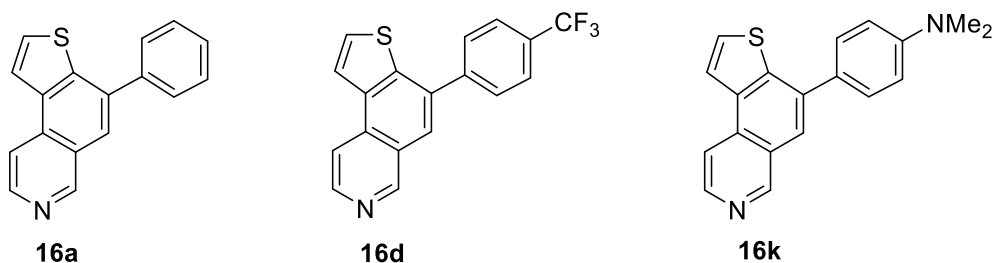
Figure 15. Selected compounds for the determination of optical properties (**16a**, **19d** and **16k**).

Table 22. Absorption and emission spectroscopic data of **16a**, **16d** and **16k**.

Comp	$\lambda_{1, abs}$ (nm)	log $\varepsilon_{\lambda 1}$	$\lambda_{2, abs}$ (nm)	log $\varepsilon_{\lambda 2}$	ϕ_{fluo} (%)
16a	259	4.50	300	4.06	2
16d	259	4.41	304	4.02	2
16k	255	4.33	306	4.09	10

The studied structures in the UV/Vis spectra showed the absorption band in the range of 255-306 nm (figure 16). Spectra from compound **16a** and **16d** did not show significant differences, this should be attributed to the fact that the CF_3 substituent in the aryl ring did not affect the chemical shift. In contrast, compound **16k** exhibited a red shifted absorption at 306 nm in comparison with **16a** and **16d**. That could be attributed to the effect of the strongly electron donating dimethylamine substituent on the phenyl ring which induces a certain push-pull system between the electron deficient isoquinoline ring and the dimethylaniline moiety.
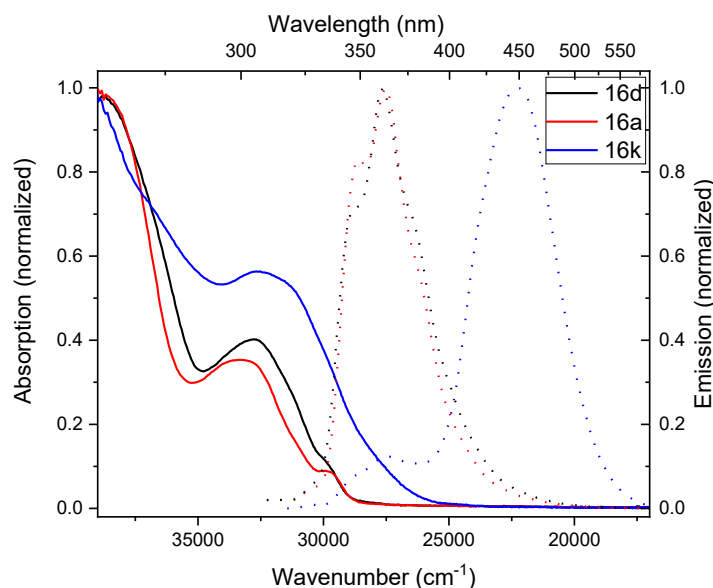
Figure 16. Normalized absorption and emission spectra of compounds **16a**, **16d** and **16k**.

The emission spectra were measured in EtOAc at 300 nm for all the compounds. The fluorescence quantum yields were determined by comparison to the standard quinine hemisulfate salt monohydrate with an fluorescence quantum yield of 52%.[119] Emission spectra for compounds **16a** and **16d** showed maxima around 360 nm, while a shift to a longer wavelength was observed for **16k** at 448 nm. The highest quantum yield was observed for the compound **16k** with 10% which is five times higher as for **16a** and **16d**.

3.3 Conclusion

In general, the developed methodology for the synthesis of (benzo-)thieno[3,2-*f*]quinoline, (benzo-)thieno[3,2-*f*]isoquinoline gave desired molecules in good to excellent yields. Alkynes containing aromatic substituents with the electron-donating groups as methyl, *tert*-butyl and methoxy, as well as the electron-withdrawing substituents fluorine and CF_3, and aliphatic moieties could be used. Substitution of the thiophene moiety by benzothiophene or 4-bromothiophene has no impact on the results of the reaction, indicating that this methodology is potentially feasible for the construction of longer polycyclic heteroaromatic compounds. The introduction of a bromine substituent additionally allows the fine tuning of the properties of this heterocyclic entity by follow up chemistry. The synthesis steps were mediated by Suzuki and Sonogashira cross coupling and Brønsted acid in the cycloisomerization reaction. Selected synthesized final products were studied using UV and fluorescence spectroscopy.

4 Palladium catalyzed C-C and C-N coupling reactions

4.1 Synthesis of 5- and 6-Azaindoles

Azaindoles are a group of important heterocycles present in a large number of molecules with biological activity.[121][122] Even though they rarely occur in nature,[122][123] these attractive frameworks are widely used in medicinal chemistry for the development of new drugs due to their significant antitumor activity.[124][125] A study done on a series of 2,3-bis(het)aryl-4-azaindoles, showed that they can inhibit colon cancer cell line in a concentration of 600 nM due to a potent Ras activating factor kinase (RAF-1) inhibitor, without toxic effects on normal cells.[126] Meanwhile, Prudent *et. al.* found that azaindole derivates significantly inhibit angiogenesis and tumour growth in chorioallantoic breast cancer xenografts.[127] Additionally, 5-azaindole derivates are reported as highly potent CB_2-agonists, which provide a potential active components for designing painkiller drugs, due to its analgesic effects.[128] The 6-azaindolylmaleimides show significant inhibition of protein kinases (PKs) accompanied with high kinase selectivity and potent inhibition of cell proliferation and angiogenesis, which can give versatile options in cancer treatment and is therefore highly effective in leukemic and endothelial cells, as well as against HT-29 cells in monotherapy[129] (figure 17).
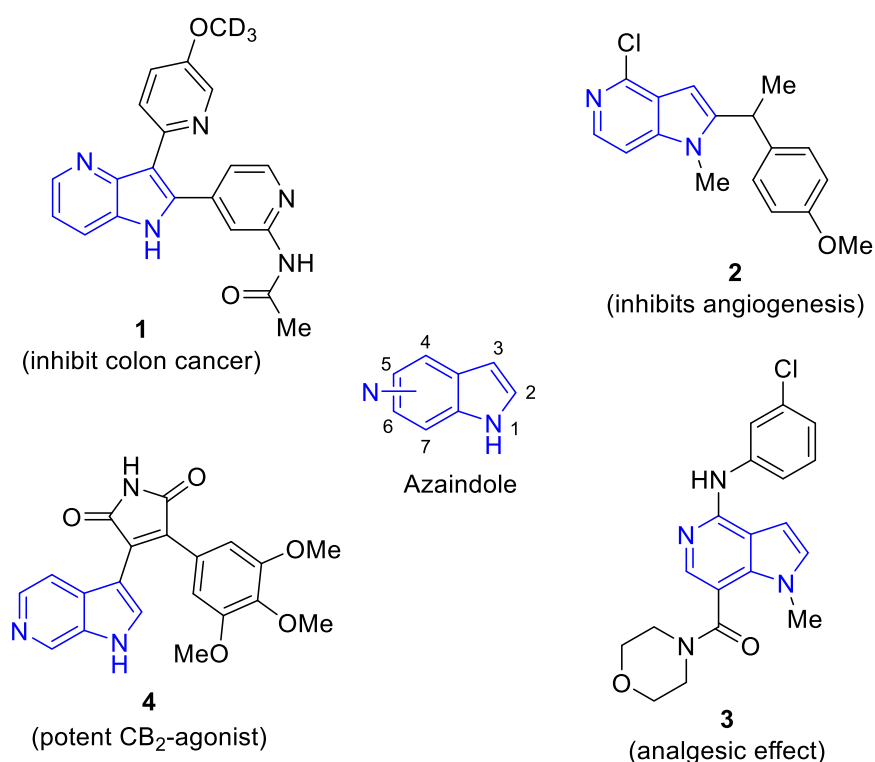
Figure 17. Azaindole derivatives with biological activity.

There are multiple structures with key azaindole core that show their potential activity as antimycobacterial agents.[130] In addition, this moieties have found applications in material science and organometallic chemistry.[131] Their interesting luminescence properties and their metal-complexes have also been extensively explored.[132]

Azaindoles, also called pyrrolopyridines, are bioisosters indoles and consist of a pyrrol ring fuse to six-membered pyridine ring. Depending on the position of the nitrogen atoms to each other four different azaindole derivatives are feasible[122] (figure 18).

Figure 18. Indole and Azaindoles frameworks.

Azaindoles have been considered as important structures in biological process regulation, in medicinal chemistry and new pharmaceutical developments. The availability of new azaindole derivatives has been increasing in the last 20 years drastically and has been fostered especially by its potential application as biological active compounds and various research areas.[121][126][133]

Due to the importance and versatility of azaindole scaffold in the development of new therapeutic agents, they have taken the attention of many researchers looking for the synthesis of new derivatives or the development of improved synthesis strategies. Generally, the key starting material for the syntheses of azaindole is a functionalized pyridine molecule which undergoes ring closure to form the annulated pyrrole ring.[134] Actually, conventional synthesis strategies adapt known synthesis procedures of indole (cf. methods developed by Fischer,[135] Bartoli,[136] Madelung,[137] Reissert,[138] and Hemetsberger[139]).

Nevertheless, these conventional synthesis strategies for azaindole formation have limited applicability and are also less efficient due to their low yields, harsh reaction conditions and limited tolerance to many functional groups.[134][136] These disadvantages could be explained by the fact that the electronic deficiency of the pyridine ring changes the behaviour of the electronic π-system over the ring, which results in several classical methods used for indole formation not being as efficient when applied to the synthesis of

azaindole analogues.[131] For example, in the Bartoli indole synthesis, the yields are usually low and it is necessary to use an excess of vinyl Grignard (scheme 18).[136] In the case of the classical Fischer indole cyclization, when pyridinyl hydrazines are used, inferior results are achieved. It also uses harsh experimental conditions and generally undergo the unfavourable electron deficient character of the pyridine ring in the [3,3]-sigmatropic rearrangement step of heterocyclization.[135] Although, Fisher indole reaction has been improved through different studies, such as Buchwald modification involving a Pd-catalyzed cross coupling reaction of aryl bromide and hydrazones.[140]

Aza-Fisher Synthesis
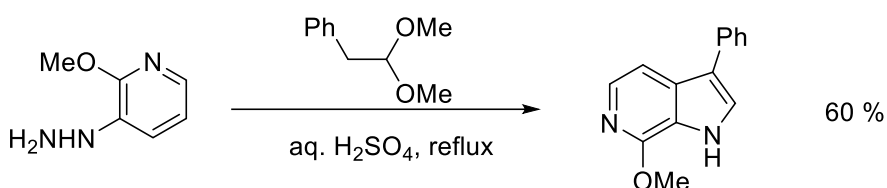
Bartoli cyclization
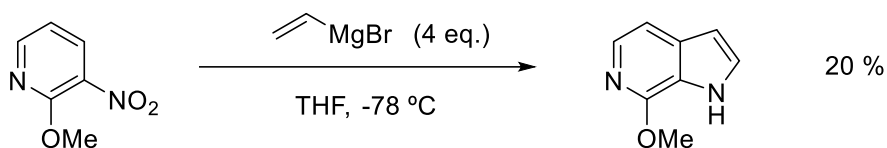
Larock Synthesis
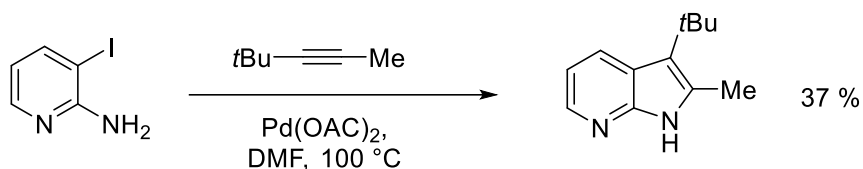
Scheme 18. Synthesis of Azaindoles derivates.

Thanks to the recent developments related to advanced synthesis methodologies using transition-metal catalysis, new and efficient pathways for constructing azaindole systems have been reported.[131] In most cases, the syntheses strategies involved are based on the use of Pd catalysis. Based on the first report by Larock's group on the synthesis of indoles by Pd-catalyzed heteroannulation of internal alkynes with anilines in 1991,[141] many related methods have been developed to access azaindoles. These include various approaches, including tandem C–N/Heck reactions,[142] Suzuki/C–N coupling reactions,[143] double C–N coupling reactions,[144] alkynyl amine cyclizations,[145] and

Larock-type reactions.[146] Recently, Marques *et. al.* reported a practical one-pot synthesis of 1,2-substituted azaindoles from amino-o-halopyridines through tandem C–N coupling/Sonogashira/cyclization reactions.[147] Additionally, a similar ultrasound-assisted one-pot synthesis of 1,2-diaryl-substituted azaindole derivatives, involving three sequential N-arylations followed by coupling–cyclization using Pd/C–Cu catalysis were published.[148]

In 2015, Langer's group reported a series of new 4- and 7-azaindole implementing the chemoselective synthesis of imines and dihalogenate pyridine by Pd-catalyzed cascade C–C and C–N coupling reactions.[149] The regioselectivity was managed by the control of the used halogen atoms substituted in the pyridine ring (scheme 19).
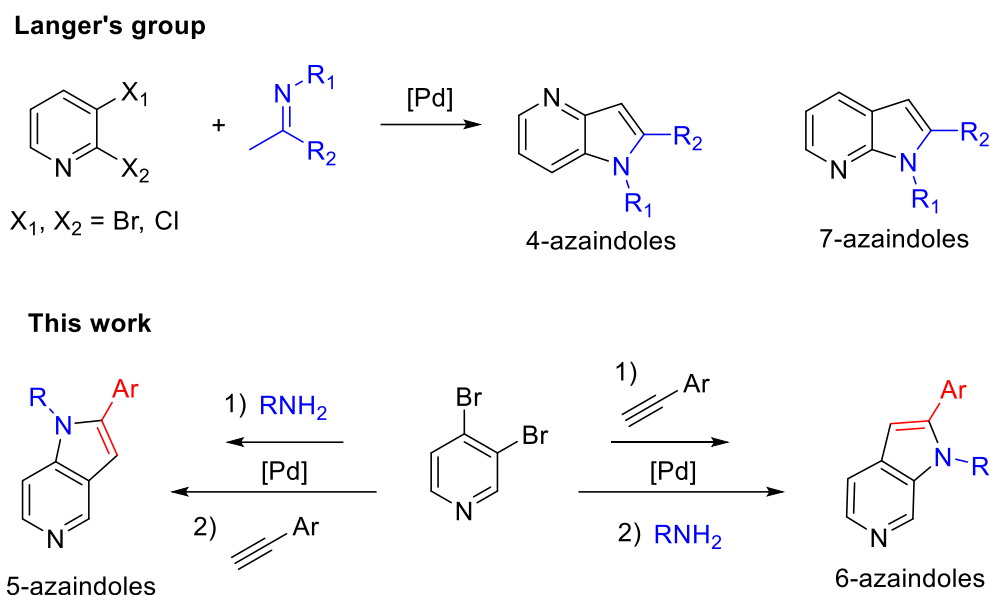
Scheme 19. Synthesis of azaindole derivates by Pd catalyzed.

Inspired by previous work of Langer's group in the synthesis of azaindoles derivatives, this research deals with the preparation of 6-azaindoles substitutes.[150] The proposed methodology includes a site-selective Pd-catalyzed Sonogashira reaction followed by a ring-closing reaction, consisting of Pd- catalyzed C–N coupling reactions and hydroamination reaction using 3,4-dibromopyridine as the key starting material (scheme 20).

55
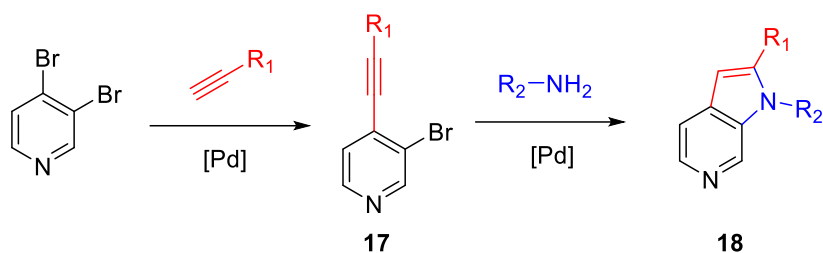
Scheme 20. Synthesis of 1-(phenylsubstituted)-2-phenylsubstituted-1*H*-pyrrolo[2,3-*c*]pyridine.

The first synthesis step involves the Sonogashira cross-coupling reaction of the commercially available 3,4-dibromopyridine with the corresponding *para*-substituted phenylacetylene (table 23). The best conditions for this reaction was obtained by the use of Pd(PPh$_3$)$_4$ as the catalyst (5 mol%) in combination with CuI as the co-catalyst. The reaction was performed at room temperature for 2 hours giving good results in the corresponding 3-bromo-4-(alkynyl)pyridine (**17**). The oxidative addition by the Pd-catalyst occurs selectively on the electron deficient 4-position of the pyridine ring.

Table 23. Synthesis of 3-bromo-4-(alkynyl)pyridine **17a-c**.

17a 72%   **17b** 84%   **17c** 81%
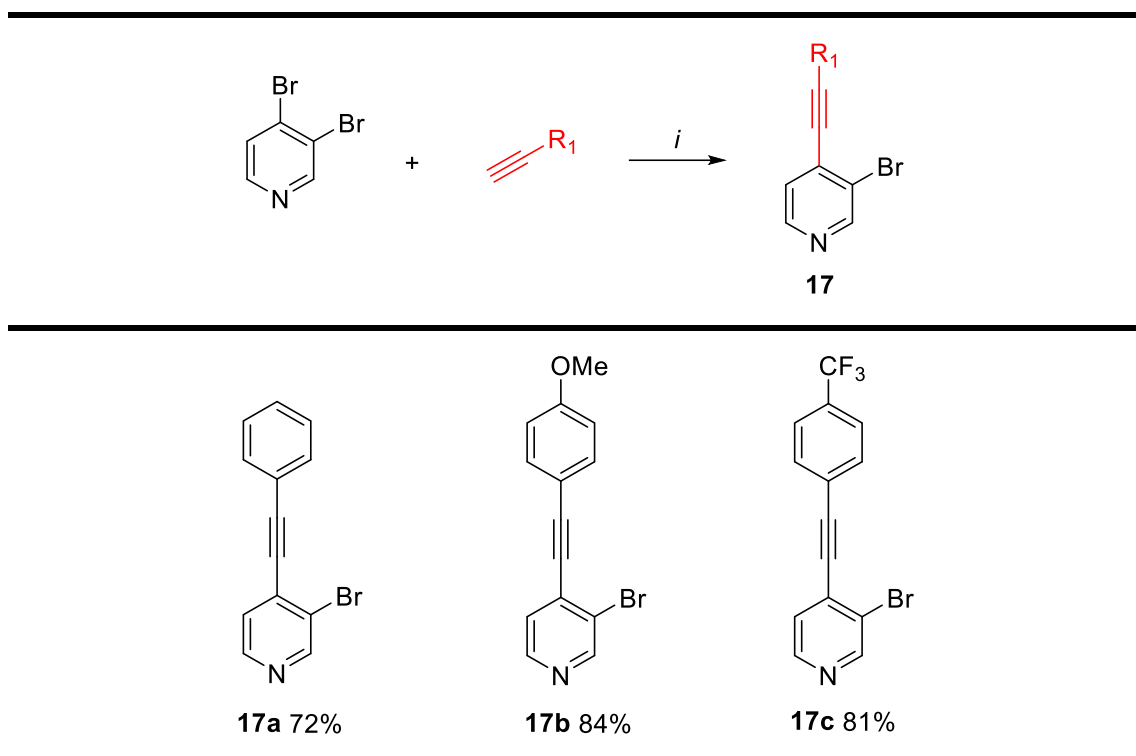
Conditions i: alkyne (1.1 equiv.), Pd(PPh$_3$)$_4$ (10 mol%), CuI (10 mol%), HN*i*Pr$_2$, r.t., 2 h.

The second synthesis step was performed by Pd-catalyst using the alkynylated bromopyridines (**17a-c**) as the starting material. The desired products were prepared via

Buchwald-Hartwig reaction by coupling substituted anilines to yield the corresponding 6-azaindoles **18a-p** (table 24). The reaction proceeds through C–N cross-coupling reaction and hydramination.

A combination of Pd(OAc)$_2$ and 4,5-bis(diphenylphosphinyl)-9,9-dimethylxanthene (Xantphos), a reagent was in the presence of the inorganic base Caesium carbonate gave good to very good yield in this domino-reaction for desired azaindole derivatives **18a-p.** [151]

Table 24. Synthesis of 6-azaindoles derivates **18a-p**.

18m 65%   **18n** 75%   **18o** 73%   **18p** 78%
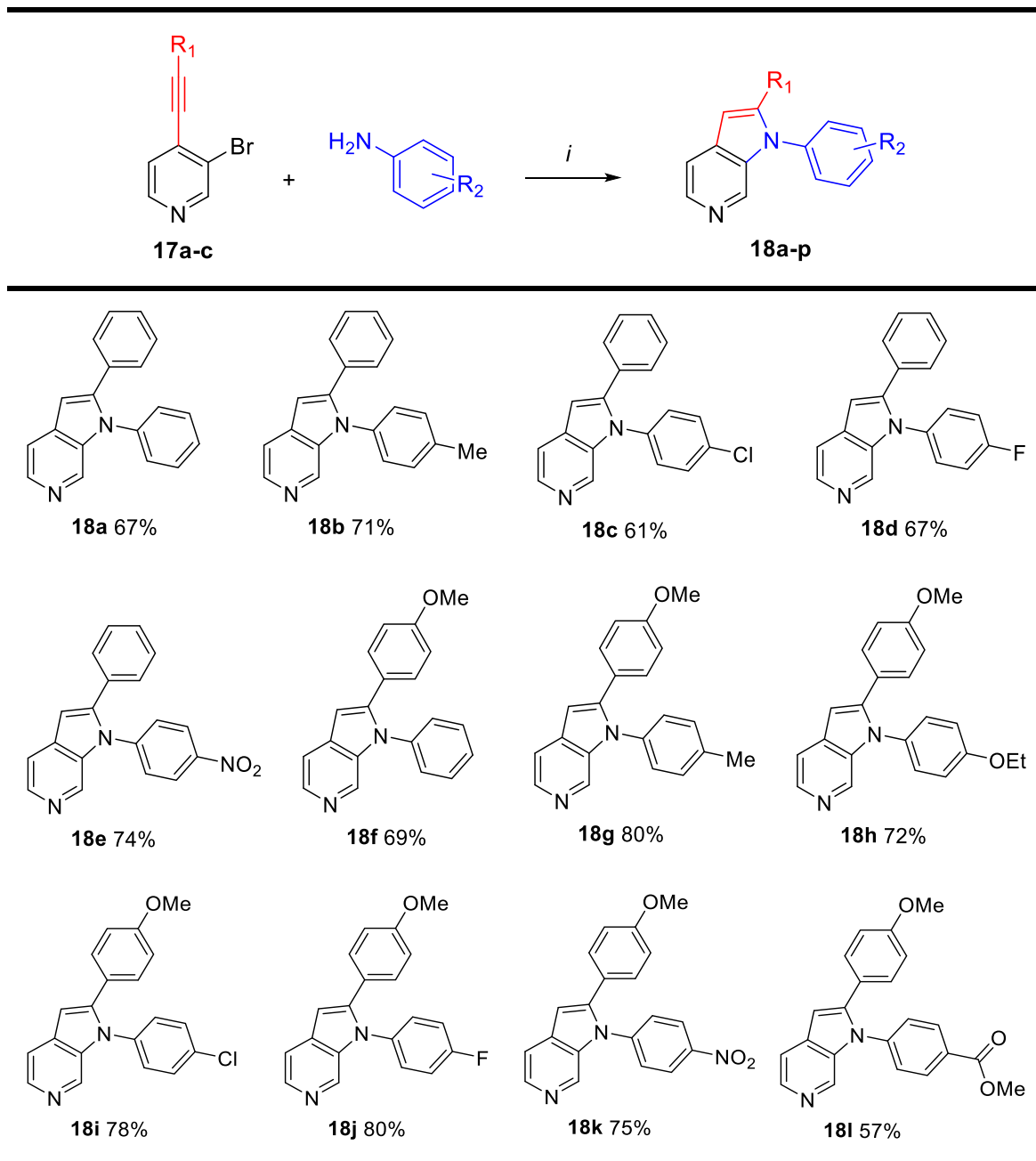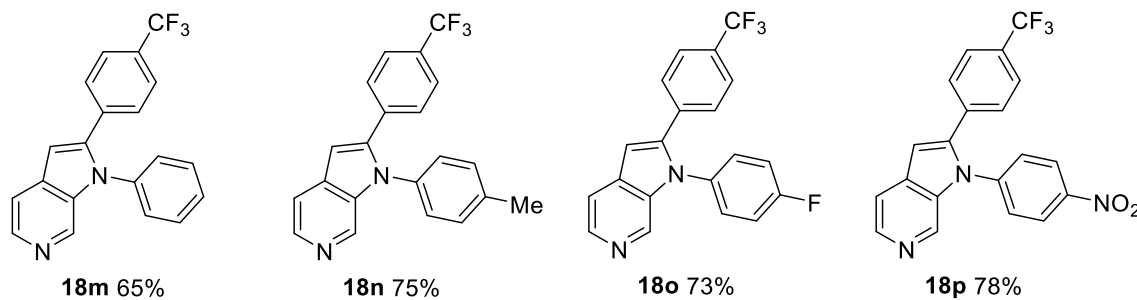
Conditions i: aniline (1.1 equiv.), Pd(OAc)$_2$ (10 mol%), Xantphos (10 mol%), Cs$_2$CO$_3$ (3.0 equiv.), DMF, 120 °C, 24 h.

Seven anilines were tested under an optimized condition. In general, 1,2-diphenyl-1*H*-pyrrolo[2,3-*c*]pyridine (**18a**) or 6-azaindole derivatives, bearing electron-donating or - withdrawing groups, achieved the corresponding products from moderate to good yields.

The employment of anilines containing electron donating substitutes (more nucleophilic) or electron withdrawing groups in *para*-position did not seem to have any significant influence on the product yields.

Encouraged by the previous results related to 6-azaindole structures and considering the importance of the 5-azaindole derivatives in the field of medicinal chemistry, an approach to get 5-azaindoles (**20**) from 3,4-dibromopyridine was developed. In order to provide the desired compounds, the order of synthesis steps (Sonogashira and C-N-coupling/hydramination) were reversed relative to the order used to obtain 6-azaindoles. In the new strategy, the initial step was carried out through a site-selective C–N coupling reaction followed by a Sonogashira coupling and an intramolecular cyclization (scheme 21).
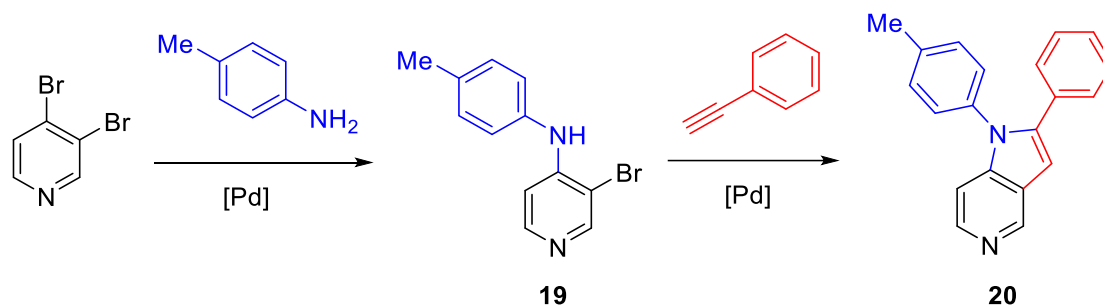
Scheme 21. Synthesis of 5-azaindole derivate.

For the reaction of this first key step, the C–N coupling reaction of 3,4-dibromopyridine with 4-methylaniline was optimized (table 25). The combination of bidentate ligands with

palladium sources for C–N coupling reactions has been sufficiently investigated.[152] However, several conditions were tested. Initially, the standard conditions for C–N coupling with Pd(OAc)$_2$/BINAP was used, but only 41% yield of coupling product **19** was obtained (entry 1). After that, the combination of Pd$_2$(dba)$_3$/BINAP as a catalyst system gave **19** in 25% yield (entry 2). The effect of bidentate ligands was tested in order to improve the yield of the desired compound. Use of (oxydi-2,1-phenylene)bis(diphenylphosphine) (DPEphos) improved the yield of the coupling product by 55%. On the other hand, the incidence of the base was performed and Cs$_2$CO$_3$ turned out to be the most suitable for this reaction (64% yield, entry 5).

Table 25. Site-selective Pd-catalized C-N coupling of 3,4-dibromopyridine.

Entry	Catalyst	Ligand	Base	Yield (%)
1	Pd(OAc)$_2$	BINAP	t-BuOK	41
2	Pd$_2$(dba)$_3$	BINAP	t-BuOK	25
3	Pd(OAc)$_2$	dppf	t-BuOK	-
4	Pd(OAc)$_2$	DPEphos	t-BuOK	55
5	Pd(OAc)$_2$	DPEphos	Cs$_2$CO$_3$	64

Conditions i: 4-methylaniline (1.1 equiv.), Pd(OAc)$_2$ (10 mol%), ligand (10 mol%), base (3.0 equiv.), DMF, 110 °C, 24 h.

The second step was carried out by Pd-catalyzed cyclization of **19** with phenylacetylene, using the standard conditions for Sonogashira coupling.[153] In this case, 5-azaindole **20** was successfully obtained with 87% yield (scheme 22). The formation of 5-azaindole presumably proceeded through an initial Sonogashira reaction to give intermediate **A**, which was subsequently cyclized to form product **20** by a Pd-catalyzed intramolecular hydroamination process.
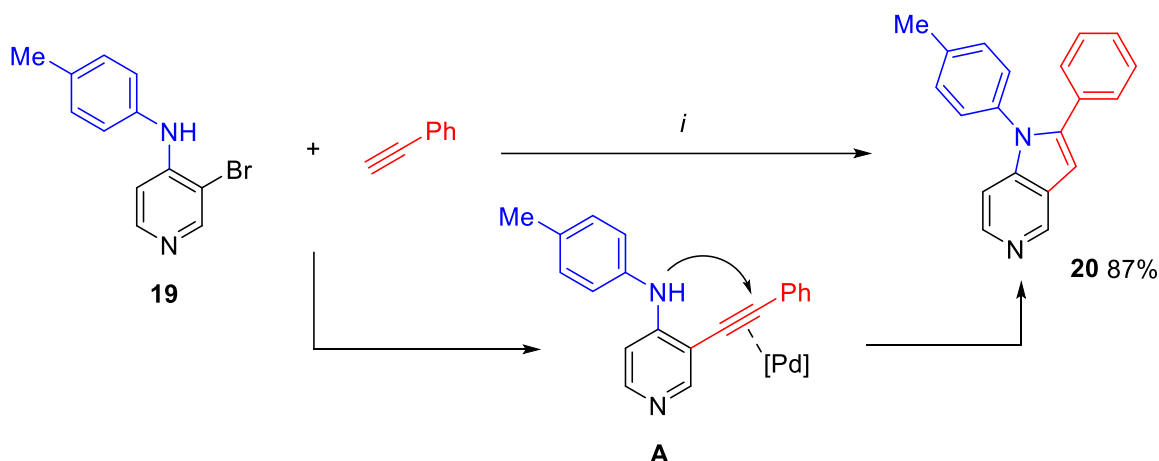
Scheme 22. Tandem Pd-catalyzed synthesis of 5-azaindole (**4**). *i*: **3** (1.0 equiv.), phenylacetylene (1.1 equiv.), Pd(PPh$_3$)$_2$Cl$_2$ (5 mol%), CuI (5 mol%), Et$_3$N, DMF, 110 °C, 20 h.

4.1.1 Absorption and fluorescence properties of 6-azaindoles

The optical properties of five selected compounds were studied by UV/Vis and fluorescence spectroscopy at 20 °C using ethyl acetate (EtOAc) as solvent. Quantum yields were calculated using quinine hemisulphate monohydrate in H$_2$SO$_4$ (0.05 M) as an external standard.[119] All results are summarized in table 26 and compared with each other.
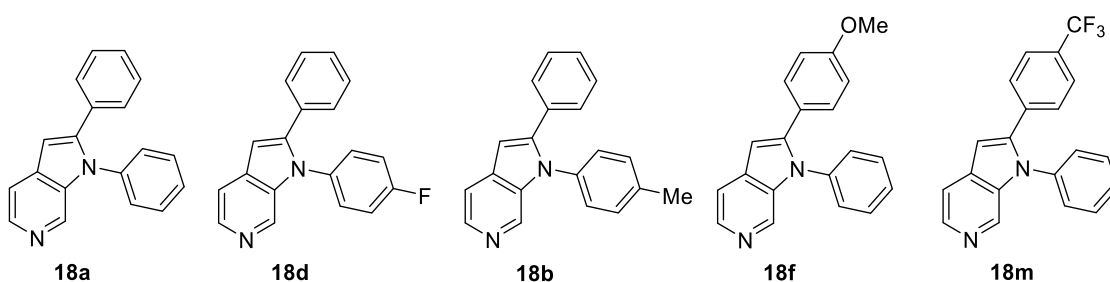
Figure 19. Selected compounds for the determination of optical properties.

Table 26. Absorption and emission spectroscopic data of **18a, 18b, 18d, 18f and 18m**.

Comp	$\lambda_{1, abs}$ (nm)	log $\varepsilon_{\lambda 1}$	$\lambda_{2, abs}$ (nm)	log $\varepsilon_{\lambda 2}$	$\lambda_{3, abs}$ (nm)	log $\varepsilon_{\lambda 3}$	λ_{em} (nm)	ϕ_{fluo} (%)
18a	254	4.17	258	4.10	289	4.27	365	40
18b	252	4.09	257	3.98	288	4.05	366	34
18d	252	4.11	255	4.00	288	4.12	364	39

18f	252	4.13	296	4.17			366	44
18m	253	4.13	257	4.04	294	4.16	379	34

The UV/Vis spectra of the studied structures exhibit an absorption band in the range of 252-296 nm (figure 20 and 21). Spectra from compound **18a**, **18b** and **18d**, do not show significant differences, it should be supposed that the substituent in the aryl ring joined to the N-pyrrole, does not affect the chemical shift.
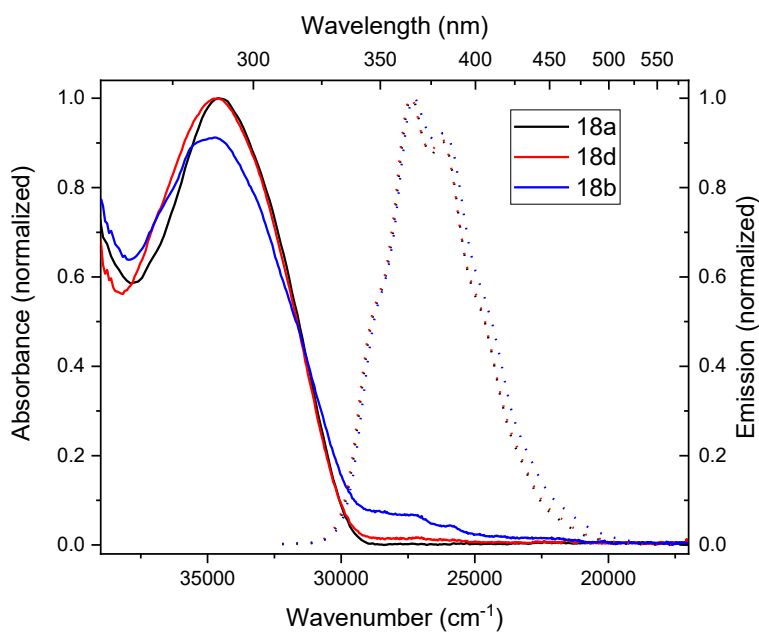
Figure 20. Normalized absorption and emission spectra of compounds **18a**, **18b** and **18d**

The absorption band of the compounds **18f** containing 4-methoxyphenyl substituents and **18m** containing trifluoromethyl substituents in comparation with **18a**, are slightly red-shifted, presumably due to the effect of the substituent in the aryl ring in position 2 on pyrrole ring.
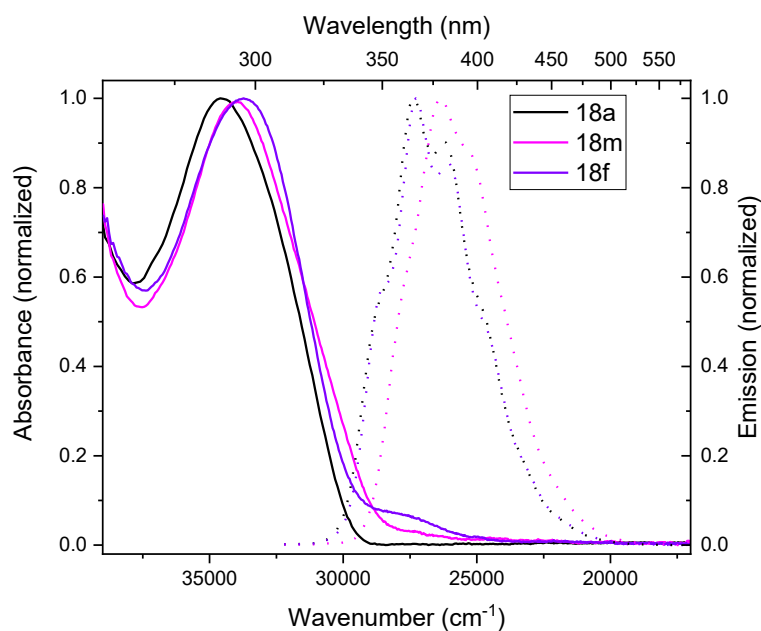
Figure 21. Normalized absorption and emission spectra of compounds **18a**, **18f** and **18m**

The emission spectra were measured in EtOAc at 300 nm. The fluorescence quantum yields were determined by comparison to the standard quinine hemisulfate salt monohydrate which exhibits a fluorescence yield of 52%.[119] All the emission spectra show maxima in the range of 360-400 nm. The emission spectra of compounds **18m** is shifted to longer wavelengths, presumable by the positive mesomeric effect of the methoxy group. All the studied compounds showed very good quantum yields, while compounds **18f** containing trifluoromethyl as substituents, exhibited the highest quantum yield with 44%.

4.2   Conclusion

In summary, the developed procedures are robust, practical, and rely on the use of commercially available starting materials. The synthesis of 5- and 6-azaindoles were successfully developed based on sequential site-selective Pd-catalyzed C–C and C–N coupling reactions. All the compounds were obtained with moderate and good yields. Some 6-azaindoles derivates were tested by UV study, resulting in good UV and fluorescence activity.

5 Summary

In this work were developed the synthesis of polycyclic heteroaromatic hydrocarbons employing the advantages offered by Palladium catalyzed cross-coupling reaction, alkyne carbonyl metathesis reactions and Brønsted acid mediated cycloisomerization. These methodologies allow for the application in most of the cases of high regio- and chemoselectivity, mild reaction conditions and the use of cheaper starting materials. The procedures developed were shown to be robust, practical and rely on the use of commercially available starting materials.

Palladium catalyzed cross-coupling reaction was employed to get the precursor structures used in the cyclization step in all of the reaction. In total, nine final compounds containing pyrrolo[1,2-*a*][1,6]naphthyridines and thieno[3,2-*f*]isoquinoline cores were synthesized. Alkyne carbonyl metathesis reaction was successfully applied yielding high performance for the cyclized final products. The strong Brønsted acid, methanesulfonic acid (MsOH) turned out to be mandatory for the reaction to proceed. In addition, were synthesis sixteen new (benzo-)thieno[3,2-*f*]quinoline and twenty three novel (benzo-)thieno[3,2-*f*]isoquinoline in good to excellent yields. The synthesis steps were mediated by Suzuki and Sonogashira cross coupling and Brønsted acid in the cycloisomerization reaction. The synthesis of 5- and 6-azaindoles were successfully developed based on sequential site-selective Pd-catalyzed C–C and C–N coupling reactions. The seventeen the compounds were obtained with moderate and good yields.

In all the cases alkynes containing aromatic substituents with the electron-donating groups as methyl, *tert*-butyl and methoxy, as well as the electron-withdrawing substituents fluorine and CF_3, and aliphatic moieties could be used. All compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry. Selected synthesized final products were studied using UV and fluorescence spectroscopy and additionally few structures were additionally confirmed by single crystal X-ray.

Appendix

Experimental Section

Methods for Compound Characterization and Analysis

NMR measurements were performed with Bruker AVANCE 250 II (built 2006), Bruker AVANCE 300 III (built 2007) and AVANCE 500 (built 2001). NMR-peaks were calibrated using standard peaks of chloroform at 7.260 ppm for ^{1}H and at 72.160 ppm for ^{13}C. For peak descriptions, following abbreviations were used: s (singlet), br-s (broad singlet), d (doublet), br-d (broad doublet), t (triplet), dd (doublet doublet), td (triplet doublet), dt (doublet triplet), ddd (double doublet doublet), q (quartet), m (multiplet).

IR measurement was completed with Nicolet 380 FT-IR spectrometer using ATR sampling technique. For peak descriptions, following abbreviations were used: w (weak), m (medium), s (strong).

GC/MS-measurements were conducted with Finnigan MAT 95-XP device using HP-5 capillary column with helium carrier gas and electron ionization (EI) scan technique at 70 eV.

For HRMS, Finnigan MAT 95 XP device was employed. Only signals with deviation of less than ±2 mDa were accounted as correct.

X-ray crystallography data were collected on a Bruker Kappa APEX II Duo diffractometer. The structure was solved by direct methods and refined by full-matrix least squares procedures on F2 with the SHELXTL software package (G. M. Sheldrick, Acta Crystallogr. 2008, A64, 112.); XP (Bruker AXS) was used for graphical representation.

UV/Vis spectroscopy was measurement with Analytic Jena Specord 50 UV/VIS spectrometer and fluorescence spectroscopy was performed with Varian Cary Eclipse spectrometer.

Melting point was carried out with Micro-Hot-Stage Galen TM III Cambridge Instrument without further corrections.

General procedures and compounds characterization

Pyrrolo[1,2-*a*][1,6]naphthyridines

1   **2**   **3**   **4**
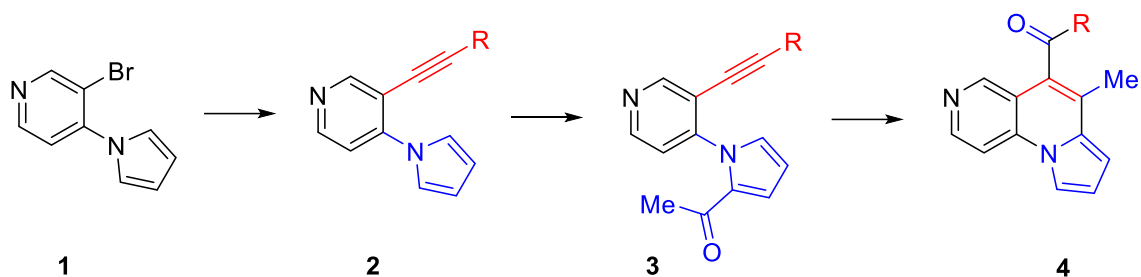
Synthesis of starting materials 1 was performed following the cited reference[90]

1
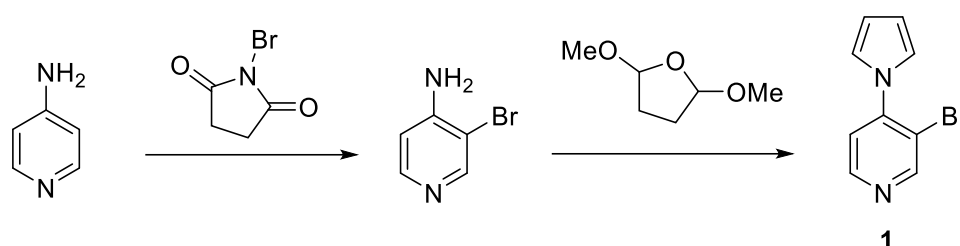
Synthesis of 3-(alkynyl)-4-(1H-pyrrol-1-yl)pyridine 2a-d
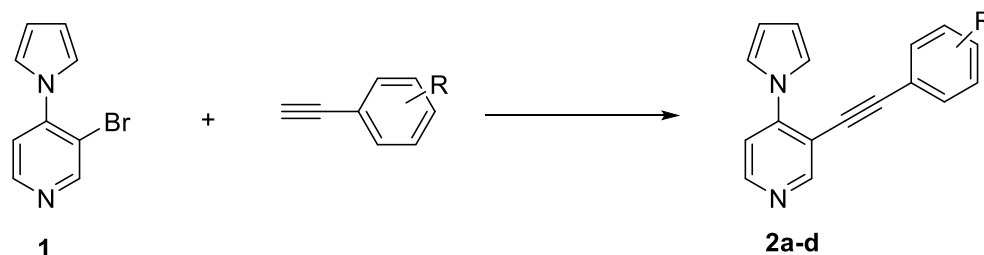
1   **2a-d**

2,3-Dibromopyridine (1.0 mmol), Pd(PPh$_3$)$_4$ (5 mol%) and CuI (2 mol%) were dissolved in 6 mL of Diisopropylamine (HN*i*Pr$_2$) under an argon atmosphere. After addition of the alkyne (1.2 equiv.) the reaction was stirred at 40 °C for 0.5 hours. After cooling to room temperature, the reaction mixture was washed with distilled water and extracted with ethyl acetate (EtOAc). The combined organic layers were collected and the solvent evaporated. The crude product was purified by column chromatography (heptane/EtOAc 4:1).

3-(phenylethynyl)-4-(1H-pyrrol-1-yl)pyridine (2a)
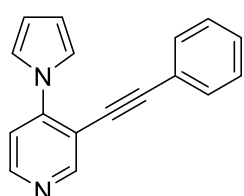
Reaction of **1** (0.45 mmol, 100 mg) and phenylacetylene (0.07 mmol, 73 µL) gave **2a** as a white solid (88 mg, 81%); mp: 68 – 69 °C. **¹H NMR (250 MHz, CDCl₃):** δ = 8.77 (br-s, 1H, CH$_{Pyr}$), 8.51 (br-s, 1H, CH$_{Pyr}$), 7.43 – 7.39 (m, 2H, CH$_{Ar}$), 7.31 (t,

^3J = 2.2 Hz, 2H, CH$_{Pyrrole}$), 7.27 – 7.25 (m, 3H, CH$_{Ar}$), 7.18 – 7.13 (m, 1H, CH$_{Pyr}$), 6.32 (t, ^3J = 2.2 Hz, 2H, CH$_{Pyrrole}$) ppm. **^{13}C NMR (62.9 MHz, CDCl$_3$):** δ = 155.0, 149.5 (CH$_{Pyr}$), 147.2 (C$_{Pyr}$), 131.6, 129.1, 128.6 (CH$_{Ar}$), 122.4 (C$_{Ar}$), 120.8 (CH$_{Pyrrole}$), 111.3 (CH$_{Pyrrole}$), 96.8, 84.2 (C$_{Alkyne}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3130 (w), 3055 (w), 2220 (w), 1562 (m), 1589 (m), 1393 (m), 1344 (m), 1185 (w), 1062 (m), 1018 (m), 920 (w), 836 (s), 749 (s), 722 (s), 685 (s), 621 (m), 562 (s). **MS (EI, 70 eV):** *m/z* (%) = 244 ([M$^+$], 100), 243 (69), 242 (36), 218 (8), 216 (7), 215 (5), 214 (5), 189 (6), 150 (8), 122 (5). **HRMS (EI):** calcd. for C$_{17}$H$_{12}$N$_2$ ([M]$^+$) 244.09950, found 244.09904.

4-(1H-pyrrol-1-yl)-3-((4-(trifluoromethyl)phenyl)ethynyl)pyridine (2b)
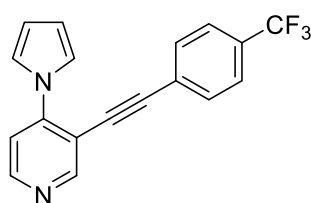
Reaction of **1** (2.02 mmol, 450 mg,) and 4-(trifluoromethyl)phenylacetylene (2.80 mmol, 494 µl) gave **2b** as a yellow solid (343 mg, 55%); mp: 75 – 76 °C. **^{1}H NMR (300 MHz, C$_6$D$_6$):** δ = 8.92 (br-s, 1H, CH$_{Pyr}$), 8.32 (br-s, 1H, CH$_{Pyr}$), 7.22 – 7.13 (m, 6H, CH$_{Ar}$), 6.58 (br-s, 1H, CH$_{Pyr}$), 6.40 (t, ^3J = 2.2 Hz, 2H, CH$_{Pyrrole}$) ppm. **^{13}C NMR (75 MHz, C$_6$D$_6$):** δ = 155.5, 150.7 (CH$_{Pyr}$), 147.3 (C$_{Pyr}$), 131.9 (CH$_{Ar}$), 130.5 (q, $^2J_{C,F}$ = 32.6 Hz, C$_{Ar}$), 126.3 (q, $^4J_{C,F}$ = 1.4 Hz, CH$_{Ar}$), 125.5 (q, $^3J_{C,F}$ = 3.8 Hz, CH$_{Ar}$), 124.4 (q, $^1J_{C,F}$ = 272.3 Hz, CF$_3$), 120.9 (CH$_{Pyrrole}$), 117.3 (CH$_{Pyr}$), 111.6 (CH$_{Pyrrole}$), 105.2 (C$_{Pyr}$), 95.1, 87.0 (C$_{Alkyne}$) ppm. **^{19}F NMR (282 MHz, C$_6$D$_6$)** δ = -62.59 ppm. **IR (ATR, cm^{-1}):** ṽ = 2929 (w), 1724 (w), 1613 (w), 1583 (w), 1557 (w), 1496 (m), 1407 (w), 1324 (s), 1163 (m), 1101 (s), 1062 (s), 1016 (m), 834 (s), 729 (s), 675 (m), 577 (m). **MS (EI, 70 eV):** *m/z* (%) = 312 ([M$^+$], 100), 311 (37), 310 (8), 293 (5), 291 (5), 286 (7), 243 (9), 242 (20), 214 (4), 199 (4). **HRMS (EI):** calcd. for C$_{18}$H$_{11}$F$_3$N$_2$ ([M]$^+$) 312.28855, found 312.28849.
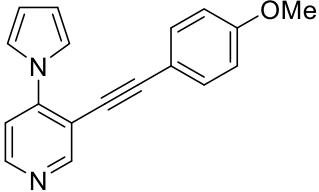
4-(1H-pyrrol-1-yl)-3-(m-tolylethynyl)pyridine (2c)
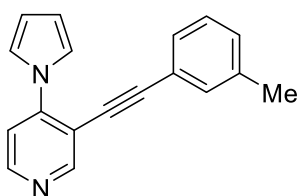
Reaction of **1** (1.35 mmol, 300 mg) and 3-tolylacetylene (2.02 mmol, 234.3 mg) gave **2c** as a white solid (304 mg, 88%); mp: 99 – 100 °C. **^{1}H NMR (250 MHz, C$_6$D$_6$):** δ = 8.91 (s, 1H, CH$_{Pyr}$), 8.21 (d, ^3J = 5.5 Hz, 1H, CH$_{Pyr}$), 7.27 (d, ^3J = 7.6 Hz, 1H, CH$_{Ar}$), 7.22 (t, ^3J = 2.2 Hz, 2H, CH$_{Pyrrole}$), 7.23 (s, 1H, CH$_{Ar}$), 6.94 (t, ^3J = 7.6 Hz, 1H, CH$_{Ar}$), 6.82 (d, ^3J = 7.6 Hz, 1H, CH$_{Ar}$), 6.52 (d, ^3J = 5.5 Hz, 1H, CH$_{Pyr}$), 6.36 (t, ^3J = 2.2 Hz, 2H, CH$_{Pyrrole}$), 1.96 (s, 3H, CH$_3$) ppm. **^{13}C NMR (62.9 MHz, C$_6$D$_6$):**

δ = 155.5, 150.1 (CH$_{Pyr}$), 147.1 (C$_{Pyr}$), 138.4 (C$_{Ar}$), 132.4, 130.1, 129.1, 128.6 (CH$_{Ar}$), 122.8 (C$_{Ar}$), 121.0 (CH$_{Pyrrole}$), 117.1 (CH$_{Pyr}$), 113.0 (C$_{Pyr}$), 111.5 (CH$_{Pyrrole}$), 97.2, 84.6 (C$_{Alkyne}$), 21.0 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 3034 (w), 2919 (w), 2207 (w), 1720 (w), 1577 (w), 1558 (m), 1498 (s), 1392 (w), 1339 (s), 1180 (w), 1062 (m), 1018 (m), 827 (w), 782 (m), 722 (s), 687 (m), 569 (m). **MS (EI, 70 eV):** *m/z* (%) = 258 ([M$^+$], 100), 257 (38), 256 (12), 255 (16), 243 (22), 242 (32), 241 (4), 231 (6), 229 (4), 214 (4), 202 (3), 164 (3), 163 (6). **HRMS (EI):** calcd. For C$_{18}$H$_{14}$N$_2$ ([M]$^+$) 258.11515, found 258.11562.

3-((4-methoxyphenyl)ethynyl)-4-(1H-pyrrol-1-yl)pyridine (2d)

Reaction of **1** (1.57 mmol, 350 mg) and 4-methoxyphenylacetylene (2.35 mmol, 311 mg) gave **2d** as a yellow solid (408 mg, 95%); mp: 89 – 90 °C. **¹H NMR (250 MHz, CDCl₃):** δ = 8.72 (br-s, 2H, CH$_{Pyr}$), 7.45 (d, ^3J = 8.9 Hz, 2H, CH$_{Ar}$), 7.45 (t, ^3J = 2.0 Hz, 2H, CH$_{Pyrrole}$), 7.31 (br-s, 1H, CH$_{Pyr}$), 6.89 (d, ^3J = 8.9 Hz, 2H, CH$_{Ar}$), 6.41 (t, ^3J = 2.0 Hz, 2H, CH$_{Pyrrole}$), 3.83 (s, 3H, CH$_3$) ppm. **¹³C NMR (62.9 MHz, CDCl₃):** δ = 160.5 (C-OCH$_3$), 133.3 (CH$_{Ar}$), 120.9 (CH$_{Pyrrole}$), 114.5 (C$_{Ar}$), 114.4 (CH$_{Ar}$), 111.5 (CH$_{Pyrrole}$), 97.5, 82.9 (C$_{Alkyne}$), 55.5 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 3035 (w), 2933 (w), 2218 (m), 1559 (m), 1504 (s), 1338 (m), 1290 (m), 1247 (s), 1174 (m), 1067 (m), 1020 (s), 826 (s), 732 (s), 686 (s), 326 (m), 542 (m). **MS (EI, 70 eV):** *m/z* (%) = 274 ([M$^+$], 100), 273 (8), 259 (36), 232 (8), 231 (46), 230 (38), 229 (34), 205 (10), 204 (9), 203 (12), 151 (7), 137 (12). **HRMS (EI):** calcd. for C$_{18}$H$_{14}$N$_2$O ([M]$^+$) 274.11006, found 274.10990.

General synthesis instructions for the acylated intermediate product 3a-d:
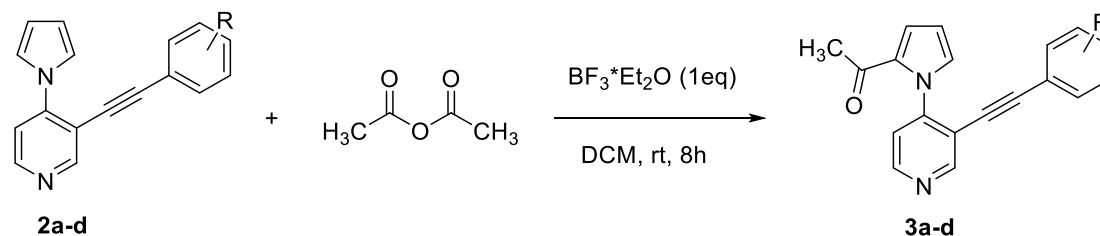
In a degassed and argon flushed Schlenk tube, a stirred solution of 3-(alkynyl)-4-(1H-pyrrol-1-y)pyridine (0.5 mmol) in CH$_2$Cl$_2$ (6 mL) at 0 °C, was added acetic anhydride (0.5 mmol) and BF$_3$·Et$_2$O (0.5 mmol). The mixture was stirred for 8 h at room temperature. After added water, the organic product was extracted with dichloromethane,

dried and solvent was removed under reduced pressure. The desired compound was purified by column chromatography.

1-(1-(3-(phenylethynyl)pyridin-4-yl)-1H-pyrrol-2-yl)ethan-1-one (3a)
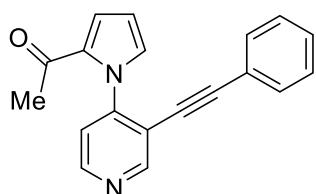
Following the general procedure, 3-(phenylethynyl)-4-(1H-pyrrol-1-yl)pyrydine (0.5 mmol, 112.15 mg), acetic anhydride (0.5 mmol, 51.05 mg) and $BF_3 \cdot Et_2O$ (0.5 mmol) gave **3a** as a yellow oil (102 mg, 71%). **^{1}H NMR** (300 MHz, CDCl$_3$) δ = 8.81 (d, ^5J = 0.7 Hz, 1H, CH$_{Pyr}$), 8.61 (d, ^3J = 5.3 Hz, 1H, CH$_{Pyr}$), 7.32 – 7.29 (m, 5H, CH$_{Ar}$), 7.25 (dd, ^3J = 5.3, ^5J = 0.7 Hz, 1H, CH$_{Pyr}$), 7.13 (dd, ^3J = 4.0, ^4J = 1.6 Hz, 1H, CH$_{Pyrrole}$), 7.01 (dd, ^3J = 2.7, ^4J = 1.6 Hz, 1H, CH$_{Pyrrole}$), 6.41 (dd, ^3J = 4.0, ^3J = 2.7 Hz, 1H, CH$_{Pyrrole}$), 2.40 (s, 3H, CH$_3$) ppm. **^{13}C NMR** (75 MHz, CDCl$_3$) δ = 187.4 (C=O), 153.3, 149.5 (CH$_{Pyr}$), 132.6 (C$_{Pyrrole}$), 131.6, 130.2 (CH$_{Ar}$), 129.1 (CH$_{Pyrrole}$), 128.5 (CH$_{Ar}$), 122.3 (C$_{Ar}$), 121.1 (CH$_{Pyrrole}$), 120.2 (CH$_{Pyr}$), 118.3 (C$_{Pyr}$), 110.4 (CH$_{Pyrrole}$), 96.3, 82.8 (C$_{Alkyne}$), 26.7 (CH$_3$) ppm. **IR (ATR, cm^{-1})**: $\tilde{v}$ = 3033 (w), 2223 (w), 1661 (s), 1484 (m), 1414 (s), 1399 (s), 1346 (m), 1107 (m), 1045 (s), 936 (m), 839 (s), 764 (s), 736 (s), 696 (s), 665 (m), 635 (m), 612 (s), 583 (s), 565 (s), 490 (m). **MS (EI, 70 eV):** m/z (%) = 287 (8), 286 ([M]$^+$, 42), 285 (40), 270 (11), 245 (6), 244 (42), 243 (100), 242 (55), 241 (11), 218 (6), 215 (8), 214 (10), 150 (7), 43 (7). **HRMS (ESI-TOF):** calcd. for C$_{19}$H$_{14}$N$_{12}$O$_1$ ([M+H]$^+$) 287.1184, found 287.1178.

1-(1-(3-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-4-yl)-1H-pyrrol-2-yl)ethan-1-one (3b)
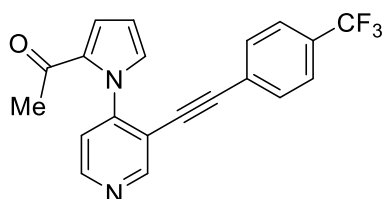
Following the general procedure, 4-(1H-pyrrol-1-yl)-3-((4-(trifluoromethyl)phenyl)ethynyl)pyridine (0.5 mmol, 156.15 mg), acetic anhydride (0.5 mmol, 51.05 mg) and $BF_3 \cdot Et_2O$ (0.5 mmol) gave **3b** as a yellow solid (160.2 mg, 90%), mp: 137 °C. **^{1}H NMR** (300 MHz, CDCl$_3$) δ = 8.83 (d, ^5J = 0.7 Hz, 1H, CH$_{Pyr}$), 8.66 (d, ^3J = 5.3 Hz, 1H, CH$_{Pyr}$), 7.59 – 7.54 (m, 2H, CH$_{Ar}$), 7.43 – 7.37 (m, 2H, CH$_{Ar}$), 7.29 (dd, ^3J = 5.3, ^5J = 0.7 Hz, 1H, CH$_{Pyr}$), 7.14 (dd, ^3J = 3.9, ^4J = 1.6 Hz, 1H, CH$_{Pyrrole}$), 7.02 (dd, ^3J = 2.7, ^5J = 1.6 Hz, 1H, CH$_{Pyrrole}$), 6.43 (dd, ^3J = 3.9, ^3J = 2.7 Hz, 1H, CH$_{Pyrrole}$), 2.40 (s, 3H, CH$_3$) ppm. **^{19}F NMR** (282 MHz, CDCl3) δ = -62.96 ppm. **^{13}C NMR** (75 MHz, CDCl$_3$) δ = 187.3 (C=O), 153.1 (CH$_{Pyr}$), 150.0 (C$_{Pyr}$), 149.8 (CH$_{Pyr}$), 132.7 (C$_{Pyrrole}$), 131.9 (CH$_{Ar}$), 130.8 (q, $^2J_{C,F}$ = 33.0 Hz, C$_{Ar}$), 130.2 (CH$_{Pyrrole}$), 126.0

(C_{Ar}), 125.5 (q, $^3J_{C,F}$ = 3.7 Hz, CH_{Ar}), 124.3 (d, $^1J_{C,F}$ = 272.1 Hz, CF_3), 121.4 ($CH_{Pyrrole}$), 120.3 (CH_{Pyr}), 117.8 (C_{Pyr}), 110.6 ($CH_{Pyrrole}$), 94.7, 85.0 (C_{Alkyne}), 26.7 (CH_3) ppm. **IR (ATR, cm^{-1}):** ṽ = 1644 (s), 1492 (m), 1447 (m), 1399 (s), 1315 (s), 1273 (s), 1160 (s), 1119 (s), 1105 (s), 1063 (s), 1047 (s), 1014 (s), 940 (s), 847 (s), 837 (s), 744 (s), 719 (s), 639 (s), 581 (s), 497 (s). **MS (EI, 70 eV):** *m/z* (%) = 355 (14), 354 ([M]$^+$, 67), 353 (29), 339 (12), 313 (10), 312 (62), 311 (100), 310 (18), 286 (12), 243 (10), 242 (30), 43 (16). **HRMS (ESI-TOF):** calcd. for $C_{20}H_{13}N_2O_1F_3$ ([M+H]$^+$) 355.1058, found 355.1057.

1-(1-(3-(m-tolylethynyl)pyridin-4-yl)-1H-pyrrol-2-yl)ethan-1-one (3c)

Following the general procedure, 4-(1H-pyrrol-1-yl)-3-(m-tolylethynyl)yridine (0.5 mmol, 129.16 mg), acetic anhydride (0.5 mmo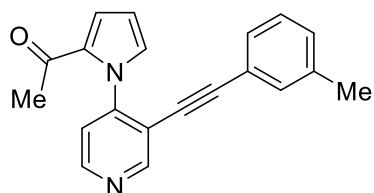l, 51.05 mg) and BF$_3$·Et$_2$O (0.5 mmol) gave **3c** as a yellow oil (113.0 mg, 75%). **^{1}H NMR** (500 MHz, CDCl$_3$) δ = 8.81 (s, 1H, CH_{Pyr}), 8.61 (d, ^3J = 5.3 Hz, 1H, CH_{Pyr}), 7.25 (d, ^3J = 5.3 Hz, 1H, CH_{Pyr}), 7.21 – 7.17 (m, 1H, CH_{Ar}), 7.14 (br-s, 2H, CH_{Ar}), 7.13 (dd, ^3J = 3.8, ^4J = 1.5 Hz, 1H, $CH_{Pyrrole}$), 7.12 – 7.09 (m, 1H, CH_{Ar}), 7.02 (dd, ^3J = 2.9, ^4J = 1.5 Hz, 1H, $CH_{Pyrrole}$), 6.41 (dd, ^3J = 3.8, ^3J = 2.9 Hz, 1H, $CH_{Pyrrole}$), 2.41 (s, 3H, CH_3(C=O)), 2.32 (s, 3H, CH_3) ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ = 187.4 (C=O), 153.3, 149.4 (CH_{Pyr}), 138.2 (C_{Ar}), 132.6 ($C_{Pyrrole}$), 132.2, 130.2, 130.0, 128.8 (CH_{Ar}), 128.4 ($CH_{Pyrrole}$), 122.2 (C_{Ar}), 121.1 ($CH_{Pyrrole}$), 120.2 (CH_{Pyr}), 118.4 (C_{Pyr}), 110.4 ($CH_{Pyrrole}$), 96.6, 82.5 (C_{Alkyne}), 26.7 (CH_3(C=O)), 21.4 (CH_3) ppm. **IR (ATR, cm^{-1}):** ṽ = 2920 (w), 2213 (w), 1657 (s), 1496 (s), 1447 (s), 1409 (s), 1399 (s), 1348 (s), 1259 (m), 1107 (m), 1088 (m), 1043 (s), 938 (s), 835 (s), 783 (s), 738 (s), 688 (s), 637 (s), 583 (s), 441 (s). **MS (EI, 70 eV):** *m/z* (%) = 300 ([M]$^+$, 50), 299 (36), 285 (20), 258 (54), 257 (100), 256 (38), 255 (47), 243 (31), 242 (81), 241 (14), 214 (13), 209 (16), 163 (14), 43 (42). **HRMS (ESI-TOF):** calcd. for $C_{20}H_{16}N_2O_1$ ([M+H]$^+$) 301.1341, found 301.1343.

4-methoxyphenyl)(6-methylpyrrolo[1,2-a][1,6]naphthyridin-5-yl)methanone (4d)
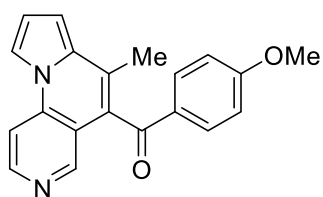
Following the general procedure, 3-((4-methoxyphenyl)ethynyl)-4-(1H-pyrrol-1-yl)Pyr (0.5 mmol, 137.16 mg), acetic anhydride (0.5 mmol, 51.05 mg) and BF$_3$·Et$_2$O (0.5 mmol) gave **4d** as a brown oil (38.2 mg, 24%). **^{1}H NMR** (500 MHz, CDCl$_3$) δ = 8.63 (s, 1H, CH_{Pyr}), 8.57 (d, ^3J = 5.8 Hz, 1H, CH_{Pyr}),

7.92 (dd, ^3J = 3.0, ^4J = 1.4 Hz, 1H, CH$_{Pyrrole}$), 7.90 (d, ^3J = 8.3 Hz, 2H, CH$_{Ar}$), 7.72 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 6.94 – 6.91 (m, 1H, CH$_{Pyrrole}$, 2H, CH$_{Ar}$), 6.72 (dd, ^3J = 3.8, ^4J = 1.4 Hz, 1H, CH$_{Pyrrole}$), 3.87 (s, 3H, O CH$_3$), 2.30 (s, 3H, CH$_3$) ppm. ^{13}**C NMR** (126 MHz, CDCl$_3$) δ = 195.7 (C=O), 164.6 (C$_{Ar}$), 148.8, 147.0 (CH$_{Pyr}$), 136.8 (C$_{Pyrrole}$), 132.4 (CH$_{Ar}$), 131.7 (C$_{Ar}$), 130.8 (C$_{Pyr}$), 127.0, 124.9 (C$_{Ar}$), 118.4 (C$_{Pyr}$), 114.9 (CH$_{Pyrrole}$), 114.4 (CH$_{Ar}$), 114.0 (CH$_{Pyrrole}$), 108.7 (CH$_{Pyr}$), 104.8 (CH$_{Pyrrole}$), 55.7 (OCH$_3$), 15.8 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3039 (w), 2932 (w), 2837 (w), 1651 (m), 1591 (s), 1570 (s), 1496 (s), 1426 (s), 1366 (s), 1306 (m), 1255 (s), 1228 (s), 1162 (s), 1022 (s), 841 (s), 814 (s), 773 (s), 703 (s), 598 (s), 552 (s). **MS (EI, 70 eV):** *m/z* (%) = 317 (21), 316 ([M]$^+$, 100), 315 (48), 301 (22), 299 (18), 286 (8), 285 (34), 209 (8), 181 (10), 179 (6), 135 (17), 77 (10). **HRMS (ESI-TOF):** calcd. for C$_{20}$H$_{16}$N$_2$O$_2$ ([M+H]$^+$) 317.1290, found 317.1290.

Cycloisomerization of the acylated intermediate product 4a-c
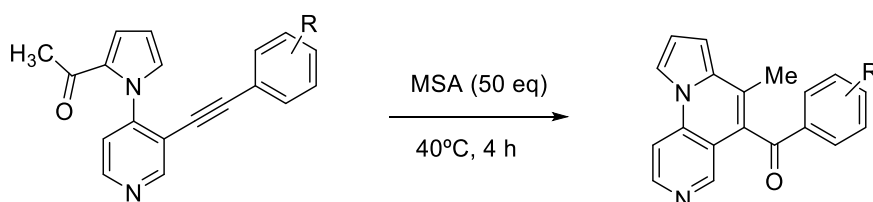
A small round bottom flask was charged with corresponding starting material (0.23 mmol) and MsOH (50 equiv.). The solution was stirred at 40 °C for 4 h. The reaction mixture was washed with a 10% sodium hydroxide solution and extracted with ethyl acetate (EtOAc). The combined organic layers were collected and the solvent evaporated. The crude product was purified by column chromatography.

(6-methylpyrrolo[1,2-*a*][1,6]naphthyridin-5-yl)(phenyl)methanone (4a)
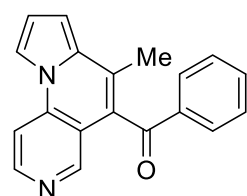
According to general procedure, the reaction of **3a** (0.23 mmol, 65.86 mg), and MsOH (11.5 mmol, 0.75 mL), affords product **4a** as a crystalline yellow solid (62 mg, 94%), mp: 152 – 154 °C. ^{1}**H NMR** (500 MHz, CDCl$_3$) δ = 8.61 (s, 1H, CH$_{Pyr}$), 8.58 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 7.95 – 7.91 (m, 2H, CH$_{Ar}$, 1H, CH$_{Pyrrole}$), 7.75 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 7.62 (tt, ^3J = 7.3, ^5J = 1.4 Hz, 1H, CH$_{Ar}$), 7.47 (t, ^3J = 7.9 Hz, 2H, CH$_{Ar}$), 6.94 (dd, ^3J = 3.8, ^4J = 3.0 Hz, 1H, CH$_{Pyrrole}$), 6.75 (dd, ^3J = 3.8, ^4J = 1.4 Hz, 1H, CH$_{Pyrrole}$), 2.30 (s, 3H, CH$_3$) ppm. ^{13}**C NMR** (126 MHz, CDCl$_3$) δ = 197.4 (C=O), 148.6, 146.9 (CH$_{Pyr}$), 137.7 (C$_{Pyr}$), 136.9 (C$_{Pyrrole}$), 134.4 (CH$_{Ar}$), 131.6 (C$_{Ar}$), 129.9, 129.2 (CH$_{Ar}$),

127.6, 124.5 (C_{Ar}), 118.4 (C_{Pyr}), 115.0, 114.2 ($CH_{Pyrrole}$), 108.7 (CH_{Pyr}), 105.1 ($CH_{Pyrrole}$), 15.9 (CH_3) ppm. **IR** (ATR, cm^{-1}): ṽ = 3058 (w), 2922 (w), 2852 (w), 1661 (s), 1593 (s), 1496 (m), 1449 (m), 1366 (s), 1313 (m), 1263 (s), 1222 (s), 1175 (s), 1065 (m), 999 (s), 907 (m), 816 (s), 719 (s), 686 (s), 639 (s), 552 (s). **MS (EI, 70 eV):** *m/z* (%) = 287 (19), 286 ([M]$^+$, 100), 285 (88), 271 (7), 270 (6), 269 (23), 257 (6), 209 (21), 181 (17), 179 (6), 77 (16). **HRMS (EI):** calcd. for $C_{19}H_{13}N_2O_1$ ([M]$^+$) 285.10224, found 285.10222; calcd. for $C_{19}H_{14}N_2O_1$ ([M]$^+$) 286.11006, found 286.10929.

(6-methylpyrrolo[1,2-*a*][1,6]naphthyridin-5-yl)(4-(trifluoromethyl)phenyl)methanone (4b)
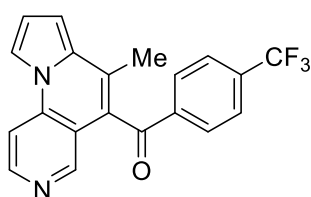
According to general procedure, the reaction of **3b** (0.23 mmol, 81.5 mg), and MsOH (11.5 mmol, 0.75 mL), affords product **4b** as a brown oil (75.8 mg, 93%). **^{1}H NMR** (500 MHz, CDCl$_3$) δ = 8.60 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.57 (s, 1H, CH$_{Pyr}$), 8.04 (d, ^3J = 8.1 Hz, 2H, CH$_{Ar}$), 7.96 (dd, ^3J = 2.9, ^4J = 1.4 Hz, 1H, CH$_{Pyrrole}$), 7.77 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 7.74 (d, ^3J = 8.1 Hz, 2H, CH$_{Ar}$), 6.96 (dd, ^3J = 3.8, ^3J = 2.9 Hz, 1H, CH$_{Pyrrole}$), 6.79 (dd, ^3J = 3.8, ^4J = 1.4 Hz, 1H, CH$_{Pyrrole}$), 2.31 (s, 3H, CH$_3$) ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ = 196.3 (C=O), 148.2, 147.0 (CH$_{Pyr}$), 140.3 (C$_{Pyr}$), 136.9 (C$_{Pyrrole}$), 135.5 (q, $^2J_{C,F}$ = 32.7 Hz, C$_{Ar}$), 131.3 (C$_{Ar}$), 130.1 (CH$_{Ar}$), 128.3 (C$_{Ar}$), 126.3 (q, $^3J_{C,F}$ = 3.7 Hz, CH$_{Ar}$), 123.9 (q, $^1J_{C,F}$ = 272.6 Hz, CF$_3$), 123.6 (C$_{Ar}$), 118.1 (C$_{Pyr}$), 115.3, 114.6 (CH$_{Pyrrole}$), 108.9 (CH$_{Pyr}$), 105.8 (CH$_{Pyrrole}$), 16.0 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3046 (w), 2922 (w), 1669 (m), 1585 (m), 1496 (m), 1409 (m), 1321 (s), 1263 (m), 1220 (m), 1164 (s), 1125 (s), 1107 (s), 1063 (s), 1014 (s), 1004 (s), 851 (s), 814 (s), 707 (s), 550 (s). **MS (EI, 70 eV):** *m/z* (%) = 355 (20), 354 ([M]$^+$, 100), 353 (57), 337 (21), 285 (19), 209 (26), 185 (21), 179 (6), 145 (12). **HRMS (EI):** calcd. for $C_{20}H_{12}F_3N_2O_1$ ([M]$^+$) 353.08962, found 353.08926; calcd. for $C_{20}H_{13}F_3N_2O_1$ ([M]$^+$) 354.09745, found 354.09665.

### (6-methylpyrrolo[1,2-*a*][1,6]naphthyridin-5-yl)(m-tolyl)methanone (4c)
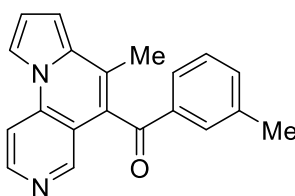
According to general procedure, the reaction of **3c** (0.23 mmol, 69.08 mg), and MsOH (11.5 mmol, 0.75 mL), affords product **4c** as a brown oil (61.5 mg, 89%). **^{1}H NMR** (250 MHz, CDCl$_3$) δ = 8.62 (s, 1H, CH$_{Pyr}$), 8.60 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 7.94 (dd, ^3J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Pyrrole}$), 7.78 – 7.74 (m,

1H, CH$_{Pyr}$, 1H, CH$_{Ar}$), 7.71 – 7.66 (m, 1H, CH$_{Ar}$), 7.46 – 7.40 (m, 1H, CH$_{Ar}$), 7.35 (d, ^3J = 7.6 Hz, 1H, CH$_{Ar}$), 6.95 (dd, ^3J = 3.8, ^3J = 3.0 Hz, 1H, CH$_{Pyrrole}$), 6.75 (dd, ^3J = 3.8, ^4J = 1.3 Hz, 1H, CH$_{Pyrrole}$), 2.38 (s, 3H, CH$_3$), 2.30 (s, 3H, CH$_3$) ppm. **^{13}C NMR** (63 MHz, CDCl$_3$) δ = 197.5 (C=O), 148.5, 146.7 (CH$_{Pyr}$), 139.2 (C$_{Pyr}$), 137.8 (C$_{Ar}$), 136.9 (C$_{Pyrrole}$), 135.3 (CH$_{Ar}$), 131.7 (C$_{Ar}$), 130.1, 129.1 (CH$_{Ar}$), 127.5 (C$_{Ar}$), 127.3 (CH$_{Ar}$), 124.8 (C$_{Ar}$), 118.5 (C$_{Pyr}$), 115.1, 114.2 (CH$_{Pyrrole}$), 108.8 (CH$_{Pyr}$), 105.1 (CH$_{Pyrrole}$), 21.4 (CH$_3$), 15.9 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3039 (w), 2918 (w), 2856 (w), 1657 (s), 1585 (s), 1496 (s), 1428 (s), 1366 (s), 1306 (s), 1267 (s), 1205 (s), 1173 (s), 1036 (s), 1010 (s), 950 (s), 812 (s), 738 (s), 707 (s), 686 (s), 556 (s). **MS (EI, 70 eV):** m/z (%) = 301 (22), 300 ([M]$^+$, 100), 299 (56), 286 (14), 285 (74), 284 (16), 283 (19), 209 (25), 181 (21), 179 (8), 128 (10), 91 (21). **HRMS (EI):** calcd. For C$_{20}$H$_{16}$N$_2$O$_1$ ([M]$^+$) 300.12571, found 300.12566.

3-(3-bromopyridin-4-yl)thiophene-2-carbaldehyde (5)

3,4-dibromopyridine (0.5 mmol, 118.44 mg,), (2-formylthiophen-3-yl)boronic acid (1.2 equiv.), Pd(PPh$_3$)$_4$ (5 mol%) and K$_2$CO$_3$ (2.0 equiv.) were dissolved in dioxane/H$_2$O (6:1, 3.5 mL). The reaction mixture was stirred for 24 h at 90 °C. After cooling to room temperature, the reaction mixture was washed with distilled water and the crude product was extracted with EtOAc. The organic phases were evaporated under vacuum and the crude product was purified by column chromatography (heptane/EtOAc 3:1) to yield compound **5** as a yellow solid.
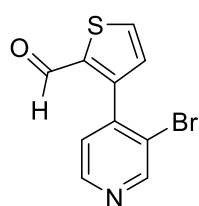
3,4-dibromopyridine (0.5 mmol, 118.44 mg,) and (2-formylthiophen-3-yl)boronic acid (0.6 mmol, 93.56 mg) gave **5** as a yellow solid (62 mg, 52%); mp: 132 – 134 °C. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 9.65 (d, ^5J = 1.3 Hz, 1H, CHO), 8.88 (br-s, 1H, CH$_{Pyr}$), 8.62 (d, ^3J = 4.9 Hz, 1H, CH$_{Pyr}$), 7.82 (dd, ^3J = 5.0, ^5J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.30 (dd, ^3J = 4.9, ^5J = 0.7 Hz, 1H, CH$_{Pyr}$), 7.19 (d, ^3J = 5.0 Hz, 1H, CH$_{Thioph}$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 182.5 (CHO), 152.8, 148.3 (CH$_{Pyr}$), 145.7 (C$_{Pyr}$), 143.0, 140.1 (C$_{Thioph}$), 134.4, 130.4 (CH$_{Thioph}$), 126.3 (CH$_{Pyr}$), 121.7 (C$_{Pyr}$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3112 (w), 2961 (w), 2922 (w), 1649 (s), 1583 (m), 1422 (s), 1399 (s), 1364 (s), 1259 (s), 1203 (s), 1090 (s), 1020 (s), 845 (s), 828 (s), 756 (s), 742 (s), 666 (s), 647 (s). **MS (EI, 70 eV):** m/z (%) = 189 (12), 188 ([M$^+$], 100), 160 (3), 159 (4), 133 (5), 89 (6). **HRMS (EI):** calcd. for C$_{10}$H$_5$O$_1$N$_1$Br$_1$S$_1$ ([M]$^+$)

265.92697, found 265.92723. Calcd. for $C_{10}H_5O_1N_1{}^{81}Br_1S_1$ ([M]$^+$) 267.92493, found 267.92569.

Synthesis of 3-(3-(alkynyl)pyridin-4-yl)thiophene-2-carbaldehyde (6a-e)

3-(3-bromopyridin-4-yl)thiophene-2-carbaldehyde (1.0 equiv.), PdCl$_2$(CH$_3$CN)$_2$ (5 mol%), XPhos (10 mol%) and CuI (2 mol%) we dissolved in HN*i*Pr$_2$. After degassed the reaction mixture, the corresponding alkyne (1.2 equiv.) was added and the reaction was stirred for 20 h at 80 °C. The reaction was washed with water and extracted with EtOAc. The crude product was purified by column chromatography (heptane/EtOAc 3:1) to yield compounds **6a-e**.

3-(3-(p-tolylethynyl)pyridin-4-yl)thiophene-2-carbaldehyde (6a)
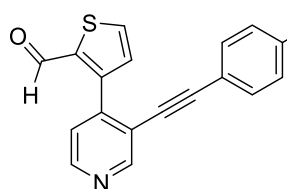
5 (0.4 mmol, 106.86 mg,) and 4-methylphenylacetylene (0.48 mmol, 0.062 mL) gave **6a** as a yellow solid (108.8 mg, 89%); mp: 78 – 80 °C. **¹H NMR (500 MHz, CDCl₃)** δ = 9.86 (d, ^5J = 1.3 Hz, 1H, CHO), 8.89 (s, 1H, CH$_{Pyr}$), 8.63 (d, ^3J = 5.0 Hz, 1H, CH$_{Pyr}$), 7.81 (dd, ^3J = 5.0, ^5J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.34 (d, ^3J = 5.0 Hz, 1H, CH$_{Pyr}$), 7.32 (d, ^3J = 5.0 Hz, 1H, CH$_{Thioph}$), 7.23 (d, ^3J = 8.0 Hz, 2H, CH$_{Ar}$), 7.12 (d, ^3J = 8.0 Hz, 2H, CH$_{Ar}$), 2.34 (s, 3H, CH$_3$) ppm. **¹³C NMR (126 MHz, CDCl₃)** δ = 183.1 (CHO), 153.3, 148.5 (CH$_{pyr}$), 145.9 (C$_{Pyr}$), 143.2, 140.4 (C$_{Thioph}$), 139.6 (C$_{Ar}$), 134.0 (CH$_{Ar}$), 131.6 (CH$_{Ar}$), 130.8 (CH$_{Thioph}$), 129.4 (CH$_{Ar}$), 124.3 (CH$_{Pyr}$), 120.3 (C$_{Pyr}$), 119.0 (C$_{Ar}$), 97.0, 84.4 (C$_{Alkyne}$), 21.7 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3027 (w), 2920 (w), 2852 (w), 2213 (w), 1659 (s), 1578 (m), 1508 (m), 1418 (s), 1405 (s), 1370 (m), 1197 (s), 1179 (m), 845 (m), 814 (s), 736 (s), 674 (s), 651 (s). **MS (EI, 70 eV):** *m/z* (%) = 303 (17), 302 ([M]$^+$, 26), 288 (23), 276 (21), 275 (100), 274 (51), 273 (16), 272 (13), 260 (21), 259 (19). **HRMS (EI):** calcd. for $C_{19}H_{12}O_1N_1S_1$ (M)$^+$ 302.06341, found 302,06360.

3-(3-(phenylethynyl)pyridin-4-yl)thiophene-2-carbaldehyde (6b)
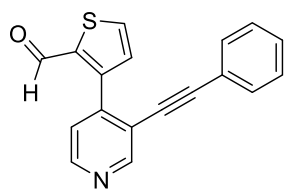
5 (0.4 mmol, 106.86 mg,) and phenylacetylene (0.48 mmol, 0.053 mL) gave **6b** as a yellow oil (108.4 mg, 94%). **¹H NMR (500 MHz, CDCl₃)** δ = 9.85 (d, ^5J = 1.4 Hz, 1H, CHO), 8.89 (s, 1H, CH$_{Pyr}$), 8.63 (d, ^3J = 5.0 Hz, 1H, CH$_{Pyr}$), 7.80 (dd, ^3J = 5.0, ^5J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.36 – 7.28 (m, 7H, CH$_{Ar/Het}$) ppm. **¹³C NMR (126 MHz,**

CDCl₃) δ = 183.0 (CHO), 153.3, 148.7 (CH$_{pyr}$), 145.8 (C$_{Pyr}$), 143.2, 140.4 (C$_{Thioph}$), 134.0 (CH$_{Thioph}$), 131.6, 130.8 (CH$_{Ar}$), 129.2 (CH$_{Thioph}$), 128.6 (CH$_{Ar}$), 124.3 (CH$_{Pyr}$), 122.0 (C$_{Ar}$), 120.0 (C$_{Pyr}$), 96.6, 84.9 (C$_{Alkyne}$) ppm. **IR (ATR, cm⁻¹):** ṽ = 3054 (w), 2852 (w), 2215 (w), 1657 (s), 1578 (m), 1490 (s), 1418 (s), 1362 (m), 1201 (s), 911 (m), 843 (m), 752 (s), 734 (s), 688 (s), 670 (s), 651 (s), 579 (s), 550 (s). **MS (EI, 70 eV):** *m/z* (%) = 290 ([M]⁺, 3), 289 (13), 288 (34), 262 (21), 261 (100), 260 (62), 259 (19), 232 (9), 189 (8). **HRMS (ESI-TOF):** calcd. for C₁₈H₁₁O₁N₁S₁ ([M+H]⁺) 290.0639, found 290.0639.

3-(3-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-4-yl)thiophene-2-carbaldehyde (6c)
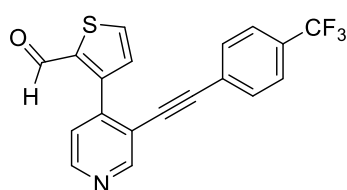
5 (0.3 mmol, 80.14 mg,) and 4-trifluoromethylphenylacetyle (0.36 mmol, 0.059 mL) gave **6c** as a brown oil (97.3 mg, 91%). **¹H NMR (300 MHz, CDCl₃)** δ = 9.86 (d, ⁵J = 1.3 Hz, 1H, CHO), 8.92 (d, ⁵J = 0.8 Hz, 1H, CH$_{Pyr}$), 8.68 (d, ³J = 5.1 Hz, 1H, CH$_{Pyr}$), 7.83 (dd, ³J = 5.0, ⁵J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.58 (m, 2H, CH$_{Ar}$), 7.44 (m, 2H, CH$_{Ar}$), 7.38 (dd, ³J = 5.1, ⁵J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.31 (d, ³J = 5.0 Hz, 1H, CH$_{Thioph}$) ppm. **¹⁹F NMR (282 MHz, CDCl₃)** δ = -62.99 (s, 3F, CF₃) ppm. **¹³C NMR (75 MHz, C₆D₆):** δ = 155.5, 150.7 (CH$_{pyridine}$), 147.3 (C$_{pyridine}$), 131.9 (CH$_{Ar}$), 130.5 (q, ²$J_{C,F}$ = 32.6 Hz, C$_{Ar}$), 126.3 (C$_{Ar}$), 125.5 (q, ³$J_{C,F}$ = 3.8 Hz, CH$_{Ar}$), 124.4 (q, ¹$J_{C,F}$ = 272.3 Hz, CF₃), 120.9 (CH$_{pyrrole}$), 117.3 (CH$_{pyridine}$), 111.6 (CH$_{pyrrole}$), 105.2 (C$_{pyridine}$), 95.1, 87.0 (C$_{alkyne}$) ppm. **IR (ATR, cm⁻¹):** ṽ = 3112 (w), 2858 (w), 1653 (s), 1611 (m), 1405 (m), 1317 (s), 1203 (m), 1164 (s), 1107 (s), 1063 (s), 1014 (s), 845 (s), 750 (s), 653 (s), 593 (m). **MS (EI, 70 eV):** *m/z* (%) = 357 ([M]⁺, 4), 356 (11), 330 (21), 329 (100), 328 (36), 260 (14), 259 (17). **HRMS (ESI-TOF):** calcd. for C₁₉H₁₀O₁N₁S₁F₃ ([M+H]⁺) 358.0513, found 358.0510.
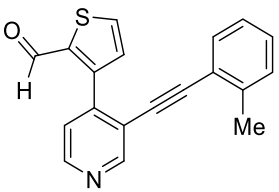
3-(3-(oct-1-yn-1-yl)pyridin-4-yl)thiophene-2-carbaldehyde (6d)
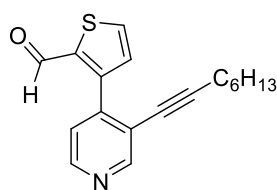
5 (0.4 mmol, 106.86 mg,) and 1-octyne (0.48 mmol, 0.071 mL) gave **6d** as a yellow oil (94.9 mg, 80%). **¹H NMR (250 MHz, CDCl₃)** δ = 9.77 (d, ⁵J = 1.3 Hz, 1H, CHO), 8.75 (br-s, 1H, CH$_{Pyr}$), 8.57 (d, ³J = 5.1 Hz, 1H, CH$_{Pyr}$), 7.76 (dd, ³J = 5.1, ⁵J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.27 (dd, ³J = 5.1, ⁵J = 0.7 Hz, 1H, CH$_{Pyr}$), 7.23 (d, ³J = 5.0 Hz, 1H, CH$_{Thioph}$), 2.29 (t, ³J = 7.0 Hz, 2H, CH₂), 1.53 – 1.35 (m, 2H, CH₂),

1.33 – 1.17 (m, 6H, CH$_2$), 0.92 – 0.79 (m, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 183.1 (CHO), 153.5, 147.8 (CH$_{pyr}$), 146.0 (C$_{Pyr}$), 143.5, 140.2 (C$_{Thioph}$), 133.8, 130.7 (CH$_{Thioph}$), 124.2 (CH$_{pyr}$), 120.9 (C$_{Pyr}$), 98.8, 76.3 (C$_{Alkyne}$), 31.4, 28.6, 28.2, 22.7, 19.6 (CH$_2$), 14.2 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3081 (w), 2953 (m), 2926 (m), 2856 (m), 2228 (w), 1663 (s), 1581 (m), 1418 (s), 1405 (m), 1377 (m), 1199 (s), 843 (m), 830 (s), 740 (s), 674 (s), 653 (s), 579 (m). **MS (EI, 70 eV):** m/z (%) = 297 ([M]$^+$, 19), 241 (22), 240 (24), 238 (32), 227 (34), 226 (17), 224 (27), 223 (22), 222 (24), 213 (17), 212 (100), 184 (38), 140 (23), 41 (16). **HRMS (ESI-TOF):** calcd. for C$_{18}$H$_{19}$O$_1$N$_1$S$_1$ ([M+H]$^+$) 298.1266, found 298.1271.

3-(3-(o-tolylethynyl)pyridin-4-yl)thiophene-2-carbaldehyde (6e)

5 (0.4 mmol, 106.86 mg,) and 2-methylphenylacetylene (0.48 mmol, 0.080 mL) gave **6e** as a brown solid (188.0 mg, 97%). **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 9.83 (d, ^5J = 1.3 Hz, 1H, CHO), 8.91 (d, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 8.64 (d, ^3J = 5.1 Hz, 1H, CH$_{Pyr}$), 7.81 (dd, ^3J = 5.0, ^5J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.35 (dd, ^3J = 5.1, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.32 (d, ^3J = 5.0 Hz, 1H, CH$_{Thioph}$), 7.37 – 7.26 (m, 1H, CH$_{Ar}$), 7.24 – 7.08 (m, 3H, CH$_{Ar}$), 2.25 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 182.9 (CHO), 153.2, 148.3 (CH$_{pyr}$), 146.0 (C$_{Pyr}$), 143.3, 140.5 (C$_{Thioph}$), 140.4 (C$_{Ar}$), 134.1, 132.2, 130.8 (CH$_{Thioph}$), 129.7, 129.4, 125.8 (CH$_{Ar}$), 124.5 (CH$_{pyr}$), 121.8 (C$_{Ar}$), 120.6 (C$_{Pyr}$), 95.8, 88.4 (C$_{Alkyne}$), 20.5 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 2957 (w), 2922 (w), 2850 (w), 2209 (w), 1644 (s), 1581 (m), 1420 (m), 1397 (m), 1368 (m), 1199 (m), 841 (s), 826 (m), 773 (m), 750 (s), 740 (s), 711 (m), 666 (s), 651 (s). **MS (EI, 70 eV):** m/z (%) = 303 ([M]$^+$, 20), 302 (29), 288 (78), 287 (22), 286 (94), 276 (21), 275 (89), 274 (100), 273 (73), 272 (44), 270 (25). **HRMS (ESI-TOF):** calcd. for C$_{19}$H$_{13}$O$_1$N$_1$S$_1$ ([M+H]$^+$) 304.0796, found 304.0796.

Synthesis of aryl(thieno[3,2-*f*]isoquinolin-5-yl)methanone 7a-e
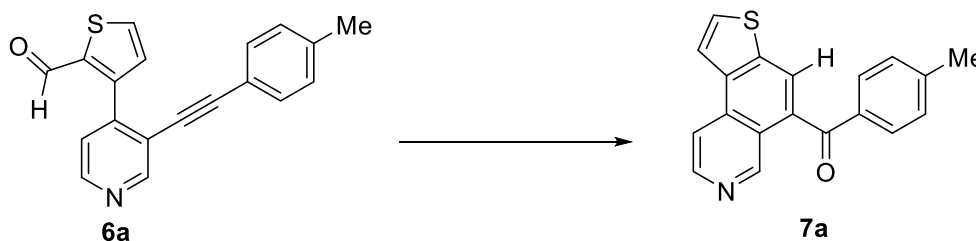
The corresponding starting material **6a-e** (0.23 mmol) was mixed with MsOH (50 equiv.) and stirred for 1 h at room temperature. After that, the reaction mixture was washed with saturated 10 % sodium hydroxide solution. This was followed by extraction of the crude product with EtOAc and purification by column chromatography (heptane/EtOAc 4:1) to obtain the cyclization products **7a-e**.

Thieno[3,2-*f*]isoquinolin-5-yl(p-tolyl)methanone (7a)
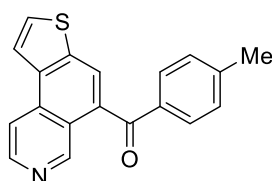
6a (0.23 mmol, 70.0 mg,) and MsOH (11.5 mmol, 0.75 mL) gave **7a** as a yellow oil (64.5 mg, 92%). **¹H NMR (250 MHz, CDCl₃)** δ = 9.55 (d, ^5J = 1.0 Hz, 1H, CH$_{Pyr}$), 8.72 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.17 (dd, ^3J = 5.8, ^5J = 1.0 Hz, 1H, CH$_{Pyr}$), 8.12 (d, ^5J = 0.8 Hz, 1H, CH$_{Ar}$), 8.06 (dd, ^3J = 5.4, ^5J = 0.8 Hz, 1H, CH$_{Thioph}$), 7.83 (d, ^3J = 5.4 Hz, 1H, CH$_{Thioph}$), 7.80 (d, ^3J = 8.1 Hz, 2H, CH$_{Ar}$), 7.29 (d, ^3J = 8.1 Hz, 2H, CH$_{Ar}$), 2.45 (s, 3H, CH₃) ppm. **¹³C NMR (63 MHz, CDCl₃)** δ = 196.0 (C=O), 150.8 (CH$_{Pyr}$), 144.8 (C$_{Ar}$), 144.4 (CH$_{Pyr}$), 139.4 (C$_{Thioph}$), 136.3 (C$_{Pyr}$), 135.6 (C$_{Ar}$), 133.2 (C$_{Thioph}$), 132.9 (C$_{Ar}$), 130.7 (CH$_{Ar}$), 130.0 (CH$_{Thioph}$), 129.5, 124.5 (CH$_{Ar}$), 124.2 (C$_{Pyr}$), 122.4 (CH$_{Thioph}$), 117.1 (CH$_{Pyr}$), 21.9 (CH₃) ppm. **IR (ATR, cm⁻¹):** ṽ = 3093 (w), 2920 (w), 1649 (s), 1601 (s), 1294 (m), 1257 (s), 1208 (m), 1173 (s), 1102 (m), 1032 (s), 872 (s), 826 (s), 795 (s), 744 (s), 723 (s), 692 (s). **MS (EI, 70 eV):** *m/z* (%) = 304 (23), 303 ([M]⁺, 100), 302 (64), 289 (18), 288 (85). **HRMS (ESI-TOF):** calcd. For C₁₉H₁₃O₁N₁S₁ ([M+H]⁺) 304.0796, found 304.0796.

Phenyl(thieno[3,2-*f*]isoquinolin-5-yl)methanone (7b)
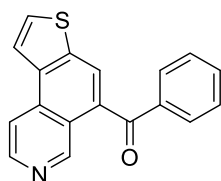
6b (0.23 mmol, 66.5 mg,) and MsOH (11.5 mmol, 0.75 mL) gave **7b** as a brown oil (63.9 mg, 96%). **¹H NMR (300 MHz, CDCl₃)** δ = 9.60 (br-s, 1H, CH$_{Pyr}$), 8.73 (d, ^3J = 5.7 Hz, 1H, CH$_{Pyr}$), 8.17 (dd, ^3J = 5.7, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.13 (d, ^5J = 0.8 Hz, 1H, CH$_{Ar}$), 8.06 (dd, ^3J = 5.4, ^5J = 0.8 Hz, 1H, CH$_{Thioph}$),), 7.92 – 7.88 (m, 2H, CH$_{Ar}$), 7.84 (d, ^3J = 5.4 Hz, 1H, CH$_{Thioph}$), 7.67 – 7.61 (m, 1H, CH$_{Ar}$), 7.53 – 7.46 (m, 2H, CH$_{Ar}$) ppm. **¹³C NMR (75 MHz, CDCl₃)** δ = 196.3 (C=O), 150.8, 144.6 (CH$_{Pyr}$), 139.2 (C$_{Thioph}$), 138.2 (C$_{Ar}$), 136.5 (C$_{Pyr}$), 133.7 (CH$_{Ar}$), 132.9 (C$_{Thioph}$), 132.8 (C$_{Ar}$), 130.5 (CH$_{Ar}$), 130.2 (CH$_{Thioph}$), 128.8, 124.9 (CH$_{Ar}$), 124.2 (C$_{Pyr}$), 122.4 (CH$_{Thioph}$), 117.1 (CH$_{Pyr}$) ppm. **IR (ATR, cm⁻¹):** ṽ = 3095 (w), 3056 (w), 2924 (w), 1649 (s), 1597 (s), 1447 (m), 1290 (m), 1255 (s), 1210 (m), 1173 (m), 1022 (m), 870 (s), 826 (s), 713 (s), 690 (s), 672 (s), 661 (s), 626 (s).

MS (EI, 70 eV): m/z (%) = 290 (23), 289 ([M]$^+$, 98), 288 (93), 260 (37), 212 (29), 184 (40), 140 (44), 113 (30), 105 (38), 77 (100), 51 (33). **HRMS (ESI-TOF):** calcd. for $C_{18}H_{11}O_1N_1S_1$ ([M+H]$^+$) 290.0639, found 290.0639.

Thieno[3,2-*f*]isoquinolin-5-yl(4-(trifluoromethyl)phenyl)methanone (7c)
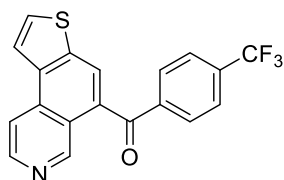
6c (0.23 mmol, 82.2 mg,) and MsOH (11.5 mmol, 0.75 mL) gave **7c** as a yellow solid (70.1 mg, 85%); mp: 130 – 132 °C. **^{1}H NMR (300 MHz, CDCl₃)** δ = 9.69 (s, 1H, CH$_{Pyr}$), 8.79 (br-s, 1H, CH$_{Pyr}$), 8.21 (d, ^3J = 5.7 Hz, 1H, CH$_{Pyr}$), 8.14 (d, ^5J = 0.8 Hz, 1H, CH$_{Ar}$), 8.09 (dd, ^3J = 5.4, ^5J = 0.8 Hz, 1H, CH$_{Thioph}$), 8.01 (d, ^3J = 8.4 Hz, 2H, CH$_{Ar}$), 7.90 (d, ^3J = 5.4 Hz, 1H, CH$_{Thioph}$), 7.78 (d, ^3J = 8.4 Hz, 2H, CH$_{Ar}$) ppm. **^{19}F NMR (282 MHz, CDCl₃)** δ = -63.10 (s, 3F, CF₃) ppm. **^{13}C NMR (75 MHz, CDCl₃)** δ = 195.2 (C=O), 150.7, 144.9 (CH$_{Pyr}$), 141.2 (C$_{Thioph}$), 139.0 (C$_{Ar}$), 137.1 (C$_{Pyr}$), 134.8 (q, $^2J_{CF}$ = 32.9 Hz, C$_{Ar}$), 133.0 (C$_{Thioph}$), 131.7 (C$_{Ar}$), 131.0 (CH$_{Thioph}$), 130.7 (CH$_{Ar}$), 125.9 (q, $^3J_{CF}$ = 3.8 Hz, CH$_{Ar}$), 125.8 (CH$_{Ar}$), 123.7 (q, $^1J_{CF}$ = 272.8 Hz, CF₃), 122.5 (CH$_{Thioph}$), 117.3 (CH$_{Pyr}$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3089 (w), 3044 (w), 1646 (s), 1323 (s), 1253 (s), 1162 (s), 1100 (s), 1067 (s), 1036 (s), 1016 (s), 853 (s), 826 (s), 748 (s), 736 (s), 709 (s), 666 (s). **MS (EI, 70 eV):** m/z (%) = 358 (19), 357 ([M]$^+$, 82), 356 (44), 288 (90), 212 (58), 184 (68), 145 (100), 140 (60), 113 (37). **HRMS (ESI-TOF):** calcd. for $C_{19}H_{10}O_1N_1S_1F_3$ ([M+H]$^+$) 358.0513, found 358.0510.

1-(thieno[3,2-*f*]isoquinolin-5-yl)heptan-1-one (7d)
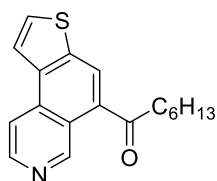
6d (0.23 mmol, 68.4 mg,) and MsOH (11.5 mmol, 0.75 mL) gave **7d** as a yellow solid (54.7 mg, 80%); mp: 95 – 97 °C. **^{1}H NMR (250 MHz, CDCl₃)** δ = 10.01 (br-s, 1H, CH$_{Pyr}$), 8.73 (d, ^3J = 5.7 Hz, 1H, CH$_{Pyr}$), 8.41 (d, ^5J = 0.8 Hz, 1H, CH$_{Ar}$), 8.13 (dd, ^3J = 5.7, ^5J = 0.8 Hz, 1H, CH$_{Thioph}$), 8.02 (dd, ^3J = 5.4, ^5J = 0.8 Hz, 1H, CH$_{Thioph}$), 7.86 (d, ^3J = 5.4 Hz, 1H, CH$_{Thioph}$), 3.20 – 3.07 (m, 2H, CH$_{Ar}$), 1.90 – 1.77 (m, 2H, CH$_{Ar}$), 1.45 – 1.24 (m, 6H, CH$_{Ar}$), 0.94 – 0.85 (m, 3H, CH$_{Ar}$) ppm. **^{13}C NMR (63 MHz, CDCl₃)** δ = 203.1 (C=O), 151.1, 144.4 (CH$_{Pyr}$), 139.3 (C$_{Thioph}$), 137.1 (C$_{Pyr}$), 133.1 (C$_{Thioph}$), 132.9 (C$_{Ar}$), 130.7 (CH$_{Thioph}$), 124.2 (CH$_{Ar}$), 123.3 (C$_{Pyr}$), 122.5 (CH$_{Thioph}$), 117.0 (CH$_{Pyr}$), 42.0, 31.8, 29.2, 24.9, 22.7 (CH₂), 14.2 (CH₃) ppm. **IR** (ATR, cm^{-1}): ṽ = 3054 (w), 2955 (m), 2922 (s), 2850 (m), 1669 (s), 1603 (m), 1461 (m), 1290 (m), 1238 (s), 1203 (m), 1131 (s), 1102 (m), 1028 (m), 837 (s), 793 (s), 729 (s). **MS (EI, 70 eV):** m/z (%) = 297 ([M]$^+$, 11), 228

(6), 227 (32), 226 (6), 214 (6), 213 (14), 212 (100), 185 (8), 184 (40), 183 (6), 140 (22), 113 (9). **HRMS (ESI-TOF):** calcd. for $C_{18}H_{19}O_1N_1S_1$ ($[M+H]^+$) 298.1266, found 298.1267.

Thieno[3,2-*f*]isoquinolin-5-yl(o-tolyl)methanone (7e)
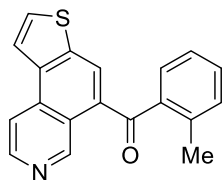
6e (0.23 mmol, 69.8 mg,) and MsOH (11.5 mmol, 0.75 mL) gave **7e** as a white solid (54.0 mg, 78%); mp: 137 – 139 °C. **¹H NMR (250 MHz, CDCl₃)** δ = 9.99 (s, 1H, CH_{Pyr}), 8.76 (br-s, 1H, CH_{Pyr}), 8.17 (d, ^3J = 5.7 Hz, 1H, CH_{Pyr}), 8.08 (s, 1H, CH_{Ar}), 8.05 (d, ^3J = 5.4 Hz, 1H, CH_{Thioph}), 7.85 (d, ^3J = 5.4 Hz, 1H, CH_{Thioph}), 7.50 – 7.32 (m, 3H, CH_{Ar}), 7.28 – 7.20 (m, 1H, CH_{Ar}), 2.49 (s, 3H, CH_3) ppm. **¹³C NMR (63 MHz, CDCl₃)** δ = 198.6 (C=O), 151.1, 144.7 (CH_{Pyr}), 139.1 (C_{Thioph}), 139.1, 138.5 (C_{Ar}), 137.2 (C_{Pyr}), 133.2 (C_{Thioph}), 133.0 (C_{Ar}), 131.7, 131.6, 131.0 (CH_{Ar}), 130.5 (CH_{Thioph}), 127.1, 125.7 (CH_{Ar}), 122.5 (CH_{Thioph}), 117.1 (CH_{Pyr}), 20.8 (CH_3) ppm. **IR (ATR, cm⁻¹):** ṽ = 3099 (w), 2959 (w), 2922 (m), 2850 (w), 1649 (s), 1599 (m), 1457 (m), 1414 (m), 1298 (m), 1251 (s), 1193 (m), 1030 (s), 876 (s), 828 (s), 802 (m), 744 (s), 732 (s), 655 (s). **MS (EI, 70 eV):** *m/z* (%) = 304 (24), 303 ($[M]^+$, 100), 302 (82), 288 (34), 287 (16), 286 (65), 286 (28), 212 (26), 184 (41), 140 (43), 119 (39), 91 (83). **HRMS (ESI-TOF):** calcd. for $C_{19}H_{13}O_1N_1S_1$ ($[M+H]^+$) 304.0796, found 304.0789.

Synthesis of 2-(alkynyl)-3-bromopyridines (8a-g).

2,3-Dibromopyridine (1.0 mmol), Pd(PPh₃)₄ (5 mol%) and CuI (2 mol%) were dissolved in 6 mL of Diisopropylamine (HNiPr₂) under an argon atmosphere. After addition of the alkyne (1.2 equiv.) the reaction was stirred at 40 °C for 0.5 hours. After cooling to room temperature, the reaction mixture was washed with distilled water and extracted with ethyl acetate (EtOAc). The combined organic layers were collected and the solvent evaporated. The crude product was purified by column chromatography (heptane/EtOAc 4:1).

3-bromo-2-((4-(*tert*-butyl)phenyl)ethynyl)pyridine (8a)
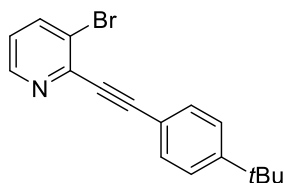
Following the general procedure, 2,3-dibromopyridine (1.0 mmol, 236.89 mg) and 4-*tert*-butylphenylacetylene (1.2 mmol, 0.216 mL) gave **8a** as a yellow solid (283 mg, 90%), mp: 77 °C. **¹H NMR (250 MHz, CDCl₃)** δ = 8.54 (dd, ^3J = 4.7, ^4J = 1.5 Hz, 1H, CH$_{Pyr}$), 7.94 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 1H, CH$_{Pyr}$), 7.60 (d, ^3J = 8.7 Hz, 2H, CH$_{Ar}$), 7.40 (d, ^3J = 8.7 Hz, 2H, CH$_{Ar}$), 7.12 (dd, ^3J = 8.1, ^3J = 4.7 Hz, 1H, CH$_{Pyr}$), 1.33 (s, 9H, CH$_{3-tBu}$) ppm. **¹³C NMR (63 MHz, CDCl₃)** δ = 153.1 (C$_{Ar}$), 148.1 (CH$_{Pyr}$), 143.8 (C$_{Pyr}$), 140.2 (CH$_{Pyr}$), 132.2 (CH$_{Ar}$), 125.6 (CH$_{Ar}$), 124.0 (C$_{Pyr}$), 123.5 (CH$_{Pyr}$), 118.9 (C$_{Ar}$), 95.3, 86.9 (C$_{Alkyne}$), 35.1 (C$_{tBu}$), 31.3 (CH$_{3-tBu}$) ppm. **IR (ATR, cm⁻¹):** ṽ = 2959 (m), 2901 (m), 2860 (m), 2217 (m), 1562 (s), 1508 (m), 1422 (s), 1362 (m), 1265 (m), 1123 (m), 1102 (m), 1059 (m), 1018 (s), 847 (s), 830 (s), 787 (s), 748 (s), 622 (m), 567 (s). **MS (EI, 70 eV):** m/z (%) = 315 ([M]⁺, 32), 313 ([M]⁺, 33), 300 (97), 298 (100), 117 (24), 151 (24), 95 (36), 51 (36), 41 (67), 39 (37). **HRMS (EI):** calcd. for C₁₇H₁₆N₁Br₁ (M)⁺ 313.04606, found 313.04585; calcd. for C₁₇H₁₆N₁⁸¹Br₁ (M)⁺ 315.04402, found 315.04406.

3-bromo-2-((4-methoxyphenyl)ethynyl)pyridine (8b)
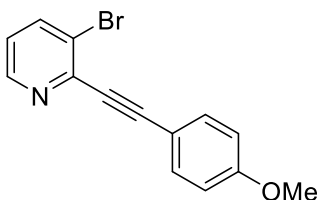
Following the general procedure, 2,3-dibromopyridine (1.0 mmol, 236.89 mg) and 4-methoxyphenylacetylene (1.2 mmol, 0.156 mL) gave **8b** as an orange oil (273.5 mg, 95%). **¹H NMR (500 MHz, CDCl₃)** δ = 8.52 (dd, ^3J = 4.6, ^4J = 1.5 Hz, 1H, CH$_{Pyr}$), 7.90 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 1H, CH$_{Pyr}$), 7.58 (d, ^3J = 8.8 Hz, 2H, CH$_{Ar}$), 7.08 (dd, ^3J = 8.1, ^3J = 4.6 Hz, 1H, CH$_{Pyr}$), 6.89 (d, ^3J = 8.8 Hz, 2H, CH$_{Ar}$),

3.83 (s, 3H, OCH$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 160.65 (C$_{Ar}$), 148.4 (CH$_{Pyr}$), 144.2 (C$_{Pyr}$), 139.9 (CH$_{Pyr}$), 133.9 (CH$_{Ar}$), 123.6 (C$_{Pyr}$), 123.3 (CH$_{Pyr}$), 114.3 (CH$_{Ar}$), 114.1 (C$_{Ar}$), 94.6, 86.7 (C$_{Alkyne}$), 55.5 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3044 (w), 2957 (w), 2918 (w), 2835 (w), 2217 (m), 1603 (s), 1564 (s), 1508 (s), 1434 (m), 1416 (s), 1288 (s), 1247 (s), 1177 (m), 1156 (s), 1125 (m), 1014 (s), 828 (s), 789 (s), 748 (s), 530 (s). **MS (EI, 70 eV):** *m/z* (%) = 289 ([M]$^+$, 98), 287 ([M]$^+$, 100), 274 (31), 272 (31), 246 (7), 244 (8), 165 (33), 164 (28), 138 (17), 137 (9). **HRMS (ESI-TOF):** calcd. for C$_{14}$H$_{10}$O$_1$N$_1$Br$_1$ ([M+H]$^+$) 288.0024, found 288.0027.

3-bromo-2-((4-(trifluoromethyl)phenyl)ethynyl)pyridine (8c)

Following the general procedure, 2,3-dibromopyridine (1.0 mmol, 236.89 mg) and 4-trifluoromethylphenylacetylene (1.2 mmol, 0.196 mL) gave **8c** as a yellow solid (306.2 mg, 94%), mp: 75 °C. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.57 (dd, ^3J = 4.6, ^4J = 1.4 Hz, 1H, CH$_{Pyr}$), 7.95 (dd, ^3J = 8.2, ^4J = 1.4 Hz, 1H, CH$_{Pyr}$), 7.75 (d, ^3J = 8.2 Hz, 2H, CH$_{Ar}$), 7.64 (d, ^3J = 8.2 Hz, 2H, CH$_{Ar}$), 7.17 (dd, ^3J = 8.2, ^3J = 4.6 Hz, 1H, CH$_{Pyr}$) ppm. **^{19}F NMR (282 MHz, CDCl$_3$)** δ = -62.95 (s, 3F, CF$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 148.6 (CH$_{Pyr}$), 143.3 (C$_{Pyr}$), 140.1 (CH$_{Pyr}$), 132.6 (CH$_{Ar}$), 131.1 (q, $^2J_{C,F}$ = 33.0 Hz, C$_{Ar}$), 125.9 (C$_{Ar}$), 125.9 (C$_{Pyr}$), 125.5 (q, $^3J_{C,F}$ = 3.8 Hz, CH$_{Ar}$), 124.2 (CH$_{Pyr}$), 123.9 (q, $^1J_{C,F}$ = 272.3 Hz, CF$_3$), 92.0, 89.4 (C$_{Alkyne}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3046 (w), 2225 (w), 1418 (m), 1403 (m), 1315 (s), 1154 (s), 1102 (s), 1057 (s), 1018 (s), 1010 (s), 975 (m), 835 (s), 787 (s), 748 (s), 721 (m), 655 (m). **MS (EI, 70 eV):** *m/z* (%) = 327 ([M]$^+$, 99), 325 ([M]$^+$, 100), 246 (27), 226 (60), 199 (24), 177 (42), 150 (20), 98 (23), 51 (39), 50 (20). **HRMS (EI):** calcd. for C$_{14}$H$_7$N$_1$Br$_1$F$_3$ (M)$^+$ 324.97085 found 324.97135; calcd. for C$_{14}$H$_7$N$_1$^{81}Br$_1$F$_3$ (M)$^+$ 326.96880, found 326.96935.

3-bromo-2-(oct-1-yn-1-yl)pyridine (8d)
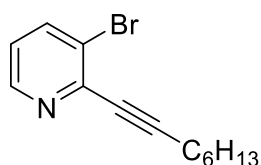
Following the general procedure, 2,3-dibromopyridine (1.0 mmol, 236.89 mg) and 1-octyne (1.2 mmol, 0.177 mL) gave **8d** as a brown oil (261.6 mg, 94%). **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.47 (dd, ^3J = 4.7, ^4J = 1.5 Hz, 1H, CH$_{Pyr}$), 7.86 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 1H, CH$_{Pyr}$), 7.06 (dd, ^3J = 8.1 Hz, ^3J = 4.7 Hz, 1H, CH$_{Pyr}$), 2.50 (t, ^3J = 7.0 Hz, 2H, CH$_2$), 1.73 – 1.60 (m, 2H, CH$_2$), 1.56 – 1.44 (m, 2H, CH$_2$), 1.35 – 1.29

(m, 4H, CH$_2$), 0.90 (t, ^3J = 7.0 Hz, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 148.2 (CH$_{Pyr}$), 144.3 (C$_{Pyr}$), 139.8 (CH$_{Pyr}$), 123.6 (C$_{Pyr}$), 123.2 (CH$_{Pyr}$), 96.8, 79.4 (C$_{Alkyne}$), 31.5, 28.7, 28.3, 22.7, 19.7 (CH$_2$), 14.2 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 2953 (m), 2928 (m), 2856 (m), 2232 (m), 1566 (m), 1422 (s), 1125 (m), 1069 (m), 1016 (s), 789 (s), 750 (s), 723 (m), 645 (m). **MS (EI, 70 eV):** *m/z* (%) = 267 ([M]$^+$, 2), 265 ([M]$^+$, 2), 224 (24), 222 (25), 210 (48), 208 (47), 197 (34), 195 (30), 186 (100), 158 (37), 117 (28), 116 (59), 115 (69), 114 (30), 102 (27), 89 (43), 88 (41), 75 (26), 63 (36), 62 (34), 51 (39), 43 (70), 41 (94), 39 (56), 29 (74). **HRMS (EI):** calcd. for C$_{13}$H$_{16}$N$_1$Br$_1$ (M)$^+$ 265.04606 found 265.04569; calcd. for C$_{13}$H$_{16}$N$_1$^{81}Br$_1$ (M)$^+$ 267.04402, found 267.04374.
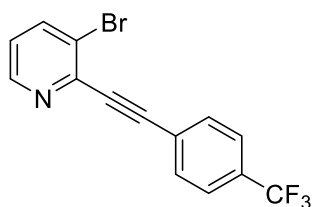
3-bromo-2-(*m*-tolylethynyl)pyridine (8e)

Following the general procedure, 2,3-dibromopyridine (1.0 mmol, 236.89 mg) and 3-methylphenylacetylene (1.2 mmol, 0.155 mL) gave **8e** as a yellow solid (262.3 mg, 96%), mp: 65 °C. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.54 (dd, ^3J = 4.6, ^4J = 1.5 Hz, 1H, CH$_{Pyr}$), 7.92 (dd, ^3J = 8.2, ^4J = 1.5 Hz, 1H, CH$_{Pyr}$), 7.48 – 7.46 (m, 1H, CH$_{Ar}$), 7.48 – 7.43 (m, 1H, CH$_{Ar}$), 7.30 – 7.23 (m, 1H, CH$_{Ar}$), 7.23 – 7.18 (m, 1H, CH$_{Ar}$), 7.11 (dd, ^3J = 8.2, ^3J = 4.6 Hz, 1H, CH$_{Pyr}$), 2.37 (s, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 148.4 (CH$_{Pyr}$), 144.0 (C$_{Pyr}$), 139.9 (CH$_{Pyr}$), 138.3 (C$_{Ar}$), 132.9, 130.4, 129.4, 128.5 (CH$_{Ar}$), 123.9 (C$_{Ar}$), 123.6 (CH$_{Pyr}$), 121.9 (C$_{Pyr}$), 94.5, 87.3 (C$_{Alkyne}$), 21.4 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3039 (w), 2963 (w), 2924 (w), 2209 (w), 1558 (w), 1484 (m), 1430 (m), 1401 (m), 1125 (m), 1057 (m), 1014 (s), 898 (m), 804 (s), 779 (s), 748 (s), 684 (s), 554 (m), 439 (m). **MS (EI, 70 eV):** *m/z* (%) = 273 ([M]$^+$, 96), 271 ([M]$^+$, 100), 192 (16), 191 (49), 190 (21), 165 (13), 164 (13), 163 (16), 96 (11), 82 (13). **HRMS (EI):** calcd. for C$_{14}$H$_{10}$N$_1$Br$_1$ (M)$^+$ 270.99911 found 270.99903; calcd. for C$_{14}$H$_{10}$N$_1$^{81}Br$_1$ (M)$^+$ 272.99707, found 272.99724.

4-((3-bromopyridin-2-yl)ethynyl)-*N*,*N*-dimethylaniline (8f)
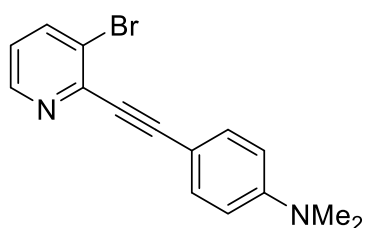
Following the general procedure, 2,3-dibromopyridine (1.0 mmol, 236.89 mg) and 4-dimethylaminophenylacetylene (1.2 mmol, 174.0 mg) gave **8f** as a yellow crystalline solid (166 mg, 55%), mp: 92 – 94 °C. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.50 (dd,

$^3J = 4.7$, $^4J = 1.5$ Hz, 1H, CH$_{Pyr}$), 7.88 (dd, $^3J = 8.1$, $^4J = 1.5$ Hz, 1H, CH$_{Pyr}$), 7.52 (d, $^3J = 9.0$ Hz, 2H, CH$_{Ar}$), 7.03 (dd, $^3J = 8.1$, $^3J = 4.7$ Hz, 1H, CH$_{Pyr}$), 6.65 (d, $^3J = 9.0$ Hz, 2H, CH$_{Ar}$), 3.00 (s, 6H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 150.9 (C$_{Ar}$), 148.3 (CH$_{Pyr}$), 144.6 (C$_{Pyr}$), 139.8 (CH$_{Pyr}$), 133.7 (CH$_{Ar}$), 123.3 (C$_{Pyr}$), 122.7 (CH$_{Pyr}$), 111.8 (CH$_{Ar}$), 108.5 (C$_{Ar}$), 96.6, 86.5 (C$_{Alkyne}$), 40.2 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 2897 (m), 2852 (m), 2815 (m), 2205 (s), 1601 (s), 1562 (s), 1523 (s), 1420 (s), 1366 (s), 1226 (s), 1197 (s), 1152 (s), 1125 (s), 1059 (s), 1018 (s), 816 (s), 806 (s), 787 (s), 746 (s), 525 (s). **MS (EI, 70 eV):** m/z (%) = 302 ([M]$^+$, 97), 301 (69), 300 ([M]$^+$, 100), 299 (56), 286 (11), 284 (11), 177 (14), 151 (11), 150 (14), 110 (13), 97 (7). **HRMS (ESI-TOF):** calcd. for C$_{15}$H$_{13}$N$_2$Br$_1$ ([M+H]$^+$) 301.0340 found 301.0342.
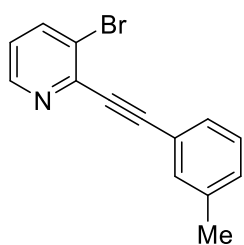
3-bromo-2-(phenylethynyl)pyridine (8g)
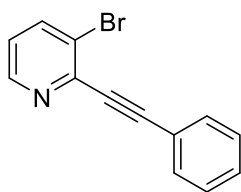
Following the general procedure, 2,3-dibromopyridine (1.0 mmol, 236.89 mg) and phenylacetylene (1.2 mmol, 0.132 mL) gave **8g** as a colourless oil (200 mg, 77%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.55 (dd, $^3J = 4.6$, $^4J = 1.3$ Hz, 1H, CH$_{Pyr}$), 7.92 (dd, $^3J = 8.1$, $^4J = 1.3$ Hz, 1H, CH$_{Pyr}$), 7.65 (dd, $^3J = 7.4$, $^4J = 2.2$ Hz, 2H, CH$_{Ar}$), 7.41 – 7.35 (m, 3H, CH$_{Ar}$), 7.12 (dd, $^3J = 8.1$, $^3J = 4.6$ Hz, 1H, CH$_{Pyr}$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 148.4 (CH$_{Pyr}$), 143.9 (C$_{Pyr}$), 140.0 (CH$_{Pyr}$), 132.3, 129.5, 128.6 (CH$_{Ar}$), 124.0 (C$_{Pyr}$), 123.7 (CH$_{Pyr}$), 122.1 (C$_{Ar}$), 94.2, 87.6 (C$_{Alkyne}$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 3044 (w), 2219 (m), 1562 (m), 1490 (s), 1432 (m), 1418 (s), 1059 (m), 1018 (s), 789 (s), 750 (s), 732 (m), 686 (s), 565 (m), 546 (m), 521 (m). **MS (EI, 70 eV):** m/z (%) = 259 ([M]$^+$, 99), 258 (18), 257 ([M]$^+$, 100), 178 (31), 177 (29), 152 (12), 151 (42), 150 (26), 89 (10), 75 (16), 51 (11). **HRMS (ESI-TOF):** calcd. for C$_{13}$H$_8$N$_1$Br$_1$ ([M+H]$^+$) 257.9918 found 257.9919.

Synthesis of 2-(alkynyl)-3-thiophenpyridines (9a-k).

2-(alkynyl)-3-bromopyridine (0.525 mmol), Pd(PPh$_3$)$_4$ (5 mol%), K$_2$CO$_3$ (2.0 equiv.) and the corresponding boronic acid (3-thiopheneboronic acid or 3-benzothiopheneboronic acid) (1.7 equiv.) were dissolved in 1,4-dioxane (3.0 mL) and water (0.5 mL) under an argon atmosphere. The reaction was stirred overnight at 90 °C. Afterwards the reaction mixture was washed with distilled water and extracted with ethyl acetate (EtOAc). The combined organic layers were collected and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography to yield desired compounds (heptane/EtOAc 4:1).

2-((4-(*tert*-butyl)phenyl)ethynyl)-3-(thiophen-3-yl)pyridine (9a)
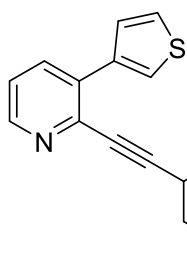
Following the general procedure, **8a** (0.525 mmol, 165.0 mg) and 3-thiopheneboronic acid (0.893 mmol, 114.2 mg) gave **9a** as a yellow oil (78.4 mg, 45%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.45 (dd, ^3J = 4.6, ^4J = 1.6 Hz, 1H, CH$_{Pyr}$), 7.66 (dd, ^3J = 7.8, ^4J = 1.6 Hz, 1H, CH$_{Pyr}$), 7.63 (dd, ^4J = 2.9, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.42 (dd, ^3J = 4.9, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.35 (d, ^3J = 8.2 Hz, 2H, CH$_{Ar}$), 7.31 (dd, ^3J = 4.9, ^4J = 2.9 Hz, 1H, CH$_{Thioph}$), 7.26 (d, ^3J = 8.2 Hz, 2H, CH$_{Ar}$), 7.15 (dd, ^3J = 7.8, ^3J = 4.6 Hz, 1H, CH$_{Pyr}$), 1.21 (s, 9H, CH$_{3\text{-}tBu}$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 152.4 (C$_{Ar}$), 148.3 (CH$_{Pyr}$), 140.9 (C$_{Pyr}$), 138.4 (C$_{Thioph}$), 136.4 (CH$_{Pyr}$), 134.4 (C$_{Pyr}$), 131.7 (CH$_{Ar}$), 128.4 (CH$_{Thioph}$), 125.5 (CH$_{Ar}$), 125.4 (CH$_{Thioph}$), 124.6 (CH$_{Pyr}$), 122.7 (CH$_{Thioph}$), 119.4 (C$_{Ar}$), 92.7, 88.4 (C$_{Alkyne}$), 34.9 (C$_{tBu}$), 31.2 (CH$_{3\text{-}tBu}$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 2959 (m), 2924 (w), 2864 (w), 2217 (w), 1424 (s), 1362 (m), 1102 (m), 855 (m), 835 (s), 779 (s), 647 (s), 626 (m), 563 (s). **MS (EI, 70 eV):** *m/z* (%) = 317 ([M]$^+$, 42), 303 (22), 302 (100), 286 (17), 274 (11), 273 (17), 260 (27), 136 (32), 63 (10), 41 (30), 39 (18). **HRMS (EI):** calcd. for C$_{21}$H$_{19}$N$_1$S$_1$ (M)$^+$ 317.12327 found 317.12326.

2-((4-methoxyphenyl)ethynyl)-3-(thiophen-3-yl)pyridine (9b)
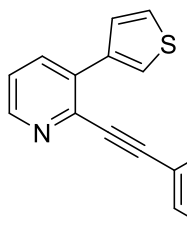
Following the general procedure, **8b** (0.525 mmol, 151.3 mg) and 3-thiopheneboronic acid (0.8925 mmol, 114.2 mg) gave **9b** as a yellow oil (150 mg, 98%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.55 (dd, ^3J = 4.7, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.78 (dd, ^3J = 7.9, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.74 (dd, ^4J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.52 (dd, ^3J = 5.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.44 (d, ^3J = 8.7 Hz, 2H, CH$_{Ar}$), 7.42 (dd, ^3J = 5.0, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.27 (dd, ^3J = 7.9, ^3J = 4.7 Hz, 1H, CH$_{Pyr}$), 6.86 (d, ^3J = 8.7 Hz, 2H, CH$_{Ar}$), 3.81 (s, 3H, CH$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 160.4 (C$_{Ar}$), 148.2 (CH$_{Pyr}$), 141.0 (C$_{Pyr}$), 138.5 (C$_{Thioph}$), 136.6 (CH$_{Pyr}$), 134.3 (C$_{Pyr}$), 133.6 (CH$_{Ar}$), 128.4, 125.5 (CH$_{Thioph}$), 124.6 (CH$_{Pyr}$), 122.7 (CH$_{Thioph}$), 114.5 (C$_{Ar}$), 114.2 (CH$_{Ar}$), 93.1, 87.8 (C$_{Alkyne}$), 55.4 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 2209 (m), 1603 (s), 1506 (s), 1440 (m), 1424 (s), 1288 (s), 1247 (s), 1173 (s), 1152 (s), 1107 (s), 1024 (s), 830 (s), 777 (s), 647 (s), 532 (s). **MS (EI, 70 eV):** *m/z* (%) = 292 (19), 291 ([M]$^+$, 100), 290 (19), 276 (33), 275 (14), 249 (10), 248 (38), 247 (65), 246 (18),

203 (7), 124 (7), 45 (10). **HRMS (ESI-TOF):** calcd. for $C_{18}H_{13}O_1N_1S_1$ ([M+H]$^+$) 292.0796 found 292.0798.

3-(thiophen-3-yl)-2-((4-(trifluoromethyl)phenyl)ethynyl)pyridine (9c)
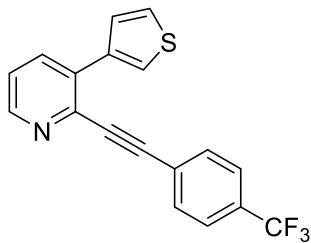
Following the general procedure, **8c** (0.525 mmol, 171.2 mg) and 3-thiopheneboronic acid (0.8925 mmol, 114.2 mg) gave **9c** as a yellow solid (165.3 mg, 96%), mp: 50 – 52 ºC. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.60 (dd, ^3J = 4.7, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.82 (dd, ^3J = 7.9, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.71 (dd, ^4J = 2.9, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.59 (s, 4H, CH$_{Ar}$), 7.51 (dd, ^3J = 5.0, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.45 (dd, ^3J = 5.0, ^4J = 2.9 Hz, 1H, CH$_{Thioph}$), 7.34 (dd, ^3J = 7.9, ^3J = 4.7 Hz, 1H, CH$_{Pyr}$) ppm. **^{19}F NMR (282 MHz, CDCl$_3$)** δ = -62.92 (s, 3F, CF$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 148.7 (CH$_{Pyr}$), 140.3 (C$_{Pyr}$), 138.4 (C$_{Thioph}$), 136.7 (CH$_{Pyr}$), 135.1 (C$_{Pyr}$), 132.3 (CH$_{Ar}$), 130.8 (q, $^2J_{C,F}$ = 33.0 Hz, C$_{Ar}$), 128.4 (CH$_{Thioph}$), 125.8 (CH$_{Thioph}$), 125.5 (q, $^3J_{C,F}$ = 3.8 Hz, CH$_{Ar}$), 124.8 (CH$_{Thioph}$), 124.2 (q, $^1J_{C,F}$ = 272.0 Hz, CF$_3$), 124.8 (C$_{Ar}$), 123.5 (CH$_{Pyr}$), 91.0, 90.6 (C$_{Alkyne}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 1613 (m), 1426 (m), 1323 (s), 1166 (s), 1102 (s), 1065 (s), 1016 (s), 835 (s), 785 (s), 767 (s), 717 (m), 694 (m), 659 (s), 651 (s), 591 (s). **MS (EI, 70 eV):** *m/z* (%) = 330 (33), 329 ([M]$^+$, 100), 328 (99), 310 (11), 284 (12), 260 (29), 259 (30), 258 (26), 130 (7), 108 (8). **HRMS (EI):** calcd. for $C_{18}H_{10}F_3N_1S_1$ (M)$^+$ 329.04806 found 329.04708.

2-(oct-1-yn-1-yl)-3-(thiophen-3-yl)pyridine (9d)
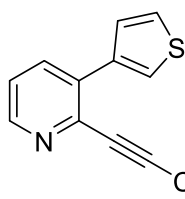
Following the general procedure, **8d** (0.525 mmol, 139.74 mg) and 3-thiopheneboronic acid (0.8925 mmol, 114.2 mg) gave **9d** as a brown solid (114.7 mg, 81%), mp: 50 ºC. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.48 (dd, ^3J = 4.7, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.73 (dd, ^3J = 7.9, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.68 (dd, ^4J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.45 (dd, ^3J = 5.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.37 (dd, ^3J = 5.0, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.23 (dd, ^3J = 7.9, ^3J = 4.7 Hz, 1H, CH$_{Pyr}$), 2.41 (t, ^3J = 7.0 Hz, 2H, CH$_2$), 1.65 – 1.48 (m, 2H, CH$_2$), 1.44 – 1.30 (m, 2H, CH$_2$), 1.33 – 1.22 (m, 4H, CH$_2$), 0.87 (t, ^3J = 6.9 Hz, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 148.1 (CH$_{Pyr}$), 141.1 (C$_{Pyr}$), 138.6 (C$_{Thioph}$), 136.5 (CH$_{Pyr}$), 134.0 (C$_{Pyr}$), 128.3, 125.3, 124.4 (CH$_{Thioph}$), 122.5 (CH$_{Pyr}$), 95.0, 80.3 (C$_{Alkyne}$), 31.5, 28.8, 28.2, 22.6, 19.7 (CH$_2$), 14.2 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 2953 (w), 2926

(m), 2856 (m), 2228 (w), 1556 (w), 1449 (m), 1426 (s), 1354 (w), 1189 (w), 1113 (w), 863 (m), 779 (s), 721 (m), 649 (s). **MS (EI, 70 eV):** m/z (%) = 269 ([M]$^+$, 4), 268 (5), 212 (46), 210 (19), 200 (25), 199 (100), 198 (61), 197 (20), 186 (29), 173 (44), 172 (20), 154 (20), 63 (11), 43 (20), 41 (32), 39 (15), 29 (24). **HRMS (EI):** calcd. for C$_{17}$H$_{18}$N$_1$S$_1$ (M)$^+$ 268.11545 found 268.11546; calcd. for C$_{17}$H$_{19}$N$_1$S$_1$ (M)$^+$ 269.12327 found 269.12268.

3-(thiophen-3-yl)-2-(*m*-tolylethynyl)pyridine (9e)
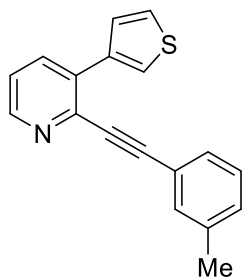
Following the general procedure, **8e** (0.525 mmol, 142.88 mg) and 3-thiopheneboronic acid (0.8925 mmol, 114.2 mg) gave **9e** as a yellow oil (116 mg, 80%). **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.57 (dd, ^3J = 4.7, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.80 (dd, ^3J = 7.9, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.75 (dd, ^4J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.53 (dd, ^3J = 5.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.44 (dd, ^3J = 5.0, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.33 – 7.28 (m, 2H, CH$_{Ar}$), 7.29 (dd, ^3J = 7.9, ^3J = 4.7 Hz, 1H, CH$_{Pyr}$), 7.26 – 7.19 (m, 1H, CH$_{Ar}$), 7.19 – 7.14 (m, 1H, CH$_{Ar}$), 2.34 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 148.6 (CH$_{Pyr}$), 141.0 (C$_{Pyr}$), 138.6 (C$_{Thioph}$), 138.2 (C$_{Ar}$), 136.5 (CH$_{Pyr}$), 134.5 (C$_{Pyr}$), 132.6, 130.0, 129.2, 128.5 (CH$_{Ar}$), 128.4, 125.5 (CH$_{Thioph}$), 124.7 (CH$_{Pyr}$), 122.9 (CH$_{Thioph}$), 122.4 (C$_{Ar}$), 92.6, 88.8 (C$_{Alkyne}$), 21.4 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3097 (w), 3037 (w), 2918 (w), 2207 (w), 1556 (m), 1484 (m), 1449 (m), 1426 (s), 1397 (m), 1356 (m), 1111 (m), 863 (m), 777 (s), 688 (s), 647 (s), 618 (m), 563 (m), 519 (m), 441 (m). **MS (EI, 70 eV):** m/z (%) = 276 (20), 275 ([M]$^+$, 92), 274 (100), 273 (20), 272 (13), 260 (25), 259 (15), 230 (8), 136 (8). **HRMS (ESI-TOF):** calcd. for C$_{18}$H$_{13}$N$_1$S$_1$ ([M+H]$^+$) 276.0847 found 276.0848.

N,*N*-dimethyl-4-((3-(thiophen-3-yl)pyridin-2-yl)ethynyl)aniline (9f)
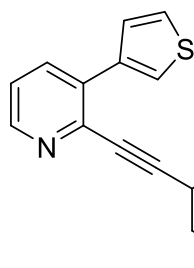
Following the general procedure, **8f** (0.525 mmol, 158.12 mg) and 3-thiopheneboronic acid (0.8925 mmol, 114.2 mg) gave **9f** as a brown oil (140.1 mg, 88%). **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.53 (dd, ^3J = 4.7, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.77 (dd, ^4J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.76 (dd, ^3J = 7.7, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.55 (dd, ^3J = 5.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.42 (dd, ^3J = 5.0, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.38 (d, J = 9.0 Hz, 2H, CH$_{Ar}$), 7.22 (dd, ^3J = 7.7, ^4J = 4.7 Hz, 1H, CH$_{Pyr}$), 6.64 (d, J = 9.0 Hz, 2H, CH$_{Ar}$), 2.99 (s, 6H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 150.7 (C$_{Ar}$), 148.4 (CH$_{Pyr}$), 141.7

(C_{Pyr}), 138.9 (C_{Thioph}), 136.3 (CH_{Pyr}), 133.7 (C_{Pyr}), 133.3 (CH_{Ar}), 128.6, 125.2, 124.5 (CH_{Thioph}), 122.1 (CH_{Pyr}), 111.8 (CH_{Ar}), 109.1 (C_{Ar}), 94.4, 87.7 (C_{Alkyne}), 40.2 (CH_3) ppm. **IR** (ATR, cm^{-1}): ṽ = 3039 (w), 2891 (w), 2854 (w), 2802 (w), 2201 (m), 1603 (s), 1519 (s), 1424 (s), 1354 (s), 1185 (s), 1148 (s), 1125 (m), 1109 (s), 944 (m), 814 (s), 779 (s), 732 (s), 690 (m), 647 (s), 528 (s). **MS (EI, 70 eV):** *m/z* (%) = 305 (23), 304 ([M]$^+$, 100), 303 (47), 288 (13), 287 (25), 261 (6), 260 (20), 259 (14), 258 (6), 151 (6), 130 (8) **HRMS (ESI-TOF):** calcd. for $C_{19}H_{16}N_2S_1$ ([M+H]$^+$) 305.1112 found 305.1113; calcd. for $C_{19}H_{16}N_2S_1$ ([M+Na]$^+$) 327.0926 found 327.0933.

3-(benzo[*b*]thiophen-3-yl)-2-((4-(*tert*-butyl)phenyl)ethynyl)pyridine (9g)
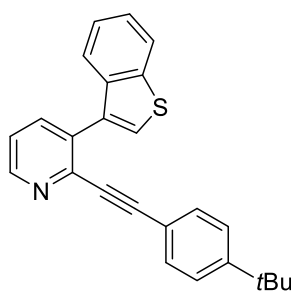
Following the general procedure, **8a** (0.525 mmol, 164.25 mg) and 3-benzothiopheneboronic acid (0.8925 mmol, 158.87 mg) gave **9g** as a yellow oil (182.0 mg, 94%), mp: 125 – 127 ºC. **¹H NMR (250 MHz, CDCl₃)** δ = 8.68 (dd, ^3J = 4.8, ^4J = 1.7 Hz, 1H, CH_{Pyr}), 8.00 – 7.94 (m, 1H, $CH_{Benzothioph}$), 7.83 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1H, CH_{Pyr}), 7.75 – 7.69 (m, 1H, $CH_{Benzothioph}$), 7.67 (s, 1H, CH_{thioph}), 7.43 – 7.38 (m, 2H, $CH_{Benzothioph}$), 7.36 (dd, ^3J = 7.8, ^3J = 4.8 Hz, 1H, CH_{Pyr}), 7.23 (d, ^3J = 8.6 Hz, 2H, (CH_{Ar}), 7.04 (d, ^3J = 8.6 Hz, 2H, (CH_{Ar}), 1.26 (s, 9H, CH_{3-tBu}) ppm. **¹³C NMR (63 MHz, CDCl₃)** δ = 152.4 (C_{Ar}), 149.2 (CH_{Ar}), 143.0, 140.1, 138.2 (C_{Ar}), 137.6 (CH_{Ar}), 134.3, 133.9 (C_{Ar}), 131.8, 126.5, 125.4, 124.7, 124.6, 123.2, 123.0, 122.5 (CH_{Ar}), 119.2(C_{Ar}), 93.3, 88.0 (C_{Alkyne}), 34.9 (C_{tBu}), 31.2(CH_{3-tBu}) ppm. **IR** (ATR, cm^{-1}): ṽ = 3089 (w), 3062 (w), 2953 (m), 2862 (w), 2219 (w), 1508 (m), 1426 (m), 1412 (s), 1362 (m), 1094 (m), 849 (m), 826 (s), 802 (m), 783 (s), 767 (s), 760 (m), 754 (s), 732 (s), 565 (s), 424 (m). **MS (EI, 70 eV):** *m/z* (%) = 368 (12), 367 ([M]$^+$, 42), 366 (100), 352 (12), 351 (13), 350 (21), 336 (21), 310 (16), 161 (10). **HRMS (ESI-TOF):** calcd. for $C_{25}H_{21}N_1S_1$ ([M+H]$^+$) 368.1473, found 368.1473.

3-(benzo[*b*]thiophen-3-yl)-2-((4-methoxyphenyl)ethynyl)pyridine (9h)
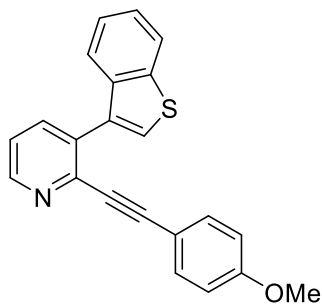
Following the general procedure, **8b** (0.525 mmol, 151.27 mg) and 3-benzothiopheneboronic acid (0.8925 mmol, 158.87 mg) gave **9h** as a yellow solid (165.9 mg, 93%), mp: 106 – 108 ºC. **¹H NMR (250 MHz, CDCl₃)** δ = 8.66 (dd, ^3J = 4.8, ^4J = 1.7 Hz, 1H, CH_{Pyr}), 7.99 – 7.94 (m, 1H, $CH_{Benzothioph}$), 7.82 (dd, ^3J = 7.8,

^4J = 1.7 Hz, 1H, CH$_\text{Pyr}$), 7.74 – 7.69 (m, 1H, CH$_\text{Benzothioph}$), 7.67 (s, 1H, CH$_\text{thioph}$), 7.42 – 7.36 (m, 2H, CH$_\text{Benzothioph}$), 7.34 (dd, ^3J = 7.8, ^3J = 4.8 Hz, 1H, CH$_\text{Pyr}$), 7.02 (d, ^3J = 8.9 Hz, 2H, CH$_\text{Ar}$), 6.73 (d, ^3J = 8.9 Hz, 2H, CH$_\text{Ar}$), 3.76 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 160.2 (C$_\text{Ar}$), 149.2 (CH$_\text{Pyr}$), 143.1, 140.1, 138.2 (C$_\text{Ar}$), 137.5 (CH$_\text{Ar}$), 134.1, 134.0 (C$_\text{Ar}$), 133.5, 126.4, 124.6, 124.5, 123.3, 122.9, 122.3 (CH$_\text{Ar}$), 114.3 (C$_\text{Ar}$), 114.0 (CH$_\text{Ar}$), 93.4, 87.6 (C$_\text{Alkyne}$), 55.4 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 2840 (w), 2215 (m), 1603 (m), 1508 (s), 1424 (m), 1290 (m), 1249 (s), 1024 (s), 832 (s), 789 (s), 758 (s), 729 (s), 542 (s), 525 (s), 418 (s). **MS (EI, 70 eV):** *m/z* (%) = 342 (13), 341 ([M]$^+$, 47), 340 (100), 325 (11), 298 (25), 297 (80), 296 (38), 155 (11), 149 (46), 148 (10), 135 (16), 114 (14), 63 (12), 39 (12). **HRMS (ESI-TOF):** calcd. for C$_{22}$H$_{15}$N$_1$O$_1$S$_1$ ([M+H]$^+$) 342.0952, found 342.0955.

3-(benzo[*b*]thiophen-3-yl)-2-((4-(trifluoromethyl)phenyl)ethynyl)pyridine (9i)
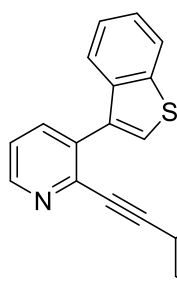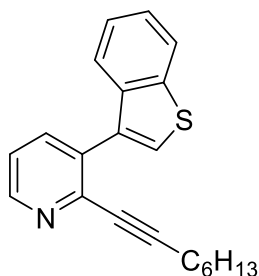

Following the general procedure, **8c** (0.525 mmol, 171.21 mg) and 3-benzothiopheneboronic acid (0.8925 mmol, 158.87 mg) gave **9i** as a yellow solid (154.9 mg, 78%), mp: 162 – 164 ºC. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.71 (dd, ^3J = 4.8, ^4J = 1.7 Hz, 1H, CH$_\text{Pyr}$), 7.99 – 7.97 (m, 1H, CH$_\text{Benzothioph}$), 7.86 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1H, CH$_\text{Pyr}$), 7.72 – 7.69 (m, 1H, CH$_\text{Benzothioph}$), 7.64 (s, 1H, CH$_\text{thioph}$), 7.45 (dd, ^3J = 8.7, ^4J = 0.8 Hz, 2H, CH$_\text{Ar}$), 7.41 (dd, ^3J = 7.8, ^3J = 4.8 Hz, 1H, CH$_\text{Pyr}$), 7.41 – 7.37 (m, 2H, CH$_\text{Benzothioph}$), 7.13 (dd, ^3J = 8.7, ^4J = 0.8 Hz, 2H, CH$_\text{Ar}$) ppm. **^{19}F NMR (471 MHz, CDCl$_3$)** δ = -62.95 (s, 3F, CF$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 149.4 (CH$_\text{Pyr}$), 142.2, 140.1, 138.0 (C$_\text{Ar}$), 137.8 (CH$_\text{Ar}$), 135.0, 133.7 (C$_\text{Ar}$), 132.1 (CH$_\text{Ar}$), 130.5 (q, $^2J_\text{C,F}$ = 33.0 Hz, C$_\text{Ar}$), 126.6 (CH$_\text{Ar}$), 126.0 (C$_\text{Ar}$), 124.8 (CH$_\text{Ar}$), 125.3 (q, $^3J_\text{C,F}$ = 3.8 Hz, CH$_\text{Ar}$), 124.6 (CH$_\text{Ar}$), 123.9 (q, $^1J_\text{C,F}$ = 272.3 Hz, CF$_3$), 123.2, 123.2 (CH$_\text{Ar}$), 123.0 (CH$_\text{Pyr}$), 91.2, 90.5 (C$_\text{Alkyne}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3079 (w), 1611 (w), 1552 (w), 1426 (m), 1325 (s), 1160 (s), 1146 (m), 1115 (s), 1102 (s), 1065 (s), 1014 (m), 837 (s), 800 (s), 760 (s), 736 (s), 711 (m), 701 (s), 596 (m). **MS (EI, 70 eV):** *m/z* (%) = 380 (9), 379 ([M]$^+$, 30), 378 (100), 309 (10), 308 (13), 155 (10), 139 (7), 114 (7), 69 (9). **HRMS (ESI-TOF):** calcd. for C$_{22}$H$_{12}$N$_1$S$_1$F$_3$ ([M+H]$^+$) 380.0721, found 380.0715.

3-(benzo[*b*]thiophen-3-yl)-2-(oct-1-yn-1-yl)pyridine (9j)

Following the general procedure, **8d** (0.525 mmol, 139.75 mg) and 3-benzothiopheneboronic acid (0.8925 mmol, 158.87 mg) gave **9n** as a red oil (121.8 mg, 73%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.60 (dd, ^3J = 4.8, ^4J = 1.8 Hz, 1H, CH$_{Pyr}$), 7.92 – 7.90 (m, 1H, CH$_{Benzothioph}$), 7.74 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1H, CH$_{Pyr}$), 7.64 – 7.61 (m, 1H, CH$_{Benzothioph}$), 7.57 (s, 1H, CH$_{thioph}$), 7.40 – 7.33 (m, 2H, CH$_{Benzothioph}$), 7.30 (dd, ^3J = 7.8, ^3J = 4.8 Hz, 1H, CH$_{Pyr}$), 2.17 (t, ^3J = 7.0 Hz, 2H, CH$_2$), 1.25 – 1.13 (m, 4H, CH$_2$), 1.12 – 1.02 (m, 4H, CH$_2$), 0.83 (t, ^3J = 7.2 Hz, 3H, CH$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 149.0 (CH$_{Ar}$), 143.2, 140.1, 138.2 (C$_{Ar}$), 137.6 (CH$_{Ar}$), 134.1, 133.9 (C$_{Ar}$), 126.1, 124.5, 124.3, 123.2, 122.8 (CH$_{Ar}$), 122.1 (CH$_{Pyr}$), 95.1, 79.9 (C$_{Alkyne}$), 31.4, 28.4, 27.9, 22.5, 19.4 (CH$_2$), 14.2 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3056 (w), 2953 (m), 2926 (m), 2856 (m), 2228 (w), 1552 (m), 1457 (m), 1440 (m), 1426 (s), 1414 (s), 1337 (w), 1102 (m), 837 (m), 806 (m), 783 (m), 775 (m), 758 (s), 732 (s), 699 (m), 433 (m). **MS (EI, 70 eV):** *m/z* (%) = 319 ([M]$^+$, 27), 318 (21), 290 (13), 276 (22), 263 (18), 262 (70), 261 (13), 260 (39), 250 (33), 249 (100), 248 (97), 247 (95), 246 (58), 236 (51), 235 (25), 224 (23), 223 (97), 222 (46), 221 (14), 176 (12). **HRMS (ESI-TOF):** calcd. for C$_{21}$H$_{21}$N$_1$S$_1$ ([M+H]$^+$) 320.1473, found 320.1474.
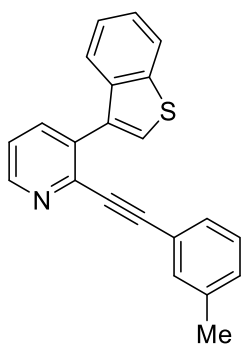
3-(benzo[*b*]thiophen-3-yl)-2-(*m*-tolylethynyl)pyridine (9k)

Following the general procedure, **8e** (0.525 mmol, 142.88 mg) and 3-benzothiopheneboronic acid (0.8925 mmol, 158.87 mg) gave **9k** as an orange oil (153.8 mg, 90%). **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.68 (dd, ^3J = 4.8, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.99 – 7.95 (m, 1H, CH$_{Ar}$), 7.84 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.74 – 7.70 (m, 1H, CH$_{Ar}$), 7.67 (s, 1H, CH$_{Pyr}$), 7.45 – 7.35 (m, 2H, CH$_{Ar}$), 7.37 (dd, ^3J = 7.8, ^3J = 4.8 Hz, 1H, CH$_{Pyr}$), 7.13 – 7.04 (m, 2H, CH$_{Ar}$), 6.95 – 6.90 (m, 1H, CH$_{Ar}$), 6.84 – 6.82 (m, 1H, CH$_{Ar}$), 2.23 (s, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 149.2 (CH$_{Pyr}$), 142.9, 140.2, 138.2, 138.0 (C$_{Ar}$), 137.6 (CH$_{Pyr}$), 134.4, 133.9 (C$_{Ar}$), 132.6, 129.9, 129.0, 128.2, 126.5, 124.6, 124.6, 123.3, 122.9, 122.6 (CH$_{Ar}$), 122.0 (C$_{Ar}$), 93.3, 88.3 (C$_{Alkyne}$), 21.3 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3052 (w), 2918 (w), 2207 (w), 1550 (m), 1484 (m), 1426 (s), 1405 (m), 1096 (m), 841 (m), 781 (s),

758 (s), 732 (s), 709 (m), 688 (s), 569 (m), 441 (m), 424 (s). **MS (EI, 70 eV):** *m/z* (%) = 326 (8), 325 ([M]$^+$, 32), 324 (100), 323 (8), 310 (9), 309 (8), 308 (7), 162 (9), 161 (8), 155 (14), 139 (8), 114 (8), 63 (8), 39 (9). **HRMS (ESI-TOF):** calcd. for $C_{22}H_{15}N_1S_1$ ([M+H]$^+$) 326.1003, found 326.1006.

Synthesis of 2-(alkynyl)-3-(3-bromothiophen)pyridines (9l-n).

2-(alkynyl)-3-bromopyridine (0.5 mmol), Pd(OAc)$_2$ (5 mol %), S-Phos (10 mol %), K$_2$CO$_3$ (2.0 equiv.) and 4-bromo-3-thiopheneboronic acid (1.1 equiv.) were dissolved in CH$_3$CN (1.5 mL) and water (0.5 mL) under an argon atmosphere. The reaction was stirred 24 hours at 100 °C. After cooling to room temperature, the reaction mixture was washed with distilled water and extracted with ethyl acetate (EtOAc). The combined organic layers were collected and the solvent evaporated. The crude product was purified by column chromatography to yield desired compounds (heptane/EtOAc 4:1).

3-(4-bromothiophen-3-yl)-2-(*m*-tolylethynyl)pyridine (9l)

Following the general procedure, **8e** (0.5 mmol, 136.07 mg) and 4-bromo-3-thiopheneboronic acid (0.55 mmol, 113.77 mg) gave **9l** as a brown solid (101.7 mg, 57%), mp: 91 ºC. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.64 (dd, ^3J = 4.8, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.74 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.54 (d, ^4J = 3.4 Hz, 1H, CH$_{Thioph}$), 7.42 (d, ^4J = 3.4 Hz, 1H, CH$_{Thioph}$), 7.31 (dd, ^3J = 7.8, ^3J = 4.8 Hz, 1H, CH$_{Pyr}$), 7.20 – 7.16 (m, 3H, CH$_{Ar}$), 7.16 – 7.11 (m, 1H, CH$_{Ar}$), 2.31 (s, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, DMSO)** δ = 149.5 (CH$_{Ar}$), 141.9, 138.1, 137.9 (C$_{Ar}$), 137.8 (CH$_{Ar}$), 134.0 (C$_{Ar}$), 131.8, 130.2, 128.7, 128.5, 127.2, 124.6, 122.9 (CH$_{Ar}$), 121.3, 111.3 (C$_{Ar}$), 91.8, 88.0 (C$_{Alkyne}$), 20.7 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3087 (m), 2207 (m), 1556 (m), 1486 (m), 1422 (s), 1405 (m), 1344 (m), 1111 (m), 1045 (m), 915 (m), 855 (m), 818 (s), 800 (s), 783 (s), 771 (s), 686 (s), 672 (m), 554 (m), 511 (m), 443 (m). **MS (EI, 70 eV):** *m/z* (%) = 355 ([M]+, 5), 353 ([M]+, 5), 276 (6), 275 (21), 274 (100), 273 (32), 272 (18), 271 (5), 260 (4), 259 (21), 136 (11), 123 (4). **HRMS (ESI-TOF):** calcd. for $C_{18}H_{12}N_1Br_1S_1$ ([M+H]$^+$) 353.9952, found 353.9952.

3-(4-bromothiophen-3-yl)-2-(phenylethynyl)pyridine (9m)
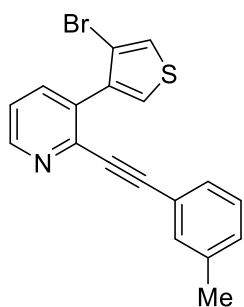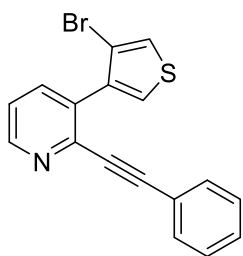
Following the general procedure, **8g** (0.5 mmol, 129.06 mg) and 4-bromo-3-thiopheneboronic acid (0.55 mmol, 113.77 mg) gave **9m** as a yellow solid (104.0 mg, 61%), mp: 95 – 97 ºC. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.65 (dd, ^3J = 4.8, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.74 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.53 (d, ^4J = 3.4 Hz, 1H, CH$_{Thioph}$), 7.43 (d, ^4J = 3.4 Hz, 1H, CH$_{Thioph}$), 7.40 – 7.35 (m, 2H, CH$_{Ar}$), 7.32 (dd, ^3J = 7.8, ^3J = 4.8 Hz, 1H, CH$_{Pyr}$), 7.32 – 7.29 (m, 3H, CH$_{Ar}$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 149.6 (CH$_{Ar}$), 143.0, 138.3 (C$_{Ar}$), 137.9 (CH$_{Ar}$), 134.0 (C$_{Ar}$), 132.1, 129.1, 128.5, 126.1, 123.7 (CH$_{Ar}$), 122.4 (C$_{Ar}$), 122.3 (CH$_{Ar}$), 112.3 (C$_{Ar}$), 92.7, 88.2 (C$_{Alkyne}$) ppm. **IR** (ATR, cm^{-1}):ṽ = 3099 (m), 2215 (m), 1556 (m), 1490 (m), 1420 (s), 1346 (m), 1259 (w), 1201 (m), 1111 (m), 1026 (m), 921 (m), 855 (m), 820 (s), 797 (s), 771 (s), 752 (s), 684 (s), 530 (m), 501 (m). **MS (EI, 70 eV):** m/z (%) = 341 ([M]$^+$, 3), 339 ([M]$^+$, 3), 261 (21), 260 (100), 259 (30), 216 (8), 214 (8), 130 (12). **HRMS (EI):** calcd. for C$_{17}$H$_{10}$N$_1$Br$_1$S$_1$ (M)$^+$ 338.97118, found 338.97071; calcd. for C$_{17}$H$_{10}$N$_1$^{81}Br$_1$S$_1$ (M)$^+$ 340.96914, found 340.96961.

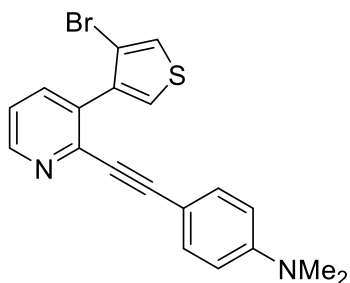### 3-(4-bromothiophen-3-yl)-2-(4-dimethylaminophenylethynyl)pyridine (9n)

Following the general procedure, **8f** (0.5 mmol, 150.59 mg) and 4-bromo-3-thiopheneboronic acid (0.55 mmol, 113.77 mg) gave **9n** as a yellow solid (113.0 mg, 59%), mp: 163 – 164 ºC. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.59 (dd, ^3J = 4.8, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.70 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 7.54 (d, ^4J = 3.5 Hz, 1H, CH$_{Thioph}$), 7.40 (d, ^4J = 3.5 Hz, 1H, CH$_{Thioph}$), 7.24 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$), 7.24 (dd, ^3J = 7.8, ^3J = 4.8 Hz, 1H, CH$_{Pyr}$), 6.59 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$), 2.97 (s, 6H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 150.7 (C$_{Ar}$), 149.4 (CH$_{Ar}$), 143.8, 138.6 (C$_{Ar}$), 137.7, 133.4 (CH$_{Ar}$), 133.1 (C$_{Ar}$), 126.0, 123.4, 121.3 (CH$_{Ar}$), 112.4 (C$_{Ar}$), 111.8 (CH$_{Ar}$), 108.9 (C$_{Ar}$), 94.9, 86.9 (C$_{Alkyne}$), 40.2 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3095 (w), 2889 (m), 2205 (m), 1607 (s), 1523 (s), 1422 (s), 1368 (s), 1344 (s), 1187 (s), 1150 (s), 1109 (m), 1065 (m), 923 (s), 853 (m), 802 (s), 795 (s), 769 (s), 519 (s), 507 (s). **MS (EI, 70 eV):** m/z (%) = 384 ([M]$^+$, 100), 383 (60), 382 (98), 381 (40), 287 (15), 260 (13), 259 (34), 191 (30), 129 (14). **HRMS (ESI-TOF):** calcd. for C$_{19}$H$_{15}$N$_2$Br$_1$S$_1$ ([M+H]$^+$) 383.0218, found 383.0211.

Synthesis of 3-(benzo[b]thiophen-3-yl)-2-chloroquinolines (11a-b).

3-bromo-2-chloroquinoline (0.83 mmol), K_3PO_4 (3.0 equiv.) and the corresponding boronic acid (benzo[*b*]thiophen-3-ylboronic acid or thiophen-3-ylboronic acid) (1.0 equiv.) were dissolved in 1,4-dioxane (3.0 mL) and water (0.75 mL). Reaction mixture were degassed for 10 minutes and the $Pd(dppf)Cl_2$ (5 mol %) was added under an argon atmosphere. The reaction was stirred during 3 hours at 100 °C. After cooling to room temperature, the reaction mixture was washed with distilled water and extracted with ethyl acetate (EtOAc). The combined organic layers were collected and the solvent evaporated. The crude product was purified by column chromatography to yield desired compounds (heptane/EtOAc 20:1).

3-(benzo[*b*]thiophen-3-yl)-2-chloroquinoline (11a)
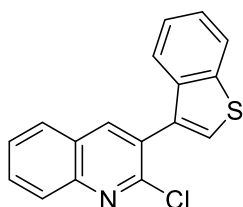
Following the general procedure, 3-bromo-2-chloroquinoline (0.83 mmol, 199.62 mg) and benzo[*b*]thiophen-3-ylboronic acid (0.83 mmol, 147.76 mg) gave **11a** as a crystalline yellow solid (197 mg, 80%), mp: 98 – 100 °C. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.23 (s, 1H, CH_{Pyr}), 8.12 (dd, ^3J = 8.5, ^4J = 1.2 Hz, 1H, CH_{Ar}), 7.99 – 7.92 (m, 1H, CH_{Ar}), 7.86 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.80 (ddd, ^3J = 8.5, ^3J = 6.9, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.62 (ddd, ^3J = 8.1, ^3J = 6.9, ^4J = 1.2 Hz, 1H), 7.58 (s, 1H, CH_{Thioph}), 7.57 – 7.52 (m, 1H, CH_{Ar}), 7.46 – 7.36 (m, 2H, CH_{Ar}) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 150.6, 147.4 (C_{Ar}), 140.0 (CH_{Ar}), 138.5, 133.0 (C_{Ar}), 130.9 (CH_{Ar}), 129.0 (C_{Ar}), 128.6, 127.7, 127.6 (CH_{Ar}), 127.1 (C_{Ar}), 126.9, 124.9, 124.7, 123.0, 123.0 (CH_{Ar}) ppm. **IR (ATR, cm^{-1}):** ṽ = 3074 (w), 3054 (w), 1484 (m), 1426 (m), 1321 (m), 1210 (m), 1133 (m), 1067 (m), 1045 (s), 878 (m), 855 (m), 822 (m), 750 (s), 732 (s), 692 (s), 641 (m), 598 (s), 474 (s), 447 (m), 418 (m). **MS (EI, 70 eV):** *m/z* (%) = 297 (38), 296 (20), 295 ([M]$^+$, 100), 261 (9), 260 (43), 259 (24), 216 (25), 214 (11), 130 (10). **HRMS (ESI-TOF):** calcd. for $C_{17}H_{10}N_1Cl_1S_1$ ([M+H]$^+$) 296.0301, found 296.0305.

2-chloro-3-(thiophen-3-yl)quinoline (11b)
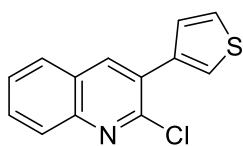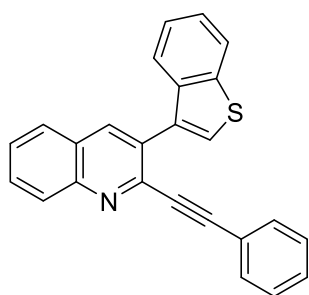
Following the general procedure, 3-bromo-2-chloroquinoline (0.83 mmol, 199.62 mg) and thiophen-3-ylboronic acid (0.83 mmol, 106.2 mg) gave **11b** as a crystalline white solid (120 mg, 59%), mp: 73 – 74 °C. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.18 (s, 1H, CH_{Pyr}), 8.05 (dd, ^3J = 8.5, ^4J = 1.1 Hz, 1H, CH_{Ar}), 7.83 (dd, ^3J = 8.2, ^4J = 1.4 Hz, 1H, CH_{Ar}), 7.74

(ddd, ^3J = 8.5, ^3J = 6.9, ^4J = 1.4 Hz, 1H, CH$_{Ar}$), 7.58 (ddd, ^3J = 8.2, ^3J = 6.9, ^4J = 1.1 Hz, 1H, CH$_{Ar}$), 7.57 (dd, ^4J = 3.1, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.44 (dd, ^3J = 5.0, ^4J = 3.1 Hz, 1H, CH$_{Thioph}$), 7.40 (dd, ^3J = 5.0, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 149.5, 146.9 (C$_{Ar}$), 138.6 (CH$_{Ar}$), 137.8 (C$_{Ar}$), 130.6 (CH$_{Ar}$), 129.9 (C$_{Ar}$), 129.0, 128.5, 127.6, 127.5 (CH$_{Ar}$), 127.4 (C$_{Ar}$), 125.7, 125.4 (CH$_{Ar}$) ppm. **IR (ATR, cm^{-1})**: ṽ = 1484 (m), 1414 (m), 1327 (m), 1131 (m), 1088 (s), 991 (m), 921 (m), 849 (s), 812 (m), 789 (s), 777 (s), 750 (s), 701 (m), 690 (m), 651 (s), 639 (s), 596 (s), 480 (s), 443 (m). **MS (EI, 70 eV):** m/z (%) = 247 ([M]+, 37), 246 (16), 245 ([M]+, 100), 211 (8), 210 (46), 209 (20), 166 (7), 164 (6), 139 (10). **HRMS (EI):** calcd. for C$_{13}$H$_8$N$_1$Cl$_1$S$_1$ (M)$^+$ 245.00605, found 245.00583, calcd. for C$_{13}$H$_8$N$_1$^{37}Cl$_1$S$_1$ (M)$^+$ 247.00310, found 247.00314.

Synthesis of 3-(benzo[b]thiophen-3-yl)-2-(phenylethynyl)quinolines (12a-b).

3-(benzo[b]thiophen-3-yl)-2-chloroquinoline (0.4 mmol), Pd(PPh$_3$)$_4$ (5 mol %) and CuI (2 mol %) were dissolved in 2.4 mL of Diisopropylamino (HNiPr$_2$) under an argon atmosphere. After addition of the alkyne (1.2 equiv.) the reaction was stirred at 70 °C for 20 h. After cooling to room temperature, the reaction mixture was washed with distilled water and extracted with ethyl acetate (EtOAc). The combined organic layers were collected and the solvent evaporated. The crude product was purified by column chromatography (heptane/EtOAc 10:1).

3-(benzo[b]thiophen-3-yl)-2-(phenylethynyl)quinoline (12a)

Following the general procedure, **11a** (0.4 mmol, 118.31 mg) and phenylacetylene (0.48 mmol, 0.053 mL) gave **12a** as a yellow solid (112.8 mg, 78%), mp: 166 – 167 ºC. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.27 (s, 1H, CH$_{Pyr}$), 8.22 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.99 (dd, ^3J = 8.2, ^4J = 1.5 Hz, 1H, CH$_{Ar}$), 7.85 (dd, ^3J = 8.2, ^4J = 1.5 Hz, 1H, CH$_{Ar}$), 7.78 (ddd, ^3J = 8.4, ^3J = 6.9, ^4J = 1.5 Hz, 1H, CH$_{Ar}$), 7.75 (dd, ^3J = 8.1, ^4J = 1.4 Hz, 1H CH$_{Ar}$), 7.71 (s, 1H, CH$_{Thioph}$), 7.60 (ddd, ^3J = 8.2, ^3J = 6.9, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.42 (ddd, ^3J = 8.1, ^3J = 7.1, ^4J = 1.5 Hz, 1H, CH$_{Ar}$), 7.38 (ddd, ^3J = 8.2, ^3J = 7.1, ^4J = 1.4 Hz, 1H, CH$_{Ar}$), 7.26 (dd, ^3J = 7.5, ^3J = 1.4 Hz, 1H, CH$_{Ar}$), 7.20 (dd, ^3J = 8.4, ^3J = 7.5 Hz, 2H, CH$_{Ar}$), 7.07 (dd, ^3J = 8.4, ^4J = 1.4 Hz, 2H, CH$_{Ar}$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 147.7, 143.6, 140.1, 138.7 (C$_{Ar}$), 136.9 (CH$_{Ar}$), 134.1 (C$_{Ar}$), 132.2 (CH$_{Ar}$), 131.5 (C$_{Ar}$), 130.4,

129.3, 129.2, 128.3, 127.7, 127.7 (CH$_{Ar}$), 127.1 (C$_{Ar}$), 126.5, 124.7, 124.6, 123.3, 122.9 (CH$_{Ar}$), 122.1 (C$_{Ar}$), 93.5, 89.1 (C$_{Alkyne}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3050 (m), 2215 (w), 1593 (m), 1490 (m), 1428 (m), 1144 (m), 1131 (m), 913 (m), 849 (m), 810 (m), 760 (s), 748 (s), 740 (s), 703 (m), 684 (s), 620 (m), 525 (m), 474 (m), 464 (m), 431 (m). **MS (EI, 70 eV):** *m/z* (%) = 362 (12), 361 (41), 360 ([M]$^+$, 100), 359 (13), 358 (15), 357 (3), 187 (2), 180 (10), 163 (2), 158 (3). **HRMS (EI):** calcd. for C$_{25}$H$_{14}$N$_1$S$_1$ (M)$^+$ 360.08415, found 360.08316.
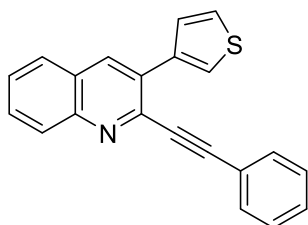
2-(phenylethynyl)-3-(thiophen-3-yl)quinoline (12b)

Following the general procedure, **11b** (0.4 mmol, 98.3 mg) and phenylacetylene (0.48 mmol, 0.053 mL) gave **11b** as a yellow solid (90.2 mg, 72%), mp: 98 – 99 ºC.

^{1}H NMR (300 MHz, CDCl$_3$) δ = 8.21 (d, ^4J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.16 (ddd, ^3J = 8.5, ^4J = 2.0, ^4J = 0.9 Hz, 1H, CH$_{Ar}$), 7.82 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 1H, CH$_{Ar}$), 7.76 (dd, ^4J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.72 (ddd, ^3J = 8.5, ^3J = 7.0, ^4J = 1.5 Hz, 1H, CH$_{Ar}$), 7.59 (dd, ^3J = 5.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.55 (ddd, ^3J = 8.1, ^3J = 7.0, ^4J = 2.0 Hz, 1H, CH$_{Ar}$), 7.55 – 7.51 (m, 2H, CH$_{Ar}$), 7.47 (dd, ^3J = 5.0, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.39 – 7.33 (m, 3H, CH$_{Ar}$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 147.2, 142.3, 138.8 (C$_{Ar}$), 135.5, 132.3 (CH$_{Ar}$), 132.0 (C$_{Ar}$), 130.1, 129.3, 129.1, 128.9, 128.5, 127.7, 127.6 (CH$_{Ar}$), 127.4 (C$_{Ar}$), 125.5, 124.7 (CH$_{Ar}$), 122.4 (C$_{Ar}$), 93.0, 89.5 (C$_{Alkyne}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3099 (w), 3054 (w), 2211 (w), 1574 (w), 1490 (m), 1420 (m), 1350 (m), 1148 (m), 913 (m), 859 (m), 791 (s), 750 (s), 727 (s), 686 (s), 666 (s), 643 (s), 620 (s), 528 (m), 495 (m), 476 (m). **MS (EI, 70 eV):** *m/z* (%) = 312 (21), 311 ([M]$^+$, 83), 310 (100), 309 (14), 308 (8), 278 (4), 266 (4), 155 (7), 139 (4), 133 (7). **HRMS (EI):** calcd. for C$_{21}$H$_{13}$N$_1$S$_1$ (M)$^+$ 311.07632, found 311.07550.

Synthesis of thieno[3,2-*f*]quinolines (13a-p).

A degassed and argon flushed Schlenk tube was charged with corresponding starting material (0.3 mmol) and MsOH (50 equiv.). The reaction was stirred at 120 °C for 1 h. After cooling to room temperature, the reaction mixture was washed with a 10% sodium hydroxide solution and extracted with ethyl acetate (EtOAc). The combined organic

layers were collected and the solvent evaporated. The crude product was purified by column chromatography (heptane/EtOAc 3:1).

4-(4-(*tert*-butyl)phenyl)thieno[3,2-*f*]quinoline (13a)
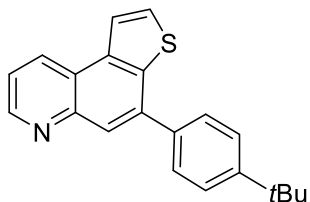
According to the general procedure, the reaction of **9a** (0.195 mmol, 62 mg) and MsOH (9.75 mmol, 0.63 mL), affords product **13a** as a yellow oil (51.8 mg, 84%). **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.95 (dd, ^3J = 4.4, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 8.68 – 8.61 (m, 1H, CH$_{Pyr}$), 8.08 (br-s, 1H, CH$_{Ar}$), 8.03 (dd, ^3J = 5.5, ^5J = 0.8 Hz, 1H, CH$_{Thiophh}$), 7.80 (d, ^3J = 8.4 Hz, 2H, CH$_{Ar}$), 7.70 (dd, ^3J = 5.5, ^6J = 0.9 Hz, 1H, CH$_{Thiophh}$), 7.58 (d, ^3J = 8.4 Hz, 2H, CH$_{Ar}$), 7.51 (dd, ^3J = 8.3, ^3J = 4.4 Hz, 1H, CH$_{Pyr}$), 1.42 (s, 9H, CH$_{3\text{-}t\text{Bu}}$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 151.9 (C$_{Ar}$), 149.2 (CH$_{Ar}$), 147.4, 139.0, 138.1, 136.9, 136.2 (C$_{Ar}$), 132.2, 128.2, 127.9, 126.0, 124.8 (CH$_{Ar}$), 123.6 (C$_{Ar}$), 122.2, 121.0 (CH$_{Ar}$), 34.9 (C$_{t\text{Bu}}$), 31.5 (CH$_{3\text{-}t\text{Bu}}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 2959 (m), 2901 (m), 2866 (w), 1735 (m), 1486 (m), 1475 (s), 1360 (s), 1238 (s), 909 (m), 884 (m), 835 (s), 769 (s), 734 (s), 686 (s), 608 (s), 550 (s). **MS (EI, 70 eV):** *m/z* (%) = 317 ([M]$^+$, 55), 303 (23), 302 (100), 286 (13), 274 (19), 273 (16), 260 (19), 137 (46), 41 (29), 39 (16) **HRMS (EI):** calcd. for C$_{21}$H$_{19}$N$_1$S$_1$ (M)$^+$ 317.12327 found 317.12319.

4-(4-methoxyphenyl)thieno[3,2-*f*]quinoline (13b)
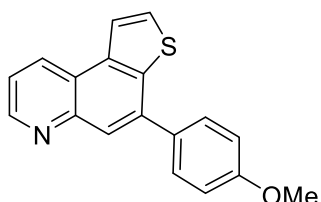
According to the general procedure, the reaction of **9b** (0.3 mmol, 87.41 mg) and MsOH (15 mmol, 1.0 mL), affords product **13b** as a yellow solid (80.1 mg, 92%), mp: 161 – 163 ºC. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.94 (dd, ^3J = 4.4, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 8.64 (ddd, ^3J = 8.3, ^4J = 1.7, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.03 (br-s, 1H, CH$_{Ar}$), 8.02 (d, ^3J = 5.5 Hz, 1H, CH$_{Thiophh}$), 7.78 (d, ^3J = 8.8 Hz, 2H, CH$_{Ar}$), 7.69 (dd, ^3J = 5.5, J = 0.5 Hz, 1H, CH$_{Thioph}$), 7.51 (dd, ^3J = 8.3, ^3J = 4.4 Hz, 1H, CH$_{Pyr}$), 7.08 (d, J = 8.8 Hz, 2H, CH$_{Ar}$), 3.90 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 160.1 (C$_{Ar}$), 149.1 (CH$_{Ar}$), 147.4, 138.8, 138.2, 136.2, 132.3 (C$_{Ar}$), 132.2, 129.7, 127.9, 124.5 (CH$_{Ar}$), 123.5 (C$_{Ar}$), 122.2, 120.9, 114.5 (CH$_{Ar}$), 55.5 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 2920 (m), 2833 (m), 1601 (m), 1488 (m), 1247 (s), 1179 (s), 1028 (s), 828 (s), 812 (s), 769 (s), 740 (s), 723 (s), 688 (s), 602 (s), 556 (s), 517 (s). **MS (EI, 70 eV):** *m/z* (%) = 292 (20), 291 ([M]$^+$, 100), 276 (19), 248 (24), 247 (30), 246 (14), 146 (5), 123 (4). **HRMS (ESI-TOF):** calcd. for C$_{18}$H$_{13}$O$_1$N$_1$S$_1$ ([M+H]$^+$) 292.0796 found 292.0798.

## 4-(4-(trifluoromethyl)phenyl)thieno[3,2-*f*]quinoline (13c)
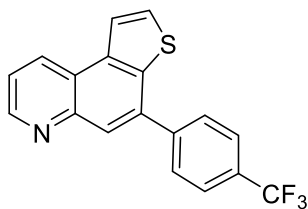
According to the general procedure, the reaction of **9c** (0.3 mmol, 98.72 mg) and MsOH (15 mmol, 1.0 mL), affords product **13c** as a yellow solid (93.8 mg, 95%), mp: 127 – 129 ºC. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.99 (br-s, 1H, CH$_{Pyr}$), 8.67 (dd, ^3J = 8.3, ^4J = 1.6 Hz, 1H, CH$_{Pyr}$), 8.07 (d, ^3J = 5.4 Hz, 1H, CH$_{Thioph}$), 8.06 (s, 1H, CH$_{Ar}$), 7.95 (d, ^3J = 8.1 Hz, 2H, CH$_{Ar}$), 7.82 (d, ^3J = 8.1 Hz, 2H, CH$_{Ar}$), 7.73 (d, ^3J = 5.4 Hz, 1H, CH$_{Thioph}$), 7.57 (dd, ^3J = 8.3, ^3J = 4.3 Hz, 1H, CH$_{Pyr}$) ppm. **^{19}F NMR (282 MHz, CDCl$_3$)** δ = -62.54 (s, 3F, CF$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 149.8 (CH$_{Ar}$), 147.4, 143.5, 137.4, 136.6 (C$_{Ar}$), 132.0 (CH$_{Ar}$), 130.8 (d, $^2J_{C,F}$ = 33.0 Hz, C$_{Ar}$), 128.9, 128.1 (CH$_{Ar}$), 126.1 (d, $^3J_{C,F}$ = 3.8 Hz, CH$_{Ar}$), 125.8 (CH$_{Ar}$), 124.3 (q, $^1J_{C,F}$ = 272.0 Hz, CF$_3$), 124.1 (C$_{Ar}$), 122.4, 121.7 (CH$_{Ar}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 1323 (s), 1152 (m), 1102 (s), 1065 (s), 1016 (s), 909 (m), 841 (s), 832 (s), 812 (m), 802 (m), 769 (s), 734 (s), 684 (s), 618 (s), 542 (m), 482 (m). **MS (EI, 70 eV):** *m/z* (%) = 330 (25), 329 ([M]$^+$, 100), 328 (41), 310 (6), 260 (9), 259 (12), 268 (6), 232 (6), 154 (6), 69 (5). **HRMS (EI):** calcd. for C$_{18}$H$_{10}$F$_3$N$_1$S$_1$ (M)$^+$ 329.04806 found 329.04776.

4-(*m*-tolyl)thieno[3,2-*f*]quinoline (13e)
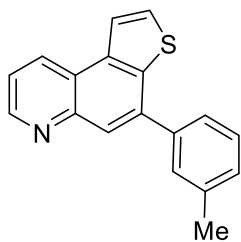
According to the general procedure, the reaction of **9e** (0.18 mmol, 51.6 mg) and MsOH (9.3 mmol, 0.60 mL), affords product **13e** as a colourless oil (43 mg, 87%). **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.96 (dd, ^3J = 4.3, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 8.63 (ddd, ^3J = 8.3, ^4J = 1.7, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 8.04 (br-s, 1H, CH$_{Ar}$), 8.03 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.69 (dd, ^3J = 5.5, J = 0.5 Hz, 1H, CH$_{Thioph}$), 7.66 – 7.63 (m, 2H, CH$_{Ar}$), 7.51 (dd, ^3J = 8.3, ^3J = 4.3 Hz, 1H, CH$_{Pyr}$), 7.48 – 7.41 (m, 1H, CH$_{Ar}$), 7.33 – 7.28 (m, 1H, CH$_{Ar}$), 2.48 (s, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 149.6 (CH$_{Ar}$), 147.8, 140.0, 138.9, 138.8, 138.0, 136.3 (C$_{Ar}$), 131.8, 129.5, 129.3, 128.9, 127.8, 125.6, 125.4 (CH$_{Ar}$), 123.6 (C$_{Ar}$), 122.2, 121.1 (CH$_{Ar}$), 21.7 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3035 (w), 2918 (w), 2854 (w), 1601 (m), 1558 (m), 1475 (s), 1354 (m), 878 (m), 824 (m), 787 (s), 769 (s), 734 (s), 705 (s), 680 (s), 616 (m), 579 (m), 474 (m), 433 (m). **MS (EI, 70 eV):** *m/z* (%) = 276 (28), 275 ([M]$^+$, 100), 274 (42), 273 (13), 272 (10), 259 (10), 137 (14), 123 (5). **HRMS (EI):** calcd. for C$_{18}$H$_{13}$N$_1$S$_1$ (M)$^+$ 275.07632 found 275.07595.

N,N-dimethyl-4-(thieno[3,2-f]quinolin-4-yl)aniline (13f)
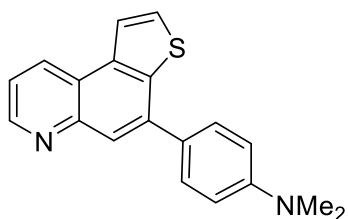
According to the general procedure, the reaction of **9f** (0.071 mmol, 21.5 mg) and MsOH (3.53 mmol, 0.24 mL), affords product **13f** as a yellow solid (14.3 mg, 66%). **mp**: 197 – 199 ºC. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.93 (dd, ^3J = 4.3, ^4J = 1.7 Hz, 1H, CH$_{Pyr}$), 8.63 (ddd, ^3J = 8.3, ^4J = 1.7, J = 0.8 Hz, 1H, CH$_{Pyr}$), 8.03 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 8.02 (br-s, 1H, CH$_{Ar}$), 7.77 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$), 7.69 (dd, ^3J = 5.5, J = 0.6 Hz, 1H, CH$_{Thioph}$), 7.48 (dd, ^3J = 8.3, ^3J = 4.3 Hz, 1H, CH$_{Pyr}$), 6.89 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$), 3.06 (s, 6H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 150.8 (C$_{Ar}$), 149.4 (CH$_{Ar}$), 147.9, 139.2, 138.3, 136.2 (C$_{Ar}$), 131.9, 129.4 (CH$_{Ar}$), 127.7 (C$_{Ar}$), 127.7, 124.2, 122.2, 120.6, 112.6 (CH$_{Ar}$), 40.6 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3093 (w), 3058 (m), 1605 (s), 1523 (s), 1486 (s), 1358 (s), 1222 (m), 1189 (s), 1170 (m), 1065 (m), 812 (s), 781 (s), 744 (s), 727 (s), 699 (s), 600 (s), 546 (s), 515 (s), 488 (m), 478 (s). **MS (EI, 70 eV):** *m/z* (%) = 305 (22), 304 ([M]$^+$, 100), 303 (47), 288 (14), 260 (16), 259 (12), 151 (13). **HRMS (EI):** calcd. for C$_{19}$H$_{16}$N$_2$S$_1$ (M)$^+$ 304.10287 found 304.10219.

6-(4-(*tert*-butyl)phenyl)benzo[4,5]thieno[3,2-f]quinoline (13g)
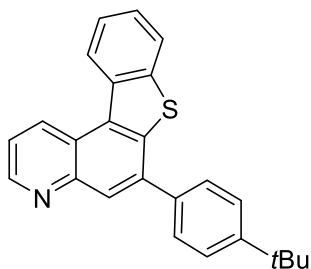
According to the general procedure, the reaction of **9g** (0.3 mmol, 110.25 mg) and MsOH (15 mmol, 1.0 mL), affords product **13g** as a yellow solid (70.3 mg, 64%), mp: 187 – 189 ºC. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 9.28 (d, ^3J = 8.7 Hz, 1H, CH$_{Benzothioph}$), 8.98 (dd, ^3J = 4.3, ^4J = 1.6 Hz, 1H, CH$_{Pyr}$), 8.73 (br-d, ^3J = 8.0 Hz, 1H, CH$_{Benzothioph}$), 8.15 (d, ^5J = 0.6 Hz, 1H, CH$_{Ar}$), 7.94 (ddd, ^3J = 7.7, ^4J = 1.6, ^5J = 0.6 Hz, 1H, CH$_{Pyr}$), 7.77 (d, ^3J = 8.6 Hz, 2H, CH$_{Ar}$), 7.59 (d, ^3J = 8.6 Hz, 2H, CH$_{Ar}$), 7.60 – 7.53 (m, 1H, CH$_{Benzothioph}$), 7.57 (dd, ^3J = 7.7, ^3J = 4.3 Hz, 1H, CH$_{Pyr}$), 7.53 – 7.45 (m, 1H, CH$_{Benzothioph}$), 1.44 (s, 9H, CH$_{3\text{-}tBu}$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 151.8 (C$_{Ar}$), 149.0 (CH$_{Ar}$), 148.1, 140.4, 139.6, 138.9, 137.0, 136.7 (C$_{Ar}$), 131.0 (CH$_{Ar}$), 129.5 (C$_{Ar}$), 128.4, 128.1, 126.0, 125.8, 125.1 (CH$_{Ar}$), 124.9 (C$_{Ar}$), 124.4, 123.3, 121.2 (CH$_{Ar}$), 34.9 (C$_{tBu}$), 31.5 (CH$_{3\text{-}tBu}$) ppm. **IR** (ATR, cm^{-1}): ṽ = 2959 (m), 1482 (m), 1459 (w), 1263 (w), 1193 (w), 1144 (m), 1117 (m), 917 (m), 886 (m), 830 (s), 806 (m), 754 (s), 723 (s), 705 (w), 624 (m), 606 (s), 550 (s), 538 (m), 511 (m), 418 (m). **MS (EI, 70 eV):** *m/z* (%) = 368 (21), 367 ([M]$^+$, 73), 354 (8), 353 (27), 352

(100), 336 (14), 324 (19), 323 (18), 311 (11), 310 (18), 309 (9), 176 (10), 162 (37). **HRMS (EI):** calcd. for $C_{25}H_{21}N_1S_1$ (M)$^+$ 367.13892, found 367.13849.
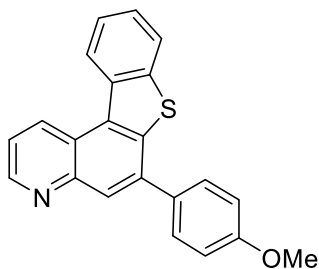
6-(4-methoxyphenyl)benzo[4,5]thieno[3,2-*f*]quinoline (13h)

According to the general procedure, the reaction of **9h** (0.1025 mmol, 35.0 mg) and MsOH (5.12 mmol, 0.34 mL), affords product **13h** as a white solid (18.6 mg, 53%), mp: 200 – 202 °C. **¹H NMR (250 MHz, CDCl₃)** δ = 9.34 (br-d, ^3J = 8.5 Hz, 1H, CH$_{Benzothioph}$), 9.00 (dd, ^3J = 4.3, 1.5 Hz, 1H, CH$_{Pyr}$), 8.79 (br-d, ^3J = 8.3 Hz, 1H, CH$_{Benzothioph}$), 8.12 (br-s,

1H, CH$_{Ar}$), 7.98 (dd, ^3J = 7.9, 1.5 Hz, 1H, CH$_{Pyr}$), 7.77 (d, ^3J = 8.8 Hz, 2H, CH$_{Ar}$), 7.65 – 7.58 (m, 1H, CH$_{Benzothioph}$), 7.61 (dd, ^3J = 7.9, ^3J = 4.3 Hz, 1H, CH$_{Pyr}$), 7.56 – 7.48 (m, 1H, CH$_{Benzothioph}$), 7.10 (d, ^3J = 8.8 Hz, 2H, CH$_{Ar}$), 3.93 (s, 3H, CH$_3$) ppm. **¹³C NMR (63 MHz, CDCl₃)** δ = 160.2 (C$_{Ar}$), 149.1 (CH$_{Ar}$), 148.2, 140.5, 139.8, 138.8, 136.9, 132.4 (C$_{Ar}$), 131.1, 130.0 (CH$_{Ar}$), 129.5 (C$_{Ar}$), 128.0, 125.9, 125.2 (CH$_{Ar}$), 124.9 (C$_{Ar}$), 124.5, 123.5, 121.3, 114.5 (CH$_{Ar}$), 55.6 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 2988 (w), 2835 (m), 1609 (m), 1515 (s), 1482 (s), 1438 (m), 1288 (m), 1249 (s), 1181 (s), 1032 (s), 915 (m), 880 (s), 828 (s), 808 (s), 750 (s), 732 (m), 715 (s), 604 (s), 546 (s), 507 (s), 420 (m). **MS (EI, 70 eV):** *m/z* (%) = 342 (24), 341 ([M]$^+$, 100), 326 (12), 298 (20), 297 (36), 296 (22), 171 (13), 149 (24), 135 (9). **HRMS (EI):** calcd. for $C_{22}H_{15}N_1O_1S_1$ (M)$^+$ 341.08689, found 341.08709.

6-(4-(trifluoromethyl)phenyl)benzo[4,5]thieno[3,2-*f*]quinoline (13i)
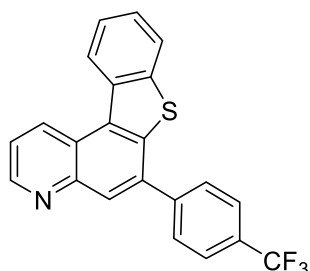
According to the general procedure, the reaction of **9i** (0.12 mmol, 46.0 mg) and MsOH (6.06 mmol, 0.39 mL), affords product **13i** as a white solid (43.0 mg, 94%), mp: 202 °C. **¹H NMR (300 MHz, CDCl₃)** δ = 9.31 (dd, ^3J = 8.7, ^4J = 1.5 Hz, 1H, CH$_{Pyr}$), 8.99 (dd, ^3J = 4.3, ^4J = 1.5 Hz, 1H, CH$_{Pyr}$), 8.75 (ddd, ^3J = 8.3, ^4J = 1.2, ^5J = 0.5 Hz, 1H, CH$_{benzothiop}$), 8.12 (s, 1H, CH$_{Ar}$), 7.94 (ddd, ^3J = 8.2, ^4J = 1.4, ^5J = 0.5 Hz, 1H, CH$_{benzothiop}$), 7.89 (dd, ^3J = 8.0, ^4J = 0.8 Hz, 2H, CH$_{Ar}$), 7.80 (m, 2H, CH$_{Ar}$), 7.62 (dd, ^3J = 8.7, ^3J = 4.3 Hz, 1H, CH$_{Pyr}$), 7.59 (ddd, ^3J = 8.3, ^3J = 7.2, ^4J = 1.4 Hz, 1H, CH$_{benzothiop}$), 7.50 (ddd, ^3J = 8.2, ^3J = 7.2, ^4J = 1.2 Hz, 1H, CH$_{benzothiop}$) ppm. **¹⁹F NMR (282 MHz, CDCl₃)** δ = -62.54 (s, 3F, CF$_3$) ppm. **¹³C**

NMR (63 MHz, CDCl₃) δ = 149.3 (CH$_{Ar}$), 147.8, 143.4, 140.3, 138.8, 137.5, 136.6 (C$_{Ar}$), 131.2 (CH$_{Ar}$), 130.2 (q, $^2J_{C,F}$ = 33.3 Hz, C$_{Ar}$), 129.2, 128.6, 126.2 (CH$_{Ar}$), 126.1 (d, $^3J_{C,F}$ = 3.8 Hz, CH$_{Ar}$), 125.4, 124.5 (CH$_{Ar}$), 124.3 (q, $^1J_{C,F}$ = 272.3 Hz, CF₃), 123.5 (CH$_{Ar}$), 121.9 (CH$_{Ar}$) ppm. **IR (ATR, cm⁻¹):** ṽ = 3052 (w), 2922 (w), 1929 (w), 1613 (w), 1484 (w), 1407 (m), 1325 (s), 1261 (m), 1168 (m), 1098 (s), 1065 (s), 1016 (s), 915 (s), 841 (s), 808 (s), 752 (s), 719 (s), 676 (m), 624 (m), 608 (m). **MS (EI, 70 eV):** *m/z* (%) = 380 (25), 379 ([M]⁺, 100), 378 (25), 309 (10), 189 (11), 179 (15), 155 (10), 69 (17). **HRMS (EI):** calcd. for C₂₂H₁₂N₁F₃S₁ (M)⁺ 379.06371, found 379.06323.
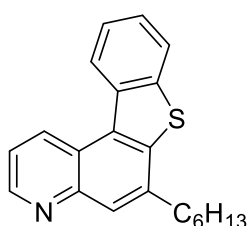
6-hexylbenzo[4,5]thieno[3,2-*f*]quinoline (13j)

According to the general procedure, the reaction of **9j** (0.22 mmol, 71.0 mg) and MsOH (11.1 mmol, 0.74 mL), affords product **13j** as a yellow solid (50.0 mg, 71%), mp: 49 – 51 ºC. **¹H NMR (300 MHz, CDCl₃)** δ = 9.27 (ddd, ^3J = 8.6, ^4J = 1.6, ^5J = 0.8 Hz, 1H, CH$_{Benzothioph}$), 8.95 (dd, ^3J = 4.2, ^4J = 1.5 Hz, 1H, CH$_{Pyr}$), 8.74 (br-d, ^3J = 8.2 Hz, 1H, CH$_{Benzothioph}$), 8.03 (ddd, ^3J = 7.8, ^4J = 1.5, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.98 (d, ^5J = 0.8 Hz, 1H, CH$_{Ar}$), 7.63 – 7.56 (m, 1H, CH$_{Benzothioph}$), 7.56 (dd, ^3J = 7.8, ^3J = 4.2 Hz, 1H, CH$_{Pyr}$), 7.55 – 7.48 (m, 1H, CH$_{Benzothioph}$), 3.06 (t, ^3J = 7.7 Hz, 2H, CH₂), 2.00 – 1.87 (m, 2H, CH₂), 1.56 – 1.43 (m, 2H, CH₂), 1.43 – 1.28 (m, 4H, CH₂), 0.91 (t, ^3J = 7.1 Hz, 3H, CH₃) ppm. **¹³C NMR (75 MHz, CDCl₃)** δ = 147.6 (CH$_{Ar}$), 147.0, 139.2, 138.7, 137.8, 135.9 (C$_{Ar}$), 129.8 (CH$_{Ar}$), 127.7 (C$_{Ar}$), 125.8, 124.6, 124.0, 123.3 (CH$_{Ar}$), 123.2 (C$_{Ar}$), 122.4, 119.7 (CH$_{Ar}$), 34.1, 30.7, 28.2, 27.8, 21.6 (CH₂), 13.1 (CH₃) ppm. **IR (ATR, cm⁻¹):** ṽ = 2957 (m), 2926 (s), 2852 (m), 1486 (m), 1457 (m), 1247 (m), 1195 (m), 1076 (m), 1030 (m), 868 (m), 808 (s), 760 (s), 750 (s), 732 (s), 715 (s), 596 (m), 575 (s), 501 (m), 441 (m), 416 (m). **MS (EI, 70 eV):** *m/z* (%) = 319 ([M]⁺, 32), 262 (13), 260 (9), 250 (21), 249 (100), 248 (51), 247 (19), 222 (7). **HRMS (EI):** calcd. for C₂₁H₂₁N₁S₁ (M)⁺ 319.13892, found 319.13890.

6-(*m*-tolyl)benzo[4,5]thieno[3,2-*f*]quinoline (13k)
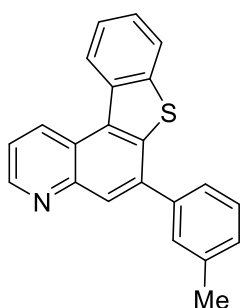
According to the general procedure, the reaction of **9k** (0.077 mmol, 25 mg) and MsOH (3.84 mmol, 0.256 mL), affords product **13k** as a yellow solid (20 mg, 80%), mp: 128 – 130 ºC. **¹H NMR (300 MHz, CDCl₃)** δ = 9.36 (d, ^3J = 8.4 Hz, 1H, CH$_{Benzothioph}$), 9.01 (dd, ^3J = 4.3, ^4J = 1.6 Hz, 1H, CH$_{Pyr}$), 8.80 (d, ^3J = 8.2 Hz, 1H, CH$_{Benzothioph}$), 8.15 (s, 1H, CH$_{Ar}$), 7.99 (dd, ^3J = 7.8, ^4J = 1.6 Hz, 1H,

CH$_{Pyr}$), 7.66 – 7.47 (m, 6H, CH$_{Ar}$), 7.33 (d, ^3J = 7.8 Hz, 1H, CH$_{Ar}$), 2.50 (s, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 149.1 (CH$_{Ar}$), 148.1, 140.5, 139.9, 139.7, 139.2, 138.8, 136.8 (C$_{Ar}$), 131.2, 129.6 (CH$_{Ar}$), 129.5 (C$_{Ar}$), 129.5, 128.9, 128.1, 125.9, 125.8, 125.2 (CH$_{Ar}$), 125.1 (C$_{Ar}$), 124.5, 123.5, 121.4 (CH$_{Ar}$), 21.7 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 2916 (w), 2852 (w), 1585 (w), 1545 (w), 1482 (m), 1346 (m), 1321 (m), 1263 (m), 1030 (m), 886 (m), 808 (s), 785 (s), 756 (s), 727 (s), 705 (s), 608 (m), 507 (s), 427 (s). **MS (EI, 70 eV):** m/z (%) = 326 (25), 325 ([M]$^+$, 100), 324 (26), 162 (30), 155 (11), 148 (9), 146 (10). **HRMS (EI):** calcd. for C$_{22}$H$_{15}$N$_1$S$_1$ (M)$^+$ 325.09197, found 325.09208.
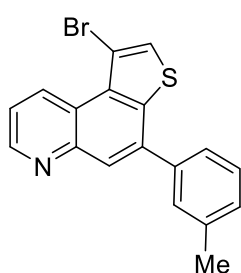
1-bromo-4-(*m*-tolyl)thieno[3,2-*f*]quinoline (13l)

According to the general procedure, the reaction of **9l** (0.11 mmol, 39 mg) and MsOH (5.5 mmol, 0.356 mL), affords product **13l** as a white solid (32 mg, 82%), mp: 138 – 140 ºC. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 9.98 (ddd, ^3J = 8.6, ^4J = 1.6, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 8.98 (dd, ^3J = 4.3, ^4J = 1.6 Hz, 1H, CH$_{Pyr}$), 8.04 (s, 1H, CH$_{Thioph}$), 7.68 (d, ^5J = 0.8 Hz, 1H, CH$_{Ar}$), 7.58 – 7.53 (m, 2H, CH$_{Ar}$), 7.54 (dd, ^3J = 8.6, ^3J = 4.3 Hz, 1H, CH$_{Pyr}$), 7.43 (pt, ^3J = 7.8 Hz, 1H, CH$_{Ar}$), 7.31 (d, ^3J = 7.8 Hz, 1H, CH$_{Ar}$), 2.47 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 149.8 (CH$_{Ar}$), 148.2, 138.9, 138.8, 138.5 (C$_{Ar}$), 130.6 (CH$_{Pyr}$), 130.4 (C$_{Ar}$), 129.7, 129.4, 129.0, 127.1, 126.6, 125.7, 124.2 (C$_{Ar}$), 120.6 (CH$_{Ar}$), 107.4 (C$_{Ar}$), 21.7 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3095 (w), 3044 (m), 1554 (m), 1480 (m), 1467 (m), 1313 (s), 1203 (m), 919 (s), 870 (s), 857 (m), 781 (s), 764 (s), 725 (m), 699 (s), 624 (s), 581 (m), 546 (s), 503 (m), 433 (m). **MS (EI, 70 eV):** m/z (%) = 355 ([M]$^+$, 91), 354 (22), 353 ([M]$^+$, 92), 274 (37), 273 (23), 272 (28), 259 (35), 136 (100). **HRMS (ESI-TOF):** calcd. for C$_{18}$H$_{12}$N$_1$Br$_1$S$_1$ ([M+H]$^+$) 353.9952, found 353.9952.

1-bromo-4-phenylthieno[3,2-*f*]quinoline (13m)
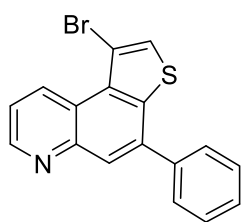
According to the general procedure, the reaction of **9m** (0.258 mmol, 88 mg) and MsOH (12.9 mmol, 0.84 mL), affords product **13m** as a white solid (68.2 mg, 77%), mp: 166 ºC. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 9.99 (dd, ^3J = 8.6, ^4J = 1.6 Hz, 1H, CH$_{Pyr}$), 8.98 (dd, ^3J = 4.3, ^4J = 1.6 Hz, 1H, CH$_{Pyr}$), 8.06 (s, 1H, CH$_{Thioph}$), 7.74 (dd, ^3J = 7.9, ^4J = 1.7 Hz, 2H, CH$_{Ar}$), 7.68 (s, 1H, CH$_{Ar}$), 7.59 – 7.54 (m, 2H, CH$_{Ar}$), 7.55 (dd, ^3J = 8.6, ^3J = 4.3 Hz, 1H, CH$_{Pyr}$), 7.54 – 7.47 (m, 1H, CH$_{Ar}$) ppm.

^{13}C NMR (75 MHz, CDCl$_3$) δ = 149.7 (CH$_{Ar}$), 148.1, 138.9, 138.7, 138.4 (C$_{Ar}$), 130.7 (CH$_{Ar}$), 130.5 (C$_{Ar}$), 129.1, 129.0, 128.7, 127.1, 126.7 (CH$_{Ar}$), 124.2 (C$_{Ar}$), 120.7 (CH$_{Ar}$), 107.4 (C$_{Ar}$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 3093 (m), 3023 (m), 1480 (m), 1463 (m), 1434 (m), 1313 (m), 1201 (m), 1072 (m), 1032 (m), 915 (s), 861 (m), 841 (m), 806 (m), 762 (s), 752 (s), 696 (s), 608 (s), 577 (s), 548 (s). **MS (EI, 70 eV):** *m/z* (%) = 341 ([M]$^+$, 100), 339 ([M]$^+$, 96), 260 (54), 259 (41), 232 (26), 189 (23), 130 (34), 116 (20), 94 (20). **HRMS (EI):** calcd. for C$_{17}$H$_{10}$N$_1$Br$_1$S$_1$ (M)$^+$ 338.97118, found 338.97149; calcd. for C$_{17}$H$_{10}$N$_1$^{81}Br$_1$S$_1$ (M)$^+$ 340.96914, found 340.97009.
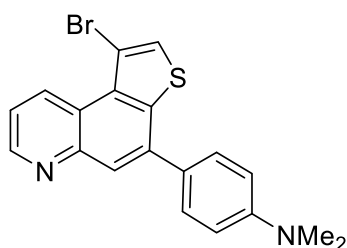
1-bromo-4-(4-(dimethylamino)phenyl)thieno[3,2-*f*]quinoline (13n)

According to the general procedure, the reaction of **9n** (0.14 mmol, 53.7 mg) and MsOH (7.0 mmol, 0.454 mL), affords product **13n** as a yellow solid (44 mg, 83%), mp: 199 – 202 °C. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 9.97 (ddd, ^3J = 8.6, ^4J = 1.6, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 8.96 (dd, ^3J = 4.3, ^4J = 1.6 Hz, 1H, CH$_{Pyr}$), 8.02 (s, 1H, CH$_{Thioph}$), 7.68 (d, ^5J = 0.8 Hz, 1H, CH$_{Ar}$), 7.67 (d, ^3J = 8.9 Hz, 2H, CH$_{Ar}$), 7.51 (dd, ^3J = 8.6, ^3J = 4.3 Hz, 1H, CH$_{Pyr}$), 6.87 (d, ^3J = 8.9 Hz, 2H, CH$_{Ar}$), 3.06 (s, 6H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 150.9 (C$_{Ar}$), 149.5 (CH$_{Ar}$), 148.4, 139.2, 138.7 (C$_{Ar}$), 130.7 (CH$_{Ar}$), 130.3 (C$_{Ar}$), 129.5, 126.6, 126.1 (CH$_{Ar}$), 123.9, 123.7 (C$_{Ar}$), 120.1, 112.5 (CH$_{Ar}$), 107.3 (C$_{Ar}$), 40.5 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 3093 (m), 2805 (m), 1611 (s), 1595 (m), 1525 (s), 1477 (s), 1465 (m), 1445 (m), 1360 (s), 1313 (s), 1234 (m), 1195 (s), 915 (s), 878 (m), 810 (s), 795 (s), 764 (s), 606 (s), 546 (s), 513 (s). **MS (EI, 70 eV):** *m/z* (%) = 384 ([M]$^+$, 100), 383 (60), 382 ([M]$^+$, 97), 381 (40), 287 (15), 260 (15), 259 (38), 191 (31), 129 (16). **HRMS (ESI-TOF):** calcd. for C$_{19}$H$_{15}$N$_2$Br$_1$S$_1$ ([M+H]$^+$) 383.0218, found 383.0216.

Synthesis of thieno[3,2-*f*]quinolines (13o-p).

A degassed and argon flushed Schlenk tube was charged with corresponding starting material (0.13 mmol) and MsOH (50 equiv.). The reaction was stirred at 120 °C for 6 h. After cooling to room temperature, the reaction mixture was washed with a 10 % sodium hydroxide solution and extracted with ethyl acetate (EtOAc). The combined organic layers were collected and the solvent evaporated. The crude product was purified by column chromatography (heptane/EtOAc 8:1).

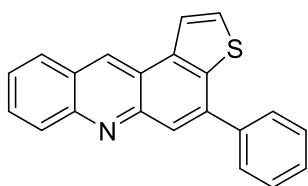## 6-phenylbenzo[4,5]thieno[3,2-*a*]acridine (13o)
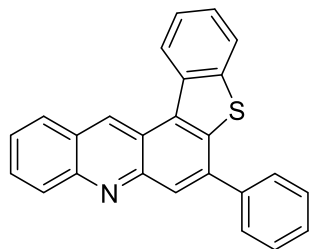
According to the general procedure, the reaction of **12a** (0.13 mmol, 46.5 mg) and MsOH (6.45 mmol, 0.42 mL), affords product **13o** as a yellow solid (43.4 mg, 93%), mp: 193 – 195 ºC. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 9.81 (s, 1H, CH$_{Pyr}$), 8.94 (dd, ^3J = 8.3, ^4J = 1.4 Hz, 1H, CH$_{Ar}$), 8.29 (dd, ^3J = 8.7, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 8.25 (d, ^5J = 0.9 Hz, 1H, CH$_{Ar}$), 8.17 (dd, ^3J = 8.4, ^4J = 1.1 Hz, 1H, CH$_{Ar}$), 7.99 (dd, ^3J = 8.1, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.86 (dd, ^3J = 8.0, ^4J = 1.6 Hz, 2H, CH$_{Ar}$), 7.83 (ddd, ^3J = 8.7, ^3J = 6.6, ^4J = 1.4 Hz, 1H, CH$_{Ar}$), 7.67 (ddd, ^3J = 8.4, ^3J = 7.1, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.63 (ddd, ^3J = 8.3, ^3J = 6.6, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.60 – 7.53 (m, 3H, CH$_{Ar}$), 7.53 (ddd, ^3J = 8.1, ^3J = 7.1, ^4J = 1.1 Hz, 1H, CH$_{Ar}$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 149.0, 147.7, 140.4, 140.2, 139.8, 139.3, 137.1 (C$_{Ar}$), 130.8, 130.3, 129.2, 129.1, 129.0 (CH$_{Ar}$), 128.9 (C$_{Ar}$), 128.7, 128.6, 128.0 (CH$_{Ar}$), 126.6 (C$_{Ar}$), 126.4, 125.7, 125.4, 124.3 (CH$_{Ar}$), 123.6 (C$_{Ar}$), 123.5 (CH$_{Ar}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3054 (w), 3029 (w), 1498 (m), 1447 (m), 1286 (w), 1129 (m), 884 (m), 767 (m), 729 (s), 713 (s), 694 (s), 670 (m), 596 (s), 563 (m), 530 (m), 462 (m), 422 (m). **MS (EI, 70 eV):** *m/z* (%) = 362 (27), 361 ([M]+, 100), 360 (32), 359 (14), 358 (6), 357 (4), 332 (2), 180 (16), 179 (6), 166 (2). **HRMS (EI):** calcd. for C$_{25}$H$_{15}$N$_1$S$_1$ (M)$^+$ 361.09197, found 361.09125.

4-phenylthieno[3,2-*a*]acridine (13p)
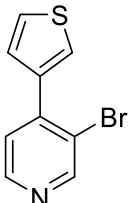
According to the general procedure, the reaction of **12b** (0.13 mmol, 40.2 mg) and MsOH (6.45 mmol, 0.42 mL), affords product **13p** as a yellow solid (36.95 mg, 92%), mp: 148 – 150 ºC. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 9.14 (br-s, 1H, CH$_{Pyr}$), 8.28 (ddd, ^3J = 8.8, ^4J = 1.9, ^5J = 0.9 Hz, 1H, CH$_{Ar}$), 8.18 (d, ^3J = 5.4 Hz, 1H, CH$_{Thioph}$), 8.13 (br-s, 1H, CH$_{Ar}$), 8.07 (ddd, ^3J = 8.4, ^4J = 1.6, ^5J = 0.7 Hz, 1H, CH$_{Ar}$), 7.89 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 2H, CH$_{Ar}$), 7.81 (ddd, ^3J = 8.8, ^3J = 6.8, ^4J = 1.6 Hz, 1H, CH$_{Ar}$), 7.72 (dd, ^3J = 5.4, ^6J = 0.6 Hz, 1H, CH$_{Thioph}$), 7.62 – 7.47 (m, 4H, CH$_{Ar}$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 149.0, 148.4, 140.1, 139.9, 137.3, 136.2 (C$_{Ar}$), 131.1, 130.1, 129.4, 129.1, 128.9, 128.5, 128.2, 127.6 (CH$_{Ar}$), 126.5 (C$_{Ar}$), 126.1, 125.3, 123.0 (CH$_{Ar}$), 122.5 (C$_{Ar}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3052 (w), 1480 (m), 1438 (m), 1360 (m), 1092 (m), 905 (m), 878 (m), 868 (m), 789 (m), 746 (s), 711 (s), 690 (s), 672 (s), 655 (m), 620 (m), 600

(s), 560 (m), 528 (m), 468 (m), 437 (m). **MS (EI, 70 eV):** *m/z* (%) = 312 (24), 311 ([M]$^+$, 100), 310 (40), 309 (14), 308 (5), 155 (11), 133 (6). **HRMS (EI):** calcd. for C$_{21}$H$_{13}$N$_1$S$_1$ (M)$^+$ 311.07632, found 311.07647.

Synthesis of 3-(2-bromophenyl)thiophene and 3-(2-bromophenyl)benzo[*b*]thiophene 14a-b.

In a dry pressure tube were charged 3,4-dibromopyridine (1.0 mmol), the corresponding boronic acid (3-thiopheneboronic acid or 3-benzothiopheneboronic acid) (1.1 equiv.), Pd(PPh$_3$)$_4$ (5 mol%) and K$_2$CO$_3$ (2.0 equiv.). The solids were dissolved in a mixture of 1,4-dioxane/H$_2$O (6:1) (7.0 mL) and the reaction was purged with argon. The mixture was stirred at 90°C for 3 hours. After cooled to r.t. the mixture was washed with water and extracted with ethyl acetate. Organic phase was treated with anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (Heptane/EtOAc 5:1).
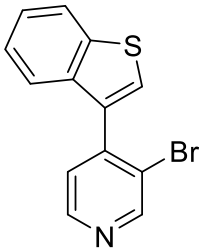
3-bromo-4-(thiophen-3-yl)pyridine (14a)

According to the synthetic procedure, 3,4-dibromopyridine (1.05 mmol, 240.0 mg) was reacted with 3-thiopheneboronic (1.155 mmol, 147.8 mg) to give the yellow oil **14a** (224.1 mg, 89%). **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.80 (s, 1H, CH$_{Pyr}$), 8.51 (d, ^3J = 5.0 Hz, 1H, CH$_{Pyr}$), 7.63 (dd, ^4J = 3.0, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.43 (dd, ^3J = 5.0, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.35 (dd, ^3J = 5.0, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.33 (d, ^3J = 5.0 Hz, 1H, CH$_{Pyr}$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 153.0, 148.4 (CH$_{Pyr}$), 144.5 (C$_{Pyr}$), 138.3 (C$_{Thioph}$), 128.1 (CH$_{Pyr}$), 125.9, 125.4 (CH$_{Thioph}$), 120.5 (C$_{Pyr}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3101 (w), 3037 (w), 1578 (s), 1463 (m), 1393 (m), 1362 (m), 1092 (m), 1018 (s), 865 (m), 837 (s), 820 (m), 783 (s), 736 (s), 711 (s), 692 (m), 664 (s), 645 (s), 608 (s), 552 (s), 418 (m). **MS (EI, 70 eV):** *m/z* (%) = 241 ([M]$^+$, 99), 239 ([M]$^+$, 100), 160 (41), 133 (23), 89 (33), 75 (14), 74 (15), 69 (13), 63 (19), 62 (18), 50 (21), 45 (49). **HRMS (EI):** calcd. for C$_9$H$_6$N$_1$Br$_1$S$_1$ (M)$^+$ 238.93988, found 238.93995; calcd. for C$_9$H$_6$N$_1$^{81}Br$_1$S$_1$ (M)$^+$ 240.93784, found 240.93799.

**4-(benzo[*b*]thiophen-3-yl)-3-bromopyridine (14b)**

Following the synthetic procedure, 3,4-dibromopyridine (1.0 mmol, 240.0 mg) was reacted with 3-benzothiopheneboronic acid (1.1 mmol, 198.4 mg) to give the pure product **14b** as a light violet solid. (211.7 mg, 73%), mp: 78 °C. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.90 (s, 1H, CH$_{pyr}$), 8.61 (d, ^3J = 4.9 Hz, 1H, CH$_{pyr}$), 7.95 – 7.93 (m, 1H,

CH$_{Ar}$), 7.56 (s, 1H, CH$_{Thioph}$), 7.54 – 7.52 (m, 1H, CH$_{Ar}$), 7.42 – 7.39 (m, 2H, CH$_{Ar}$), 7.37 (d, ^3J = 4.9 Hz, 1H, CH$_{pyr}$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 152.5, 147.9 (CH$_{pyr}$), 145.0 (C$_{pyr}$), 140.1, 137.3, 133.5 (C$_{Ar}$), 127.0 (CH$_{Ar}$), 126.5 (C$_{pyr}$), 125.0, 124.8, 123.0 (CH$_{Ar}$), 122.9 (CH$_{pyr}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3072 (m), 1581 (s), 1424 (m), 1393 (s), 1339 (m), 1084 (m), 1057 (m), 1020 (s), 950 (m), 830 (s), 756 (s), 734 (s), 696 (s), 637 (s), 624 (m), 589 (s), 521 (m), 429 (s). **MS (EI, 70 eV):** *m/z* (%) = 291 ([M]$^+$, 100), 290 (16), 289 ([M]$^+$, 99), 210 (34), 209 (16), 183 (15), 182 (16), 166 (16), 139 (36), 138 (14), 74 (14), 69 (15), 45 (26). **HRMS (EI):** calcd. for C$_{13}$H$_8$Br$_1$N$_1$S$_1$ (M)$^+$ 288.95553 found 288.95573; calcd. for C$_{13}$H$_8$^{81}Br$_1$N$_1$S$_1$ (M)$^+$ 290.95349 found 290.95378.

Synthesis of 3-(benzo[*b*]&thieno)-3-(alkynyl)pyridines 15a-w

Corresponding 2-bromo-3-heteroarylpyridine (0.4 mmol), Pd(PPh$_3$)$_4$ (5 mol%) and CuI (2 mol%) were dissolved under argon atmosphere in Et$_3$N (3.0 mL). After addition of acetylene (1.5 equiv.) the reaction was stirred for 20 h at 80 °C. After cooling to room temperature, the reaction was washed with water and the crude product was extracted with EtOAc. By evaporation of the collected organic phases and purification by column chromatography (Heptane/EtOAc 5:1), the substrates **15a-w** were obtained.

3-(phenylethynyl)-4-(thiophen-3-yl)pyridine (15a)
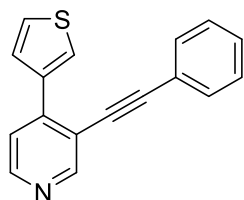
The corresponding 2-bromo-3-heteroarylpyridine (0.4 mmol, 96.05 mg) reacted with phenylacetylene (0.6 mmol, 0.066 mL) to give **15a** (101.5 mg, 97%) as yellow oil. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.83 (br-s, 1H, CH$_{Pyr}$), 8.53 (d, ^3J = 5.3 Hz, 1H, CH$_{Pyr}$), 7.99 (dd, ^4J = 3.0, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.61 (dd, ^3J = 5.1, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.52 – 7.47 (m, 2H, CH$_{Ar}$), 7.45 (dd, ^3J = 5.1, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.42 (d, ^3J = 5.3 Hz, 1H, CH$_{Pyr}$), 7.39 – 7.35 (m, 3H, CH$_{Ar}$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 154.2, 148.9 (CH$_{Pyr}$), 144.2 (C$_{Pyr}$), 138.4 (C$_{Thioph}$), 131.7, 128.9, 128.6 (CH$_{Ar}$), 127.8, 125.9, 125.9 (CH$_{Thioph}$), 122.9 (C$_{Ar}$), 122.5 (CH$_{Pyr}$), 117.7 (C$_{Pyr}$), 95.6, 86.7 (C$_{Alkyne}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3099 (w), 3079 (w), 3054 (w), 3031 (w), 2213 (w), 1578 (s), 1490 (m), 1412 (m), 1166 (w), 1041 (m), 837 (m), 789 (s), 748 (s), 686 (s), 668 (s), 645 (s), 614 (m), 575 (m), 554 (s), 484 (m). **MS (EI, 70 eV):** *m/z* (%) = 262 (13), 261 (63), 260 ([M]$^+$, 100), 259 (20), 130 (11), 98 (18), 74 (10), 58 (11), 45 (29). **HRMS (EI):** calcd. for C$_{17}$H$_{10}$N$_1$S$_1$ (M)$^+$ 260.05285, found 260.05282.

4-(thiophen-3-yl)-3-(p-tolylethynyl)pyridine (15b)
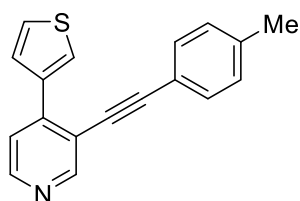
The corresponding 2-bromo-3-heteroarylpyridine (0.4 mmol, 96.05 mg) reacted with 4-methylphenylacetylene (0.6 mmol, 0.108 mL) to give **15b** (105.0 mg, 95%) as yellow solid. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.81 (br-s, 1H, CH$_{Pyr}$), 8.51 (d, ^3J = 5.3 Hz, 1H, CH$_{Pyr}$), 7.99 (dd, ^4J = 3.0, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.61 (dd, ^3J = 5.1, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.43 (dd, ^3J = 5.1, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.40 (dd, ^3J = 5.3, ^5J = 5.3 Hz, 1H, CH$_{Pyr}$), 7.39 (d, ^3J = 8.2 Hz, 2H, CH$_{Ar}$), 7.17 (d, ^3J = 8.2 Hz, 2H, CH$_{Ar}$), 2.38 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 154.1, 148.7 (CH$_{Pyr}$), 144.0 (C$_{Pyr}$), 139.2 (C$_{Ar}$), 138.5 (C$_{Thioph}$), 131.5, 129.4 (CH$_{Ar}$), 127.8, 125.9, 125.8 (CH$_{Thioph}$), 122.5 (CH$_{Pyr}$), 119.8 (C$_{Ar}$), 117.9 (C$_{Pyr}$), 95.9, 86.1 (C$_{Alkyne}$), 21.7 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): $\tilde{v}$ = 3114 (w), 3027 (w), 2914 (w), 2852 (w), 2211 (w), 1576 (s), 1506 (m), 1387 (m), 1026 (w), 816 (s), 795 (s), 748 (s), 666 (m), 641 (m), 554 (s), 525 (m), 503 (m). **MS (EI, 70 eV):** m/z (%) = 276 (22), 275 ([M]$^+$, 100), 274 (85), 273 (17), 272 (12), 260 (28), 259 (25), 139 (9), 45 (14). **HRMS (EI):** calcd. for C$_{18}$H$_{13}$N$_1$S$_1$ (M)$^+$ 275.07632, found 275.07567.
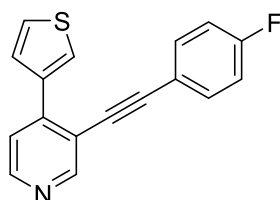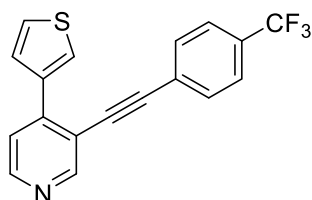
3-((4-fluorophenyl)ethynyl)-4-(thiophen-3-yl)pyridine (15c)

The corresponding 2-bromo-3-heteroarylpyridine (0.4 mmol, 96.05 mg) reacted with 4-fluorophenylacetylene (0.6 mmol, 0.069 mL) to give **15c** (106.2 mg, 95%) as yellow solid. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.81 (br-s, 1H, CH$_{Pyr}$), 8.53 (d, ^3J = 5.2 Hz, 1H, CH$_{Pyr}$), 7.95 (dd, ^4J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.59 (dd, ^3J = 5.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.47 (d, ^3J = 8.8 Hz, 1H, CH$_{Ar}$), 7.46 (d, ^3J = 8.8 Hz, 1H, CH$_{Ar}$), 7.44 (dd, ^3J = 5.0, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.41 (d, ^3J = 5.2, ^5J = 0.6 Hz, 1H, CH$_{Pyr}$), 7.08 (d, ^3J = 8.8 Hz, 1H, CH$_{Ar}$), 7.05 (d, ^3J = 8.8 Hz, 1H, CH$_{Ar}$) ppm. **^{19}F NMR (471 MHz, CDCl$_3$)** δ = -109.78 (s, 1F, CF) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 162.9 (d, $^1J_{C,F}$ = 250.4 Hz, CF), 154.1, 148.9 (CH$_{Pyr}$), 144.3 (C$_{Pyr}$), 138.4 (C$_{Thioph}$), 133.6 (d, $^3J_{C,F}$ = 8.4 Hz, CH$_{Ar}$), 127.8, 125.9, 125.8 (CH$_{Thioph}$), 122.6 (CH$_{Pyr}$), 119.0 (d, $^4J_{C,F}$ = 3.6 Hz, C$_{Ar}$), 117.6 (C$_{Pyr}$), 116.0 (d, $^2J_{C,F}$ = 22.3 Hz, CH$_{Ar}$), 94.5 (C$_{Alkyne}$), 86.4 (d, $^5J_{C,F}$ = 1.0 Hz, C$_{Alkyne}$) ppm. **IR** (ATR, cm^{-1}): $\tilde{v}$ = 3109 (w), 2215 (w), 1576 (m), 1504 (s), 1228 (s), 1218 (s), 1156 (m), 1090 (m), 1036 (m), 830 (s), 793 (s), 746 (s), 639 (m), 550 (m), 525 (s), 505 (s). **MS (EI, 70 eV):** m/z (%) = 280 (21), 279 ([M]$^+$, 91), 278 (100), 277

(20), 252 (11), 234 (11), 207 (13), 144 (10), 45 (24). **HRMS (EI):** calcd. for $C_{17}H_{10}N_1F_1S_1$ (M)$^+$ 279.05125, found 275.05053.

4-(thiophen-3-yl)-3-((4-(trifluoromethyl)phenyl)ethynyl)pyridine (15d)

The corresponding 2-bromo-3-heteroarylpyridine (0.4 mmol, 96.05 mg) reacted with 4-trifluoromethylphenylacetyle (0.6 mmol, 0.098 mL) to give **15d** (118.0 mg, 90%) as yellow solid. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.84 (d, ^5J = 0.7 Hz, 1H, CH$_{Pyr}$), 8.57 (d, ^3J = 5.2 Hz, 1H, CH$_{Pyr}$), 7.93 (dd, ^4J = 3.0, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.62 (d, ^3J = 8.2 Hz, 2H, CH$_{Ar}$), 7.58 (dd, ^3J = 5.1, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.57 (d, ^3J = 8.2 Hz, 2H, CH$_{Ar}$), 7.46 (dd, ^3J = 5.1, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.43 (dd, ^3J = 5.2, ^5J = 0.7 Hz, 1H, CH$_{Pyr}$) ppm. **^{19}F NMR (471 MHz, CDCl$_3$)** δ = -62.86 (s, 3F, CF$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 154.3, 149.4 (CH$_{Pyr}$), 144.7 (C$_{Pyr}$), 138.3 (C$_{Thioph}$), 131.9 (CH$_{Ar}$), 130.6 (q, $^2J_{C,F}$ = 32.7 Hz, C$_{Ar}$), 127.8 (CH$_{Thioph}$), 126.6 (C$_{Ar}$), 126.1, 126.0 (CH$_{Thioph}$), 125.6 (q, $^3J_{C,F}$ = 3.9 Hz, CH$_{Ar}$), 124.0 (q, $^1J_{C,F}$ = 272.2 Hz, CF$_3$),122.7 (CH$_{Pyr}$), 117.1 (C$_{Pyr}$), 93.9, 89.0 (C$_{Alkyne}$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 3079 (w), 1613 (m), 1581 (m), 1414 (w), 1325 (s), 1160 (s), 1111 (s), 1100 (s), 1067 (s), 1016 (s), 835 (s), 800 (s), 752 (s), 715 (m), 699 (m), 670 (m), 647 (s), 593 (m), 569 (s), 490 (m). **MS (EI, 70 eV):** *m/z* (%) = 330 (21), 329 ([M]$^+$, 79), 328 (100), 260 (19), 259 (15), 257 (11), 232 (9), 69 (39), 45 (18). **HRMS (EI):** calcd. for $C_{18}H_{10}N_1F_3S_1$ (M)$^+$ 329.04806, found 329.04712.

3-((4-(*tert*-butyl)phenyl)ethynyl)-4-(thiophen-3-yl)pyridine (15e)
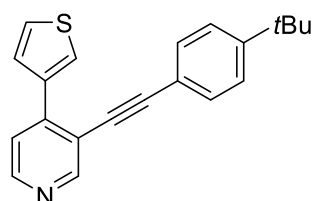
The corresponding 2-bromo-3-heteroarylpyridine (0.5 mmol, 120.06 mg) reacted with 4-*tert*-butylphenylacetylene (0.75 mmol, 0.135 mL) to give **15e** (96.3 mg, 80%) as yellow oil. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.82 (s, 1H, CH$_{Pyr}$), 8.52 (d, ^3J = 5.2 Hz, 1H, CH$_{Pyr}$), 8.00 (dd, ^4J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.61 (dd, ^3J = 5.1, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.43 (dd, ^3J = 5.1, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.46 – 7.34 (m, 5H, CH$_{Pyr/Ar}$), 1.33 (s, 9H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 154.2 (CH$_{Pyr}$), 152.4 (C$_{Ar}$), 148.7 (CH$_{Pyr}$), 144.1 (C$_{Pyr}$), 138.5 (C$_{Thioph}$), 131.4 (CH$_{Ar}$), 127.8, 125.9, 125.8 (CH$_{Thioph}$), 125.7 (CH$_{Ar}$), 122.5 (CH$_{Pyr}$), 119.8 (C$_{Ar}$), 117.9 (C$_{Pyr}$), 95.9, 86.1 (C$_{Alkyne}$), 35.0 (C$_{tBu}$), 31.3 (CH$_{3-tBu}$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 3033 (w), 2959

(m), 2922 (m), 2864 (w), 2213 (w), 1578 (m), 1504 (m), 1465 (m), 1393 (m), 1364 (m), 1265 (m), 1102 (m), 832 (s), 789 (s), 750 (s), 670 (m), 639 (m), 560 (s), 499 (m). **MS (EI, 70 eV):** m/z (%) = 318 (11), 317 ([M]$^+$, 45), 304 (7), 303 (22), 302 (100), 286 (7), 274 (7), 273 (5), 272 (5), 260 (7), 136 (19). **HRMS (EI):** calcd. for $C_{21}H_{19}N_1S_1$ (M)$^+$ 317.12327, found 317.12325.
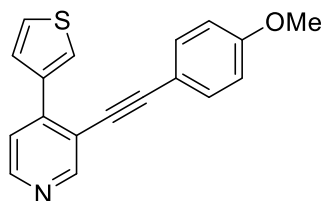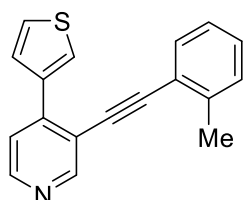
3-((4-methoxyphenyl)ethynyl)-4-(thiophen-3-yl)pyridine (15f)

The corresponding 2-bromo-3-heteroarylpyridine (0.5 mmol, 120.06 mg) reacted with 4-methoxyphenylacetylene (0.75 mmol, 0.097 mL) to give **15f** (121.5 mg, 84%) as yellow oil. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.80 (s, 1H, CH$_{Pyr}$), 8.51 (d, ^3J = 5.2 Hz, 1H, CH$_{Pyr}$), 7.99 (dd, ^4J = 2.9, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.61 (dd, ^3J = 5.0, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.43 (dd, ^3J = 5.0, ^4J = 2.9 Hz, 2H, CH$_{Thioph}$), 7.43 (d, ^3J = 8.9 Hz, 2H, CH$_{Ar}$), 7.40 (d, ^3J = 5.2 Hz, 1H, CH$_{Pyr}$), 6.89 (d, ^3J = 8.9 Hz, 2H, CH$_{Ar}$), 3.83 (s, 3H, CH$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 160.2 (C$_{Ar}$), 154.0, 148.5 (CH$_{Pyr}$), 143.9 (C$_{Pyr}$), 138.5 (C$_{Thioph}$), 133.2(CH$_{Ar}$), 127.8, 125.8, 125.8 (CH$_{Thioph}$), 122.5 (CH$_{Pyr}$), 118.0 (C$_{Pyr}$), 114.9 (C$_{Ar}$), 114.3 (CH$_{Ar}$), 95.7, 85.5 (C$_{Alkyne}$), 55.5 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3101 (w), 3002 (w), 2955 (w), 2932 (w), 2835 (w), 2211 (w), 1603 (s), 1578 (m), 1506 (s), 1461 (m), 1288 (s), 1245 (s), 1168 (s), 1026 (s), 828 (s), 789 (vs), 748 (s), 643 (s), 532 (s), 490 (s). **MS (EI, 70 eV):** m/z (%) = 292 (21), 291 ([M]$^+$, 100), 290 (15), 277 (7), 276 (36), 275 (8), 260 (6), 249 (7), 248 (28), 247 (48), 246 (16), 123 (14). **HRMS (EI):** calcd. for $C_{18}H_{13}O_1N_1S_1$ (M)$^+$ 291.07124, found 291.07079.

4-(thiophen-3-yl)-3-(o-tolylethynyl)pyridine (15g)

The corresponding 2-bromo-3-heteroarylpyridine (0.5 mmol, 120.06 mg) reacted with 2-methylphenylacetylene (0.75 mmol, 0.135 mL) to give **15g** (83.5 mg, 60%) as yellow oil. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.84 (d, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 8.53 (d, ^3J = 5.2 Hz, 1H, CH$_{Pyr}$), 7.97 (dd, ^4J = 3.0, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.59 (dd, ^3J = 5.1, ^4J = 1.4 Hz, 1H, CH$_{Thioph}$), 7.48 – 7.44 (m, 1H, CH$_{Ar}$), 7.43 (dd, ^3J = 5.1, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.41 (dd, ^3J = 5.2, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.27 – 7.23 (m, 2H, CH$_{Ar}$), 7.22 – 7.15 (m, 1H, CH$_{Ar}$), 2.44 (s, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 154.3, 148.8 (CH$_{Pyr}$), 144.1 (C$_{Pyr}$), 140.4 (C$_{Ar}$), 138.5 (C$_{Thioph}$), 132.2, 129.8, 129.0

(CH$_{Ar}$), 127.9 (CH$_{Thioph}$), 125.9 (CH$_{Ar}$), 125.9, 125.8 (CH$_{Thioph}$), 122.6 (C$_{Ar}$), 122.6 (CH$_{Pyr}$), 118.1 (C$_{Pyr}$), 94.7, 90.3 (C$_{Alkyne}$), 20.9 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 3107 (w), 3072 (w), 2924 (s), 2850 (m), 2223 (w), 1583 (m), 1445 (m), 1366 (m), 1041 (w), 863 (m), 841 (s), 814 (m), 795 (s), 748 (s), 692 (m), 666 (m), 645 (m), 616 (m), 550 (m), 484 (m). **MS (EI, 70 eV):** m/z (%) = 276 (22), 275 ([M]$^+$, 99), 274 (100), 273 (49), 272 (20), 260 (16), 242 (23), 241 (22), 230 (13), 136 (11). **HRMS (ESI-TOF):** calcd. for C$_{18}$H$_{13}$N$_1$S$_1$ ([M+H]$^+$) 276.0847, found 276.0844.
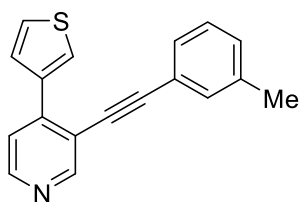
4-(thiophen-3-yl)-3-(m-tolylethynyl)pyridine (15h)

The corresponding 2-bromo-3-heteroarylpyridine (0.5 mmol, 120.06 mg) reacted with 3-methylphenylacetylene (0.75 mmol, 0.111 mL) to give **15h** (68.2 mg, 90%) as brown oil. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.79 (d, ^5J = 0.7 Hz, 1H, CH$_{Pyr}$), 8.50 (d, ^3J = 5.3 Hz, 1H, CH$_{Pyr}$), 7.98 (dd, ^4J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.59 (dd, ^3J = 5.1, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.42 (dd, ^3J = 5.1, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.39 (dd, ^3J = 5.3, ^5J = 0.7 Hz, 1H, CH$_{Pyr}$), 7.30 – 7.26 (m, 2H, CH$_{Ar}$), 7.26 – 7.22 (m, 1H, CH$_{Ar}$), 7.18 – 7.13 (m, 1H, CH$_{Ar}$), 2.34 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 154.3, 148.8 (CH$_{Pyr}$), 144.1 (C$_{Pyr}$), 138.5 (C$_{Thioph}$), 138.4 (C$_{Ar}$), 132.2, 129.9, 128.8, 128.5 (CH$_{Ar}$), 127.8, 125.9, 125.9 (CH$_{Thioph}$), 122.7 (C$_{Ar}$), 122.5 (CH$_{Pyr}$), 117.8 (C$_{Pyr}$), 95.8, 86.4 (C$_{Alkyne}$), 21.4 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 3097 (w), 3033 (w), 2918 (w), 2854 (w), 2207 (w), 1576 (s), 1486 (m), 1041 (m), 868 (m), 837 (m), 824 (m), 783 (s), 748 (s), 688 (s), 668 (s), 645 (s), 558 (m), 542 (m), 439 (m). **MS (EI, 70 eV):** m/z (%) = 276 (21), 275 ([M]$^+$, 100), 274 (84), 273 (14), 272 (10), 261 (6), 260 (30), 259 (24), 247 (6). **HRMS (ESI-TOF):** calcd. for C$_{18}$H$_{13}$N$_1$S$_1$ ([M+H]$^+$) 276.0847, found 276.0841.

3-(cyclohexylethynyl)-4-(thiophen-3-yl)pyridine (15i)
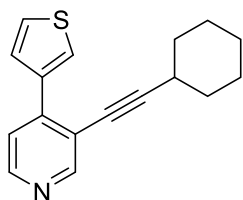
The corresponding 2-bromo-3-heteroarylpyridine (0.5 mmol, 120.06 mg) reacted with ethynylcyclohexane (0.75 mmol, 0.097 mL) to give **15h** (80.0 mg, 60%) as yellow solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.68 (d, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 8.46 (d, ^3J = 5.2 Hz, 1H, CH$_{Pyr}$), 7.96 (dd, ^4J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.55 (dd, ^3J = 5.1, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.39 (dd, ^3J = 5.1, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.34 (dd, ^3J = 5.2, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 2.63 (tt, ^3J = 9.3, ^3J = 3.8 Hz, 1H, CH), 1.92 – 1.84 (m,

2H, CH$_2$), 1.77 – 1.69 (m, 2H, CH$_2$), 1.59 – 1.48 (m, 3H, CH$_2$), 1.42 – 1.31 (m, 3H, CH$_2$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 154.5, 148.2 (CH$_{Pyr}$), 143.9 (C$_{Pyr}$), 138.6 (C$_{Thioph}$), 127.8, 125.7, 125.5 (CH$_{Thioph}$), 122.3 (CH$_{Pyr}$), 118.4 (C$_{Pyr}$), 101.1, 77.9 (C$_{Alkyne}$), 32.4 (CH$_2$), 30.1 (CH), 26.0, 25.0 (CH$_2$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3095 (w), 3056 (w), 3021 (w), 2918 (w), 2850 (w), 2209 (w), 1578 (m), 1488 (m), 1366 (w), 1166 (w), 1041 (m), 837 (m), 789 (s), 748 (s), 713 (m), 692 (m), 668 (m), 645 (m), 563 (m), 449 (s). **MS (EI, 70 eV):** *m/z* (%) = 267 ([M]$^+$, 77), 266 (34), 238 (39), 224 (69), 223 (32), 212 (60), 211 (38), 210 (39), 199 (95), 198 (52), 186 (61), 185 (100). **HRMS (ESI-TOF):** calcd. for C$_{17}$H$_{17}$N$_1$S$_1$ ([M+H]$^+$) 268.1160, found 268.1163.

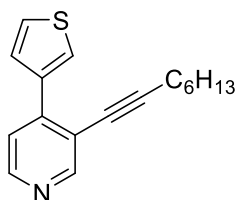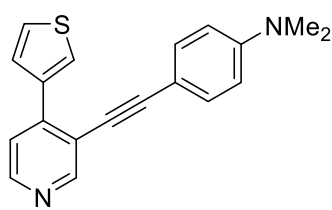### 3-(hept-1-yn-1-yl)-4-(thiophen-3-yl)pyridine (15j)

The corresponding 2-bromo-3-heteroarylpyridine (0.5 mmol, 120.06 mg) reacted with 1-octyne (0.75 mmol, 0.110 mL) to give **15j** (68.2 mg, 51%) as yellow oil. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.68 (d, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 8.46 (d, ^3J = 5.3 Hz, 1H, CH$_{Pyr}$), 7.94 (dd, ^4J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.54 (dd, ^3J = 5.1, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.38 (dd, ^3J = 5.1, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.34 (dd, ^3J = 5.3, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 2.43 (t, ^3J = 7.0 Hz, 2H, CH$_2$), 1.67 – 1.53 (m, 2H, CH$_2$), 1.48 – 1.36 (m, 2H, CH$_2$), 1.36 – 1.26 (m, 4H, CH$_2$), 0.93 – 0.86 (m, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 154.6, 148.2 (CH$_{Pyr}$), 143.9 (C$_{Pyr}$), 138.6 (C$_{Thioph}$), 127.7, 125.6, 125.6 (CH$_{Thioph}$), 122.4 (CH$_{Pyr}$), 118.4 (C$_{Pyr}$), 97.3, 77.9 (C$_{Alkyne}$), 31.5, 28.8, 28.5, 22.7, 19.8 (CH$_2$), 14.2 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3035 (w), 2953 (m), 2926 (m), 2856 (m), 2225 (w), 1578 (s), 1477 (m), 1465 (m), 1412 (w), 1366 (w), 1164 (w), 1041 (w), 837 (m), 822 (m), 789 (s), 750 (s), 668 (m), 645 (m), 569 (m), 492 (m). **MS (EI, 70 eV):** *m/z* (%) = 269 ([M]$^+$, 6), 226 (11), 212 (21), 200 (31), 199 (100), 198 (58), 197 (12), 186 (18), 185 (17), 173 (11). **HRMS (ESI-TOF):** calcd. for C$_{17}$H$_{19}$N$_1$S$_1$ ([M+H]$^+$) 270.1316, found 270.1320.
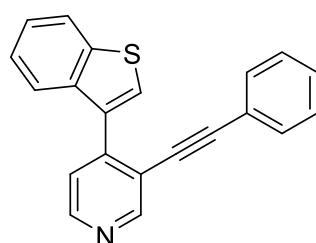
N,N-dimethyl-4-((4-(thiophen-3-yl)pyridin-3-yl)ethynyl)aniline (15k)

The corresponding 2-bromo-3-heteroarylpyridine (0.35 mmol, 84.04 mg) reacted with 4-dimethylaminophenylacetylene (0.525 mmol, 76.2 mg) to give **15k** (103.3 mg, 97%) as

yellow solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.79 (d, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 8.47 (d, ^3J = 5.3 Hz, 1H, CH$_{Pyr}$), 8.03 (dd, ^4J = 3.0, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.63 (dd, ^3J = 5.1, ^4J = 1.3 Hz, 1H, CH$_{Thioph}$), 7.42 (dd, ^3J = 5.1, ^4J = 3.0 Hz, 1H, CH$_{Thioph}$), 7.39 (dd, ^3J = 5.3, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.37 (d, ^3J = 9.1 Hz, 2H, CH$_{Ar}$), 6.66 (d, ^3J = 9.1 Hz, 2H, CH$_{Ar}$), 3.00 (s, 6H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 153.9 (CH$_{Pyr}$), 150.6 (C$_{Ar}$), 148.0 (CH$_{Pyr}$), 143.4 (C$_{Pyr}$), 138.7 (CH$_{Thioph}$), 132.8 (CH$_{Ar}$), 127.9, 125.8, 125.6 (CH$_{Thioph}$), 122.4 (CH$_{Pyr}$), 118.6 (C$_{Pyr}$), 112.0 (CH$_{Ar}$), 109.5 (CH$_{Ar}$), 97.3, 84.9 (C$_{Alkyne}$), 40.3 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3033 (m), 2891 (m), 2796 (m), 2203 (m), 1605 (s), 1574 (s), 1519 (s), 1360 (s), 1222 (s), 1193 (s), 1119 (m), 1055 (s), 812 (s), 795 (s), 746 (s), 666 (s), 643 (s), 552 (s), 540 (m), 513 (s). **MS (EI, 70 eV):** *m/z* (%) = 305 (22), 304 ([M]$^+$, 100), 303 (37), 288 (8), 287 (8), 260 (15), 259 (11), 130 (7). **HRMS (EI):** calcd. for C$_{19}$H$_{16}$N$_2$S$_1$ (M)$^+$ 304.10287, found 304.10251.

4-(benzo[*b*]thiophen-3-yl)-3-(phenylethynyl)pyridine (15l)

Yellow oil. (101.1 mg, 88%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.93 (br-s, 1H, CH$_{Pyr}$), 8.66 (br-s, 1H, CH$_{Pyr}$), 8.00 – 7.93 (m, 1H, CH$_{Ar}$), 7.81 (s, 1H, CH$_{Thioph}$), 7.83 – 7.76 (m, 1H, CH$_{Ar}$), 7.50 (d, ^3J = 5.1 Hz, 1H, CH$_{Pyr}$), 7.46 – 7.36 (m, 2H, CH$_{Ar}$), 7.28 – 7.24 (m, 3H, CH$_{Ar}$), 7.18 – 7.12 (m, 2H, CH$_{Ar}$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 153.3, 148.2 (CH$_{Pyr}$), 145.4 (C$_{Pyr}$), 140.3, 137.5, 133.4 (C$_{Thioph}$), 131.9 (C$_{Ar}$), 131.6, 128.9, 128.4, 127.5, 124.9 (CH$_{Ar}$), 124.7 (CH$_{Thioph}$), 123.2, 123.0 (CH$_{Ar}$), 122.5 (C$_{Pyr}$), 96.3, 85.9 (C$_{Alkyne}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3054 (w), 3029 (w), 2217 (w), 1578 (m), 1490 (m), 1426 (m), 1397 (m), 1055 (m), 828 (m), 752 (s), 732 (s), 688 (s), 645 (s), 593 (s), 540 (s), 503 (m), 468 (m), 424 (s). **MS (EI, 70 eV):** *m/z* (%) = 312 (12), 311 (46), 310 ([M]$^+$, 100), 309 (30), 308 (7), 307 (4), 283 (3), 282 (7), 237 (3), 155 (6), 154 (4). **HRMS (EI):** calcd. for C$_{21}$H$_{13}$N$_1$S$_1$ (M)$^+$ 310.06850 found 310.06819.

4-(benzo[*b*]thiophen-3-yl)-3-((4-(*tert*-butyl)phenyl)ethynyl)pyridine (15m)
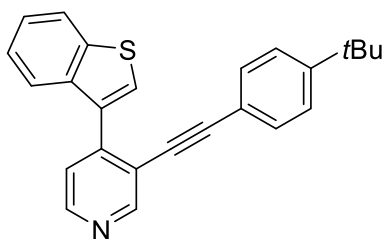
Yellow oil. (103.9 mg, 79%). **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.93 (br-s, 1H, CH$_{Pyr}$), 8.65 (br-s, 1H, CH$_{Pyr}$), 8.00 – 7.95 (m, 1H, CH$_{Ar}$), 7.82 (s, 1H, CH$_{Thioph}$), 7.84 – 7.77 (m, 1H, CH$_{Ar}$), 7.46 – 7.41 (m, 2H, CH$_{Pyr/Ar}$), 7.28 (d, ^3J = 8.3 Hz, 3H, CH$_{Ar}$), 7.11 (d, ^3J = 8.5 Hz, 2H, CH$_{Ar}$), 1.28 (s, 9H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 153.0 (C$_{Ar}$), 152.3, 147.8 (CH$_{Pyr}$), 145.4 (C$_{Pyr}$), 140.3, 137.5, 133.4 (C$_{Thioph}$), 131.4, 127.5, 125.5, 124.9 (CH$_{Ar}$), 124.7 (CH$_{Thioph}$), 123.2 (CH$_{Ar}$), 123.0 (CH$_{Pyr}$), 119.5 (C$_{Pyr}$), 96.6, 85.2 (C$_{Alkyne}$), 35.0 (C$_{tBu}$), 31.2 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): $\tilde{v}$ = 3056 (w), 3031 (w), 2959 (m), 2901 (w), 2864 (w), 2215 (w), 1578 (m), 1504 (m), 1457 (m), 1397 (m), 1261 (m), 832 (s), 760 (s), 732 (s), 651 (m), 635 (m), 593 (s), 560 (s), 507 (m), 424 (m). **MS (EI, 70 eV):** *m/z* (%) = 368 (23), 367 ([M]$^+$, 75), 366 (65), 353 (38), 352 (100), 350 (27), 336 (21), 334 (20), 311 (31), 310 (80), 309 (29), 162 (20), 41 (42), 39 (28). **HRMS (EI):** calcd. for C$_{25}$H$_{21}$N$_1$S$_1$ (M)$^+$ 367.13892 found 367.13842.

4-(benzo[*b*]thiophen-3-yl)-3-(p-tolylethynyl)pyridine (15n)
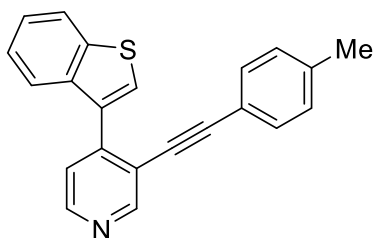
Yellow oil. (93.9 mg, 89%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.90 (s, 1H, CH$_{Pyr}$), 8.62 (d, ^3J = 5.0 Hz, 1H, CH$_{Pyr}$), 7.97 – 7.95 (m, 1H, CH$_{Ar}$), 7.81 – 7.79 (m, 1H, CH$_{Ar}$), 7.79 (s, 1H, CH$_{Thiop}$), 7.46 (d, ^3J = 5.0 Hz, 1H, CH$_{Pyr}$), 7.43 – 7.40 (m, 2H, CH$_{Ar}$), 7.05 (br-s, 4H, CH$_{Ar}$), 2.32 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 140.3 (C$_{Pyr}$), 139.2, 137.4 (C$_{Thioph}$), 135.6 (C$_{Ar}$), 133.6 (C$_{Thioph}$), 131.6, 129.2, 127.3, 124.9 (CH$_{Ar}$), 124.7 (CH$_{thiop}$), 123.2 (CH$_{Ar}$), 123.0 (CH$_{Pyr}$), 119.4 (C$_{Ar}$), 97.0, 83.0 (C$_{Alkyne}$), 21.6 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): $\tilde{v}$ = 3052 (w), 3027 (w), 2918 (w), 2852 (w), 2215 (w), 1581 (s), 1506 (m), 1426 (m), 1397 (m), 814 (s), 760 (s), 746 (s), 732 (s), 707 (m), 641 (s), 593 (s), 540 (s), 525 (m), 470 (m), 424 (s). **MS (EI, 70 eV):** *m/z* (%) = 326 (16), 325 ([M]$^+$, 60), 324 (100), 322 (15), 321 (10), 310 (50), 309 (52), 308 (13), 296 (10), 155 (15), 51 (10). **HRMS (EI):** calcd. for C$_{22}$H$_{14}$N$_1$S$_1$ (M)$^+$ 324.08415 found 324.08434.

4-(benzo[*b*]thiophen-3-yl)-3-(cyclohexylethynyl)pyridine (15o)
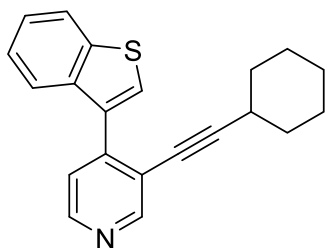
Brown oil. (105.3 mg, 95%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.77 (br-s, 1H, CH$_{Pyr}$), 8.56 (d, ^3J = 4.9 Hz, 1H, CH$_{Pyr}$), 7.93 – 7.91 (m, 1H, CH$_{Ar}$), 7.71 (dd, ^3J = 4.9, 1.8 Hz, 1H, CH$_{Pyr}$), 7.69 (s, 1H, CH$_{Thioph}$), 7.40 – 7.37 (m, 3H, CH$_{Ar}$), 2.45 – 2.39 (m, 1H, CH), 1.62 – 1.57 (m, 2H, CH$_2$), 1.49 – 1.43 (m, 2H, CH$_2$), 1.26 – 1.15 (m, 6H, CH$_2$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 153.6, 147.8 (CH$_{Pyr}$), 145.1 (C$_{Pyr}$), 140.2, 137.6, 133.8 (C$_{Thiop}$), 126.8, 124.7 (CH$_{Ar}$), 124.5 (CH$_{Thioph}$), 124.0, 123.3 (CH$_{Ar}$), 122.9 (CH$_{Pyr}$), 120.7 (C$_{Pyr}$), 101.7, 77.0 (C$_{Alkyne}$), 32.1 (CH$_2$), 29.7 (CH), 25.9, 24.6 (CH$_2$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3056 (w), 3031 (w), 2953 (w), 2926 (m), 2854 (m), 2225 (w), 1581 (s), 1455 (m), 1426 (m), 1395 (m), 1022 (m), 830 (s), 758 (s), 732 (s), 696 (m), 639 (s), 593 (s), 540 (m), 433 (m). **MS (EI, 70 eV):** *m/z* (%) = 318 (24), 317 ([M]$^+$, 84), 316 (23), 288 (28), 274 (46), 249 (48), 248 (42), 246 (36), 235 (100), 222 (33), 55 (23), 39 (42). **HRMS (EI):** calcd. for C$_{21}$H$_{19}$N$_1$S$_1$ (M)$^+$ 317.12327 found 317.12290.

4-(benzo[*b*]thiophen-3-yl)-3-(oct-1-yn-1-yl)pyridine (15p)
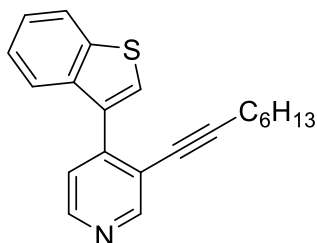
Brown oil. (120.5 mg, 59%). **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.92 (s, 1H, CH$_{Pyr}$), 8.64 (s, 1H, CH$_{Pyr}$), 7.97 – 7.89 (m, 1H, CH$_{Ar}$), 7.77 – 7.66 (m, 1H, CH$_{Thiop}$), 7.59 – 7.49 (m, 1H, CH$_{Ar}$), 7.45 – 7.35 (m, 3H, CH$_{Pyr/Ar}$), 2.22 (t, ^3J = 6.9 Hz, 2H, CH$_2$), 1.40 – 1.01 (m, 8H, CH$_2$), 0.85 (t, ^3J = 6.9 Hz, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl3)** δ = 140.2 (C$_{Pyr}$), 137.5 (C$_{Ar}$), 133.7 (C$_{Thioph}$), 126.9, 125.0, 124.7, (CH$_{Ar}$), 123.2 (CH$_{Thioph}$), 123.0 (CH$_{Ar}$), 122.9 (CH$_{Pyr}$), 122.9 (C$_{Pyr}$), 97.9, 77.4 (C$_{Alkyne}$), 31.4, 28.5, 28.2, 22.6, 19.6 (CH$_2$), 14.2 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3056 (w), 3029 (w), 2924 (s), 2850 (m), 2223 (w), 1581 (m), 1447 (m), 1426 (m), 1397 (m), 1348 (m), 1059 (m), 956 (m), 830 (m), 791 (m), 760 (s), 732 (s), 645 (s), 596 (s), 540 (m), 422 (m). **MS (EI, 70 eV):** *m/z* (%) = 319 ([M]$^+$, 33), 276 (32), 250 (35), 249 (100), 248 (79), 247 (48), 246 (50), 235 (29), 223 (38), 222 (33), 41 (41). **HRMS (EI):** calcd. for C$_{21}$H$_{21}$N$_1$S$_1$ (M)$^+$ 319.13892 found 319.13863.

4-(benzo[*b*]thiophen-3-yl)-3-((4-ethylphenyl)ethynyl)pyridine (15q)
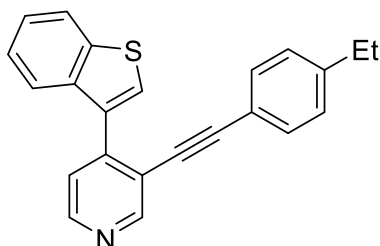
Light brown oil (102.2 mg, 68%). ^{1}H NMR (250 MHz, CDCl$_3$) δ = 8.00 – 7.93 (m, 1H, CH$_{Ar}$), 7.83 – 7.77 (m, 2H, CH$_{Thioph/Ar}$), 7.45 – 7.39 (m, 2H, CH$_{Pyr/Ar}$), 7.08 (br-s, 3H, CH$_{Ar}$), 2.62 (q, ^3J = 7.6 Hz, 2H, CH$_2$), 1.20 (t, ^3J = 7.6 Hz, 3H, CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$) δ = 145.4, 140.3, 137.3, 133.9 (C$_{Ar}$), 131.7, 128.0 (CH$_{Ar}$), 127.0 (CH$_{Thioph}$), 124.8, 124.7, 123.2, 123.0 (CH$_{Ar}$), 119.6 (C$_{Pyr}$), 97.1, 86.5 (C$_{Alkyne}$), 28.9 (CH$_2$), 15.4 (CH$_3$) ppm. IR (ATR, cm^{-1}): ṽ = 3027 (w), 2962 (m), 2873 (w), 2215 (w), 1579 (m), 1507 (m), 1426 (m), 1397 (m), 1052 (m), 951 (m), 829 (m), 760 (s), 732 (s), 642 (m), 594 (s). LRMS (GC-MS) cald for C$_{23}$H$_{17}$NS m/z 339, found 338 (M-H$^+$), 323 (M-CH4$^+$), 310 (M-Et$^+$). HRMS (EI): cald for C$_{23}$H$_{16}$NS m/z 338. 09980, found 317.09934 (M-H$^+$). MS (EI, 70 eV): *m/z* (%) = 340 (18), 339 ([M]$^+$, 100), 325 (15), 324 (49), 323 (15), 322 (15), 162 (9). HRMS (EI): calcd. for C$_{23}$H$_{17}$N$_1$S$_1$ (M)$^+$ 339.10762 found 339.10754.

4-(benzo[*b*]thiophen-3-yl)-3-((4-fluorophenyl)ethynyl)pyridine (15r)
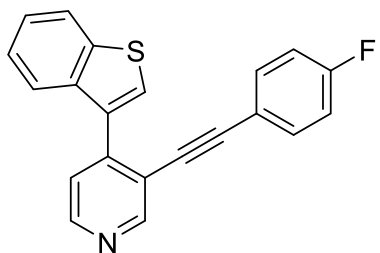
Brown oil. (72.0 mg, 79%). **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 7.99 – 7.93 (m, 1H, CH$_{Ar}$), 7.83 – 7.73 (m, 2H, CH$_{Thioph/Ar}$), 7.47 – 7.37 (m, 3H, CH$_{Pyr/Ar}$), 7.14 – 7.06 (m, 2H, CH$_{Ar}$), 7.02 – 6.87 (m, 2H, CH$_{Ar}$) ppm. **^{19}F NMR (471 MHz, CDCl$_3$)** δ = -109.87 ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 162.8 (d, $^1J_{C,F}$ = 250.6 Hz, CF), 153.2, 148.5 (CH$_{Pyr}$), 145.3 (C$_{Pyr}$), 140.3, 137.4 (C$_{Thioph}$), 133.5 (d, $^3J_{C,F}$ = 8.5 Hz, CH$_{Ar}$), 128.7 (C$_{Thioph}$), 127.3 (CH$_{Thioph}$), 124.9, 124.7 (CH$_{Ar}$), 123.2 (CH$_{Pyr}$), 123.0 (C$_{Ar}$), 118.6 (d, $^4J_{C,F}$ = 3.6 Hz, C$_{Ar}$), 115.8 (d, $^2J_{C,F}$ = 22.3 Hz, CH$_{Ar}$), 95.2, 85.7 (C$_{Alkyne}$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3118 (w), 3046 (m), 2219 (w), 1583 (m), 1504 (vs), 1401 (m), 1222 (s), 1162 (m), 1096 (m), 830 (s), 789 (s), 754 (s), 723 (s), 709 (s), 643 (s), 591 (s), 540 (s), 517 (s), 499 (s), 418 (s). **MS (EI, 70 eV):** *m/z* (%) = 330 (16), 329 ([M]$^+$, 45), 328 (100), 327 (23), 168 (7), 164 (6), 150 (8), 144 (6), 122 (6), 87 (6), 57 (6). **HRMS (EI):** calcd. for C$_{21}$H$_{12}$F$_1$N$_1$S$_1$ (M)$^+$ 329.06690 found 329.06599.

4-(benzo[*b*]thiophen-3-yl)-3-((4-(trifluoromethyl)phenyl)ethynyl)pyridine (15s)
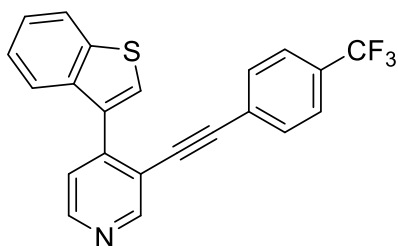
Brown solid. (89.6 mg, 82%), mp 74 – 76 °C. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.97 (br-s, 2H, CH$_{Pyr}$), 7.99 – 7.95 (m, 1H, CH$_{Ar}$), 7.81 – 7.75 (m, 1H, CH$_{Ar}$), 7.75 (s, 1H, CH$_{Thioph}$), 7.49 (d, ^3J = 8.4 Hz, 2H, CH$_{Ar}$), 7.47 – 7.39 (m, 3H, CH$_{Ar/Pyr}$), 7.19 (d, ^3J = 8.4 Hz, 2H, CH$_{Ar}$) ppm. **^{19}F NMR (471 MHz, CDCl$_3$)** δ = -62.92 (s, 3F, CF$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 153.1, 145.3 (CH$_{Pyr}$), 140.3 (C$_{Pyr}$), 137.3, 133.6, 132.2 (C$_{Thioph}$), 131.8 (CH$_{Ar}$), 130.4 (q, $^2J_{C,F}$ = 32.9 Hz, C$_{Ar}$), 128.7 (CH$_{Ar}$), 127.2 (CH$_{Thioph}$), 126.3 (C$_{Ar}$), 125.4 (q, $^3J_{C,F}$ = 3.7 Hz, CH$_{Ar}$), 124.9, 124.7 (CH$_{Ar}$), 124.1 (q, $^1J_{C,F}$ = 272.2 Hz, CF$_3$), 123.2 (CH$_{Ar}$), 123.1 (CH$_{Pyr}$), 94.7, 88.6 (C$_{Alkyne}$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 3093 (w), 3031 (w), 1578 (m), 1325 (s), 1156 (s), 1102 (s), 1067 (s), 1016 (s), 841 (s), 832 (s), 797 (s), 762 (s), 752 (s), 727 (s), 715 (s), 641 (m), 593 (s), 583 (s), 540 (s), 490 (m). **MS (EI, 70 eV):** *m/z* (%) = 380 (16), 379 ([M]$^+$, 65), 378 (100), 377 (12), 311 (8), 310 (29), 309 (28), 308 (8), 307 (8), 69 (16). **HRMS (EI):** calcd. for C$_{22}$H$_{11}$F$_3$N$_1$S$_1$ (M)$^+$ 378.05588 found 378.05545.

4-(benzo[*b*]thiophen-3-yl)-3-(o-tolylethynyl)pyridine (15t)
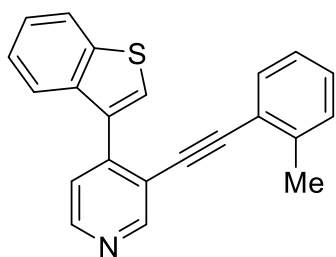
Light green solid. (120.1 mg. 98%), mp: 76 – 79 °C. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.93 (s, 1H, CH$_{Pyr}$), 8.63 (d, ^3J = 5.1 Hz, 1H, CH$_{Pyr}$), 7.96 – 7.92 (m, 1H, CH$_{Ar}$), 7.75 (s, 1H, CH$_{Thioph}$), 7.77 – 7.72 (m, 1H, CH$_{Ar}$), 7.46 (d, ^3J = 5.1 Hz, 1H, CH$_{Pyr}$), 7.42 – 7.38 (m, 2H, CH$_{Ar}$), 7.19 – 7.15 (m, 2H, CH$_{Ar}$), 7.15 – 7.03 (m, 2H, CH$_{Ar}$), 2.04 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 153.6, 148.4 (CH$_{Pyr}$), 145.0 (C$_{Pyr}$), 140.4 (C$_{Ar}$), 140.3, 137.6, 133.8 (C$_{Thioph}$), 132.2, 129.6, 128.9, 127.0, 125.6, 124.9, 124.7 (CH$_{Ar}$), 124.2 (CH$_{Thioph}$), 123.2 (CH$_{Ar}$), 123.0 (CH$_{Pyr}$), 122.4 (C$_{Ar}$), 120.4 (C$_{Pyr}$), 95.0, 89.5 (C$_{Alkyne}$), 20.3 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** $\tilde{v}$ = 3114 (w), 3023 (w), 2918 (w), 1578 (m), 1488 (m), 1426 (m), 1389 (m), 839 (m), 791 (m), 756 (s), 742 (s), 727 (s), 709 (s), 647 (m), 596 (m), 540 (m), 447 (m), 424 (s). **MS (EI, 70 eV):** *m/z* (%) = 318 (24), 317 ([M]$^+$, 84), 316 (23), 288 (28), 274 (46), 249 (48), 248 (42), 246 (36), 235 (100), 222 (33), 55 (23), 39 (42). **HRMS (EI):** calcd. for C$_{22}$H$_{14}$N$_1$S$_1$ (M)$^+$ 324.08415 found 324.08412.

4-(benzo[*b*]thiophen-3-yl)-3-((4-methoxyphenyl)ethynyl)pyridine (15u)
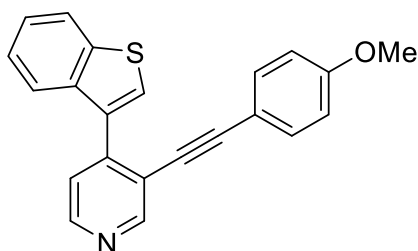
Light orange solid. (103.8 mg, 67%), mp: 120 – 123 °C. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.90 (s, 1H, CH$_{Pyr}$), 8.62 (s, 1H, CH$_{Pyr}$), 7.97 – 7.95 (m, 1H, CH$_{Ar}$), 7.81 – 7.79 (m, 1H, CH$_{Ar}$), 7.78 (s, 1H, CH$_{thioph}$), 7.47 (d, ^3J = 4.4 Hz, 1H, CH$_{Pyr}$), 7.43 – 7.40 (m, 2H, CH$_{Ar}$), 7.08 (d, ^3J = 8.9 Hz, 2H, CH$_{Ar}$), 6.77 (d, ^3J = 8.9 Hz, 2H, CH$_{Ar}$), 3.78 (s, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 160.1 (C$_{Ar}$), 151.7, 140.3 (C$_{Pyr}$), 137.5, 133.8 (C$_{Thioph}$), 133.1, 127.2, 124.8 (CH$_{Ar}$), 124.6 (CH$_{thiop}$), 123.3 (CH$_{Ar}$), 123.0 (CH$_{Pyr}$), 114.1 (C$_{Ar}$), 96.5, 87.6 (C$_{Alkyne}$), 55.4 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3118 (w), 3066 (w), 2932 (w), 2840 (m), 2213 (m), 1605 (m), 1508 (s), 1292 (m), 1249 (s), 1181 (m), 1144 (m), 1024 (s), 826 (s), 756 (s), 744 (s), 732 (s), 643 (s), 593 (m), 530 (s), 420 (s). **MS (EI, 70 eV):** *m/z* (%) = 342 (25), 341 ([M]$^+$, 100), 340 (49), 326 (40), 310 (21), 298 (37), 297 (68), 296 (46), 270 (19), 149 (23). **HRMS (EI):** calcd. for C$_{22}$H$_{15}$O$_1$N$_1$S$_1$ (M)$^+$ 341.08689 found 341.08603.

### 4-(benzo[*b*]thiophen-3-yl)-3-(m-tolylethynyl)pyridine (15v)
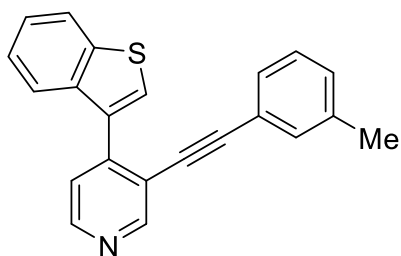
Light yellow oil. (123.5 mg, 96%). **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.91 (br-s, 1H, CH$_{Pyr}$), 8.63 (d, ^3J = 5.1 Hz, 1H, CH$_{Pyr}$), 7.99 – 7.94 (m, 1H, CH$_{Ar}$), 7.83 – 7.78 (m, 1H, CH$_{Ar}$), 7.79 (s, 1H, CH$_{Thiop}$), 7.47 (dd, ^3J = 5.1, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 7.44 – 7.40 (m, 2H, CH$_{Ar}$), 7.14 – 7.07 (m, 2H, CH$_{Ar}$), 6.99 – 6.93 (m, 2H, CH$_{Ar}$), 2.27 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ 153.5, 148.5 (CH$_{Pyr}$), 145.1 (C$_{Pyr}$), 140.3 (C$_{Ar}$), 138.1, 137.5, 133.6 (C$_{Thioph}$), 132.2, 129.7, 128.6, 128.3, 127.3, 124.8, 124.7 (CH$_{Ar}$), 124.0 (CH$_{Thioph}$), 123.2 (CH$_{Ar}$), 123.0 (CH$_{Pyr}$), 122.4 (C$_{Ar}$), 119.9 (C$_{Pyr}$), 96.4, 85.7 (C$_{Alkyne}$), 21.3 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3052 (w), 3029 (w), 2918 (w), 2856 (w), 2209 (w), 1578 (s), 1486 (m), 1426 (m), 1395 (m), 832 (m), 783 (s), 760 (s), 732 (s), 688 (s), 645 (s), 596 (s), 540 (m), 507 (m), 439 (m), 424 (s). **MS (EI, 70 eV):** *m/z* (%) = 326 (17), 325 ([M]$^+$, 62), 324 (100), 323 (9), 322 (9), 321 (5), 311 (10), 310 (43), 309 (42), 155 (6), 39 (6). **HRMS (EI):** calcd. for C$_{22}$H$_{14}$N$_1$S$_1$ (M)$^+$ 324.08415 found 324.08416.

4-((4-(benzo[*b*]thiophen-3-yl)pyridin-3-yl)ethynyl)-N,N-dimethylaniline (15w)
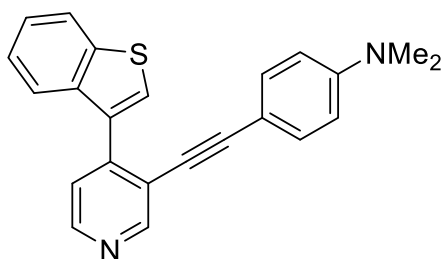
Yellow oil. (131.4 mg, 97%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.87 (br s, 1H, CH$_{Pyr}$), 8.57 (d, ^3J = 5.1 Hz, 1H, CH$_{Pyr}$), 7.97 – 7.94 (m, 1H, CH$_{Ar}$), 7.83 – 7.80 (m, 1H, CH$_{Ar}$), 7.81 (s, 1H, CH$_{Thioph}$), 7.44 (dd, ^3J = 5.1, ^5J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.42 – 7.40 (m, 2H, CH$_{Ar}$), 7.03 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$), 6.54 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$), 2.95 (s, 6H, CH$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ 153.2 (CH$_{Pyr}$), 150.4 (C$_{Ar}$), 147.7 (CH$_{Pyr}$), 144.2 (C$_{Pyr}$), 140.2, 137.7, 133.8 (C$_{Thioph}$), 132.8, 127.2, 124.7, 124.6 (CH$_{Ar}$), 123.9 (CH$_{Thioph}$), 123.3 (CH$_{Ar}$), 122.9 (CH$_{Pyr}$), 120.7 (C$_{Pyr}$), 111.8 (CH$_{Ar}$), 109.2 (C$_{Ar}$), 97.8, 84.3 (C$_{Alkyne}$), 40.2 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3039 (w), 2914 (m), 2891 (m), 2850 (m), 2800 (m), 2205 (m), 1603 (s), 1578 (s), 1519 (s), 1442 (s), 1358 (s), 1193 (s), 1140 (s), 1057 (s), 944 (s), 814 (s), 760 (s), 732 (s), 641 (s), 593 (s), 528 (s). **MS (EI, 70 eV):** *m/z* (%) = 355 (27), 354 ([M]$^+$, 100), 353(29), 339 (12), 338 (12), 337 (18), 311 (10), 310 (28), 309 (32), 155 (16). **HRMS (ESI-TOF):** calcd. for C$_{23}$H$_{18}$N$_2$S$_1$ ([M+H]$^+$) 355.1269 found 355.1273.

Synthesis of benzo[4,5]- and thieno[3,2-*f*]isoquinolines 16a-w

The corresponding starting material **15a-w** (0.2 mmol) was mixed with MsOH (30 equiv.) and stirred for 1 h at 120 °C. After cooling to room temperature, the reaction mixture was washed with saturated 10 % sodium hydroxide solution. This was followed by extraction of the crude product with EtOAc and purification by column chromatography (heptane/EtOAc 4:1) to obtain the cyclization products **16a-w**.

4-phenylthieno[3,2-*f*]isoquinoline (16a)
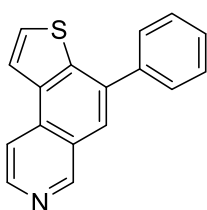
Yellow oil. (27.7 mg, 53%). **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 9.34 (br-s, 1H, CH$_{Pyr}$), 8.68 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.09 (dd, ^3J = 5.8, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.05 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.81 (br-s, 1H, CH$_{Ar}$), 7.80 – 7.77 (m, 2H, CH$_{Ar}$), 7.69 (dd, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.59 – 7.48 (m, 3H, CH$_{Ar}$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 152.5, 144.2

(CH$_{Pyr}$), 141.6 (C$_{Thioph}$), 139.9 (C$_{Ar}$), 136.9 (C$_{Thioph}$), 135.2 (C$_{Pyr}$), 131.7 (C$_{Ar}$), 129.1 (CH$_{Ar}$), 128.7 (CH$_{Thioph}$), 128.5, 127.6 (CH$_{Ar}$), 127.2 (C$_{Pyr}$), 122.8 (CH$_{Thioph}$), 122.4 (CH$_{Ar}$), 116.9 (CH$_{Pyr}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3060 (w), 3025 (w), 2918 (w), 2850 (w), 1609 (w), 1558 (w), 1484 (m), 1358 (m), 1179 (m), 1076 (m), 1036 (m), 878 (m), 762 (s), 729 (s), 699 (s), 676 (s), 596 (m), 552 (m), 490 (s), 470 (m). **MS (EI, 70 eV):** *m/z* (%) = 263 (14), 262 (30), 261 ([M]$^+$, 100), 260 (36), 259 (16), 130 (18), 74 (13), 50 (9), 45 (10). **HRMS (EI):** calcd. for C$_{17}$H$_{11}$N$_1$S$_1$ (M)$^+$ 261.06067, found 261.06057.

4-(p-tolyl)thieno[3,2-*f*]isoquinoline (16b)
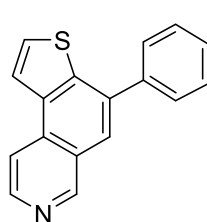
White solid. (50.2 mg, 70%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 9.33 (br-s, 1H, CH$_{Pyr}$), 8.67 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.09 (dd, ^3J = 5.8, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.05 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.79 (br-s, 1H, CH$_{Ar}$), 7.69 (d, ^3J = 7.9 Hz, 2H, CH$_{Ar}$), 7.68 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.36 (d, ^3J = 7.9 Hz, 2H, CH$_{Ar}$), 2.47 (s, 3H, CH$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 152.5, 144.1 (CH$_{Pyr}$), 141.7 (C$_{Thioph}$), 138.6 (C$_{Ar}$), 137.0 (C$_{Thioph}$), 136.8 (C$_{Ar}$), 135.1 (C$_{Pyr}$), 131.5 (C$_{Ar}$), 129.8, 128.4 (CH$_{Ar}$), 127.5 (CH$_{Thioph}$), 127.3 (C$_{Pyr}$), 122.6 (CH$_{Thioph}$), 122.4 (CH$_{Ar}$), 116.9 (CH$_{Pyr}$), 21.5 (CH$_3$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3054 (w), 3023 (w), 2918 (w), 2854 (w), 1609 (m), 1558 (m), 1492 (s), 1360 (m), 1212 (m), 1183 (m), 1096 (m), 1036 (m), 816 (s), 727 (s), 678 (s), 657 (m), 593 (s), 552 (m), 497 (s). **MS (EI, 70 eV):** *m/z* (%) = 276 (20), 275 ([M]$^+$, 100), 274 (24), 273 (10), 272 (7), 259(5), 137 (9). **HRMS (ESI-TOF):** calcd. for C$_{18}$H$_{13}$N$_1$S$_1$ ([M+H]$^+$) 276.0847, found 276.0847.
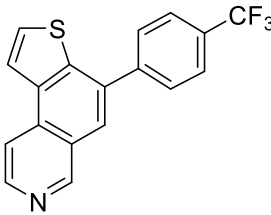
4-(4-fluorophenyl)thieno[3,2-*f*]isoquinoline (16c)
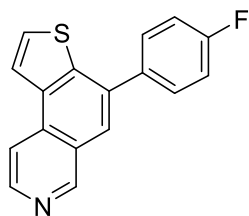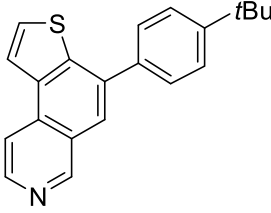
Yellow solid. (55.6 mg, 99%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 9.33 (d, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.68 (d, ^3J = 5.7 Hz, 1H, CH$_{Pyr}$), 8.09 (dd, ^3J = 5.7, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.05 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.76 (d, ^5J = 0.9 Hz, 1H, CH$_{Ar}$), 7.75 (d, ^3J = 8.7 Hz, 1H, CH$_{Ar}$), 7.74 (d, ^3J = 8.7 Hz, 1H, CH$_{Ar}$), 7.69 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.24 (d, ^3J = 8.7 Hz, 1H, CH$_{Ar}$), 7.22 (d, ^3J = 8.7 Hz, 1H, CH$_{Ar}$) ppm. **^{19}F NMR (471 MHz, CDCl$_3$)** δ = -112.94 (s, 1F, CF) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 163.04 (d, $^1J_{C,F}$ = 248.2 Hz, CF), 152.5, 144.3 (CH$_{Pyr}$), 141.5 (C$_{Thioph}$), 135.90 (d, $^4J_{C,F}$ = 3.2 Hz, C$_{Ar}$), 135.8 (C$_{Thioph}$), 135.2 (C$_{Pyr}$), 131.6 (C$_{Ar}$), 130.2 (d, $^3J_{C,F}$ = 7.8 Hz,

CH$_{Ar}$), 127.6 (CH$_{Thioph}$), 127.1 (C$_{Pyr}$), 122.8 (CH$_{Thioph}$), 122.6 (CH$_{Ar}$), 116.9 (CH$_{Pyr}$), 116.1 (d, $^2J_{C,F}$ = 21.6 Hz, CH$_{Ar}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3052 (w), 3019 (w), 2922 (w), 1607 (m), 1513 (s), 1492 (s), 1358 (m), 1216 (s), 1158 (s), 1096 (s), 826 (s), 789 (s), 727 (s), 715 (s), 676 (s), 589 (s), 544 (s), 507 (s), 470 (s). **MS (EI, 70 eV):** *m/z* (%) = 281 (9), 280 (16), 279 ([M]$^+$, 100), 278 (34), 277 (9), 250 (8), 207 (8), 69 (6). **HRMS (EI):** calcd. for C$_{17}$H$_{10}$N$_1$F$_1$S$_1$ (M)$^+$ 279.05125, found 274.05106.

4-(4-(trifluoromethyl)phenyl)thieno[3,2-*f*]isoquinoline (16d)

Yellow oil. (56.7 mg, 87%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 9.36 (s, 1H, CH$_{Pyr}$), 8.71 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.11 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.08 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.91 (d, ^3J = 8.1 Hz, 2H, CH$_{Ar}$), 7.82 (s, 1H, CH$_{Ar}$), 7.82 (d, ^3J = 8.1 Hz, 1H, CH$_{Ar}$), 7.72 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$) ppm. **^{19}F NMR (471 MHz, CDCl$_3$)** δ = -62.54 (s, 3F, CF$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 152.7, 144.7 (CH$_{Pyr}$), 143.4 (C$_{Ar}$), 140.9, 135.5 (C$_{Thioph}$), 135.4 (C$_{Pyr}$), 132.0 (C$_{Ar}$), 130.8 (q, $^2J_{C,F}$ = 32.6 Hz, C$_{Ar}$), 128.9 (CH$_{Ar}$), 127.8 (CH$_{Thioph}$), 127.0 (C$_{Pyr}$), 126.1 (q, $^3J_{C,F}$ = 3.7 Hz, CH$_{Ar}$), 124.2 (q, $^1J_{C,F}$ = 272.2 Hz, CF$_3$), 123.3 (CH$_{Thioph}$), 122.6 (CH$_{Ar}$), 116.9 (CH$_{Pyr}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3064 (w), 2926 (w), 2856 (w), 1613 (m), 1418 (m), 1323 (s), 1168 (s), 1096 (s), 1065 (vs), 1041 (s), 1016 (s), 876 (m), 845 (s), 832 (s), 802 (m), 723 (s), 676 (s), 614 (s), 548 (m), 470 (m). **MS (EI, 70 eV):** *m/z* (%) = 331 (5), 330 (21), 329 ([M]$^+$, 100), 328 (15), 259 (7), 232 (5), 164 (5), 69 (15). **HRMS (EI):** calcd. for C$_{18}$H$_{10}$N$_1$F$_3$S$_1$ (M)$^+$ 329.04806, found 329.04783.

4-(4-(*tert*-butyl)phenyl)thieno[3,2-*f*]isoquinoline (16e)

Yellow oil. (60.0 mg, 94%). **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 9.34 (br-s, 1H, CH$_{Pyr}$), 8.67 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.10 (dd, ^3J = 5.8, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.07 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.82 (br-s, 1H, CH$_{Ar}$), 7.75 (d, ^3J = 8.5 Hz, 2H, CH$_{Ar}$), 7.70 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.57 (d, ^3J = 8.5 Hz, 2H, CH$_{Ar}$), 1.42 (s, 9H, CH$_{3-tBu}$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 152.5 (CH$_{Pyr}$), 151.9 (C$_{Ar}$), 144.1 (CH$_{Pyr}$), 141.6, 136.9 (C$_{Thioph}$), 136.8 (C$_{Ar}$), 135.2 (C$_{Pyr}$), 131.6 (C$_{Ar}$), 128.1 (CH$_{Ar}$), 127.5 (CH$_{Thioph}$), 127.3 (C$_{Pyr}$), 126.0 (CH$_{Ar}$), 122.7 (CH$_{Thioph}$), 122.4 (CH$_{Ar}$), 116.9 (CH$_{Pyr}$), 34.9 (C$_{tBu}$), 31.5 (CH$_{3-tBu}$) ppm. **IR (ATR, cm^{-1}):** ṽ = 3056 (w), 3029 (w), 2959 (m), 2901 (w), 2866

(w), 1611 (m), 1556 (w), 1492 (m), 1362 (m), 1267 (m), 1096 (m), 832 (s), 800 (m), 725 (s), 678 (s), 655 (w), 639 (m), 602 (s), 540 (s). **MS (EI, 70 eV):** m/z (%) = 318 (13), 317 ([M]$^+$, 55), 303 (23), 302 (100), 286 (9), 274 (19), 273 (11), 260 (11), 137 (19), 41 (8). **HRMS (ESI-TOF):** calcd. for $C_{21}H_{19}N_1S_1$ ([M+H]$^+$) 318.1316, found 318.1312.

4-(o-tolyl)thieno[3,2-*f*]isoquinoline (16g)
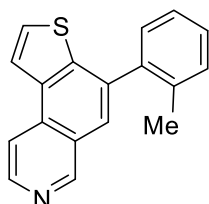
Yellow oil. (52.3 mg, 95%). **¹H NMR (250 MHz, CDCl₃)** δ = 9.33 (br-s, 1H, CH$_{Pyr}$), 8.70 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.12 (dd, ^3J = 5.8, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.05 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.68 (br-s, 1H, CH$_{Ar}$), 7.66 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.42 – 7.33 (m, 4H, CH$_{Ar}$), 2.19 (s, 3H, CH₃) ppm. **¹³C NMR (63 MHz, CDCl₃)** δ = 152.4, 144.2 (CH$_{Pyr}$), 143.1 (C$_{Ar}$), 139.2, 136.6 (C$_{Thioph}$), 136.3 (C$_{Pyr}$), 134.5, 131.7 (C$_{Ar}$), 130.7, 129.6, 128.7 (CH$_{Ar}$), 127.8 (CH$_{Thioph}$), 127.0 (C$_{Pyr}$), 126.1 (CH$_{Ar}$), 123.2 (CH$_{Thioph}$), 122.4 (CH$_{Ar}$), 116.9 (CH$_{Pyr}$), 20.0 (CH₃) ppm. **IR (ATR, cm⁻¹):** ṽ = 3058 (w), 3019 (w), 2920 (w), 2852 (w), 1613 (m), 1564 (w), 1484 (m), 1358 (m), 1098 (m), 1036 (m), 847 (m), 824 (m), 760 (s), 725 (s), 688 (s), 674 (s), 635 (m), 598 (m), 554 (m), 474 (s) ppm. **MS (EI, 70 eV):** m/z (%) = 276 (23), 275 ([M]$^+$, 100), 274 (56), 273 (24), 272 (12), 260 (10), 242 (9), 241 (8), 137 (12), 123 (7). **HRMS (EI):** calcd. for $C_{18}H_{13}N_1S_1$ (M)$^+$ 275.07632, found 275.07614.

4-(m-tolyl)thieno[3,2-*f*]isoquinoline (16h)
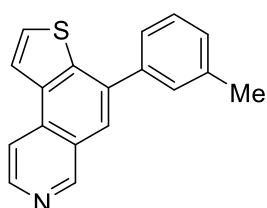
Yellow oil. (54 mg, 98%). **¹H NMR (250 MHz, CDCl₃)** δ = 9.34 (br-s, 1H, CH$_{Pyr}$), 8.67 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.09 (dd, ^3J = 5.8, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.05 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.80 (br-s, 1H, CH$_{Ar}$), 7.68 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.62 – 7.58 (m, 2H, CH$_{Ar}$), 7.44 (t, ^3J = 7.9 Hz, 1H, CH$_{Ar}$), 7.33 – 7.28 (m, 1H, CH$_{Ar}$), 2.48 (s, 3H, CH₃) ppm. **¹³C NMR (63 MHz, CDCl₃)** δ = 152.5, 144.2 (CH$_{Pyr}$), 141.6 (C$_{Ar}$), 139.9 (C$_{Thioph}$), 138.8(C$_{Ar}$), 137.0 (C$_{Thioph}$), 135.2 (C$_{Pyr}$), 131.6 (C$_{Ar}$), 129.5, 129.2, 129.0 (CH$_{Ar}$), 127.6 (CH$_{Thioph}$), 127.3 (C$_{Pyr}$), 125.5 (CH$_{Ar}$), 122.7 (CH$_{Thioph}$), 122.4 (CH$_{Ar}$), 116.9 (CH$_{Pyr}$), 21.7 (CH₃) ppm. **IR (ATR, cm⁻¹):** ṽ = 3099 (w), 3023 (w), 2918 (m), 2850 (w), 1609 (m), 1562 (m), 1480 (m), 1356 (m), 1212 (m), 1096 (m), 1036 (m), 868 (m), 822 (s), 785 (s), 725 (s), 705 (s), 676 (s), 633 (m), 554 (m). **MS (EI, 70 eV):** m/z

(%) = 276 (21), 275 ([M]$^+$, 100), 274 (17), 273 (9), 259 (6), 137 (9). **HRMS (ESI-TOF):** calcd. for C$_{18}$H$_{13}$N$_1$S$_1$ ([M+H]$^+$) 276.0847, found 276.0848.

4-cyclohexylthieno[3,2-*f*]isoquinoline (16i)
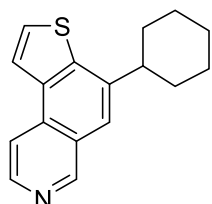
Yellow oil. (45.5 mg, 85%). **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 9.27 (d, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.61 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.04 (dd, ^3J = 5.8, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.00 (d, ^3J = 5.4 Hz, 1H, CH$_{Thioph}$), 7.65 (br-s, 1H, CH$_{Ar}$), 7.64 (d, ^3J = 5.4 Hz, 1H, CH$_{Thioph}$), 2.97 (tt, ^3J = 11.7, ^3J = 3.3 Hz, 1H, CH), 2.21 – 2.13 (m, 2H, CH$_2$), 2.00 – 1.92 (m, 2H, CH$_2$), 1.72 – 1.33 (m, 6H, CH$_2$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 152.2, 143.5 (CH$_{Pyr}$), 142.3, 142.1 (C$_{Thioph}$), 134.5 (C$_{Pyr}$), 131.3 (C$_{Ar}$), 127.4 (C$_{Pyr}$), 126.2, 122.7 (CH$_{Thioph}$), 118.9 (CH$_{Ar}$), 116.8 (CH$_{Pyr}$), 44.0 (CH), 33.4, 27.0, 26.4 (CH$_2$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3058 (w), 2922 (s), 2848 (m), 1677 (w), 1613 (m), 1568 (m), 1496 (m), 1447 (m), 1377 (m), 1214 (m), 1080 (m), 1034 (m), 859 (s), 816 (s), 787 (m), 723 (s), 678 (s), 552 (s), 472 (s). **MS (EI, 70 eV):** *m/z* (%) = 268 (19), 267 ([M]$^+$, 100), 225 (11), 224 (39), 223 (18), 212 (18), 211 (28), 210 (15), 199 (43), 198 (25), 185 (15). **HRMS (ESI-TOF):** calcd. for C$_{17}$H$_{17}$N$_1$S$_1$ ([M+H]$^+$) 268.1160, found 268.1162.
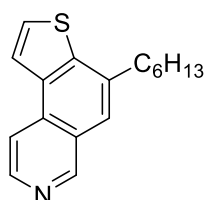

4-hexylthieno[3,2-*f*]isoquinoline (16j)

Yellow oil. (50.2 mg, 93%). **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 9.27 (br-s, 1H, CH$_{Pyr}$), 8.62 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.04 (dd, ^3J = 5.8, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.00 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.65 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.62 (br-s, 1H, CH$_{Ar}$), 3.03 (t, ^3J = 7.7 Hz, 2H, CH$_2$), 1.95 – 1.83 (m, 2H, CH$_2$), 1.47 – 1.32 (m, 6H, CH$_2$), 0.90 (t, ^3J = 7.7 Hz, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 152.0, 143.6 (CH$_{Pyr}$), 142.6, 136.9 (C$_{Thioph}$), 134.5 (C$_{Pyr}$), 131.3 (C$_{Ar}$), 127.3 (C$_{Pyr}$), 126.4, 122.6 (CH$_{Thioph}$), 121.4 (CH$_{Ar}$), 116.8 (CH$_{Pyr}$), 35.2, 31.8, 29.4, 29.1, 22.7 (CH$_2$), 14.2 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3112 (w), 2957 (m), 2920 (s), 2848 (m), 1613 (m), 1570 (w), 1463 (m), 1377 (m), 1216 (m), 1183 (m), 1074 (m), 868 (m), 853 (s), 828 (m), 808 (m), 793 (m), 729 (s), 674 (m), 548 (m), 474 (m). **MS (EI, 70 eV):** *m/z* (%) = 270 (9), 269 ([M]$^+$, 47), 212 (9), 201 (5), 200 (16), 199 (100), 198 (59), 197 (6), 171 (8), 154 (8). **HRMS (ESI-TOF):** calcd. for C$_{17}$H$_{19}$N$_1$S$_1$ ([M+H]$^+$) 270.1316, found 270.1320.

N,N-dimethyl-4-(thieno[3,2-*f*]isoquinolin-4-yl)aniline (16k)
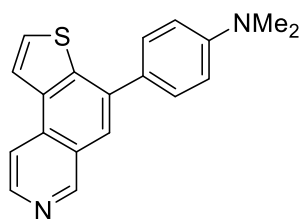
Yellow oil. (55 mg, 90%). **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 9.32 (br-s, 1H, CH$_{Pyr}$), 8.63 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.06 (dd, ^3J = 5.8, ^5J = 0.9 Hz, 1H, CH$_{Pyr}$), 8.03 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 7.76 (br-s, 1H, CH$_{Ar}$), 7.70 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$), 7.67 (d, ^3J = 5.5 Hz, 1H, CH$_{Thioph}$), 6.87 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$), 3.05 (s, 6H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 152.3 (CH$_{Pyr}$), 150.7 (C$_{Ar}$), 143.6 (CH$_{Pyr}$), 141.9, 137.1 (C$_{Thioph}$), 135.0 (C$_{Pyr}$), 131.2 (C$_{Ar}$), 129.2 (CH$_{Ar}$), 127.6 (C$_{Ar}$), 127.5 (C$_{Pyr}$), 127.3, 122.4 (CH$_{Thioph}$), 121.7 (CH$_{Ar}$), 116.8 (CH$_{Pyr}$), 112.5 (CH$_{Ar}$), 40.5 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 2918 (w), 2850 (w), 2800 (w), 1605 (vs), 1521 (s), 1492 (s), 1442 (m), 1356 (s), 1195 (s), 1168 (s), 948 (m), 814 (s), 721 (s), 678 (s), 591 (s), 548 (s). **MS (EI, 70 eV):** *m/z* (%) = 306 (6), 305 (22), 304 ([M]$^+$, 100), 303 (45), 289 (5), 288 (13), 260 (9), 259 (7), 152 (11). **HRMS (ESI-TOF):** calcd. for C$_{17}$H$_{17}$N$_1$S$_1$ ([M+H]$^+$) 268.1160, found 268.1162.

6-phenylbenzo[4,5]thieno[3,2-*f*]isoquinoline (16l)
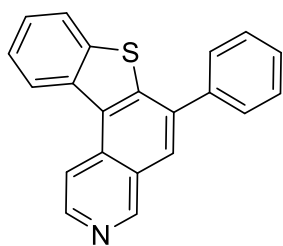
Yellow solid. (63.1 mg, 80%). mp: 127 – 129 ºC. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 9.45 (br-s, 1H, CH$_{Pyr}$), 8.83 (dd, ^3J = 8.4, ^4J = 1.3 Hz, 1H, CH$_{Ar}$), 8.75 (br-s, 1H, CH$_{Pyr}$), 7.79 – 7.75 (m, 2H, CH$_{Ar/Pyr}$)7.94 (br-s, 1H, CH$_{Ar}$), 7.79 – 7.75 (m, 2H, CH$_{Ar}$), 7.64 (d, ^3J = 8.4, 1H, CH$_{Ar}$), 7.60 – 7.50 (m, 4H, CH$_{Ar}$). **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 152.4, 144.0 (CH$_{Pyr}$), 141.9, 136.6 (C$_{Thioph}$), 135.2 (C$_{Pyr}$), 132.4, 131.5 (C$_{Ar}$), 129.6, 127.6, 122.8, 122.4 (CH$_{Ar}$), 118.0 (CH$_{Pyr}$), 114.5 (CH$_{Ar}$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3054 (w), 3025 (w), 2920 (w), 1607 (m), 1566 (w), 1484 (m), 1440 (m), 1344 (m), 1119 (m), 1026 (m), 977 (m), 806 (m), 754 (m), 717 (s), 692 (s), 622 (s), 600 (s), 482 (s), 420 (m). **MS (EI, 70 eV):** *m/z* (%) = 312 (21), 311 ([M]$^+$, 100), 310 (12), 309 (7), 283 (4), 282 (7), 155 (9), 51 (4). **HRMS (EI):** calcd. for C$_{21}$H$_{13}$N$_1$S$_1$ (M)$^+$ 311.07632 found 311.07644.

6-(4-(*tert*-butyl)phenyl)benzo[4,5]thieno[3,2-*f*]isoquinoline (16m)
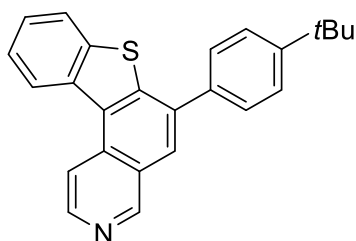
Yellow solid. (66.4 mg, 72%). mp: 197 – 199 ºC.

^{1}H NMR (500 MHz, CDCl₃) δ = 9.43 (br s, 1H, CH$_{Pyr}$), 8.84 (d, ^3J = 8.2 Hz, 1H, CH$_{Ar}$), 8.75 (br s, 2H, CH$_{Pyr}$), 7.98 (d, ^3J = 8.1 Hz, 1H, CH$_{Ar}$), 7.94 (s, 1H, CH$_{thiop}$), 7.73 (br d, ^3J = 8.2 Hz, 2H, CH$_{Ar}$), 7.64 (ddd, ^3J = 8.2, ^3J = 7.2, ^4J = 1.1 Hz, 2H, CH$_{Ar}$), 7.59 (br d, ^3J = 8.2 Hz, 2H, CH$_{Ar}$), 7.54 (ddd, ^3J = 8.1, ^3J = 7.2, ^4J = 1.0 Hz, 2H, CH$_{Ar}$), 1.43 (s, 9H, CH₃). **^{13}C NMR (63 MHz, CDCl₃)** δ = 153.3 (CH$_{Pyr}$), 152.0 (C$_{Ar}$), 144.3 (CH$_{Pyr}$), 143.8 (C$_{Ar}$), 140.1, 137.2, 136.8 (C$_{Thioph}$), 136.6(C$_{Pyr}$), 132.4 (C$_{Thioph}$), 128.6 (C$_{Ar}$), 128.4, 126.1, 126.0, 125.8, 125.4, 124.6, 123.3 (CH$_{Ar}$), 116.4 (CH$_{Pyr}$), 35.0 (C$_{tBu}$), 31.5 (CH₃) ppm. **IR (ATR, cm⁻¹):** ṽ = 3033 (w), 2957 (m), 2866 (w), 1607 (m), 1515 (m), 1463 (m), 1341 (m), 1265 (m), 1107 (m), 1022 (m), 919 (m), 832 (s), 810 (s), 750 (m), 723 (s), 701 (m), 647 (m), 602 (s), 540 (s), 420 (m). **MS (EI, 70 eV):** *m/z* (%) = 368 (21), 367 ([M]$^+$, 81), 353 (20), 352 (100), 324 (20), 162 (23), 41 (19), 39 (12). **HRMS (EI):** calcd. for C₂₅H₂₁N₁S₁ (M)$^+$ 367.13892 found 367.13850.
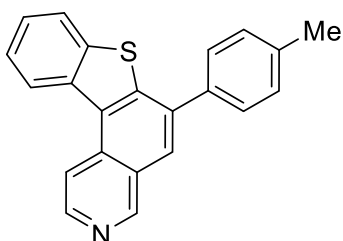
6-(p-tolyl)benzo[4,5]thieno[3,2-*f*]isoquinoline (16n)

Yellow solid. (73.6 mg, 92%). mp: 171 – 174 ºC. **^{1}H NMR (500 MHz, CDCl₃)** δ = 9.41 (br s, 1H, CH$_{Pyr}$), 8.83 (dt, ^3J = 8.2, ^4J = 1.0 Hz, 1H, CH$_{Ar}$), 8.77 (br s, 1H, CH$_{Pyr}$), 8.73 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 7.97 (dt, ^3J = 8.0, ^4J = 1.0 Hz, 1H, CH$_{Ar}$), 7.92 (s, 1H, CH$_{thiop}$), 7.67 (d, ^3J = 8.1 Hz, 2H, CH$_{Ar}$), 7.64 (ddd, ^3J = 8.2, ^3J = 7.1, ^4J = 1.0 Hz, 1H, CH$_{Ar}$), 7.53 (ddd, ^3J = 8.0, ^3J = 7.1, ^4J = 1.0 Hz, 1H, CH$_{Ar}$), 7.38 (d, ^3J = 8.1 Hz, 2H, CH$_{Ar}$), 2.49 (s, 3H, CH₃). **^{13}C NMR (63 MHz, CDCl₃)** δ = 144.4 (C$_{Pyr}$), 140.1 (C$_{Ar}$), 139.0, 138.7 (C$_{Thioph}$), 136.7 (C$_{Ar}$), 136.5 (C$_{Thioph}$), 129.9, 128.6, 126.3, 125.9, 125.5 (CH$_{Ar}$), 124.6 (CH$_{thiop}$), 123.3 (CH$_{Ar}$), 21.5 (CH₃) ppm. **IR (ATR, cm⁻¹):** ṽ = 3019 (w), 2918 (w), 2852 (w), 1607 (m), 1564 (w), 1510 (m), 1488 (m), 1442 (m), 1344 (m), 1263 (m), 1210 (m), 1181 (m), 1111 (m), 979 (m), 857 (m), 808 (s), 744 (m), 721 (s), 670 (m), 596 (s). **MS (EI, 70 eV):** *m/z* (%) = 326 (23), 325 ([M]$^+$,100), 324 (17), 323 (3), 295 (6), 162 (11), 95 (6), 39 (6). **HRMS (EI):** calcd. for C₂₂H₁₅N₁S₁ (M)$^+$ 325.09197 found 325.09224.

6-(4-ethylphenyl)benzo[4,5]thieno[3,2-*f*]isoquinoline (16o)
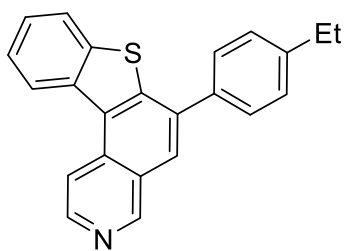
Yellow solid. (72.4 mg, 81%). mp: 158 – 161 ºC. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 9.46 (s, 1H, CH$_{Pyr}$), 8.94 – 8.62 (m, 3H, CH$_{Ar/Pyr}$), 7.98 (d, ^3J = 8.1 Hz, 1H, CH$_{Ar}$), 7.94 – 7.91 (m, 1H, CH$_{Ar}$), 7.70 (d, ^3J = 7.9 Hz, 2H, CH$_{Ar}$), 7.68 – 7.60 (m, 1H, CH$_{Ar}$), 7.58 – 7.51 (m, 1H, CH$_{Ar}$), 7.41 (d, ^3J = 7.9 Hz, 2H, CH$_{Ar}$), 2.79 (q, ^3J = 7.6 Hz, 2H, CH$_2$), 1.35 (t, ^3J = 7.6 Hz, 3H, CH$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 153.4, 145.1 (CH$_{Pyr}$), 144.5, 143.6, 140.0, 137.2, 137.1, 136.6, 132.2 (C$_{Ar}$), 128.7, 128.6, 126.0, 125.8, 125.4, 124.6 (CH$_{Ar}$), 123.2 (CH$_{Pyr}$), 28.9 (CH$_2$), 15.6 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3023 (w), 2961 (m), 2924 (w), 2873 (w), 1609 (m), 1488 (m), 1418 (m), 1344 (m), 1261 (m), 1187 (m), 1121 (m), 1024 (m), 979 (m), 882 (m), 826 (s), 806 (s), 750 (s), 719 (s), 668 (m), 600 (s). **MS (EI, 70 eV):** *m/z* (%) = 340 (18), 339 ([M]$^+$, 100), 325 (15), 324 (49), 323 (15), 322 (15), 162 (9). **HRMS (EI):** calcd. for C$_{23}$H$_{17}$N$_1$S$_1$ (M)$^+$ 339.10762 found 339.10754.

6-(4-fluorophenyl)benzo[4,5]thieno[3,2-*f*]isoquinoline (16p)
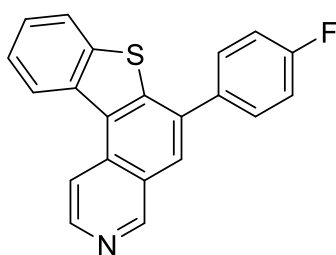
Yellow solid. (53.9 mg, 47%). mp: 203 – 206 ºC.

^{1}H NMR (500 MHz, CDCl$_3$) δ = 9.43 (s, 1H, CH$_{Pyr}$), 8.84 (d, ^3J = 8.1 Hz, 1H, CH$_{Ar}$), 8.82 – 8.70 (m, 2H, CH$_{Pyr}$), 7.98 (d, ^3J = 8.1 Hz, 1H, CH$_{Ar}$), 7.91 (s, 1H, CH$_{Ar}$), 7.76 – 7.72 (m, 2H, CH$_{Ar}$), 7.65 (ddd, ^3J = 8.1, ^3J = 7.1, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.55 (ddd, ^3J = 8.1, ^3J = 7.1, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.29 – 7.24 (m, 2H, CH$_{Ar}$) ppm. **^{19}F NMR (471 MHz, CDCl$_3$)** δ = -112.72 (s, 1F, CF) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 163.1 (d, $^1J_{C,F}$ = 248.6 Hz, CF), 153.4, 144.8 (CH$_{Pyr}$), 143.4, 139.9, 136.6 (C$_{Ar}$), 136.1 (C$_{Pyr}$), 135.8 (d, $^4J_{C,F}$ = 3.7 Hz, C$_{Ar}$), 132.4 (C$_{Ar}$), 130.6 (d, $^3J_{C,F}$ = 8.3 Hz, CH$_{Ar}$), 128.7 (C$_{Pyr}$), 126.2, 126.0, 125.5, 124.7 (CH$_{Ar}$), 123.3 (CH$_{Pyr}$), 116.1 (d, $^2J_{C,F}$ = 21.6 Hz, CH$_{Ar}$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3017 (w), 1603 (m), 1508 (s), 1488 (m), 1344 (m), 1222 (s), 1152 (m), 1024 (m), 979 (m), 917 (m), 826 (s), 746 (s), 717 (s), 694 (m), 596 (s). **MS (EI, 70 eV):** *m/z* (%) = 330 (27), 329 ([M]$^+$, 100), 328 (19), 327 (6), 302 (4), 301 (5), 300 (8), 165 (9). **HRMS (EI):** calcd. for C$_{21}$H$_{11}$F$_1$N$_1$S$_1$ (M)$^+$ 328.05907 found 328.05858.

6-(o-tolyl)benzo[4,5]thieno[3,2-*f*]isoquinoline (16q)
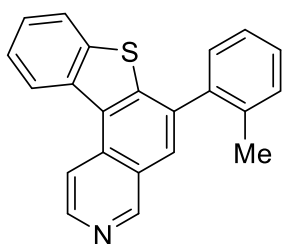
Yellow oil: 73.8 mg (0.23 mmol, 88%). **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 9.40 (br s, 1H, CH$_{Pyr}$), 8.85 (dt, ^3J = 8.4, ^4J = 0.9 Hz, 1H, CH$_{Ar}$), 8.80 (d, ^3J = 6.1 Hz, 1H, CH$_{Pyr}$), 8.76 (d, ^3J = 6.1 Hz, 1H, CH$_{Pyr}$), 7.93 (dt, ^3J = 7.9, ^4J = 1.0 Hz, 1H, CH$_{Ar}$), 7.85 (br s, 1H, CH$_{Ar}$), 7.65 (ddd, ^3J = 8.4, ^3J = 7.2, ^4J = 1.3 Hz, 1H, CH$_{Ar}$), 7.53 (ddd, ^3J = 8.1, ^3J = 7.2, ^4J = 1.1 Hz, 1H, CH$_{Ar}$), 7.46 – 7.40 (m, 2H, CH$_{Ar}$), 7.40 – 7.34 (m, 2H, CH$_{Ar}$), 2.19 (s, 3H, CH$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 153.4 (CH$_{Pyr}$), 144.9 (C$_{Pyr}$), 144.7 (CH$_{Pyr}$), 140.2 (C$_{Thioph}$), 139.1 (C$_{Ar}$), 136.8, 136.7 (C$_{Thioph}$), 136.5(C$_{Ar}$), 132.5(C$_{Thioph}$), 130.7, 129.7, 129.0 (CH$_{Ar}$), 128.1 (C$_{Ar}$), 127.5 (C$_{Pyr}$), 126.2, 126.1, 126.0, 125.4, 124.6, 123.4 (CH$_{Ar}$), 116.3 (CH$_{Pyr}$), 20.0 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3056 (w), 3021 (w), 2920 (w), 2852 (w), 1609 (m), 1568 (m), 1484 (m), 1445 (m), 1344 (m), 1261 (m), 1212 (w), 1107 (m), 1024 (m), 979 (m), 919 (m), 878 (w), 810 (s), 752 (s), 723 (s), 618 (s). **MS (EI, 70 eV):** *m/z* (%) = 326 (19), 325 ([M]$^+$, 100), 324 (35), 323 (13), 322 (12), 295 (9), 162 (9), 39 (9). **HRMS (EI):** calcd. for C$_{22}$H$_{15}$N$_1$S$_1$ (M)$^+$ 325.09197 found 325.09175.

6-(m-tolyl)benzo[4,5]thieno[3,2-*f*]isoquinoline (3r)
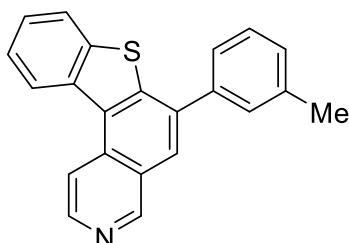
Yellow solid. (66.5 mg, 77%). mp: 136 – 139 ºC. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 9.40 (s, 1H, CH$_{Pyr}$), 8.83 (dd, ^3J = 8.2, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 8.77 (d, ^3J = 6.1 Hz, 1H, CH$_{Pyr}$), 8.73 (d, ^3J = 6.1 Hz, 1H, CH$_{Pyr}$), 7.97 (dd, ^3J = 8.2, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.93 (s, 1H, CH$_{Ar}$), 7.64 (ddd, ^3J = 8.2, ^3J = 7.1, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.59 – 7.57 (m, 2H, CH$_{Ar}$), 7.54 (ddd, ^3J = 8.2, ^3J = 7.1, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.46 (t, ^3J = 7.9 Hz, 1H, CH$_{Ar}$), 7.35 – 7.32 (m, 1H, CH$_{Ar}$), 2.50 (s, 3H, CH$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 153.5, 144.7 (CH$_{Pyr}$), 143.6, 140.0, 139.7, 138.9, 137.3, 136.6, 132.4 (C$_{Ar}$), 129.6, 129.4, 129.0 (CH$_{Ar}$), 128.6 (C$_{Ar}$), 127.7 (C$_{Pyr}$), 126.1, 125.8, 125.8, 125.4, 124.6, 123.2 (CH$_{Ar}$), 116.3 (CH$_{Pyr}$), 21.7 (CH$_3$) ppm. **IR** (ATR, cm^{-1}): ṽ = 3033 (m), 2914 (w), 2854 (w), 1605 (m), 1564 (m), 1484 (m), 1453 (m), 1344 (m), 1263 (m), 1216 (m), 1119 (m), 1018 (w), 925 (m), 874 (m), 804 (s), 779 (m), 717 (s), 705 (s), 612 (s), 579 (m). **MS (EI, 70 eV):** *m/z* (%) = 326 (25), 325 ([M]$^+$, 100), 324 (14), 295 (6), 162 (7), 148 (5), 63 (5). **HRMS (EI):** calcd. for C$_{22}$H$_{15}$N$_1$S$_1$ (M)$^+$ 325.09197 found 325.09158.

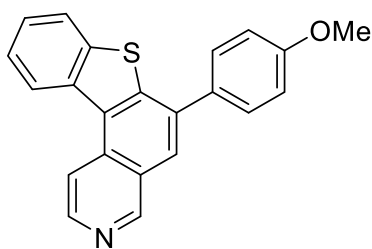**6-(4-methoxyphenyl)benzo[4,5]thieno[3,2-*f*]isoquinoline (16s)**

Yellow solid. (78.2 mg, 87%). mp: 200 – 202 ºC. **¹H NMR (500 MHz, CDCl₃)** δ = 9.39 (s, 1H, CH_{Py}), 8.83 (br-d, ^3J = 8.4 Hz, 1H, CH_{Ar}), 8.76 (d, ^3J = 6.1 Hz, 1H, CH_{Pyr}), 8.72 (d, ^3J = 6.1 Hz, 1H, CH_{Pyr}), 7.97 (br-d, ^3J = 8.4 Hz, 1H, CH_{Ar}), 7.90 (s, 1H, CH_{Ar}), 7.71 (d, ^3J = 8.9 Hz, 2H, CH_{Ar}), 7.63 (ddd, ^3J = 8.4, ^3J = 7.1, ^4J = 1.2 Hz, 1H, CH_{Ar}), 7.53 (ddd, ^3J = 8.4, ^3J = 7.1, ^4J = 1.2 Hz, 1H, CH_{Ar}), 7.10 (d, ^3J = 8.9 Hz, 2H, CH_{Ar}) ppm. **¹³C NMR (126 MHz, CDCl₃)** δ = 160.1 (C_{Ar}), 153.4, 144.5 (CH_{Pyr}), 143.8, 140.0, 136.8, 136.7, 132.2 (C_{Ar}), 130.0 (CH_{Ar}), 128.5 (C_{Ar}), 127.8 (C_{Pyr}), 126.0, 125.6, 125.4, 124.6, 123.2 (CH_{Ar}), 116.3 (CH_{Pyr}), 114.5 (CH_{Ar}), 55.6 (CH_3), 3.93 (s, 3H, CH_3) ppm. **IR (ATR, cm⁻¹):** ṽ = 3019 (w), 2918 (m), 2837 (m), 1607 (s), 1515 (s), 1346 (m), 1292 (m), 1249 (s), 1179 (s), 1113 (m), 1026 (s), 977 (m), 828 (s), 806 (s), 750 (s), 721 (s), 696 (m), 647 (m), 614 (s), 598 (s). **MS (EI, 70 eV):** *m/z* (%) = 342 (29), 341 ([M]⁺, 100), 326 (9), 298 (14), 297 (26), 296 (14), 148 (10). **HRMS (EI):** calcd. for $C_{22}H_{15}O_1N_1S_1$ (M)⁺ 341.08689 found 341.08669.

6-cyclohexylbenzo[4,5]thieno[3,2-*f*]isoquinoline (16t)
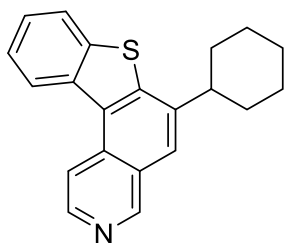
Yellow solid. (57.9 mg, 70%). mp: 123 – 126 ºC. **¹H NMR (500 MHz, CDCl₃)** δ = 9.35 (s, 1H, CH_{Pyr}), 8.79 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 8.71 (d, ^3J = 6.1 Hz, 1H, CH_{Pyr}), 8.66 (d, ^3J = 6.1 Hz, 1H, CH_{Pyr}), 8.02 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.81 (s, 1H, CH_{thiop}), 7.62 (ddd, ^3J = 8.2, ^3J = 7.0, ^4J = 1.2 Hz, 1H, CH_{Ar}), 7.54 (ddd, ^3J = 8.0, ^3J = 7.0, ^3J = 1.0 Hz, 1H, CH_{Ar}), 3.00 (tt, ^3J = 11.7, ^3J = 3.1 Hz, 1H, CH), 2.25 – 2.18 (m, 2H, CH_2), 2.01 – 1.96 (m, 2H, CH_2), 1.92 – 1.84 (m, 1H, CH_2), 1.74 – 1.63 (m, 2H, CH_2), 1.64 – 1.51 (m, 2H, CH_2), 1.46 – 1.34 (m, 1H, CH_2) ppm. **¹³C NMR (126 MHz, CDCl₃)** δ = 153.1, 144.1 (CH_{Pyr}), 144.0 (C_{Pyr}), 142.1, 139.3, 137.0, 131.9(C_{thiop}), 128.0 (C_{Ar}), 125.9, 125.3, 124.6, 123.3, 122.0 (CH_{Ar}), 116.2 (CH_{Pyr}), 44.0 (CH), 33.4, 27.1, 26.4 (CH_2) ppm. **IR (ATR, cm⁻¹):** ṽ = 3058 (w), 2918 (m), 2844 (m), 1607 (m), 1566 (w), 1442 (m), 1344 (m), 1249 (w), 1156 (m), 1078 (m), 993 (m), 921 (m), 857 (m), 806 (s), 750 (s), 719 (s), 688 (m), 633 (m), 602 (s), 587 (m). **MS (EI, 70 eV):** *m/z* (%) = 318 (31), 317 ([M]⁺, 100), 274 (31), 261 (30), 260 (17), 249 (29), 248

(25), 233 (18), 41 (32), 39 (16). **HRMS (EI):** calcd. for $C_{21}H_{19}N_1S_1$ (M)$^+$ 317.12327 found 317.12320.

6-hexylbenzo[4,5]thieno[3,2-*f*]isoquinoline (16u)
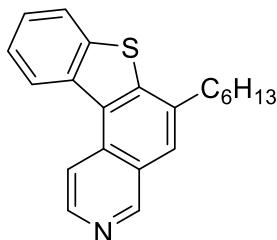
Dark yellow solid. (34.5 mg, 73%). mp: 75 – 78 ºC. **¹H NMR (500 MHz, CDCl₃)** δ = 9.35 (br s, 1H, CH$_{Pyr}$), 8.78 (dt, ^3J = 8.2, ^4J = 0.9 Hz, 1H, CH$_{Ar}$), 8.73 (br s, 1H, CH$_{Pyr}$), 8.66 (d, ^3J = 5.8 Hz, 1H, CH$_{Pyr}$), 8.02 (dt, ^3J = 7.9, ^4J = 0.8 Hz, 3H, CH$_{Ar}$), 7.76 (br s, 1H, CH$_{Ar}$), 7.62 (ddd, ^3J = 8.4, ^3J = 7.1, ^4J = 1.3 Hz, 1H, CH$_{Ar}$), 7.54 (ddd, ^3J = 8.1, ^3J = 7.1, ^3J = 1.2 Hz, 1H, CH$_{Ar}$), 3.04 (t, ^3J = 7.7 Hz, 2H, CH₂), 1.94 – 1.88 (m, 2H, CH₂), 1.52 – 1.46 (m, 2H, CH₂), 1.42 – 1.31 (m, 4H, CH₂), 0.92 (t, ^3J = 7.2 Hz, 3H, CH₃) ppm. **¹³C NMR (126 MHz, CDCl₃)** δ 152.9, 144.2 (CH$_{Pyr}$), 144.0 (C$_{Ar}$), 139.4, 136.9, 136.8 (C$_{Thioph}$), 131.9 (C$_{Ar}$), 128.0 (C$_{Pyr}$), 125.9, 125.3, 124.6, 124.5, 123.4 (CH$_{Ar}$), 116.3 (CH$_{Pyr}$), 35.2, 31.8, 29.4, 29.0, 22.7 (CH₂), 14.2 (CH₃) ppm. **IR (ATR, cm⁻¹):** ṽ = 3056 (w), 2951 (m), 2924 (s), 2852 (m), 1609 (m), 1574 (w), 1463 (m), 1370 (w), 1257 (w), 1197 (m), 1026 (m), 919 (m), 853 (s), 812 (s), 746 (m), 721 (s), 674 (s), 628 (m), 575 (s), 546 (s). **MS (EI, 70 eV):** *m/z* (%) = 320 (16), 319 ([M]$^+$, 68), 250 (20), 249 (100), 248 (71), 247 (16), 246 (14), 233 (46), 43 (25), 41 (29). **HRMS (EI):** calcd. for $C_{21}H_{21}N_1S_1$ (M)$^+$ 319.13892 found 319.13893.

6-(4-(trifluoromethyl)phenyl)benzo[4,5]thieno[3,2-*f*]isoquinoline (16v)
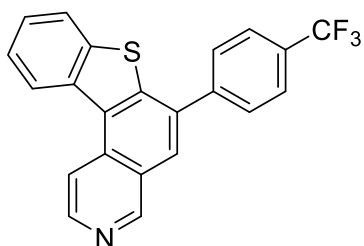
White solid. (67.1 mg, 96%), mp: 187 – 190 ºC. **¹H NMR (500 MHz, CDCl₃)** δ = 9.44 (s, 1H, CH$_{Pyr}$), 8.85 (dt, ^3J = 8.4, ^4J = 0.8 Hz, 1H, CH$_{Ar}$), 8.82 (br s, 1H, CH$_{Pyr}$), 8.75 (d, ^3J = 6.0 Hz, 1H, CH$_{Pyr}$), 7.99 (dt, ^3J = 8.1, ^4J = 0.8 Hz, 1H, CH$_{Ar}$), 7.94 (br s, 1H, CH$_{Ar}$), 7.90 (d, ^3J = 8.1 Hz, 2H, CH$_{Ar}$), 7.84 (d, ^3J = 8.2 Hz, 2H, CH$_{Ar}$), 7.66 (ddd, ^3J = 8.2, ^3J = 7.1, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.57 (ddd, ^3J = 8.1, ^3J = 7.2, ^4J = 1.1 Hz, 1H, CH$_{Ar}$). **¹⁹F NMR (471 MHz, CDCl₃)** δ = -62.56 (s, 3F, CF₃) ppm. **¹³C NMR (126 MHz, CDCl₃)** δ = 153.6, 145.2 (CH$_{Pyr}$), 143.3, 142.7 (C$_{Ar}$), 139.8, 136.5 (C$_{Thioph}$), 135.6 (C$_{Ar}$), 132.7 (C$_{Thioph}$), 131.0 (q, $^2J_{C,F}$ = 32.7 Hz, C$_{Ar}$), 129.2 (CH$_{Ar}$), 129.0, 126.4, 126.3 (CH$_{Ar}$), 126.1 (q, $^3J_{C,F}$ = 3.7 Hz, CH$_{Ar}$), 125.6, 124.7 (CH$_{Ar}$), 124.2 (q, $^1J_{C,F}$ = 272.5 Hz, CF₃), 123.3 (CH$_{Ar}$), 116.4 (CH$_{Pyr}$) ppm. **IR (ATR, cm⁻¹):** ṽ = 3054 (w), 3025 (w), 1609 (m), 1564 (w), 1416 (m), 1325 (s), 1218 (w), 1156 (s), 1115 (s), 1065 (s), 1016 (m), 917 (m), 835 (s),

812 (s), 750 (s), 723 (s), 690 (m), 618 (m), 591 (m). **MS (EI, 70 eV):** *m/z* (%) = 380 (24), 379 ([M]$^+$, 100), 360 (4), 309 (5), 282 (4), 189 (3), 141 (3), 69 (13). **HRMS (EI):** calcd. for $C_{22}H_{12}F_3N_1S_1$ (M)$^+$ 379.06371 found 379.06345.

4-(benzo[4,5]thieno[3,2-*f*]isoquinolin-6-yl)-N,N-dimethylaniline (16w)
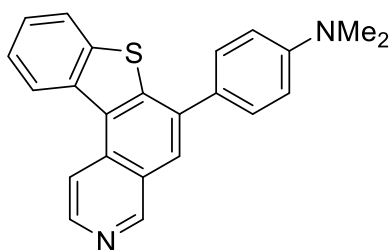
Yellow solid. (67.2 mg, 73%). mp: 215 – 218 ºC.

¹H NMR (500 MHz, CDCl₃) δ = 9.36 (s, 1H, CH$_{Pyr}$), 8.80 (br-d, ^3J = 8.2 Hz, 1H, CH$_{Ar}$), 8.72 (d, ^3J = 6.1 Hz, 1H, CH$_{Pyr}$), 8.68 (d, ^3J = 6.1 Hz, 1H, CH$_{Pyr}$), 7.96 (br-d, ^3J = 8.2 Hz, 1H, CH$_{Ar}$), 7.87 (s, 1H), 7.67 (d, ^3J = 8.9 Hz, 2H, CH$_{Ar}$), 7.61 (ddd, ^3J = 8.2, ^3J = 7.1, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 7.51 (ddd, ^3J = 8.2, ^3J = 7.1, ^4J = 1.2 Hz, 1H, CH$_{Ar}$), 6.88 (d, ^3J = 8.9 Hz, 2H, CH$_{Ar}$), 3.07 (s, 6H, CH₃) ppm. **¹³C NMR (126 MHz, CDCl₃)** δ = 153.2 (CH$_{Pyr}$), 150.6 (C$_{Ar}$), 144.1 (CH$_{Pyr}$), 144.0 (C$_{Pyr}$), 139.9, 137.3, 136.6 (C$_{Thioph}$), 131.8 (C$_{Ar}$), 129.4 (CH$_{Ar}$), 128.3, 127.8 (C$_{Ar}$), 127.4 (C$_{Pyr}$), 125.7, 125.1, 124.9, 124.4, 123.1 (CH$_{Ar}$), 116.1 (CH$_{Pyr}$), 112.3 (CH$_{Ar}$), 40.4 (CH₃) ppm. **IR** (ATR, cm^{-1}): ṽ = 3017 (w), 2850 (w), 2794 (w), 1605 (s), 1521 (s), 1490 (m), 1366 (s), 1230 (m), 1189 (s), 1119 (m), 1065 (m), 977 (m), 946 (m), 868 (m), 806 (s), 748 (s), 717 (s), 645 (m), 596 (s). **MS (EI, 70 eV):** *m/z* (%) = 355 (27), 354 ([M]$^+$, 100), 353 (34), 338 (12), 310 (8), 309 (6), 177 (26), 155 (7). **HRMS (ESI-TOF):** calcd. for $C_{23}H_{18}N_2S_1$ ([M+H]$^+$) 355.1269 found 355.1191.

Synthesis of 5- and 6-Azaindoles
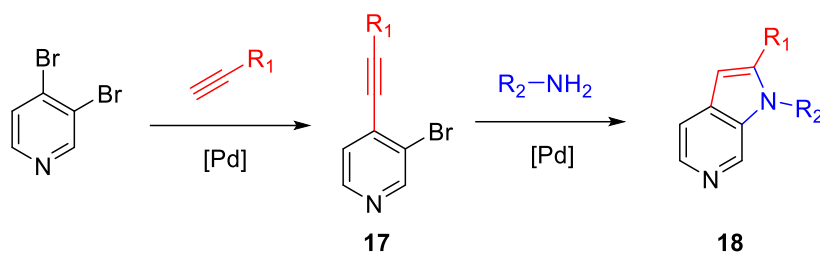
## Synthesis of 3-bromo-4-(arylethynyl)pyridine (17a-c)

3,4-Dibromopyridine (1 mmol), phenylacetylene (1.1 equiv.), Pd(PPh$_3$)$_4$ (10 mol%), CuI (10 mol%) and diisopropylamine (2 mL) were added into a dried pressure tube equipped with a septum. The reaction was back-filled with argon three times and the septum was replaced by a Teflon cap. The reaction mixture was stirred at room temperature for 2 hours. Then reaction mixture was extracted by ethyl acetate, washed organic layer 3 times by water, dried by Na$_2$SO$_4$, and the product was obtained after flash chromatography on a silica gel column with n-hexane: ethyl acetate.

3-bromo-4-(phenylethynyl)pyridine (17a):
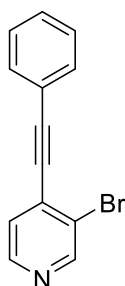
It was prepared following general procedure using 3,4-dibromopyridine (1 mmol, 237 mg) and phenylacetylene (1.1 mmol, 102 mg). The product was purified by flash chromatography (heptane/ethyl acetate 8:2) to yield **17a** (185 mg, 72 %) as a brow oil. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.63 (d, ^4J = 0.6 Hz, 1H, CH$_{Pyr}$), 8.34 (d, ^3J = 5.0 Hz, 1H, CH$_{Pyr}$), 7.59 – 7.37 (m, 2H, CH$_{Ar}$), 7.29 – 7.20 (m, 4H, CH$_{Ar/Pyr}$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 152.08, 148.08 (CH$_{Pyr}$), 133.43 (C$_{Pyr}$), 132.37, 129.96, 128.88 (CH$_{Ar}$), 126.87 (C$_{Ar}$), 123.39 (CH$_{Pyr}$), 122.12 (C$_{Pyr}$), 99.05, 85.95 (C$_{Alkyne}$) ppm. **MS (EI, 70 eV):** m/z (%) = 259 ([M]$^+$, 100), 257 (97), 177 (34), 151 (96), 98 (38), 75 (65).

3-bromo-4-((4-methoxyphenyl)ethynyl)pyridine (17b)
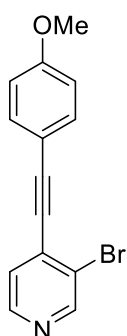
It was prepared following the general procedure using 3,4-dibromopyridine (3.0 mmol, 711 mg,) and 1-ethynyl-4-methoxybenzene (3.3 mmol, 396 mg). The product was purified by flash chromatography (heptane/ethyl acetate 8:2) to yield **17b** (720 mg, 84 %) as a brow oil. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.76 (d, ^4J = 0.6 Hz, 1H, CH$_{Pyr}$), 8.47 (d, ^3J = 5.0 Hz, 1H, CH$_{Pyr}$), 7.60 – 7.49 (m, 2H, CH$_{Ar}$), 7.38 (dd, ^3J = 5.0,

$^4J = 0.6$ Hz, 1H, CH$_{Pyr}$), 6.97 – 6.85 (m, 2H, CH$_{Ar}$), 3.85 (s, 3H, CH$_3$). **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 161.09 (C$_{Ar}$), 152.01, 148.02 (CH$_{Pyr}$), 133.92, 126.67 (CH$_{Ar}$), 114.59 (CH$_{Pyr}$), 99.60, 85.14 (C$_{Alkyne}$), 55.74 (CH$_3$). **MS (EI, 70 eV):** m/z (%) = 289 ([M]$^+$, 100), 287 (97), 274 (24), 164 (26), 138 (32).

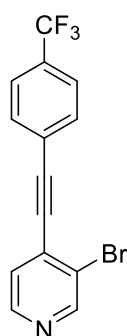### 3-bromo-4-((4-(trifluoromethyl)phenyl)ethynyl)pyridine (17c)

It was prepared following general procedure using 3,4-dibromopyridine (1.07 mmol, 253 mg,) and 1-ethynyl-4-(trifluoromethyl)benzene (1.17 mmol, 200 mg,). The product was purified by flash chromatography (heptane/ethyl acetate 8:2) to yield **17c** (282.1 mg, 81 %) as a yellow crystalline solid. **^{1}H NMR (500 MHz, CDCl$_3$)** δ = 8.80 (s, 1H, CH$_{Pyr}$), 8.53 (d, $^3J = 5.0$ Hz, 1H, CH$_{Pyr}$), 7.71 (d, $^3J = 8.6$ Hz, 2H, CH$_{Ar}$), 7.65 (d, $^3J = 8.5$ Hz, 2H, CH$_{Ar}$), 7.42 (d, $^3J = 5.0$ Hz, 1H, CH$_{Pyr}$) ppm. **^{19}F NMR (471 MHz, CDCl$_3$)** δ = -62.98 (s, 3F, CF$_3$) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 152.0, 148.0 (CH$_{Pyr}$), 132.5 (C$_{Ar}$), 132.4 (CH$_{Ar}$), 131.4 (q, $^2J_{C,F} = 32.9$ Hz, C$_{Ar}$), 126.7 (CH$_{Ar}$), 125.6 (q, $^3J_{C,F} = 3.9$ Hz, CH$_{Ar}$), 123.9 (q, $^1J_{C,F} = 272.5$ Hz, CF$_3$), 123.3 (CH$_{Pyr}$), 96.8, 87.6 (C$_{Alkyne}$) ppm.

Synthesis of 6-azaindoles
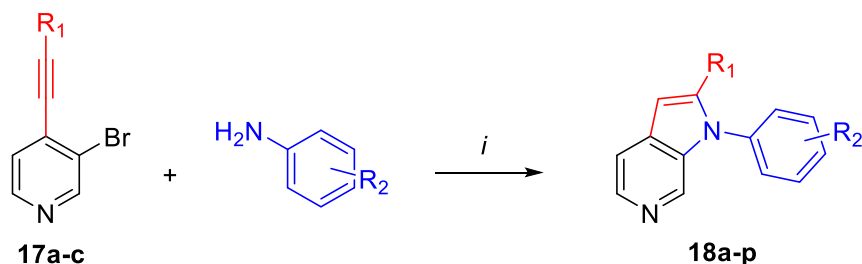
1,2-diphenyl-1H-pyrrolo[2,3-c]pyridine (18a) [147]
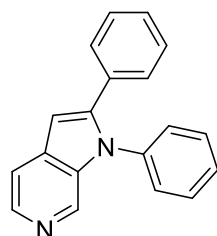
3-Bromo-2-(phenylethynyl)pyridine (**17a**) (1.0 equiv, 0.3 mmol; 77.4 mg), aniline (1.1 equiv., 0.33 mmol, 30.7 mg), Pd(OAc)$_2$ (10 mol%, 0.03 mmol, 6.7 mg), Xantphos (10 mol%, 0.03 mmol, 17.6 mg), and Cs$_2$CO$_3$ (3.0 equiv., 0.9 mmol, 293.22 mg.) were placed in a dried pressure tube equipped with a septum. Then dried and degassed DMF (4.0 mL) was added under argon. The reaction was back-filled with argon three times and the septum was replaced by a Teflon cap. The reaction mixture was allowed to stir at 120 °C for 24 h. Then the reaction mixture was cooled to room

temperature and filtered through a pad of Celite. The filtrate was dried under reduced pressure, and the product 17a was obtained after flash chromatography on a silica gel column with ethyl acetate to yield 1,2-diphenyl-1H-pyrrolo[2,3-c]pyridine **18a** (54,3 mg, 67 %) as a white solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.62 (s, 1H, CH$_{Pyr}$), 8.29 (d, ^3J = 5.5 Hz, 1H, CH$_{Pyr}$), 7.54 (dd, ^3J = 5.5, ^4J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.46 – 7.33 (m, 3H, CH$_{Ar}$), 7.24 – 7.22 (m, 3H, CH$_{Ar}$), 6.76 (d, ^4J = 0.8 Hz, 1H, CH$_{Pyrrole}$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 143.99, 139.82 (CH$_{Pyr}$), 133.92, 132.92 (C$_{Ar}$), 131.37, 129.46, 129.16, 128.29, 128.21 (CH$_{Ar}$), 127.85 (C$_{Pyr}$), 127.70 (CH$_{Ar}$), 114.61 (CH$_{Pyr}$), 102.63 (CH$_{Pyrrole}$) ppm. **MS (EI, 70 eV):** m/z (%) = 270 ([M]$^+$, 100), 135 (25), 77 (27), 51 (25).

2-phenyl-1-(*p*-tolyl)-1H-pyrrolo[2,3-c]pyridine (18b) [147]
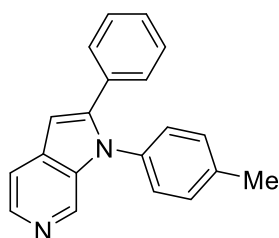
Following general procedure and using compound **17a** (0.3 mmol, 77.4 mg) and 4-methylaniline (0.33 mmol, 35.3 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18b** (60.6 mg, 71 %) a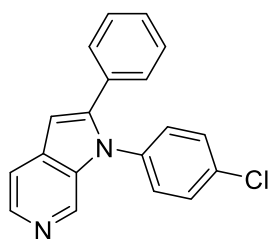s a yellowish solid. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.60 (s, 1H, CH$_{Pyr}$), 8.28 (d, ^3J = 5.4 Hz, 1H, CH$_{Pyr}$), 7.52 (dd, ^3J = 5.4, ^4J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.29 – 7.17 (m, 4H, CH$_{Ar/Pyr}$), 7.15 – 7.07 (m, 2H, CH$_{Ar}$), 6.73 (d, ^4J = 0.8 Hz, 1H, CH$_{Pyrrole}$), 2.38 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 144.26, 139.77 (CH$_{Pyr}$), 138.00, 134.81, 134.12, 133.03 (C$_{Ar}$), 131.63, 130.27, 129.33, 128.40, 127.61 (CH$_{Ar}$), 114.76 (CH$_{Pyr}$), 102.56 (CH$_{Pyrrole}$), 21.29 (CH$_3$) ppm.

1-(4-chlorophenyl)-2-phenyl-1H-pyrrolo[2,3-c]pyridine (18c)

Following general procedure and using compound **17a** (77.4 mg; 0.3 mmol) and 4-chloroaniline (0.33 mmol, 42.1 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18c** (55.3 mg, 61 %) as a yellowish solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.49 (s, 1H, CH$_{Pyr}$), 8.19 (d, ^3J = 5.4 Hz, 1H, CH$_{Pyr}$), 7.42 (dd, ^3J = 5.4, ^4J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.31 – 7.22 (m, 2H, CH$_{Ar}$), 7.21 – 7.10 (m, 5H, CH$_{Ar}$), 7.10 – 7.03 (m, 2H, CH$_{Ar}$), 6.64 (d, ^4J = 0.8 Hz, 1H, CH$_{Pyrrole}$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 144.30, 140.42 (CH$_{Pyr}$), 136.09, 134.00, 133.46 (C$_{Ar}$), 131.40, 130.12, 129.55, 129.22, 128.83 (CH$_{Ar}$), 115.12 (CH$_{Pyr}$), 103.46 (CH$_{Pyrrole}$) ppm.

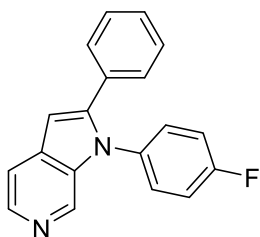## 1-(4-fluorophenyl)-2-phenyl-1H-pyrrolo[2,3-*c*]pyridine (18d)

Following general procedure and using compound **17a** (0.3 mmol, 77.4 mg) and 4-fluoroaniline (0.33 mmol, 36.7 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18d** (57.9 mg, 67 %) as a yellowish solid. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.57 (s, 1H, CH$_{Pyr}$), 8.30 (d, ^3J = 5.4 Hz, 1H, CH$_{Pyr}$), 7.53 (dd, ^3J = 5.4, ^4J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.31 – 7.16 (m, 7H, CH$_{Ar}$), 7.10 (t, ^3J = 8.6 Hz, 2H, CH$_{Ar}$), 6.74 (d, ^4J = 0.8 Hz, 1H, CH$_{Pyrrole}$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 163.9 (d, $^1J_{C,F}$ = 248.6 Hz, CF), 144.2 (C$_{Ar}$), 140.1 (CH$_{Pyr}$), 136.0 (C$_{Ar}$),133.8 (CH$_{Pyr}$), 131.5 (d, $^4J_{C,F}$ = 3.2 Hz, C$_{Ar}$), 133.1, 131.3 (C$_{Ar}$),129.5 (d, $^3J_{C,F}$ = 8.7 Hz, CH$_{Ar}$), 129.3, 128.6, 128.5 (CH$_{Ar}$), 116.7 (d, $^2J_{C,F}$ = 22.9 Hz, CH$_{Ar}$), 114.9 (CH$_{Pyr}$), 102.9 (CH$_{Pyrrole}$) ppm. **MS (EI, 70 eV):** m/z (%) = 289 (([M]$^+$, 100), 274 (31), 164 (34), 138 (42).
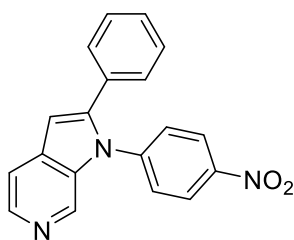
## 1-(4-nitrophenyl)-2-phenyl-1H-pyrrolo[2,3-*c*]pyridine (18e)

Following general procedure 2 and using compound **3a** (0.3 mmol, 77.4 mg) and 4-nitroaniline (0.33 mmol, 45.6 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **17e** (62.9 mg, 74 %) as a yellow solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.55 (s, 1H, CH$_{Pyr}$), 8.20 (d, ^3J = 5.4 Hz, 1H, CH$_{Pyr}$), 8.16 – 8.08 (m, 2H, CH$_{Ar}$), 7.41 (dd, ^3J = 5.4, ^4J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.29 – 7.20 (m, 2H, CH$_{Ar}$), 7.20 – 7.10 (m, 3H, CH$_{Ar}$), 7.09 – 7.01 (m, 2H, CH$_{Ar}$), 6.65 (d, ^4J = 0.8 Hz, 1H, CH$_{Pyrrole}$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 146.79, 144.16 (C$_{Ar}$), 143.34, 141.13 (CH$_{Pyr}$), 135.42, 134.06, 133.57 (C$_{Ar}$), 130.99, 129.59, 129.11, 128.33, 125.35 (CH$_{Ar}$), 115.45 (CH$_{Pyr}$), 105.02 (CH$_{Pyrrole}$) ppm.

2-(4-methoxyphenyl)-1-phenyl-1H-pyrrolo[2,3-*c*]pyridine (18f)
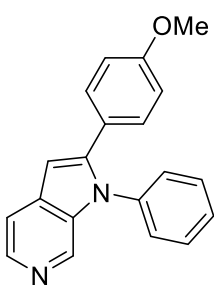
Following general procedure and using compound **17b** (0.20 mmol, 57.62 mg) and aniline (0.22 mmol, 20.46 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18f** (41.4 mg, 69 %) as a light yellow solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.61 (s, 1H, CH$_{Pyr}$), 8.30 (d, ^3J = 5.4 Hz, 1H, CH$_{Pyr}$), 7.54 (dd, ^3J = 5.4, ^4J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.49 – 7.39 (m, 3H, CH$_{Ar}$), 7.31 – 7.24 (m, 4H, CH$_{Ar}$), 7.24 – 7.18 (m, 2H, CH$_{Ar}$), 6.84 – 6.78 (m, 2H, CH$_{Ar}$),

6.71 (d, ^4J = 0.8 Hz, 1H, CH$_{Pyrrole}$), 3.79 (s, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 160.00 (C$_{Ar}$), 144.42, 140.15 (CH$_{Pyr}$), 137.82, 136.06, 134.06, 133.46 (C$_{Ar}$), 130.84 (CH$_{Ar}$), 129.88 (C$_{Ar}$), 128.21, 128.15, 124.14 (CH$_{Ar}$), 114.82 (CH$_{Pyr}$), 114.21 (CH$_{Ar}$), 102.19 (CH$_{Pyrrole}$), 55.59 (CH$_3$) ppm. **MS (EI, 70 eV):** m/z (%) = 300 ([M]$^+$, 100), 285 (28), 255 (24), 77 (32).

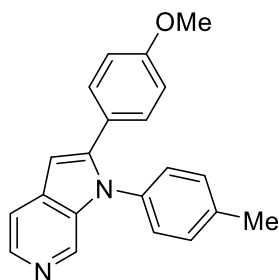### 2-(4-methoxyphenyl)-1-(p-tolyl)-1H-pyrrolo[2,3-c]pyridine (18g)

Following general procedure and using compound **17b** (0.20 mmol, 57.62 mg) and 4-methylaniline (0.22 mmol, 23.54 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18g** (50.3 mg, 80 %) as a white solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.62 (s, 1H, CH$_{Pyr}$), 8.31 (d, ^3J = 5.4 Hz, 1H, CH$_{Pyr}$), 7.55 (dd, ^3J = 5.4, ^4J = 0.8 Hz, 1H, CH$_{Pyr}$), 7.28 (m, 1H, CH$_{Ar}$), 7.27 – 7.24 (m, 2H, CH$_{Ar}$), 7.24 – 7.21 (m, 1H, CH$_{Ar}$), 7.20 – 7.14 (m, 2H, CH$_{Ar}$), 6.87 – 6.84 (m, 1H, CH$_{Ar}$), 6.83 – 6.81 (m, 1H, CH$_{Ar}$), 6.72 (d, ^4J = 0.8 Hz, 1H, CH$_{Pyrrole}$), 3.82 (s, 3H, CH$_3$), 2.44 (s, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 159.92 (C$_{Ar}$), 144.45, 139.92 (CH$_{Pyr}$), 138.12, 136.15, 135.12, 134.08, 133.35 (C$_{Ar}$), 130.79 (CH$_{Ar}$), 130.46 (C$_{Ar}$), 127.85, 124.21 (CH$_{Ar}$), 114.74 (CH$_{Pyr}$), 114.16 (CH$_{Ar}$), 101.90 (CH$_{Pyrrole}$), 55.54 (CH$_3$), 21.50 (CH$_3$) ppm. **MS (EI, 70 eV):** m/z (%) = 314 ([M]$^+$, 100), 299 (28), 255 (24), 91 (15).

1-(4-ethoxyphenyl)-2-(4-methoxyphenyl)-1H-pyrrolo[2,3-c]pyridine (18h)
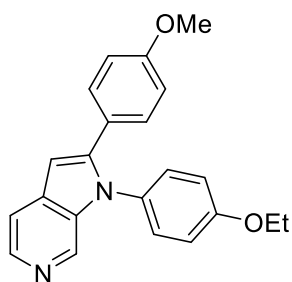
Following general procedure and using compound **17b** (0.20 mmol, 57.62 mg,) and 4-ethoxyaniline (0.22 mmol, 30.14 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18h** (49.6 mg, 72 %) as a white solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.61 (s, 1H, CH$_{Pyr}$), 8.33 (d, ^3J = 5.3 Hz, 1H, CH$_{Pyr}$), 7.58 (d, ^3J = 5.3 Hz, 1H, CH$_{Pyr}$), 7.33 – 7.17 (m, 4H, CH$_{Ar}$), 7.03 – 6.95 (m, 2H, CH$_{Ar}$), 6.90 – 6.82 (m, 2H), 6.74 (s, 1H, CH$_{Pyrrole}$), 4.12 (t, ^3J = 7.0 Hz, 2H, CH$_2$), 3.84 (s, 3H, CH$_3$), 1.50 (q, ^3J = 7.0 Hz, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 159.92, 158.76 (C$_{Ar}$), 144.69, 139.68 (CH$_{Pyr}$), 136.35, 133.92, 133.29 (C$_{Ar}$), 130.79 (CH$_{Ar}$), 130.26, 129.22 (C$_{Ar}$), 124.14, 115.50 (CH$_{Ar}$), 114.73 (CH$_{Pyr}$), 114.17 (CH$_{Ar}$), 101.62 (CH$_{Pyrrole}$), 64.08 (CH$_2$), 55.54 (CH$_3$), 15.11 (CH$_3$) ppm.

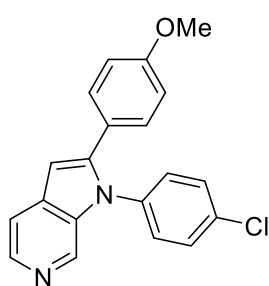## 1-(4-chlorophenyl)-2-(4-methoxyphenyl)-1H-pyrrolo[2,3-c]pyridine (18i)

Following general procedure and using compound **17b** (0.20 mmol, 57.62 mg) and 4-chloroaniline (0.22 mmol, 27.61 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18i** (52.2 mg, 78 %) as a brow solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.60 (s, 1H, CH$_{Pyr}$), 8.31 (d, ^3J = 5.4 Hz, 1H, CH$_{Pyr}$), 7.54 (dd, ^3J = 5.4, 0.8 Hz, 1H, CH$_{Pyr}$), 7.48 – 7.36 (m, 2H, CH$_{Ar}$), 7.25 – 7.14 (m, 4H, CH$_{Ar}$), 6.89 – 6.78 (m, 2H, CH$_{Ar}$), 6.71 (d, ^3J = 0.8 Hz, 1H, CH$_{Pyrrole}$), 3.80 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 159.81 (C$_{Ar}$), 144.03, 140.04 (CH$_{Pyr}$), 136.03, 135.55, 133.67, 133.40, 133.30 (C$_{Ar}$), 130.67 (CH$_{Ar}$), 130.04 (C$_{Ar}$), 128.97, 123.40 (CH$_{Ar}$), 114.63 (CH$_{Pyr}$), 114.04 (CH$_{Ar}$), 102.31 (CH$_{Pyrrole}$), 55.29 (CH$_3$) ppm. **MS (EI, 70 eV):** m/z (%) = 334 (100), 284 (35), 255 (34), 75(18).
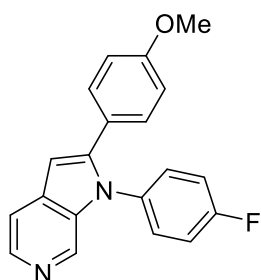
1-(4-fluorophenyl)-2-(4-methoxyphenyl)-1H-pyrrolo[2,3-c]pyridine (18j)

Following general procedure and using compound **17b** (0.20 mmol, 57.62 mg,) and 4-fluoroaniline (0.22 mmol, 22.2 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18j** (49.3 mg, 80 %) as a yellow solid. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.65 (s, 1H, CH$_{Pyr}$), 8.39 (d, ^3J = 5.4 Hz, 1H, CH$_{Pyr}$), 7.62 (dd, ^3J = 5.4, ^4J = 1.1 Hz, 1H, CH$_{Pyr}$), 7.40 – 7.15 (m, 6H, H$_{Ar}$), 6.91 (d, ^3J = 8.9 Hz, 2H, CH$_{Ar}$), 6.79 (d, ^4J = 0.8 Hz, 1H, CH$_{Pyrrole}$), 3.88 (s, 3H, CH$_3$) ppm. **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 161.9 (d, $^1J_{C,F}$ = 248.6 Hz, CF), 159.9, 144.3 (C$_{Ar}$), 140.1 (CH$_{Pyr}$), 136.0 (C$_{Ar}$), 133.7 (CH$_{Pyr}$), 133.6 (d, $^4J_{C,F}$ = 3.9 Hz, C$_{Ar}$), 130.7 (CH$_{Ar}$), 129.6 (d, $^3J_{C,F}$ = 8.7 Hz, CH$_{Ar}$), 123.7 (C$_{Ar}$), 116.7 (d, $^2J_{C,F}$ = 22.9 Hz, CH$_{Ar}$), 114.7 (CH$_{Pyr}$), 114.1 CH$_{Ar}$), 102.1 (CH$_{Pyrrole}$), 55.4 (CH$_3$) ppm.

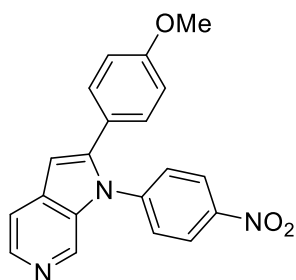## 2-(4-methoxyphenyl)-1-(4-nitrophenyl)-1*H*-pyrrolo[2,3-c]pyridine (18k)

Following general procedure and using compound **17b** (0.20 mmol, 57.62 mg) and 4-nitroaniline (0.22 mmol, 30.38 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18k** (51.8 mg, 75 %) as a yellow solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.80 (s, 1H, CH$_{Pyr}$), 8.52 – 8.37 (m, 3H, CH$_{Ar/Pyr}$), 7.70 (dd, ^3J = 5.5,

$^4J = 1.0$ Hz, 1H, CH$_{Pyr}$), 7.60 – 7.50 (m, 2H, CH$_{Ar}$), 7.39 – 7.22 (m, 2H, CH$_{Ar}$), 7.00 – 6.85 (m, 3H, CH$_{Ar/Pyrrole}$), 3.92 (s, 3H, CH$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 160.83, 147.15 (C$_{Ar}$), 145.09 (CH$_{Pyr}$), 143.62 (C$_{Ar}$), 140.67 (CH$_{Pyr}$), 134.83, 133.10 (C$_{Ar}$), 131.24 (CH$_{Ar}$), 128.69 (C$_{Ar}$), 125.70, 123.33, 115.67 (CH$_{Ar}$), 114.95 (CH$_{Pyr}$), 104.55 (CH$_{Pyrrole}$), 55.96 (CH$_3$) ppm. **MS (EI, 70 eV):** m/z (%) = 345 ([M]$^+$, 100), 299 (25), 255 (34), 228 (18).

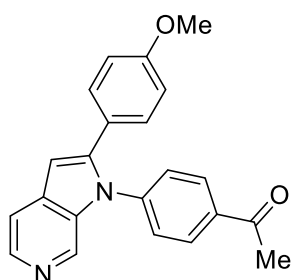## 1-(4-carbomethoxyphenyl)-2-(4-methoxyphenyl)-1H-pyrrolo[2,3-c]pyridine (18l)

Following general procedure and using compound **17b** (0.20 mmol, 57.62 mg) and 4-acetylaniline (0.22 mmol, 29.7 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18l** (40.9 mg, 57 %) as a yellow solid. **^{1}H NMR (250 MHz, CDCl$_3$)** δ = 8.67 (s, 1H, CH$_{Pyr}$), 8.33 (d, $^3J = 5.4$ Hz, 1H, CH$_{Pyr}$), 8.12 (d, $^3J = 8.8$ Hz, 2H, CH$_{Ar}$), 7.55 (dd, $^3J = 5.4$, 0.8 Hz, 1H, CH$_{Pyr}$), 7.37 – 7.31 (m, 2H, CH$_{Ar}$), 7.23 – 7.14 (m, 2H, CH$_{Ar}$), 6.87 – 6.78 (m, 2H, CH$_{Ar}$), 6.74 (d, $^4J = 0.8$ Hz, 1H, CH$_{Pyrrole}$), 3.95 (s, 3H, CH$_3$), 3.80 (s, 3H, CH$_3$). **^{13}C NMR (63 MHz, CDCl$_3$)** δ = 166.55, 160.23 (C$_{Ar}$), 144.42 (CH$_{Pyr}$), 141.85 (C$_{Ar}$), 140.46 (CH$_{Pyr}$), 133.95, 133.65, 131.29 (C$_{Ar}$), 130.88 (CH$_{Ar}$), 129.69 (C$_{Ar}$), 127.83, 123.69, 115.05 (CH$_{Ar}$), 114.42 (CH$_{Pyr}$), 103.22 (CH$_{Pyrrole}$), 55.62 (CH$_3$), 52.71 (CH$_3$) ppm.

1-phenyl-2-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-c]pyridine (18m)
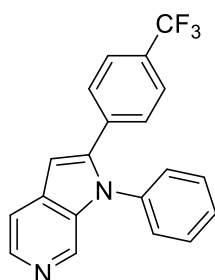
Following general procedure and using compound **17c** (0.25 mmol, 81.50 mg) and aniline (0.275 mmol, 25.57 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18m** (54.9 mg, 65 %) as a yellowish solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.67 (br-s, 1H, CH$_{Pyr}$), 8.35 (d, $^3J = 5.4$ Hz, 1H, CH$_{Pyr}$), 7.58 (dd, $^3J = 5.4$, $^4J = 1.1$ Hz, 1H, CH$_{Pyr}$), 7.56 – 7.52 (m, 2H, CH$_{Ar}$), 7.49 – 7.43 (m, 3H, CH$_{Ar}$), 7.43 – 7.37 (m, 2H, CH$_{Ar}$), 7.30 – 7.25 (m, 2H, CH$_{Ar}$), 6.86 (d, $^5J = 0.8$ Hz, 1H, CH$_{Pyrrole}$) ppm. **^{19}F NMR (282 MHz, CDCl$_3$)** δ = -62.72 (s, 3F, CF$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 142.2 (C$_{Ar}$), 140.3 (CH$_{Pyr}$), 137.1, 136.2, 135.2 (C$_{Ar}$), 134.5 (CH$_{Pyr}$), 132.8 (C$_{Ar}$), 130.5 (q, $^2J_{C,F} = 32.8$ Hz, C$_{Ar}$), 129.9, 129.5, 128.4,

127.8 (CH$_{Ar}$), 125.5 (q, $^3J_{C,F}$ = 3.7 Hz, CH$_{Ar}$), 125.1 (q, $^1J_{C,F}$ = 272.3 Hz, CF$_3$), 115.0 (CH$_{Pyr}$), 104.0 (CH$_{Pyrrole}$) ppm.

1-(4-methylphenyl)-2-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-c]pyridine (18n)
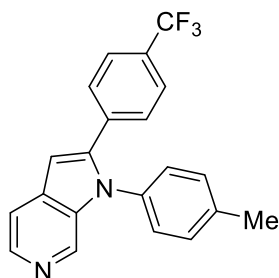
Following general procedure and using compound **17c** (0.25 mmol, 81.50 mg,) and 4-methylaniline (0.275 mmol, 29.42 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18n** (64.1 mg, 75 %) as a yellowish solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.65 (s, 1H, CH$_{Pyr}$), 8.33 (d, ^3J = 5.4 Hz, 1H, CH$_{Pyr}$), 7.63 – 7.58 (m, 3H, CH$_{Ar/Pyr}$), 7.44 – 7.38 (m, 2H, CH$_{Ar}$), 7.31 – 7.25 (m, 2H, CH$_{Ar}$), 7.14 (d, ^3J = 8.2 Hz, CH$_{Ar}$), 6.83 (d, ^4J = 0.8 Hz, 1H, CH$_{Pyrrole}$), 2.43 (s, 3H, CH$_3$) ppm. **^{19}F NMR (282 MHz, CDCl$_3$)** δ -62.69 (s, 3F, CF$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 142.3 (C$_{Ar}$), 140.1 (CH$_{Pyr}$), 138.5, 136.3, 135.3 (C$_{Ar}$), 134.5 (CH$_{Pyr}$), 134.5, 132.7 (C$_{Ar}$), 130.5 (CH$_{Ar}$), 130.2 (q, $^2J_{C,F}$ = 32.8 Hz, C$_{Ar}$), 129.4, 127.6 (CH$_{Ar}$), 125.5 (q, $^3J_{C,F}$ = 3.9 Hz, CH$_{Ar}$), 124.1 (q, $^1J_{C,F}$ = 272.4 Hz, CF$_3$), 115.0 (CH$_{Pyr}$), 103.7 (CH$_{Pyrrole}$), 21.3 (CH$_3$) ppm.
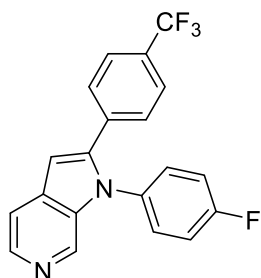
1-(4-fluorophenyl)-2-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-c]pyridine (18o)

Following general procedure and using compound **17c** (0.25 mmol, 81.50 mg) and 4-fluoroaniline (0.275 mmol, 27.77 mg) gave a crude product, which was purified by flash chromatography (ethyl acetate) to yield **18o** (63.1 mg, 73 %) as a yellowish solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.63 (s, 1H, CH$_{Pyr}$), 8.36 (d, ^3J = 5.5 Hz, 1H, CH$_{Pyr}$), 7.60 – 7.54 (m, 3H, CH$_{Ar/Pyr}$), 7.43 – 7.37 (m, 2H, CH$_{Ar}$), 7.29 – 7.22 (m, 2H, CH$_{Ar}$), 7.21 – 7.14 (m, 2H, CH$_{Ar}$), 6.85 (d, ^3J = 0.8 Hz, 1H, CH$_{Pyrrole}$) ppm. **^{19}F NMR (282 MHz, CDCl$_3$)** δ = -62.8 (s, 3F, CF$_3$), -112.1 (s, 1F, CF) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 162.0 (d, $^1J_{C,F}$ = 249.5 Hz, CF), 142.2 (C$_{Ar}$), 140.3 (CH$_{Pyr}$), 136.2, 134.8 (C$_{Ar}$), 134.1 (CH$_{Pyr}$), 133.0 (d, $^4J_{C,F}$ = 3.3 Hz, C$_{Ar}$), 132.7(C$_{Ar}$), 130.3 (q, $^2J_{C,F}$ = 32.7 Hz, C$_{Ar}$), 129.42 (d, $^3J_{C,F}$ = 8.5 Hz, CH$_{Ar}$), 129.3 (CH$_{Ar}$), 125.5 (q, $^3J_{C,F}$ = 3.9 Hz, CH$_{Ar}$), 123.9 (q, $^1J_{C,F}$ = 271.8 Hz, CF$_3$), 116.9 (d, $^2J_{C,F}$ = 23.1 Hz, CH$_{Ar}$), 115.0 (CH$_{Pyr}$), 103.9 (CH$_{Pyrrole}$) ppm.

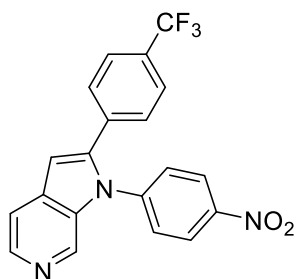**1-(4-nitrophenyl)-2-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-*c*]pyridine (18p)**

Following general procedure and using compound **17c** (0.25 mmol, 81.50 mg,) and 4-nitroaniline (0.275 mmol, 37.95 mg) gave a crude product, which was purified by flash chromatography (silica gel; ethyl acetate) to yield **18p** (74.7 mg, 78 %) as a yellowish solid. **^{1}H NMR (300 MHz, CDCl$_3$)** δ = 8.75 (s, 1H, CH$_{Pyr}$), 8.42 (d, ^3J = 5.4 Hz, 1H, CH$_{Pyr}$), 8.35 (d, ^3J = 9.2 Hz, 2H, CH$_{Ar}$), 7.64 – 7.58 (m, 3H, CH$_{Ar/Pyr}$), 7.45 (d, ^3J = 9.2 Hz, 2H, CH$_{Ar}$), 7.42 – 7.36 (m, 2H, CH$_{Ar}$), 6.92 (d, ^4J = 0.8 Hz, 1H, CH$_{Pyrrole}$) ppm. **^{19}F NMR (282 MHz, CDCl$_3$)** δ = -62.81 (s, 3F, CF$_3$) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ = 146.9, 142.7, 142.0 (C$_{Ar}$), 141.3 (CH$_{Pyr}$), 135.5, 134.4 (C$_{Ar}$), 133.8 (CH$_{Pyr}$), 133.5 (C$_{Ar}$), 131.0 (q, $^2J_{C,F}$ = 32.8 Hz, C$_{Ar}$), 129.5, 128.2 (CH$_{Ar}$), 126.0 (q, $^3J_{C,F}$ = 3.9 Hz, CH$_{Ar}$), 125.4 (CH$_{Ar}$), 123.9 (q, $^1J_{C,F}$ = 272.4 Hz, CF$_3$), 115.5 (CH$_{Pyr}$), 106.0 (CH$_{Pyrrole}$) ppm.

Crystallographic Data

	4a	7a	13o
Chemical formula	$C_{19}H_{14}N_2O$	$C_{19}H_{13}NOS$	$C_{25}H_{15}NS$
M_r	286.32	303.36	361.44
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	P 21/c	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc	-P 2ybc
Temperature (K)	123	173	123
a (Å)	16.313 (5)	7.1404 (5)	17.22 (3)
b (Å)	9.345 (3)	13.9271 (11)	5.061 (8)
c (Å)	9.473 (3)	14.8708 (11)	20.53 (4)
α (°)	90	90	90
β (°)	101.969 (6)	94.969 (3)	98.04 (6)
γ (°)	90	90	90
V ($Å^3$)	1412.6 (7)	1473.27 (19)	1772 (5)
Z	4	4	4
N_{ref}	3238	4696	3867
h,k,l_{max}	21, 12, 12	10, 20, 21	21, 6, 26
Density(g cm^{-3})	1.346	1.368	1.355
Radiation type	Mo Kα	Mo Kα	Mo Kα
μ (mm^{-1})	0.085	0.220	0.192
T_{min}, T_{max}	0.558, 0.746	0.677, 0.746	0.495, 0.746
(sin θ/λ)max ($Å^{-1}$)	0.71073	0.71073	0.71073
F(000)	600.0	632.0	752.0
N_{par}	200	200	257
R	0 .0530 (2183)	0.0421 (3845)	0.0609 (2915)
wR2	0.1286 (3238)	0.1198 (4696)	0.1556 (3867)
S	0.996	1.037	1.078

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Curriculum vitae

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Publications

1. **M. Blanco Ponce**, S. Parpart, A, Villinger, E. Torres Rodríguez, A. Flader, P. Ehlers, P. Langer. "Synthesis of Pyrrolo[1,2-*a*][1,6]- and [1,8]naphthyridines by Alkyne-Carbonyl-Metathesis". *Synthesis*. **2021**, 53, 1237-1246.

2. **2020: M. Blanco Ponce**, E. Torres Rodríguez, P. Ehlers, P. Langer. "Synthesis of thieno[2,3-*h*]-/[3,2-*h*]quinolines and thieno[2,3-*f]* quinolines by Brønsted acid mediated cycloisomerisation" *Org. Biomol. Chem.* **2020**, 18, 6531-6536.

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6. **M. Blanco Ponce**, A. Dip Gandarilla, E. Torres Rodríguez, D. Peña Fuentes, C. Vogel, M. Bullaín Galardis, L. Fajardo Cedeño "Actividad antibacteriana i*n vitro* de nuevas chalconas halogenadas". *Rev. Quim. Viva*. **2016**, 15 (2), 17-28.

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8. Y. Hernández-Molina, A. Ferrer-Serrano, **M. Blanco-Ponce**. New Amino/Amide Type Macrocycle: Synthesis, Characterization and Acidity/Basicity Constants. *Rev. Cub. Quim*. **2014**, 26, 32-36, ISSN 2224-5421.