SYNTHESIS OF IODO-SUBSTITUTED SPIRO-FUSED PYRIDINE DERIVATIVES

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SYNTHESIS OF IODO-SUBSTITUTED SPIRO-FUSED PYRIDINE DERIVATIVES

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Name, Last name: Ecem TEKE
Signature:
Spiro cyclic molecules have gained significance because of their biological activities and electronic properties. Spiro frameworks are present in importance natural products and optoelectronic materials. Moreover, due to steric strain, the presence of a spiro carbon atom induces easy rearrangements that can lead to different cyclic products. Although there are some methods to synthesize spiro compounds, the synthesis of iodo-substituted spiro-fused pyridines have not been studied. Accordingly, in this thesis, a new method for the synthesis of iodo-substituted spiro-fused pyridines have been developed via electrophilic cyclizations. After preparation of 5-alkynyl-4-(4-methoxyphenyl)pyridines, these derivatives were subjected to electrophilic cyclization in the presence of molecular iodine and NaHCO₃, which afforded iodo-substituted spiro-fused pyridines. The reaction conditions have been optimized and the limitations, scope and mechanism of these cyclizations have been studied.

**Keywords:** Spiro compound, pyridine, N-propargylic \( \beta \)-enaminone, electrophilic cyclization.
ÖZ

İYOT BAĞLI SPIRO BİRLEŞİK PİRİDİN TÜREVLERİNİN SENTEZİ

Teke, Ecem
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Zora

Şubat 2014, 109 sayfa


Anahtar Kelimeler: Spiro bileşik, piridin, N-proparjilık β-enaminon, elektrofilik halkalaşma.
To My Dear Family
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<th>Description</th>
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<tbody>
<tr>
<td>ACN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>br</td>
<td>broad (spectral)</td>
</tr>
<tr>
<td>d</td>
<td>doublet (spectral)</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublet (spectral)</td>
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<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (spectral)</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>PBD</td>
<td>(2-(4-biphenyl)-5-(4-tert-butylphenyl)-1,3, 4-oxadiazole)</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million (in NMR)</td>
</tr>
<tr>
<td>q</td>
<td>quartet (spectral)</td>
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<td>rt</td>
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</tr>
<tr>
<td>s</td>
<td>singlet (spectral)</td>
</tr>
<tr>
<td>t</td>
<td>triplet (spectral)</td>
</tr>
<tr>
<td>TAD</td>
<td>2,2',7,7'-tetrakis(N,N-diphenylamino)-9,9-spirobifluorene</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in parts per million downfield from</td>
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Organic chemistry is the study of carbon compounds from a structural property, synthesis and reaction point of view. It intersects with many areas including biochemistry, biology, medicinal chemistry, organometallic chemistry, polymer and material chemistry. Biologically functional molecules are made up by organic compounds as well. Organic compounds are important constituents of many products including drugs, food, explosives, plastics, petrochemicals and paints.\(^1\)

Most of organic compounds contain the rings of carbon atoms.\(^2\) In fact, cyclic compounds occupy one of the important classes of organic compounds. The most common cyclic compounds are those of five and six membered rings, some examples of which are shown in Figure 1.\(^3\)

![Figure 1. Examples of common cyclic compounds.](image-url)
1.1 Heterocyclic compounds

Heterocyclic compounds include at least one heteroatom other than carbon in their cyclic skeletons. Heterocyclic compounds mostly contain nitrogen, oxygen and sulfur atoms in their structures.\(^6\)

Heterocyclic compounds play an important role in pharmaceutical industry since they compose a broad range of drugs in human medicine. For instance, many antibiotics such as penicillin contain heterocyclic rings in their structures. Moreover, fundamental necessities of life as the provision of the energy, transmission of nerve impulses, metabolism and the transfer of hereditary information are based on chemical reactions involving the participation of many heterocyclic compounds. Cytosine, thymine, uracil, adenine and guanine derivatives are well known heterocycles on this matter. For instance, adenine and thymine molecules contain imidazole, purine and/or pyrimidine moieties in their structures, which participate the encoding off all genetic information (Figure 2).\(^4\)

![Figure 2. Structures of adenine and thymine heterocycles.](image)

Recently, successful treatments with leaves, fruits, barks and herbs, derived from plants and animals, are frequently triggered by the presence of various types of heterocyclic compounds. One of the most naturally occurring compounds regarding these treatments is quinine (Figure 3), which has curing ability on parasitic diseases.

In fact, quinine is a derivative of quinolone and isoquinoline alkaloids, their structures of which are given in Figure 3.
Figure 3. Structures of some quinine, quinoline and isoquinoline alkaloids.

Notably, heterocyclic alkaloids are the active ingredients in many pharmaceuticals. Most of the alkaloids occur in plants. Alkaloids are generally derived from either aromatic or hydrogenated heterocycles. Isoquinoline, pyridine, purine and quinazoline are well known alkaloids in this classification.

Heterocycles undergo many kinds of reactions. The versatile reactivity of heterocycles is related to their electron distributions in their structures. Moreover, the ability of some heterocycles to produce stable complexes with metal ions has attracted biochemical significance.

Heterocycles are critical for numerous applications including electronics, communications and aerospace technology. They also play an important role in more traditional branches of chemical industry such as dye manufacturing. Moreover, the contribution of heterocycles to the polychromism is significant.

Since heterocyclic compounds display a wide range of useful biological activities, they are generally designed according to medicinal activity studies and synthesized in the laboratory. Pyridine derivatives are one of such heterocyclic compounds.
1.2 Pyridines

In 1846, pyridine was discovered by Anderson who isolated it in a pure state from bone oil. Pyridine is a six-membered heterocyclic molecule consisting of five carbon atoms and one nitrogen atom on its skeleton. The first synthesis of pyridine was achieved in 1876 from acetylene and hydrogen cyanide. The demand for pyridine and its derivatives has increased significantly over the last fifty years due to the discovery of many pyridine containing bioactive compounds.

Pyridines are often present in the structures of biomolecules including nucleotides and alkaloids. Vitamin B₆ and nicotinamide adenine dinucleotide phosphates have significant importance in biological processes (Figure 4). Pyridines are also present in the structures of many dyes and drugs.

![Pyridine structures](image)

**Figure 4.** Structures of Vitamin B₆ and NADP+.

Pyridine has an important role in the development of medicines. For instance pyridine-containing esomeprazole, loratadine and crizotinib are used for the treatment of gastric disease, allergies and lung cancer, respectively (Figure 5).
Accordingly, many researchers have focused on the synthesis of new pyridine derivatives which can display enhanced or totally new biological activities.

![Example of pyridine-containing drugs](image)

**Figure 5.** Examples of pyridine-containing drugs.

Over the years, many methods have been developed for the synthesis of pyridines and new variants continue to appear since they have a remarkable impact in the synthesis of various drugs and natural products. In this regard, electrophilic cyclization has recently emerged as a valuable tool in organic synthesis.\textsuperscript{10,11} Electrophilic cyclizations generally occur under mild conditions in one-pot manner. Such cyclizations have also been employed in the synthesis of various pyridine derivatives.

### 1.2.1 Synthesis of pyridines

Pyridines are generally synthesized by the condensation of amines with carbonyl compounds or by the cycloaddition reactions.\textsuperscript{12} Transition metals are often used as catalyst in such reactions. Moreover, halo-substituted pyridines can be further functionalized by the metal-catalyzed cross-coupling reactions.\textsuperscript{13}
Larock and coworkers employed the Pd-catalyzed reaction of vinylic imines 4 with terminal alkynes 5 to synthesize pyridine derivatives 6 as shown in Scheme 1.\textsuperscript{14}

![Scheme 1. Palladium-catalyzed pyridine synthesis.](image)

Movassaghi and coworkers recently reported a one-pot synthesis of pyridines, where the condensation of amides 7 with alkynes 8 or vinyl ethers 9 afforded the corresponding pyridine derivatives 10 (Scheme 2). The reaction was accomplished with trifluoromethanesulfonic anhydride (Tf$_2$O) in the presence of 2-chloropyridine (2-ClPyr).\textsuperscript{12}

![Scheme 2. One-pot synthesis of pyridines.](image)

The presence of both the ambident nucleophilic character of enamine moiety and the electrophilic character of enone moiety make the $\beta$-enaminones useful synthetic intermediates. Consequently, their usage in organic synthesis have attracted current interest.\textsuperscript{15,16}
Cacchi and Fabrizi synthesized polysubstituted pyridine derivatives 12 from N-propargylic β-enaminones 11 by employing CuBr-mediated electrophilic cyclization (Scheme 3).\(^{17}\)

![Scheme 3](image)

**Scheme 3.** Synthesis of substituted pyridines.

Zora research group has recently developed a method for the synthesis of iodo-substituted pyridine derivatives, the initial results of which have been presented.\(^{18}\) In this study, iodopyridines 14 have been synthesized from N-propargylic β-enaminones 13 by molecular iodine-mediated electrophilic cyclization as depicted in Scheme 4. In addition, the synthesized iodo-substituted pyridines have been further functionalized by employing their metal-catalyzed cross-couplings with terminal alkynes to generate alkyny-substituted pyridine derivatives 15 and 16.\(^{19}\)

![Scheme 4](image)

**Scheme 4.** Synthesis of iodo-substituted pyridines via electrophilic cyclization of N-propargylic β-enaminones and their further functionalization with terminal alkynes.
1.3 Spiro compounds

Spiro compounds are bicyclic organic molecules with the rings connected through one atom, an example of which is illustrated in Figure 6. Due to steric strain, the presence of a spiro carbon atom induces easy rearrangements that can lead to different cyclic compounds.

![Figure 6. Structure of spiro[4.4]nonane.](image)

The biological activities of spiro based compounds occupied a unique position in the area of organic and pharmaceutical chemistry. One example of such spiro compounds is spiroxindole (Figure 7).\textsuperscript{20,21}

![Figure 7. Structure of spiro[cyclopentane-1,3'-indolin]-2'-one.](image)

Similarly, 2-oxindoles 17 and 18 have recently attracted the interest of researchers (Figure 8) because these spiro compounds have shown MDM2-p53, non-peptide specific small-molecule, inhibitor\textsuperscript{22} and antimalarial activities, respectively.\textsuperscript{23}
Figure 8. Structures of some 2-oxindole containing compounds.

Spiro[4,5]decanyl 19 derivatives are also found in several natural products, the basic structure of which is shown in Figure 9.\textsuperscript{24} Importantly, (+)-anhydro-β-rotunol (20) and (+)-dehydro-solanascone (21) bear a spiro[4,5]decanyl unit in their structures and display antifungal and antibacterial properties respectively (Figure 10).\textsuperscript{25,26}

Figure 9. Structure of spiro[4.5]deca-6,9-dien-8-one (19).

Figure 10. Structures of (+)-anhydro-β-rotunol (20) and (+)-dehydro-solanascone (21).
Spiro compounds are used in the organic semiconductors as well, which are often employed in the production of large area and flexible electronic devices.\textsuperscript{27} In fact, organic semiconductors are used in a wide range of devices like light-emitting diodes, field-effect transistors, and solar cells.\textsuperscript{27} Spiro compounds constitute the properties of organic optoelectronic devices. The compound known as spiro-TAD (2,2′,7,7′-tetrakis(N,N-diphenylamino)-9,9-spirobifluorene) hinders the crystallization of the molecules (Figure 11).\textsuperscript{27}

\begin{center}
\textbf{Figure 11.} Structure of spiro-TAD.
\end{center}

The integration of a spirobifluorene linkage into the structure of small molecules leads to a reduction in crystallization tendency, an enhancement in solubility and an increase in glass transition temperature (Figure 12).\textsuperscript{28} Such spiro structures have also been applied to polymeric materials, leading to enhancements in both glass transition temperature (Tg) and luminescent stability in alternating polyfluorene copolymers.\textsuperscript{29}

Moreover, electron transport materials can also be synthesized by using spiro compounds including the compound spiro-PBD (2-(4-biphenylyl)-5-(4-tert-butylphenyl)-1,3, 4-oxadiazole) (Figure 13). The electronic properties of these kind of compounds have remarkable impact on the electronic devices.\textsuperscript{27}
Furthermore, the contribution of spiro linkages to polymerization have been well documented.\textsuperscript{30} In the case of the spiro segment, polymer chain periodically zigzags at each spiro center and this structural feature not only preserves the rigidity of the polymer chain but also prevents the p-stacking of the polymer backbone, which result in an enhancement in both thermal and spectroscopic stabilities.

During the past decades, numerous frameworks have led to successful design and synthesis of diverse types of heterocyclic compounds with a spiro fused ring.\textsuperscript{31} In summary, spiro fused cyclic compounds have always been a challenge for synthetic organic chemists and electro chemists.
1.3.1 Synthesis of spiro compounds

Spiro compounds are generally synthesized by [4+2] cycloadditions or pinacol-type rearrangements. A schematic synthesis of spiro compounds via [4+2] cycloaddition, i.e., Diels-Alder reaction, is shown in Scheme 5.

**Scheme 5.** Synthesis of spiro[4.5]dec-6-ene (24) via Diels-Alder reaction.

In the synthesis of Shizukas’ acoradienol 28 (Scheme 6), the construction of spiro skeleton was performed by a [4+2] cycloaddition, where oxo-pyran-carboxylate 26 reacted with exo-double bond of methylenecyclopentene 25 to afford spiro compound 27.32

**Scheme 6.** Diels-alder approach to Shizukas’ acoradienol.
Marx research group synthesized spirosesquiterpene 30, a key intermediate for the synthesis of acorone, by [4 + 2] cycloaddition approach. The Diels-Alder reaction between methylenecyclopentanone 29 and isoprene yielded spirosesquiterpene 30 (Scheme 7).

![Scheme 7](image)

**Scheme 7.** Synthesis of spirosesquiterpene 30.

As mentioned before, spiro compounds can also be prepared by pinacol rearrangements. For instance, under acidic conditions, diol 32, prepared from cyclopentanone (31), undergoes pinacol rearrangement to furnish spiro[4,5]decan-6-one (33) (Scheme 8).

![Scheme 8](image)

**Scheme 8.** Synthesis of spiro[4.5]decan-6-one (33).
In the study carried out by Swenton and coworkers,\textsuperscript{35} intramolecular anodic carbon-carbon bond-forming reactions of oxidized phenol intermediates \textbf{35} and \textbf{37} led to the formation of spirodienones \textbf{39}. Two possible mechanisms were proposed for this reaction. One of these involves the reaction of an olefinic side chain with a phenoxonium intermediate (top mechanism), and the second includes the nucleophilic attack of a phenol on an oxidized styrene double bond (bottom mechanism) as illustrated in Scheme 9.

\textbf{Scheme 9}. Synthesis of spirocyclic 2,5-cyclohexadienones \textbf{39} with two proposed mechanisms.

When subjected to electrophilic cyclization, aryl-substituted internal alkynes produce the corresponding spiro compounds. For instance, the treatment of alkyne \textbf{40} with ICl has yielded spirocyclohexadienone derivatives \textbf{42} via intermediacy of iodonium ion \textbf{41} (Scheme 10).\textsuperscript{36}
After developing a new method for the synthesis of iodo-substituted pyridines, our research group has focused on the synthesis of spiro compounds from alkynyl-substituted pyridines. Accordingly, we have shown that under appropriate conditions, alkynyl-substituted pyridines, obtained from iodopyridines, undergo electrophilic cyclization to afford iodo-substituted spiro-fused pyridine derivatives as it will be discussed below.
1.4 Aim of the study

In this study, the electrophilic cyclizations of 5-alkynylpyridine derivatives 15 and 16 have been investigated as shown in Scheme 11. When treated with molecular iodine in the presence of sodium bicarbonate, 5-alkynylpyridine derivatives 15 and 16 have been expected to undergo electrophilic cyclization to afford iodo-substituted benzo[f]isoquinolines 43 and/or iodo-substituted spiro-fused pyridine derivatives 44. In the light of our previous studies, 5-alkynylpyridine derivatives 15 (R₂ = H) are expected to mainly produce iodo-substituted benzo[f]isoquinolines 43. On the other hand, 5-alkynylpyridine derivatives 16, which bear a methoxy group as the R₂ substituent, are expected to exclusively produce iodo-substituted spiro-fused pyridine derivatives 44. Initially, the starting materials have been prepared and then subjected to electrophilic cyclization for the synthesis of the above mentioned compounds. In summary, the limitations, scope and the proposed mechanism for these electrophilic cyclizations will be discussed in detail.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of alkynyl-substituted pyridines

The starting materials of the study, alkynyl-substituted pyridines 15 and 16, were synthesized according to the reaction scheme given in Scheme 12. Details of each step of the synthesis will be discussed in the following parts.

Scheme 12. Reaction pathway for the synthesis of alkynyl-substituted pyridines.
2.1.1 Synthesis of $N$-propargylic $\beta$-enaminone derivatives

In the first phase of the study, $N$-propargylic $\beta$-enaminones derivatives 48 were synthesized. Initially, alkynyl ketones 47 were prepared by Sonogashira cross-coupling$^{37}$ of benzoyl chloride (45) with terminal alkynes 46 (Scheme 13).

By employing these coupling reactions, four derivatives of alkynyl ketones 47, namely 1,3-diphenylprop-2-yn-1-one (47A), 1-phenyl-3-(4-(trifluoromethyl)-phenyl)prop-2-yn-1-one (47B), 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (47C) and 1-phenylhept-2-yn-1-one (47D), were synthesized in high yields (Scheme 13).

Next we carried out their reactions with propargylamine. For this purpose, alkynyl ketones 47 and propargylamine were refluxed in methanol at 65 °C for approximately 2 h. During the course of the reactions, propargylamine undergoes conjugate addition with alkynyl ketones 47 to give $N$-propargylic $\beta$-enaminones 48 (Scheme 14).
By utilizing these reactions, four derivatives of \(N\)-propargylic \(\beta\)-enaminones 48 were prepared in high yields (Scheme 14).

**Scheme 14.** Synthesis of \(N\)-propargylic \(\beta\)-enaminones 48.

Finally, the synthesized \(N\)-propargylic \(\beta\)-enaminones 48 were subjected to Sonagashira coupling with iodoaryl derivatives (Scheme 15). By this way, alkynyl moieties of \(\beta\)-enaminones 48 were further functionalized.

In the presence of palladium catalyst, CuI and amine base, \(\beta\)-enaminones 48 reacted with iodoaryl derivatives, such as iodobenzene, 4-idoanisole and 2-idoaniline furnished the arylated \(N\)-propargylic \(\beta\)-enaminone derivatives 13 in high yields (Scheme 15).
2.1.2 Synthesis of iodo-substituted pyridine derivatives via electrophilic cyclization

In the second phase of the study, we synthesized iodo-substituted pyridine derivatives 14 from N-propargylic β-enaminones 13 (Scheme 16). The syntheses of iodopyridines were achieved under the optimized conditions which were developed by our research group. In the presence of molecular iodine, N-propargylic β-enaminones 13 underwent electrophilic cyclization in refluxing acetonitrile to produce iodopyridines in good to high yields (Scheme 16).

Structural assignments of iodo-substituted pyridines 14 were made by $^1$H and $^{13}$C NMR spectroscopy. As a representative example, $^1$H and $^{13}$C NMR spectra of compound 14A are given in Figures 14 and 15, respectively. As seen in $^1$H NMR spectrum of 14A (Figure 14), the proton of pyridine at α position resonates around 9.30 ppm, which is a characteristic proton peak for such compounds. As expected, phenyl protons appear between 6.7 and 7.6 ppm of aromatic region. On the other hand, in $^{13}$C NMR spectrum of 14A (Figure 15), iodine-attached carbon resonates around 95 ppm, a specific carbon peak for iodo-substituted pyridines. In the spectrum, the peak around 190 ppm belongs to carbonyl group. Within 130-160 ppm, the peaks of phenyl carbons are observed.

Figure 14. $^1$H NMR spectrum of iodopyridine 14A.
Proposed mechanism for the formation of iodo-substituted pyridines 14 is depicted in Scheme 17. First, molecular iodine reacts with alkyne moiety of β-enaminones 13, giving iodonium ion 49. Nucleophilic attack of enamine moiety then takes place to give intermediate 50. Subsequently, hydrogen abstraction with base yields dihydropyridine 51. Finally, aerobic oxidation affords iodo-substituted pyridine derivatives 14 (Scheme 17).
2.1.3 Electrophilic cyclization of β-enaminone 13F

Initially, we also examined electrophilic cyclization of β-enaminone 13F under the same conditions (Scheme 18). Surprisingly, this reaction produced iodo-substituted benzo[c]naphthyridine derivative 52 in 25% yield, without formation of the expected iodopyridine 14F. In fact, benzo[c]naphthyridine 52 is a secondary product of the reaction and results from the initially formed iodopyridine derivative 14F via a condensation reaction between amino and carbonyl groups (Scheme 18). Importantly, electrophilic cyclizations of β-enaminones bearing 2-aminophenyl group on the alkynyl moiety (such as 13F) can provide a rapid entry to benzo[c]naphthyridine ring systems. We also tried to improve the yield of benzo[c]naphthyridine 52 by performing the electrophilic cyclizations with ZnCl₂ and AuCl₃; unfortunately these reactions afforded benzo[c]naphthyridine 52 in trace amounts, which requires further investigation.
2.1.4 Synthesis of alkynyl-substituted pyridines

Finally, we functionalized iodo-substituted pyridines 14 by palladium-catalyzed Sonogashira coupling as shown in Scheme 19 and 20. Initially, the coupling of 5-iodo-4-phenylpyridine 14A was performed with five kinds of terminal alkynes. In the presence of palladium catalyst, CuI and triethylamine, iodopyridine 14A reacted with a variety of terminal alkynes to give 5-alkynyl-4-phenylpyridines 15 in good to high yields (Scheme 19).
Scheme 19. Synthesis of 5-alkynyl-4-phenylpyridine derivatives 15.

Subsequently, Sonogashira couplings of 5-ido-4-(4-methoxyphenyl)pyridines 14B-E with five kinds of terminal alkynes were carried out (Scheme 20). Iodopyridines 14B-E underwent coupling with a variety of alkynes in the presence of palladium catalyst, CuI and triethylamine to afford 5-alkynyl-4-(4-methoxyphenyl)pyridines 16 in good yields (Scheme 20).
Scheme 20. Synthesis of 5-alkynyl-4-(4-methoxyphenyl)pyridine derivatives 16.
Structures of 5-alkynylpyridine derivatives 15 and 16 were determined by $^1$H and $^{13}$C NMR spectroscopy. As a representative example, $^1$H and $^{13}$C NMR spectra of compound 16D are given in Figures 16 and 17, respectively. As seen in the $^1$H NMR spectrum of 16D (Figure 16), the peaks of two methoxy groups are observed at 3.76 and 3.80 ppm. The $\alpha$-proton of pyridine appears around 9.0 ppm as expected. Phenyl protons resonate between 6.7 and 7.6 ppm of aromatic region. On the other hand, in $^{13}$C NMR spectrum of 16D (Figure 17), alkyne carbons appear at 84.5 and 96.5 ppm while methoxy carbons resonate at 55.2 and 55.3 ppm. The peak around 195 ppm belongs to carbonyl group. Between 115 and 160 ppm of the spectrum, phenyl carbons are observed.

![Figure 8. $^1$H NMR spectrum of 5-alkynyl-4-(4-methoxyphenyl)pyridine 16D.](image-url)
2.2 Investigation of electrophilic cyclization of alkynyl phenylpyridines 16: Synthesis of benzo[f]isoquinolines 43

Following the synthesis of 5-alkynyl-4-phenylpyridine derivatives 15A-E, we investigated their electrophilic cyclizations under our previous conditions with molecular iodine in the presence of NaHCO₃. Alkynyl-substituted pyridines 15A-E were all tested, but only pyridine derivative 15A underwent electrophilic cyclization to afford iodo-substituted benzo[f]isoquinoline 43A (Scheme 21). Unfortunately, from the reactions with alkynyl-substituted pyridines 15B-E, starting compounds were recovered with some decomposition; these reactions did not produce any desired new products. Briefly, in 15A, strong electron donating effect of p-methoxy group via resonance has an effect on the outcome of the reaction. It can be concluded from these results that the initial reaction of iodine requires a rich alkyne moiety.
Scheme 21. Synthesis of iodo-substituted benzo[f]isoquinoline 43A.

$^1$H and $^{13}$C spectra of benzo[f]isoquinolines 43A are shown in Figures 18 and 19, respectively. As seen in $^1$H NMR spectrum (Figure 18), the peak at 9.9 ppm belongs to $\alpha$-proton of pyridine. Methoxy group gives a peak around 3.8 ppm. The remaining aromatic protons resonate between 7.01 and 8.26 ppm. On the other hand, in the $^{13}$C spectrum of benzo[f]isoquinoline 43A (Figure 19), there is no alkyne carbon peaks around 85.00 ppm which implies that alkyne moiety underwent reaction. Importantly, the carbon connected to iodine appears at 103.4 ppm. The rest of aromatic carbons resonate between 105 and 160 ppm while the carbonyl carbon appears at 199 ppm.

Figure 18. $^1$H NMR spectrum of benzo[f]isoquinoline 43A.
Proposed mechanism for the formation of benzo[f]isoquinoline 43A is illustrated in Scheme 22. First, molecule iodine reacts with alkyne moiety of 5-alkynyl-4-phenylpyridine 15A giving iodonium ion 53. Nucleophilic attack of phenyl group then occurs to give intermediate 54. Finally, hydrogen abstraction with base yields benzo[f]isoquinoline 43A (Scheme 22).
2.3 Investigation of electrophilic cyclizations of alkynyl phenylpyridine 16: Synthesis of iodo-substituted spiro-fused pyridine derivatives 44

As mentioned before, in the electrophilic cyclizations of 5-alkynyl-4-phenylpyridine derivatives 15A-E, only compound 15A containing a 4-methoxyphenyl group as one of the alkyne substituents underwent the reaction to give the cyclized product 43A (Scheme 21). These results inspired us to study electrophilic cyclizations of 5-alkynyl-4-(4-methoxyphenyl)pyridine derivatives 16A-H. It was thought that the presence of 4-methoxyphenyl group at the para position of pyridine can also initiate the electrophilic cyclization. Electrophilic cyclization of 5-alkynyl-4-(4-methoxyphenyl)pyridine 16D was first examined. Interestingly, from this reaction, a spiro compound was isolated (Table 1). Accordingly, we optimized reaction conditions. As seen in entries 1 and 2 of Table 1, the electrophilic cyclizations carried out with CuI and AuCl yielded the spiro compound 44D in trace amounts and starting compounds were recovered with some decomposition. The reaction was also performed with
Cs₂CO₃, but this reaction did not produce any products (Table 1, entry 3). Then electrophilic cyclizations were conducted in the presence of molecular iodine and NaHCO₃ (Table 1, entries 4 and 5). The best yield (92%) of iodo-substituted spiro-fused pyridine 44D was obtained in the presence 3 molar equivalents of I₂ and NaHCO₃ in refluxing acetonitrile (Table 1, entry 5). The effect of NaHCO₃ might be related to ionic strength of the reaction.

**Table 1.** Optimization studies for the synthesis of iodo-substituted spiro-fused pyridine 44D.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 eq. CuI</td>
<td>1 eq. NEt₃</td>
<td>ACN</td>
<td>82°C</td>
<td>10 h</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>5 mol% AuCl</td>
<td>-</td>
<td>DCM</td>
<td>25°C</td>
<td>36 h</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>3 eq. I₂</td>
<td>3 eq. Cs₂CO₃</td>
<td>ACN</td>
<td>82°C</td>
<td>6 h</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2 eq. I₂</td>
<td>2 eq. NaHCO₃</td>
<td>ACN</td>
<td>82°C</td>
<td>4 h</td>
<td>62%</td>
</tr>
<tr>
<td>5</td>
<td>3 eq. I₂</td>
<td>3 eq. NaHCO₃</td>
<td>ACN</td>
<td>82°C</td>
<td>2.5 h</td>
<td>92%</td>
</tr>
</tbody>
</table>

Next we carried out the electrophilic cyclizations of a variety of 5-alkynl-4-(4-methoxyphenyl)pyridines 16 under optimized conditions. The results from a systematic study are given in Scheme 23. By employing these reactions, we
synthesized eight kinds of iodo-substituted spiro-fused pyridine derivatives 44 in good to high yields.

Scheme 23. Synthesis of iodo-substituted spiro-fused pyridine derivatives 44.
Structures of iodo-substituted spiro-fused pyridine derivatives 44 were elucidated by $^1$H and $^{13}$C NMR spectroscopy. As representative examples, $^1$H and $^{13}$C NMR spectra of both spiro compound 44F and its starting material 5-alkynyl-4-(4-methoxyphenyl)pyridine 16F for comparison are given in Figures 20 and 21. As seen in the $^1$H NMR spectrum of 16F, methoxy groups appear at 3.1, 3.5 and 3.7 ppm. Conversely, in the $^1$H NMR spectrum of 44F, the methoxy group which resonates at 3.1 ppm are not seen because this methoxy group initiates the cyclization and is converted to a carbonyl group. Moreover, protons of cyclohexa-2,5-dienone moiety resonate at around 5.9 and 6.2 ppm (shown by arrows); the each peak represents 2 protons. The remaining phenyl hydrogens show up between 6.5 and 7.3 ppm.

Figure 20. $^1$H NMR spectrum of 5-alkynyl-4-(4-methoxyphenyl)pyridine 16F (top) and iodo-substituted spiro-fused pyridine 44F (bottom).
$^{13}$C NMR spectra of iodo-substituted spiro-fused pyridine 44F and its starting material 5-alkynyl-4-(4-methoxyphenyl)pyridine 16F for comparison are shown in Figure 21. As expected, the alkyne peaks at 84.6 and 96.0 ppm and, particularly, the methoxy peak at 55.3 ppm in starting compound 16F disappear in the spectrum of product 44F. Prominently, in the product spectrum, another carbonyl peak appears at 184.7 ppm as shown by an arrow. Briefly, one of the methoxy group of 16F is converted to carbonyl group during spiro cyclization. Furthermore, in the spectrum of compound 44F, the existence of the new peak at 62.8 ppm (shown with an arrow), which belongs to spiro carbon, clearly proves the formation of this spiro compound. The peak at 94.4 ppm shows the iodine connected carbon atom.

Figure 21. $^{13}$C NMR spectra of 5-alkynyl-4-(4-methoxyphenyl)pyridine 16F (top) and iodo-substituted spiro-fused pyridine 44F (bottom).
Proposed mechanism for the formation of iodo-substituted spiro-fused pyridine derivatives 44 is illustrated in Scheme 24. Firstly, molecular iodine reacts with alkyne moiety of 5-alkynyl-4-(4-methoxy-phenyl)pyridine 16, yielding in situ iodonium ion 55, which initiates nucleophilic attack of 4-methoxyphenyl group to afford spiro compound 56. Finally, elimination of methyl iodide from 56 leads to the formation of iodo-substituted spiro-fused pyridine 44 (Scheme 24).

Scheme 24. Proposed mechanism for the formation of iodo-substituted spiro-fused pyridine derivatives 44.

In order to get some information about three dimensional structures of iodo-substituted spiro-fused pyridine derivatives 44, the structure of compound 44A was optimized at semi-empirical AM1 (Austin Method) level. The optimized ground state structure of 44A is given in Figure 22. Most importantly, the conjugation between 5H-cyclopenta[c]pyridine unit and its substituents (cyclohexadienone, benzoyl and phenyl groups) is severely interrupted because these substituents adopt approximately a perpendicular orientation.
Figure 22. AM1-optimized structure of iodo-substituted spiro-fused pyridine 44A.
CHAPTER 3

CONCLUSION

In summary, we investigated electrophilic cyclizations of 5-alkynyl-4-phenylpyridines 15 and 5-alkynyl-4-(4-methoxyphenyl)pyridines 16.

In the first part of the study, we prepared iodo-substituted pyridines via electrophilic cyclization of N-propargylic β-enaminones 13. Continuously, we functionalized these iodo-substituted pyridines 14 by palladium-catalyzed Sonogashira coupling with terminal alkynes to produce a broad range of 5-alkynyl-4-phenylpyridines 15 and 5-alkynyl-4-(4-methoxyphenyl)pyridines 16.

Accordingly, we examined electrophilic cyclizations of 5-alkynyl-4-phenylpyridines 15. The reactions were carried out in the presence of molecular iodine and NaHCO₃ in acetonitrile at 82 °C. Unfortunately, only alkynyl-pyridine 15A underwent electrophilic cyclization to produce the corresponding iodo-substituted benzo[f]-isoquinolines 43.

On the other hand, when treated with molecular iodine and NaHCO₃ in refluxing acetonitrile, 5-alkynyl-4-(4-methoxyphenyl)pyridines 16 afforded a variety of iodo-substituted spiro-fused pyridine derivatives 44.

Spiro structural motifs are present in some natural products as well as in some organic optoelectronic materials. Subsequently, eight different iodospiro-cyclopenta[c]-pyridine derivatives 44 were synthesized in good yields. Both the biological activities and other properties of these derivatives will be carried out by a collaborative work.
CHAPTER 4

EXPERIMENTAL

$^1$H and $^{13}$C NMR spectra were recorded at 400 and 100 MHz, respectively, by a Bruker Spectrospin Avance DPX400 Ultrashield spectrometer. The chemical shifts are reported in ppm (parts per million) downfield from an internal TMS (trimethylsilane) reference. Coupling constants ($J$) are given in Hz (Hertz), and the spin multiplicities are presented by the following symbols: br (broad), m (multiplet), q (quartet), t (triplet), d (doublet), dd (doublet of doublet) and s (singlet). Infrared Spectra (IR) were recorded on a Nicolet IS10 FTIR Spectrometer using attenuated total reflection (ATR). Band positions were counted in reciprocal centimeters (cm$^{-1}$). The reactions were accomplished by using Flash chromatography involving thick-walled glass columns using silica gel (Merck 230-400). Mass spectra (MS) were obtained on Bruker Daltonics spectrometer, using electrospray ionization (ESI) with Micro-Tof. Thin layer chromatography (TLC) was performed by using commercially available 0.25 mm silica gel plates and visualizing was effected with short wavelength UV lamp. Ethyl acetate-hexane solvent mixtures were used as eluent in Flash chromatography and their polarities were employed according to volume:volume ratio. In case of necessity, solvents used in reactions were distilled for purity. The inert atmosphere for the reactions was provided by slightly positive pressure (ca. 0.1 psi) of argon gas. All glassware was dried in oven before use.
In a round-bottomed flask, the corresponding benzoyl chloride (45) (0.70 mmol) was dissolved in THF (1.0 mL) and to the solution, PdCl₂(PPh₃)₂ (0.02 mmol) and Et₃N (0.5 mL), and CuI (0.02 mmol) were added, respectively, and stirred at room temperature under argon atmosphere. After 20 min later, terminal alkyne 46 (0.58 mmol) was added slowly and the resulting mixture was continued to be stirred for additional 40 min. When the reaction was over, water (50 mL) was added to the flask and the organic layer was extracted with ethyl acetate (2 x 25 mL). The separated organic phase was washed with water (2 x 50 mL) and then dried over MgSO₄ and filtered. The obtained crude product was purified by flash chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent.

4.1 Synthesis of 1,3-diphenylprop-2-yn-1-one (47A)

General Procedure 1 was followed by using benzoyl chloride (45) (100 mg, 0.70 mmol), PdCl₂(PPh₃)₂ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and ethynylbenzene (59 mg, 0.58 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1,3-diphenylprop-2-yn-1-one (47A) (yellow oil, 129 mg, 90% yield).

47A: ¹H NMR (400 MHz, CDCl₃): δ 8.26-8.24 (m, 2H), 7.7-7.4 (m, 8H); ¹³C NMR (100 MHz, CDCl₃): δ 178.0, 136.9, 134.2, 133.1, 130.9, 129.6, 128.7, 128.6, 120.1, 93.1, 87.0. The spectral data are matching for this compound with those reported previously.⁴⁰

4.1.2 Synthesis of 1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (47B)

General Procedure 1 was followed by using benzoyl chloride (45) (100 mg, 0.70 mmol), PdCl₂(PPh₃)₂ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (98 mg, 0.58 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1-phenyl-3-(4-(trifluoromethyl)-phenyl)prop-2-yn-1-one (47B) (brown-yellow oil, 162 mg, 85% yield).
47B: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.24-8.22 (m, 2H), 7.8-7.5 (m, 7H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 177.6, 136.6, 134.4, 133.2, 129.6, 128.8, 125.6, 124.0, 90.4, 88.1. The spectral data are matching for this compound with those reported previously.$^{39}$

4.1.3 Synthesis of 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (47C)

General Procedure 1 was followed by using benzoyl chloride (45) (100 mg, 0.70 mmol), PdCl$_2$(PPh$_3$)$_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and 1-ethynyl-2-methoxybenzene (76 mg, 0.58 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (47C) (brown solid, 148 mg, 90% yield).

47C: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.85-6.96 (m, 9H), 3.98 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 175.2, 160.9, 134.5, 134.3, 129.2, 128.7, 124.0, 121.0, 111.2, 96.1, 88.2, 55.4. The spectral data are matching for this compound with those reported previously.$^{40}$

4.1.4 Synthesis of 1-phenylhept-2-yn-1-one (47D)

General Procedure 1 was followed by using benzoyl chloride (45) (100 mg, 0.70 mmol), PdCl$_2$(PPh$_3$)$_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and hex-1-yne (47 mg, 0.58 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1-phenylhept-2-yn-1-one (47D) (yellow oil, 126 mg, 97% yield).

47D: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.16-8.14 (m, 2H), 7.61-7.47 (m, 3H), 2.52 (t, $J = 7.2$ Hz, 2H), 1.72-1.50 (m, 4H), 0.98 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.1, 136.9, 133.8, 129.5, 128.5, 96.8, 79.7, 29.8, 22.0, 18.8, 13.4. The spectral data are matching for this compound with those reported previously.$^{40}$
4.2 General Procedure 2. Synthesis of *N*-propargylic β-enaminones derivatives

In a round-bottomed flask, the corresponding alkynyl ketone **47** (0.50 mmol) was dissolved in methanol (2.0 mL) and to the solution, propargylamine (0.60 mmol) was added. The resulting reaction mixture was refluxed in methanol at 65 °C for approximately 2 h under argon atmosphere. When the reaction was over, methanol was evaporated and the resulting crude product was purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.

4.2.1 Synthesis of 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (48A)

General Procedure 2 was followed by using 1,3-diphenylprop-2-yn-1-one (**47A**) (103 mg, 0.50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**48A**) (brown-yellow solid, 128 mg, 98% yield).

**48A**: ¹H NMR (400 MHz, CDCl₃): δ 11.25 (br s, 1H), 7.80-7.33 (m, 10H), 5.85 (s, 1H), 3.88 (dd *J* = 6.4, 2.4 Hz, 2H), 2.35 (t, *J* = 2.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 188.2, 165.6, 136.5, 134.2, 129.9, 128.2, 94.4, 72.4, 68.3, 34.2. The spectral data are matching for this compound with those reported previously.¹⁷

4.2.2 Synthesis of 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (48B)

General Procedure 2 was followed by using 1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (**47B**) (137 mg, 0.50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**48B**) (yellow solid, 161 mg, 98% yield).
48B: $^1$H NMR (400 MHz, CDCl$_3$): δ 11.29 (br s, 1H), 7.93-7.40 (m, 9H), 5.85 (s, 1H), 3.89 (dd, $J = 6.4$, 2.4 Hz, 2H), 2.35 (t, $J = 1.5$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 188.4, 162.9, 138.5, 137.4, 130.3, 127.4, 127.3, 126.1, 124.7, 124.6, 93.9, 78.5, 71.7, 33.1. MS (ESI, m/z): 330.11 [M+H]$^+$; HRMS (ESI): calc. for C$_{19}$H$_{14}$F$_3$NO: 330.1100 [M+H]$^+$, found: 330.1160.

4.2.3 Synthesis of 3-(2-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-one (48C)

General Procedure 2 was followed by using 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (47C) (118 mg, 0.50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-(2-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-one (48C) (red oil, 116 mg, 80% yield).

48C: $^1$H NMR (400 MHz, CDCl$_3$): δ 11.50 (br s, 1H), 7.95-7.86 (m, 2H), 7.52-7.26 (m, 5H), 7.03 (m, 2H), 5.91-5.65 (m, 1H), 3.97-3.81 (m, 2H), 3.85 (s, 3H), 2.27 (t, $J = 2.4$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 188.9, 163.3, 156.1, 140.2, 131.3, 130.8, 129.9, 128.2, 127.1, 123.7, 121.0, 110.9, 94.1, 79.5, 72.2, 55.6, 33.9; MS (ESI, m/z): 292.13 [M+H]$^+$; HRMS (ESI): calc. for C$_{19}$H$_{17}$NO$_2$: 292.1332 [M+H]$^+$, found: 292.1347.

4.2.4 Synthesis of 1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-ene-1-one (48D)

General Procedure 2 was followed by using 1-phenylhept-2-yn-1-one (47D) (41 mg, 0.50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-ene-1-one (48D) (yellow oil, 118 mg, 98% yield).

48D: $^1$H NMR (400 MHz, CDCl$_3$): δ 11.5 (br s, 1H), 7.90-7.87 (m, 2H), 7.43-7.41 (m, 3H), 5.77 (s, 1H), 4.10 (dd, $J = 6.0$, 2.8 Hz, 2H), 2.40 (t, $J = 8.0$ Hz, 2H), 2.34 (t, $J = 2.4$ Hz, 1H), 1.66-1.42 (m, 4H), 0.99 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): 188.7, 168.1, 140.3, 130.6, 128.2, 127.0, 92.2, 79.2, 72.4, 32.2, 31.9,
4.3 General Procedure 3. Synthesis of arylated N-propargylic β-enaminone derivatives 13

In a round-bottomed flask, the corresponding N-propargylic β-enaminone 48 (0.40 mmol) was dissolved in DMF (2.0 mL) and to the solution, PdCl₂(PPh₃)₂ (5% mmol) and diisopropylamine (1.0 mL), and CuI (5% mmol) were added, respectively. Finally, iodobenzene derivative (4-iodoanisole or 2-iodoaniline) (0.40 mmol) was added and the resulting reaction mixture was stirred at room temperature for 20 h under argon atmosphere. When the reaction was over, water (50 mL) was added to the flask and the organic layer was extracted with ethyl acetate (2 x 25 mL). The separated organic phase was washed with water (2 x 50 mL) and then dried over MgSO₄ and filtered. The obtained crude product was purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.

4.3.1 Synthesis of 1,3-diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-en-1-one (13A)

General Procedure 3 was followed by using 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (48A) (104 mg, 0.40 mmol), PdCl₂(PPh₃)₂ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and iodobenzene (81 mg, 0.40 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1,3-diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-en-1-one (13A) (brown-yellow oil, 121 mg, 90% yield).

13A: ¹H NMR (400 MHz, CDCl₃): δ 11.43 (br s, 1H), 7.98-7.88 (m, 2H), 7.58-7.48 (m, 5H), 7.47-7.38 (m, 5H), 7.34-7.30 (m, 3H), 5.87 (s, 1H), 4.18 (d, J = 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 189.1, 166.0, 140.0, 135.1, 131.7, 131.0, 129.8, 128.7, 128.5, 128.3, 127.9, 127.2, 122.6, 94.6, 85.1, 84.1, 35.1; IR (neat): 1554, 1477, 1324, 1139, 1053, 1024, 747, 688, 567, 526; MS (ESI, m/z): 338.15 [M+H]^+; HRMS (ESI): calc. for C₂₄H₁₉NO: 338.1545 [M+H]^+, found: 338.1548.

4.3.2 Synthesis of 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one (13B)

General Procedure 3 was followed by using 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (48A) (104 mg, 0.40 mmol), PdCl$_2$(PPh$_3$)$_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and 4-iodoanisole (93 mg, 0.40 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one (13B) (brown-red oil, 123 mg, 84% yield).

13B: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 11.48 (br s, 1H), 8.96-7.94 (m, 2H), 7.58-7.38 (m, 10H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.89 (s, 1H), 4.18 (d, $J = 6.0$ Hz, 2H), 3.81 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 189.0, 166.0, 159.8, 140.1, 135.2, 133.2, 131.0, 129.8, 128.7, 128.3, 128.0, 127.2, 114.7, 114.0, 94.5, 84.1, 83.7, 55.3, 35.2; IR (neat): 1733, 1563, 1508, 1243, 1172, 1025, 831, 748, 692, 535; MS (ESI, $m/z$): 368.16 [M+H]$^+$; HRMS (ESI): calc. for C$_{25}$H$_{21}$NO$_2$: 368.1645 [M+H]$^+$, found: 368.1648.

4.3.3 Synthesis of 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (13C)

General Procedure 3 was followed by using phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (48B) (132 mg, 0.40 mmol), PdCl$_2$(PPh$_3$)$_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and 4-iodoanisole (93 mg, 0.40 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (13C) (brown solid, 149 mg, 86% yield).

13C: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 11.35 (br s, 1H), 7.98-7.89 (m, 2H), 7.79-7.69 (m, 3H), 7.50-7.42 (m, 4H), 7.37-7.34 (m, 2H), 6.87-6.85 (m, 2H), 5.85 (s, 1H), 4.14 (d, $J = 6.4$ Hz, 2H), 3.85 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 189.4, 164.1, 159.8, 139.8, 138.7, 133.2, 131.2, 128.5, 128.3, 127.2, 125.7, 114.4, 114.0, 94.8, 84.5, 83.4, 55.3, 36.2; IR (neat): 1596, 1508, 1321, 1247, 1165, 1109, 1066.
1016, 831, 688; MS (ESI, m/z): 436.15 [M+H]+; HRMS (ESI): calc. for C\textsubscript{26}H\textsubscript{20}F\textsubscript{3}NO\textsubscript{2}: 436.1519 [M+H]+, found: 436.1515.

4.3.4 Synthesis of 3-((2-methoxyphenyl)-3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylprop-2-en-1-one (13D)

General Procedure 3 was followed by using 3-(2-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (48C) (116 mg, 0.40 mmol), PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} (14 mg, 0.02 mmol), Cul (4 mg, 0.02 mmol) and 4-iodoanisole (93 mg, 0.40 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-(2-methoxyphenyl)-3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylprop-2-en-1-one (13D) (brown oil, 146 mg, 92% yield).

13D: \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta 11.53 (br s, 1H), 7.97-7.88 (m, 2H), 7.54-7.31 (m, 7H), 7.14-6.97 (m, 2H), 6.87-6.78 (m, 2H), 5.79 (s, 1H), 4.25-4.14 (m, 2H), 3.89 (s, 3H), 3.81 (s, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \delta 188.8, 163.4, 159.6, 156.2, 140.3, 133.1, 131.1, 130.7, 129.9, 128.1, 127.1, 124.1, 120.9, 114.9, 113.9, 110.8, 93.4, 83.7, 83.4, 55.6, 55.3, 34.8; IR (neat): 1733, 1566, 1508, 1239, 1171, 1020, 832, 752, 538; MS (ESI, m/z): 398.18 [M+H]+; HRMS (ESI): calc. for C\textsubscript{26}H\textsubscript{23}NO\textsubscript{3}: 398.1751 [M+H]+, found: 398.1754.

4.3.5 Synthesis of 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylhept-2-en-1-one (13E)

General Procedure 3 was followed by using phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (48D) (96 mg, 0.40 mmol), PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} (14 mg, 0.02 mmol), Cul (4 mg, 0.02 mmol) and 4-iodoanisole (93 mg, 0.40 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylhept-2-en-1-one (13E) (yellow-brown solid, 127 mg, 92% yield).

13E: \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta 11.59 (br s, 1H), 7.98-7.84 (m, 2H), 7.51-7.33 (m, 5H), 6.93-6.77 (m, 2H), 5.78 (s, 1H), 4.33 (d, J = 6.0 Hz, 2H), 3.82 (s, 3H), 2.52-2.43 (t, J = 8.0, 2H), 1.74-1.66 (m, 2H), 1.54-1.45 (m, 2H), 1.00 (t, J = 7.6, 3H);
\[ \text{13C NMR (100 MHz, CDCl}_3\text{): } \delta 188.5, 168.3, 159.8, 140.5, 133.2, 130.6, 128.2, 127.0, 114.6, 113.9, 92.0, 84.0, 83.0, 55.3, 33.2, 32.0, 30.3, 22.7, 13.9; \]

IR (neat): 1583, 1544, 1507, 1288, 1246, 1171, 1090, 1025, 832, 746, 690, 601, 539; MS (ESI, \( m/z \)): 348.20 [M+H]\(^+\); HRMS (ESI): calc. for C\(_{23}\)H\(_{26}\)NO\(_2\): 348.1964 [M+H]\(^+\), found: 348.1984.

### 4.3.6 Synthesis of 3-((3-(2-aminophenyl)prop-2-yn-1-yl)amino)-1,3-diphenyl-prop-2-en-1-one (13F)

General Procedure 3 was followed by using 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (48A) (104 mg, 0.40 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and 2-iodoaniline (87 mg, 0.4 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-((3-(2-aminophenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one (13F) (yellow-brown liquid, 126 mg, 90% yield).

**13F:** \( ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 11.54 \text{ (br s, 1H), 7.98 (d, } J = 6.0 \text{ Hz, 2H), 7.62-7.38 (m, 10H), 7.29-7.27 (dd, } J = 5.6, 7.6 \text{ Hz, 1H), 7.15 (m, 1H), 6.70 (m, 2H), 5.88 (s, 1H), 4.32 (d, } J = 6.0 \text{ Hz, 3H), 3.66 (br s, 1H); } ^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta 188.7, 166.7, 144.2, 140.1, 130.9, 129.7, 128.9, 128.8, 128.7, 127.1, 122.6, 126.3, 119.1, 116.4, 112.7, 94.2, 35.2. \)

### 4.4 General Procedure 4. Synthesis of iodo-subsituted pyridines 14

In a round-bottomed flask, arylated \( N \)-propargylic \( \beta \)-enaminone derivative 13 (100 mg, 0.40 mmol) was dissolved in acetonitrile (10 mL) and to this solution, I\(_2\) (303 mg, 1.20 mmol) and NaHCO\(_3\) (100 mg, 1.20 mmol) were added, respectively. The resulting reaction mixture was then refluxed at 82 °C for 5 h under air. When the reaction was over, saturated aqueous solution of Na\(_2\)S\(_2\)O\(_3\) (35 mL) was added to remove unreacted excess I\(_2\). Subsequently, the mixture was extracted with ethyl acetate (2 x 20 mL). The separated organic phase was washed with water (50 mL) and dried over MgSO\(_4\) and filtered. The obtained crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate as the eluent.
4.4.1. Synthesis of (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (14A)

General Procedure 4 was followed by using 1,3-diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-en-1-one (13A) (134 mg, 0.40 mmol), I₂ (303 mg, 1.20 mmol) and NaHCO₃ (100 mg, 1.20 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (14A) (black solid, 155 mg, 84% yield).

14A: ¹H NMR (400 MHz, CDCl₃): ¹H NMR (CDCl₃): δ 9.07 (s, 1H), 7.36-7.34 (m, 2H), 7.28 (dd, J = 8.0, 6.4 Hz, 2H), 7.20 (t, J = 7.2 Hz, 2H), 7.10-7.02 (m, 8H), 6.85 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 195.6, 157.4, 155.8, 152.4, 139.3, 138.3, 133.3, 131.9, 129.2, 129.0, 128.9, 128.6, 128.3, 128.2, 91.1; IR (neat): 1707, 1674, 1594, 1577, 1447, 1374, 1316, 1257, 1229, 1042, 954, 757, 720, 697, 653, 531; MS (ESI, m/z): 462.03 [M+H]+; HRMS (ESI): calc. for C₂₄H₁₆INO: 462.0349 [M+H]+, found: 462.0345.

4.4.2 Synthesis of (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl)methanone (14B)

General Procedure 4 was followed by using 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one (13B) (146 mg, 0.40 mmol), I₂ (303 mg, 1.20 mmol) and NaHCO₃ (100 mg, 1.20 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl) methanone (14B) (brown solid, 163 mg, 83% yield).

14B: ¹H NMR (400 MHz, CDCl₃): ¹H NMR (CDCl₃): δ 9.30 (s, 1H), 7.59-7.47 (m, 4H), 7.40 (t, J = 7.4 Hz, 1H), 7.33-7.20 (m, 6H), 6.96-6.80 (br m, 2H), 6.69 (br s, 1H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 195.8, 159.6, 157.4, 155.9, 152.2, 138.4, 137.1, 135.5, 133.3, 131.6, 129.2, 129.0, 128.9, 128.3, 113.5, 99.4, 55.1; IR (neat): 1733, 1664, 1605, 1540, 1507, 1419, 1287, 1244, 1173, 1027, 940, 827, 787, 760, 697, 573, 532, 419; MS (ESI, m/z): 492.05 [M+H]+; HRMS (ESI): calc. for C₂₅H₁₈INO₂: 492.0460 [M+H]+, found: 492.0470.
4.4.3 Synthesis of (2-butyl-5-iodo-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl) methanone (14C)

General Procedure 4 was followed by using 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylept-2-en-1-one (13E) (138 mg, 0.40 mmol), I₂ (303 mg, 1.20 mmol) and NaHCO₃ (100 mg, 1.20 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2-butyl-5-iodo-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl) methanone (14C) (yellow-brown oil, 122 mg, 65% yield).

14C: ¹H NMR (400 MHz, CDCl₃): ¹H NMR (CDCl₃): δ 8.98 (s, 1H), 7.49 - 7.43 (m, 2H), 7.39 (t, J = 6.4 Hz, 1H), 7.22 (dd, J = 16.0, 8.0 Hz, 2H), 6.85 (br s, 2H), 6.35 (br s, 2H), 3.64 (s, 3H), 2.51 (t, J = 8.0 Hz, 2H), 1.58 (s, 2H), 1.25 - 1.13 (m, 2H), 0.73 (t, J = 8.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 196.3, 159.5, 158.4, 157.1, 150.8, 136.9, 135.8, 133.7, 131.4, 129.2, 128.5, 113.4, 97.1, 55.1, 35.5, 31.6, 22.6, 13.8; IR (neat): 2956, 1734, 1668, 1608, 1510, 1428, 1246, 1175, 1029, 942, 832, 799, 729, 708, 554; MS (ESI, m/z): 472.08 [M+H⁺]; HRMS (ESI): calc. for C₂₃H₂₂INO₂: 472.0773 [M+H⁺], found: 472.0779.

4.4.4 Synthesis of (5-iodo-2-(2-methoxyphenyl)-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl)methanone (14D)

General Procedure 4 was followed by using 3-(2-methoxyphenyl)-3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylprop-2-en-1-one (13D) (159 mg, 0.40 mmol), I₂ (303 mg, 1.20 mmol) and NaHCO₃ (100 mg, 1.20 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (5-iodo-2-(2-methoxyphenyl)-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl)methanone (14D) (yellow solid, 181 mg, 87% yield).

14D: ¹H NMR (400 MHz, CDCl₃): ¹H NMR (CDCl₃): δ 9.14 (s, 1H), 7.43-7.35 (m, 2H), 7.29-7.05 (m, 6H), 6.92 (br s, 2H), 6.83 (dd, J = 8.0, 4.0 Hz, 1H), 6.64 (br s, 1H), 6.60 (t, J = 10.4 Hz, 1H), 3.65 (s, 3H), 3.27 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 194.9, 159.5, 157.3, 155.8, 154.8, 151.5, 137.0, 136.6, 132.6, 131.9, 131.4, 130.3, 129.2, 127.7, 120.5, 113.4, 110.4, 99.2, 55.1, 54.5; IR (neat): 3649, 1661,
1606, 1507, 1420, 1285, 1246, 1176, 117, 1015, 937, 836, 810, 758, 700, 651, 546; MS (ESI, m/z): 522.06 [M+H]⁺; HRMS (ESI): calc. for C_{26}H_{20}INO₃: 522.0561 [M+H]⁺, found: 522.0562.

4.4.5 Synthesis of (5-iodo-4-(4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)pyridin-3-yl)(phenyl)methanone (14E)

General Procedure 4 was followed by using 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (13C) (174 mg, 0.40 mmol), I₂ (303 mg, 1.20 mmol) and NaHCO₃ (100 mg, 1.20 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (5-iodo-4-(4-methoxyphenyl)-2-(4-(trifluoromethyl) phenyl)pyridin-3-yl)(phenyl)methanone (14E) (brown solid, 172 mg, 77% yield).

14E: °H NMR (400 MHz, CDCl₃): δ 9.16 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.47-7.27 (m, 6H), 7.15 (dd, J = 16.0, 6.4 Hz, 2H), 6.73 (br s, 3H), 3.65 (s, 3H); °C NMR (100 MHz, CDCl₃): δ 193.3, 157.4, 155.3, 152.1, 150.1, 139.6, 134.6, 131.4, 128.9, 127.1, 126.9, 126.2, 123.0, 111.3, 52.9; IR (neat): 1717, 1671, 1615, 1541, 1508, 1420, 1321, 1248, 1159, 1120, 1067, 1014, 942, 844, 798, 710, 688, 661, 559; MS (ESI, m/z): 560.03 [M+H]⁺; HRMS (ESI): calc. for C_{26}H_{17}F_{3}INO₂: 560.0329 [M+H]⁺, found: 560.0327.

4.5 Synthesis of 1-iodo-4,5-diphenylbenzo[c][2,7]naphthyridine (52)

3-((3-(2-Aminophenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one (13F) (100 mg, 0.30 mmol) was dissolved in DCM (2.0 mL), and to this solution, I₂ (303 mg, 1.2 mmol) and NaHCO₃ (100 mg, 1.2 mmol) were added, respectively. The resulting reaction mixture was then stirred at room temperature for 20 h under argon atmosphere. When the reaction was over, saturated aqueous solution of Na₂S₂O₃ (35 mL) was added to remove unreacted excess I₂. Subsequently, the mixture was extracted with ethyl acetate (2 x 20 mL). The separated organic phase was washed with water (50 mL) and dried over MgSO₄ and filtered. The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl
acetate as the eluent to afford 1-iodo-4,5-diphenylbenzo[c][2,7]naphthyridine (52) (brown oil, 34 mg, 25% yield).

52: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.07 (s, 1H), 8.32 (d, $J = 8.0$ Hz, 1H), 7.99-7.86 (m, 1H), 7.69 (s, 1H), 7.57-7.35 (m, 8H), 7.23-7.13 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.4, 157.7, 151.7, 137.5, 134.5, 134.3, 133.0, 132.0, 130.1, 129.9, 129.2, 129.0, 128.9, 126.8, 125.0, 122.7, 122.6, 96.9; IR (neat): 1653, 1576, 1508, 1457, 1437, 1360, 1298, 1073, 999, 758, 689, 624, 584.

4.6 General Procedure 5. Synthesis of alkynyl-substituted pyridines 15 and 16

The corresponding iodo-substituted pyridine derivative 14 (100 mg, 0.20 mmol) was dissolved in DMF (2 mL) and to this solution, Et$_3$N (1.5 ml), PdCl$_2$(PPh$_3$)$_2$ (7 mg, 5% mmol) and CuI (2 mg, 5% mmol) were added. Finally, terminal alkyne (25 mg, 0.24 mmol) was added to the solution and the resulting reaction mixture was heated at 65 °C for 10 h under argon atmosphere. When the reaction was over, water (50 mL) was added to the flask and the organic layer was extracted with ethyl acetate (2 x 25 ml). The separated organic phase was washed with water (2 x 50 mL) and then dried over MgSO$_4$ and filtered. The obtained crude product was purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.

4.6.1 Synthesis of (5-((4-methoxyphenyl)ethynyl)-2,4-diphenylpyridin-3-yl)-(phenyl)methanone (15A)

General Procedure 5 was followed by using (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (14A) (100 mg, 0.20 mmol), PdCl$_2$(PPh$_3$)$_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynylanisole (32 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (5-((4-methoxyphenyl)ethynyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (15A) (brown solid, 57 mg, 62% yield).

15A: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.92 (s, 1H), 7.45 (m, 4H), 7.33-7.25 (m, 1H), 7.24-7.05 (m, 12H), 6.72 (m, 2H), 3.72 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 198.0, 160.0, 152.2, 149.9, 141.4, 133.2, 133.0, 129.3, 129.1, 128.8, 128.3, 127.8, 119.2, 114.0, 96.8, 86.8, 55.3; IR (neat): 2216, 1672, 1602, 1508, 1445, 1291, 1253,
1226, 1162, 1030, 992, 876, 833, 807, 757, 697, 575, 535, 509; MS (ESI, m/z): 466.18 [M+H]^+; HRMS (ESI): calc. for C_{33}H_{23}NO_2: 466.1802 [M+H]^+, found: 466.1802.

4.6.2 Synthesis of (2,4-diphenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl) methanone (15B)

General Procedure 5 was followed by using (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (14A) (100 mg, 0.20 mmol), PdCl_2(PPh_3)_2 (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and phenylacetylene (25 mg, 0.24 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2,4-diphenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl) methanone (15B) (white-yellow solid, 74 mg, 85% yield).

15B: ^1H NMR (400 MHz, CDCl_3): δ 8.92 (s, 1H), 7.56-7.34 (m, 4H), 7.30-7.05 (m, 16H); ^13C NMR (100 MHz, CDCl_3): δ 195.2, 142.0, 136.4, 134.7, 132.2, 130.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.4, 127.3, 126.8, 92.6, 92.5, 88.7; IR (neat): 1669, 1592, 1489, 1434, 1322, 1258, 1220, 1002, 873, 754, 717, 701, 685, 591, 514; MS (ESI, m/z): 436.17 [M+H]^+; HRMS (ESI): calc. for C_{32}H_{21}NO: 436.1695 [M+H]^+, found: 436.1692.

4.6.3 Synthesis of (2,4-diphenyl-5-(thiophen-3-ylethynyl)pyridin-3-yl)(phenyl) methanone (15C)

General Procedure 5 was followed by using (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (14A) (100 mg, 0.20 mmol), PdCl_2(PPh_3)_2 (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 3-ethynylthiophene (26 mg, 0.24 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2,4-diphenyl-5-(thiophen-3-ylethynyl)pyridin-3-yl)(phenyl) methanone (15C) (white-yellow oil, 67 mg, 76% yield).

15C: ^1H NMR (400 MHz, CDCl_3): δ 9.04 (s, 1H), 7.61-7.34 (m, 4H), 7.37 (t, J = 7.2 Hz, 1H), 7.34-7.19 (m, 12H), 6.93 (dd, J = 4.8, 1.2 Hz, 1H); ^13C NMR (100 MHz, CDCl_3): δ 196.4, 155.3, 152.3, 150.2, 139.0, 137.5, 135.8, 133.7, 133.3, 129.6,
129.5, 129.3, 129.1, 128.9, 128.4, 128.3, 127.8, 125.5, 121.6, 118.9, 91.8, 85.0; IR (neat): 1730, 1710, 1698, 1683, 1653, 1635, 1558, 1541, 1520, 1507, 1489, 1436, 1027, 694, 419; MS (ESI, m/z): 442.13 [M+H]+; HRMS (ESI): calc. for C$_{30}$H$_{19}$NOS: 442.1260 [M+H]+, found: 442.1262.

4.6.4 Synthesis of (2,4-diphenyl-5-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (15D)

General Procedure 5 was followed by using (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (14A) (100 mg, 0.20 mmol), PdCl$_2$(PPh$_3$)$_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynyl-alpha,alpha,alpha-trifluorotoluene (40 mg, 0.24 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2,4-diphenyl-5-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (15D) (yellow solid, 92 mg, 92% yield).

**15D:** $^1$H NMR (400 MHz, CDCl$_3$): δ 9.08 (s, 1H), 7.67-7.50 (m, 6H), 7.40-7.22 (m, 13H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 196.1, 155.9, 152.5, 150.7, 138.9, 137.4, 135.7, 133.8, 133.4, 131.7, 130.5, 130.2, 129.5, 129.4, 129.3, 129.2, 129.0, 128.6, 128.3, 127.9, 126.3, 125.3, 122.5, 118.2, 94.9, 87.8; IR (neat): 1663, 1558, 1521, 1437, 1316, 1226, 1161, 1118, 1064, 1016, 874, 833, 756, 716, 698, 597, 520; MS (ESI, m/z): 504.16 [M+H]$^+$; HRMS (ESI): calc. for C$_{33}$H$_{20}$F$_3$NO: 504.1570 [M+H]$^+$, found: 504.1564.

4.6.5 Synthesis of (2,4-diphenyl-5-(p-tolylethynyl)pyridin-3-yl)(phenyl) methanone (15E)

General Procedure 5 was followed by using (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (14A) (100 mg, 0.20 mmol), PdCl$_2$(PPh$_3$)$_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynyltoluene (28 mg, 0.24 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2,4-diphenyl-5-(p-tolylethynyl)pyridin-3-yl)(phenyl) methanone (15E) (yellow solid, 86 mg, 96% yield).
15E: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.93 (s, 1H), 7.51-7.41 (m, 4H), 7.35-7.09 (m, 11H), 7.08-6.96 (m, 4H), 2.24 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 196.3, 152.2, 150.3, 139.1, 138.9, 137.5, 135.8, 133.2, 131.4, 129.5, 129.3, 129.2, 129.1, 128.9, 128.4, 128.3, 127.8, 119.4, 119.2, 96.9, 84.7, 21.5; IR (neat): 1733, 1670, 1558, 1507, 1437, 1225, 1174, 992, 875, 813, 569, 577, 529, 507; MS (ESI, m/z): 450.18 $^{[M+H]^+}$; HRMS (ESI): calc. for C$_{33}$H$_{23}$NO: 450.1852 $^{[M+H]^+}$, found: 450.1847.

4.6.6 Synthesis of (4-(4-methoxyphenyl)-2-phenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl)methanone (16A)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl)methanone (14B) (100 mg, 0.20 mmol), PdCl$_2$(PPh$_3$)$_2$ (7 mg, 5% mmol), CuI (2 mg 5% mmol) and phenylacetylene (25 mg, 0.24 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-2-phenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl)methanone (16A) (yellow oil, 56 mg, 60% yield).

16A: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.03 (s, 1H), 7.62-7.48 (m, 4H), 7.32 (m, 13H), 6.81 (d, $J = 8.0$ Hz, 2H), 3.78 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 196.4, 159.6, 152.6, 149.9, 131.5, 131.0, 129.3, 129.1, 128.8, 128.4, 128.3, 122.6, 119.0, 113.3, 96.4, 85.6, 55.2; IR (neat): 1733, 1716, 1683, 1558, 1507, 1457, 1009, 911, 669, 535, 471, 419; MS (ESI, m/z): 466.18 [M+H]$^+$; HRMS (ESI): calc. for C$_{33}$H$_{23}$NO$_2$: 466.1802 [M+H]$^+$, found: 466.1808.

4.6.7 Synthesis of (4-(4-methoxyphenyl)-2-phenyl-5-(p-tolylethynyl)pyridin-3-yl)(phenyl)methanone (16B)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl) methanone (14B) (100 mg, 0.20 mmol), PdCl$_2$(PPh$_3$)$_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethyltoluene (28 mg, 0.24 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-2-phenyl-
5-(p-tolylethynyl)pyridin-3-yl)(phenyl)methanone (16B) (brown solid, 84 mg, 88% yield).

16B: 1H NMR (400 MHz, CDCl3): δ 9.03 (s, 1H), 7.55 (dd, J = 6.4, 3.2 Hz, 4H), 7.43-7.33 (m, 2H), 7.32-7.18 (m, 8H), 7.13 (t, J = 6.4 Hz, 2H), 6.82 (t, J = 10.0 Hz, 2H), 3.76 (s, 3H), 2.37 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 196.6, 159.6, 155.2, 152.6, 149.7, 139.1, 139.0, 137.5, 133.8, 133.2, 131.4, 131.0, 129.3, 129.1, 128.8, 128.3, 128.2, 128.0, 119.6, 119.2, 113.3, 96.6, 85.1, 55.2, 21.54; IR (neat): 2210, 1732, 1668, 1607, 1507, 1437, 1248, 1177, 1030, 876, 846, 817, 763, 699, 595, 528, 504; MS (ESI, m/z): 480.20 [M+H]+; HRMS (ESI): calc. for C34H15NO2: 480.1958 [M+H]+, found: 480.1959.

4.6.8 Synthesis of (4-(4-methoxyphenyl)-2-phenyl-5-(thiophen-3-yethynyl)pyridin-3-yl)(phenyl)methanone (16C)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl) methanone (14B) (100 mg, 0.20 mmol), PdCl2(PPh3)2 (0.01mmol), CuI (0.01mmol) and 3-ethynylthiophene (25 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-2-phenyl-5-(thiophen-3-yethynyl) pyridin-3-yl)(phenyl)methanone (16C) (yellow solid, 77 mg, 82% yield).

16C: 1H NMR (400 MHz, CDCl3): δ 9.04 (s, 1H), 7.59-7.51 (m, 4H), 7.42-7.34 (m, 2H), 7.31-7.20 (m, 8H), 7.03-6.97 (dd, J = 4.8, 0.8 Hz, 1H) 6.80 (d, J = 8.0 Hz, 2H), 3.76 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 196.6, 159.7, 155.3, 152.4, 149.8, 139.0, 137.5, 133.9, 130.9, 129.6, 129.3, 129.1, 128.8, 128.3, 128.0, 125.5, 121.7, 119.0, 113.3, 91.5, 85.2, 55.2; IR (neat): 1733, 1716, 1699, 1668, 1607, 1576, 1541, 1507, 1435, 1249, 1175, 1029, 927, 840, 816, 784, 694, 670, 620, 420; MS (ESI, m/z): 472.14 [M+H]+; HRMS (ESI): calc. for C31H21NO2S: 472.1366 [M+H]+, found: 472.1363.
4.6.9 Synthesis of (4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-2-phenylpyridin-3-yl)(phenyl)methanone (16D)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl)methanone (14B) (100 mg, 0.20 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynylanisole (32 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-2-phenylpyridin-3-yl)(phenyl)methanone (16D) (bright yellow solid, 77 mg, 78% yield).

16D: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.06 (s, 1H), 7.53 (m, 4H), 7.42-7.34 (m, 1H), 7.33-7.20 (m, 9H), 6.84 (m, 4H), 3.81 (s, 3H), 3.76 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 196.7, 160.0, 159.6, 155.0, 152.4, 149.5, 139.1, 137.5, 133.8, 133.2, 133.0, 131.0, 129.3, 129.1, 128.7, 128.3, 128.1, 119.3, 114.7, 114.0, 113.3, 96.5, 84.5, 55.3, 55.2; IR (neat): 2205, 1671, 1604, 1507, 1438, 1289, 1247, 1172, 1019, 877, 829, 768, 701, 533; MS (ESI, \(m/z\)): 496.19 [M+H]+; HRMS (ESI): calc. for C\(_{34}\)H\(_{15}\)NO\(_3\): 496.1907 [M+H]+, found: 496.1908.

4.6.10 Synthesis of (4-(4-methoxyphenyl)-2-phenyl-5-((4-(trifluoromethyl) phenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (16E)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl)methanone (14B) (100 mg, 0.20 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynyl-alpha,alpha,alpha-trifluorotoluene (40 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-2-phenyl-5-((4-(trifluoromethyl) phenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (16E) (yellow-brown solid, 93 mg, 87% yield).

16E: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.06 (s, 1H), 7.56 (d, \(J = 5.6\) Hz, 7H), 7.45-7.34 (m, 3H), 7.33-7.19 (m, 6H), 6.82 (d, \(J = 8.0\) Hz, 2H), 3.75 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 196.4, 159.8, 156.0, 152.7, 150.3, 138.9, 137.4, 134.0, 133.4, 131.7, 130.9, 129.3, 129.2, 129.0, 128.4, 128.3, 127.8, 125.3, 118.3, 113.3, 94.6, 88.0, 55.2; IR (neat): 1734, 1669, 1607, 1507, 1437, 1320, 1246, 1172, 1106,
1061, 1017, 875, 840, 760, 698, 593, 563, 524; MS (ESI, m/z): 534.17 [M+H]^+; HRMS (ESI): calc. for C\textsubscript{34}H\textsubscript{22}F\textsubscript{3}NO: 534.1675 [M+H]^+, found: 534.1673.

### 4.6.11 Synthesis of (2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (16F)

General Procedure 5 was followed by using (5-iodo-2-(methoxyphenyl)-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl)methanone (14D) (100 mg, 0.20 mmol), PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynylanisole (32 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)pyridin-3-yl)-(phenyl)methanone (16F) (yellow-brown solid, 75 mg, 72% yield).

**16F**: ¹H NMR (400 MHz, CDCl\textsubscript{3}): δ 8.84 (s, 1H), 7.45-7.37 (m, 2H), 7.26 (dt, J = 8.0, 2.0 Hz, 1H), 7.21-7.00 (m, 8H), 6.82 (t, J = 8.0 Hz, 1H), 6.69 (dd, J = 8.0, 2.0 Hz, 2H), 6.61 (t, J = 8.0 Hz, 2H), 6.53 (d, J = 8.0 Hz, 1H), 3.67 (s, 3H), 3.60 (s, 3H), 3.14 (s, 3H); ¹³C NMR (100 MHz, CDCl\textsubscript{3}): δ 195.7, 160.0, 159.6, 155.8, 154.0, 152.4, 148.7, 137.4, 134.5, 133.0, 132.4, 131.5, 131.2, 130.1, 129.3, 128.6, 128.1, 127.7, 120.6, 119.0, 114.8, 114.0, 113.2, 110.3, 96.0, 84.6, 55.3, 55.2, 54.2; IR (neat): 1733, 1654, 1602, 1507, 1437, 1288, 1246, 1174, 1107, 1031, 876, 835, 758, 703, 593, 534; MS (ESI, m/z): 526.20 [M+H]^+; HRMS (ESI): calc. for C\textsubscript{35}H\textsubscript{27}NO\textsubscript{4}: 526.2013 [M+H]^+, found: 526.2013.

### 4.6.12 Synthesis of (4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-2-(4-(trifluoromethyl)phenyl)pyridin-3-yl)(phenyl)methanone (16G)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)pyridin-3-yl)(phenyl)methanone (14E) (100 mg, 0.20 mmol), PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynylanisole (32 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-2-(4-(trifluoromethyl)phenyl)pyridin-3-yl)(phenyl)methanone (16G) (yellow-brown solid, 79 mg, 70% yield).
16G: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.01 (s, 1H), 7.67 (d, $J = 8.0$ Hz, 2H), 7.54 (dd, $J = 6.4$, 1.6 Hz, 4H), 7.41 (t, $J = 8.0$ Hz, 1H), 7.34-7.19 (m, 6H), 6.82 (dd, $J = 16.0$, 8.0 Hz, 4H), 3.82 (s, 3H), 3.77 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 196.5, 160.1, 159.7, 153.4, 152.5, 149.5, 142.6, 137.3, 134.0, 133.6, 131.0, 129.5, 129.2, 128.5, 127.8, 125.2, 120.0, 114.5, 114.1, 113.3, 97.1, 84.2, 55.3, 55.2; IR (neat): 2215, 1664, 1605, 1507, 1441, 1321, 1292, 1247, 1157, 1110, 1066, 1028, 875, 822, 707, 660, 591, 528; MS (ESI, $m/z$): 564.18 [M+H]$^+$; HRMS (ESI): calc. for C$_{35}$H$_{24}$F$_3$NO$_3$: 564.1781 [M+H]$^+$, found: 564.1782.

4.6.13 Synthesis of (2-butyl-4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (16H)

General Procedure 5 was followed by using (2-butyl-5-iodo-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl)methanone (14C) (100 mg, 0.20 mmol), PdCl$_2$(PPh$_3$)$_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynylanisole (32 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2-butyl-4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (16H) (white-yellow solid, 66 mg, 70% yield).

16H: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.85 (s, 1H), 7.63-7.56 (m, 2H), 7.47 (t, $J = 8.0$ Hz, 1H), 7.36-7.19 (m, 6H), 6.80 (m, 4H), 3.80 (s, 3H), 3.75 (s, 3H), 2.68 (t, $J = 8.0$ Hz, 2H), 1.69 (s, 2H), 1.35-1.25 (m, 2H), 0.84 (t, $J = 8.0$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 197.3, 159.9, 159.6, 157.8, 152.3, 148.2, 137.2, 133.8, 133.5, 132.9, 131.1, 129.3, 128.4, 128.2, 117.7, 114.8, 114.0, 113.2, 95.3, 84.4, 55.3, 55.2, 36.0, 31.8, 22.7, 13.8; IR (neat): 2218, 1656, 1605, 1510, 1446, 1289, 1247, 1185, 1027, 889, 834, 808, 713, 536; MS (ESI, $m/z$): 476.22 [M+H]$^+$; HRMS (ESI): calc. for C$_{32}$H$_{29}$NO$_3$: 476.2220 [M+H]$^+$, found: 476.2218.

4.7 Synthesis of (5-iodo-6-(4-methoxyphenyl)-2-phenylbenzo[f]isoquinolin-1-yl)(phenyl)methanone (43A)

(5-((4-Methoxyphenyl)ethynyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (15A) (100 mg, 0.22 mmol) was dissolved in acetonitrile (10 mL) and to this solution, I$_2$
(166 mg, 0.66 mmol) and NaHCO₃ (55 mg, 0.66 mmol) were added. The resulting reaction mixture was then refluxed at 82 °C for 10 h under air. When the reaction was over, saturated aqueous solution of Na₂S₂O₃ (35 mL) was added to remove unreacted excess I₂. Subsequently, the mixture was extracted with ethyl acetate (2 x 20 mL). The separated organic phase was washed with water (50 mL) and dried over MgSO₄ and filtered. The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford (5-iodo-6-(4-methoxyphenyl)-2-phenylbenzo[f]isoquinolin-1-yl)(phenyl)methanone (43A) (white-yellow solid, 83 mg, 64% yield).

43A: ¹H NMR (400 MHz, CDCl₃): δ 9.89 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.68-7.60 (m, 2H), 7.44 (dd, J = 8.0, 1.2 Hz, 1H), 7.39-7.30 (m, 4H), 7.30-7.09 (m, 8H), 7.04-7.02 (m, 2H), 3.86 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 199.5, 159.5, 158.3, 153.9, 147.7, 139.4, 137.8, 136.8, 135.4, 134.6, 133.7, 131.0, 129.9, 129.5, 129.3, 129.1, 128.9, 128.7, 128.2, 127.9, 127.8, 127.0, 125.7, 114.1, 103.4, 55.4; IR (neat): 2919, 1668, 1605, 1508, 1447, 1409, 1287, 1243, 1211, 1174, 1028, 945, 884, 837, 767, 744, 694, 632, 568, 512, 438; MS (ESI, m/z): 592.08 [M+H]+; HRMS (ESI): calc. for C₃₃H₂₂INO₂: 592.0768 [M+H]+, found: 592.0756.

4.8 General Procedure 6. Synthesis of iodo-substituted spiro-fused pyridine derivatives 44

The corresponding 5-alkynyl-4-(4-methoxyphenyl)pyridine derivative 16 (100 mg, 0.4 mmol) was dissolved in acetonitrile (10 mL) and to this solution, I₂ (303 mg, 1.2 mmol) and NaHCO₃ (100 mg, 1.2 mmol) were added. The resulting reaction mixture was then refluxed at 82 °C for 2 h under air. When the reaction was over, saturated aqueous solution of Na₂S₂O₃ (35 mL) was added to remove unreacted excess I₂. Subsequently, the mixture was extracted with ethyl acetate (2 x 20 mL). The separated organic phase was washed with water (50 mL) and dried over MgSO₄ and filtered. The obtained crude product was purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.
4.8.1 Synthesis of 4'-benzoyl-7'-iodo-3',6'-diphenylspiro[cyclohexa[2,5]dien-1,5'-cyclopenta[c]pyridin]-4-one (44A)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-2-phenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl)methanone (16A) (100 mg, 0.2 mmol) and NaHCO₃ (50 mg, 0.6 mmol), I₂ (151 mg, 0.6 mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-3',6'-diphenylspiro[cyclohexa[2,5]dien-1,5'-cyclopenta[c]pyridin]-4-one (44A) (light yellow solid, 75 mg, 65% yield).

44A: ¹H NMR (400 MHz, CDCl₃): δ 8.86 (s, 1H), 7.39-7.22 (m, 6H), 7.48 (dd, J = 8.0, 2.0 Hz, 2H), 7.14 (m, 7H), 6.45-5.94 (br m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 193.5, 184.6, 155.5, 152.9, 147.4, 145.0, 140.2, 138.6, 136.2, 133.8, 133.5, 132.4, 131.1, 129.4, 129.3, 129.1, 128.8, 128.5, 94.6, 62.8; IR (neat): 1660, 1558, 1421, 1388, 1237, 1159, 1042, 916, 871, 851, 694, 671, 591, 542, 443, 420; MS (ESI, m/z): 578.06 [M+H]+; HRMS (ESI): calc. for C₃₂H₂₀INO₂: 578.0612 [M+H]+, found: 578.0603.

4.8.2 Synthesis of 4'-benzoyl-7'-iodo-3'-phenyl-6'-((p-tolyl)spiro[cyclohexa[2,5]dien-1,5'-cyclopenta[c]pyridin]-4-one (44B)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-2-phenyl-5-(p-tolylethynyl)pyridin-3-yl)(phenyl)methanone (16B) (100 mg, 0.2 mmol) and NaHCO₃ (50 mg, 0.6 mmol), I₂ (151 mg, 0.6 mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-3'-phenyl-6'-((p-tolyl)spiro[cyclohexa[2,5]dien-1,5'-cyclopenta[c]pyridin]-4-one (44B) (yellow solid, 70 mg, 60% yield).

44B: ¹H NMR (400 MHz, CDCl₃): δ 8.94 (s, 1H), 7.58-7.55 (m, 2H), 7.49-7.37 (m, 4H), 7.30-7.19 (m, 4H), 7.15-7.07 (m, 4H), 6.52-6.00 (br m, 4H), 2.35 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 193.6, 184.7, 155.5, 152.9, 147.2, 145.1, 140.2, 139.3, 138.8, 136.3, 133.8, 132.3, 131.1, 130.5, 129.4, 129.3, 129.1, 129.0, 128.6, 128.5, 128.4, 94.3, 62.8, 21.4; IR (neat): 1733, 1660, 1558, 1507, 1419, 1396, 1239, 1174, 917, 873, 854, 822, 756, 695, 672; MS (ESI, m/z): 592.08 [M+H]+; HRMS (ESI): calc. for C₃₃H₂₂INO₂: 592.0768 [M+H]+, found: 592.0757.
4.8.3 Synthesis of 4′-benzoyl-7′-iodo-3′-phenyl-6′-(thiophen-3-yl)spiro[cyclohexa[2,5]diene-1,5′-cyclopenta[c]pyridin]-4-one (44C)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-2-phenyl-5-(thiophen-3-ylethynyl)pyridin-3-yl)(phenyl)methanone (16C) (100 mg, 0.2 mmol) and NaHCO₃ (50 mg, 0.6 mmol), I₂ (151 mg, 0.6 mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4′-benzoyl-7′-iodo-3′-phenyl-6′-(thiophen-3-yl)spiro[cyclohexa[2,5]diene-1,5′-cyclopenta[c]pyridin]-4-one (44C) (yellow solid, 78 mg, 67% yield).

44C: ¹H NMR (400 MHz, CDCl₃): δ 8.85 (s, 1H), 7.50-7.41 (m, 3H), 7.32 (dd, J = 7.2, 6.0 Hz, 3H), 7.22 (d, J = 2.0 Hz, 2H), 7.15 (m, 5H), 6.45-5.90 (br m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 193.4, 184.7, 184.6, 155.5, 146.4, 145.2, 140.4, 138.7, 136.3, 133.8, 133.4, 130.9, 129.4, 129.3, 129.0, 128.5, 128.4, 127.0, 125.7, 92.9, 62.5; IR (neat): 1658, 1620, 1550, 1421, 1397, 1314, 1236, 1182, 1034, 901, 858, 797, 753, 694, 672, 624, 593, 559, 443; MS (ESI, m/z): 584.02 [M+H]+; HRMS (ESI): calc. for C₃₀H₁₈INO₂S: 584.0176 [M+H]+, found: 584.0170.

4.8.4 Synthesis of 4′-benzoyl-7′-iodo-6′-(4-methoxyphenyl)-3′-phenylspiro[cyclohexa[2,5]diene-1,5′-cyclopenta[c]pyridin]-4-one (44D)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl)methanone (16D) (100 mg, 0.20 mmol) and NaHCO₃ (50 mg, 0.60 mmol), I₂ (151 mg, 0.6 mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4′-benzoyl-7′-iodo-6′-(4-methoxyphenyl)-3′-phenylspiro[cyclohexa[2,5]diene-1,5′-cyclopenta[c]pyridin]-4-one (44D) (yellow solid, 110 mg, 92% yield).

44D: ¹H NMR (400 MHz, CDCl₃): δ 8.94 (s, 1H), 7.62-7.49 (m, 2H), 7.42 (dd, J = 16.0, 7.6 Hz, 2H), 7.32-7.11 (m, 8H), 6.83 (m, 2H), 6.47-6.08 (br m, 4H) 3.81 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 193.6, 184.7, 160.2, 147.1, 145.0, 138.8, 136.3, 133.8, 131.1, 130.1, 129.4, 129.3, 129.0, 128.5, 125.6, 113.8, 94.1, 62.8, 55.2; IR (neat): 1733, 1660, 1504, 1419, 1248, 1175, 1030, 874, 833, 759, 697, 577, 515, 444;
MS (ESI, m/z): 608.07 [M+H]+; HRMS (ESI): calc. for C_{33}H_{22}INO_3: 608.0717 [M+H]^+; found: 608.0710.

4.8.5 Synthesis of 4'-benzoyl-7'-iodo-3'-phenyl-6'-(4-(trifluoromethyl)phenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44E)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-2-phenyl-5-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (16E) (100 mg, 0.2 mmol) and NaHCO_3 (50 mg, 0.6 mmol), I_2 (151 mg, 0.6 mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-3'-phenyl-6'-(4-(trifluoromethyl)phenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44E) (white-yellow solid, 67 mg, 52% yield).

44E: ^1H NMR (400 MHz, CDCl_3): δ 8.96 (s, 1H), 7.64-7.54 (m, 4H), 7.42 (dd, J = 12.8, 7.2 Hz, 3H), 7.33 (d, J = 8.0 Hz, 2H), 7.27-7.18 (m, 5H), 6.54-6.20 (br m 4H); ^13C NMR (100 MHz, CDCl_3): δ 193.4, 184.34, 156.0, 151.2, 147.2, 145.4, 139.8, 138.6, 137.2, 136.1, 133.9, 132.5, 131.1, 129.4, 129.3, 129.2, 128.6, 128.5, 125.5, 125.4, 95.9, 62.8; IR (neat): 1667, 1653, 1395, 1322, 1244, 1158, 1124, 1063, 1015, 909, 845, 761, 709, 697, 670, 600, 504, 450; MS (ESI, m/z): 646.05 [M+H]^+; HRMS (ESI): calc. for C_{33}H_{19}F_3INO_2: 646.0485 [M+H]^+, found: 646.0476.

4.8.6 Synthesis of 4'-benzoyl-7'-iodo-3'-(2-methoxyphenyl)-6'-(4-methoxyphenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44F)

General Procedure 6 was followed by using (2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (16F) (100 mg, 0.2 mmol) and NaHCO_3 (50 mg, 0.6 mmol), I_2 (151 mg, 0.6 mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-3'-(2-methoxyphenyl)-6'-(4-methoxyphenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44F) (yellow-brown solid, 92 mg, 72% yield).

44F: ^1H NMR (400 MHz, CDCl_3): δ 8.76 (s, 1H), 7.30 (d, J = 7.2 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 7.09-6.96 (m, 6H), 6.69-6.66 (m, 3H), 6.51 (d, J = 8.26 Hz,
1H), 6.22 (d, J = 9.6 Hz, 2H), 5.96 (d, J = 9.6 Hz, 2H), 3.64 (s, 3H), 3.44 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 192.7, 184.7, 160.1, 156.3, 154.1, 152.3, 146.9, 144.7, 143.6, 140.3, 131.6, 130.5, 129.3, 128.0, 125.7, 120.3, 113.8, 110.6, 94.4, 62.8, 55.2, 54.9; IR (neat): 1660, 1558, 1498, 1437, 1393, 1237, 1174, 1019, 880, 855, 835, 754, 709, 673, 637, 583, 521, 450, 412; MS (ESI, \(m/z\)): 638.08 [M+H]\(^{+}\); HRMS (ESI): calc. for C\(_{34}\)H\(_{24}\)INO\(_4\): 638.0822 [M+H]\(^{+}\), found: 638.0811.

4.8.7 Synthesis of 4'-benzoyl-7'-iodo-6'-(4-methoxyphenyl)-3'- (4-(trifluoromethyl)phenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44G)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-2-(4-(trifluoromethyl)phenyl)pyridin-3-yl)(phenyl)methanone (16G) (100 mg, 0.2 mmol) and NaHCO\(_3\) (50 mg, 0.6 mmol), I\(_2\) (151 mg, 0.6 mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-6'-(4-methoxyphenyl)-3'- (4-(trifluoromethyl)phenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44G) (yellow solid, 84 mg, 62% yield).

44G: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.96 (s, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.46 (t, J = 8.4 Hz, 2H), 7.32-7.24 (m, 3H), 7.21-7.13 (m, 2H), 6.87 (dd, J = 6.8, 4.8 Hz, 2H), 6.47-5.98 (br m, 4H), 3.82 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 193.3, 184.5, 160.3, 147.4, 145.1, 141.0, 136.2, 134.2, 132.4, 131.4, 130.0, 129.6, 129.4, 128.7, 125.4, 125.3, 113.9, 97.6, 93.7, 62.7, 55.2; IR (neat): 1733, 1716, 1699, 1662, 1558, 1541, 1506, 1457, 1323, 1250, 1174, 1123, 1066, 851, 705, 419; MS (ESI, \(m/z\)): 676.06 [M+H]\(^{+}\); HRMS (ESI): calc. for C\(_{34}\)H\(_{21}\)F\(_3\)INO\(_3\): 676.0591 [M+H]\(^{+}\), found: 676.0581.

4.8.8 Synthesis of 4'-benzoyl-3'-butyl-7'-iodo-6'-(4-methoxyphenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44H)

General Procedure 6 was followed by using (2-butyl-4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (16H) (100 mg, 0.2 mmol) and NaHCO\(_3\) (50 mg, 0.6 mmol), I\(_2\) (151 mg, 0.6 mmol). The obtained crude product
using 9:1 hexane/ethyl acetate as the eluent was purified by flash column chromatography on silica gel to afford 4’-benzoyl-3’-butyl-7’-iodo-6’-(4-methoxyphenyl) spiro[cyclohexa[2,5]dien-1,5’-cyclopenta[c]pyridin]-4-one (44H) (yellow solid, 75 mg, 64% yield).

**44H**: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.75 (s, 1H), 7.59 (t, $J$ = 7.2 Hz, 3H), 7.41 (t, $J$ = 7.6 Hz, 2H), 7.16-7.08 (m, 2H), 6.83-6.80 (m, 2H), 6.26 (br s, 2H), 6.05 (br s, 2H), 3.78 (s, 3H), 2.72-2.61 (m, 2H), 1.68 (m, 2H), 1.32-1.23 (m, 2H), 0.82 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 194.0, 184.5, 160.1, 151.2, 145.5, 144.6, 143.8, 136.8, 134.4, 132.1, 130.0, 128.9, 125.7, 121.9, 121.1, 119.9, 113.8, 94.3, 62.4, 55.2, 31.9, 22.6, 19.4, 13.8; IR (neat): 1661, 1559, 1504, 1457, 1395, 1290, 1248, 1175, 1031, 833, 745, 706, 519; MS (ESI, m/z): 588.10 [M+H]$^+$; HRMS (ESI): calc. for C$_{31}$H$_{26}$INO$_3$: 588.1030 [M+H]$^+$, found: 588.1027.
REFERENCES


APPENDICES A

NMR DATA

$^1$H and $^{13}$C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker Spectrospin Avance DPX400 Ultrashield spectrometer.

$^1$H and $^{13}$C NMR spectra of products are given below.
Figure 23A. $^1$H NMR Spectrum of compound 48A.

Figure 24A. $^{13}$C NMR Spectrum of compound 48A.
Figure 25A. $^1$H NMR Spectrum of compound 48B.

Figure 26A. $^{13}$C NMR Spectrum of compound 48B.
Figure 27A. $^1$H NMR Spectrum of compound 48C.

Figure 28A. $^{13}$C NMR Spectrum of compound 48C.
Figure 29A. $^1$H NMR Spectrum of compound 48D.

Figure 30A. $^{13}$C NMR Spectrum of compound 48D.
Figure 31A. $^1$H NMR Spectrum of compound 13A.

Figure 32A. $^{13}$C NMR Spectrum of compound 13A.
Figure 33A. $^1$H NMR Spectrum of compound 13B.

Figure 34A. $^{13}$C NMR Spectrum of compound 13B.
Figure 35A. $^1$H NMR Spectrum of compound 13C.

Figure 36A. $^{13}$C NMR Spectrum of compound 13C.
Figure 37A. $^1$H NMR Spectrum of compound 13D.

Figure 38A. $^{13}$C NMR Spectrum of compound 13D.
Figure 39A. $^1$H NMR Spectrum of compound 13E.

Figure 40A. $^{13}$C NMR Spectrum of compound 13E.
Figure 41A. $^1$H NMR Spectrum of compound 13F.

Figure 42A. $^{13}$C NMR Spectrum of compound 13F.
Figure 43A. $^1$H NMR Spectrum of compound 14A.

Figure 44A. $^{13}$C NMR Spectrum of compound 14A.
Figure 45A. $^1$H NMR Spectrum of compound 14B.

Figure 46A. $^{13}$C NMR Spectrum of compound 14B.
Figure 47A. $^1$H NMR Spectrum of compound 14C.

Figure 48A. $^{13}$C NMR Spectrum of compound 14C.
Figure 49A. $^1$H NMR Spectrum of compound 14D.

Figure 50A. $^{13}$C NMR Spectrum of compound 14D.
Figure 51A. $^1$H NMR Spectrum of compound 14E.

Figure 52A. $^{13}$C NMR Spectrum of compound 14E.
Figure 53A. $^1$H NMR Spectrum of compound 52.

Figure 54A. $^{13}$C NMR Spectrum of compound 52.
**Figure 55A.** $^1$H NMR Spectrum of compound 15A.

**Figure 56A.** $^{13}$C NMR Spectrum of compound 15A.
Figure 57A. $^1$H NMR Spectrum of compound 15B.

Figure 58A. $^{13}$C NMR Spectrum of compound 15B.
Figure 59A. $^1$H NMR Spectrum of compound 15C.

Figure 60A. $^{13}$C NMR Spectrum of compound 15C.
Figure 61A. $^1$H NMR Spectrum of compound 15D.

Figure 62A. $^{13}$C NMR Spectrum of compound 15D.
Figure 63A. $^1$H NMR Spectrum of compound 15E.

Figure 64A. $^{13}$C NMR Spectrum of compound 15E.
Figure 65A. $^1$H NMR Spectrum of compound 16A.

Figure 66A. $^{13}$C NMR Spectrum of compound 16A.
Figure 67A. $^1$H NMR Spectrum of compound 16B.

Figure 68A. $^{13}$C NMR Spectrum of compound 16B.
Figure 69A. $^1$H NMR Spectrum of compound 16C.

Figure 70A. $^{13}$C NMR Spectrum of compound 16C.
Figure 71A. $^1$H NMR Spectrum of compound 16D.

Figure 72A. $^{13}$C NMR Spectrum of compound 16D.
Figure 73A. $^1$H NMR Spectrum of compound 16E.

Figure 74A. $^{13}$C NMR Spectrum of compound 16E.
Figure 75A. $^1$H NMR Spectrum of compound 16F.

Figure 76A. $^{13}$C NMR Spectrum of compound 16F.
Figure 77A. \(^1\)H NMR Spectrum of compound 16G.

Figure 78A. \(^{13}\)C NMR Spectrum of compound 16G.
Figure 79A. $^1$H NMR Spectrum of compound 16H.

Figure 80A. $^{13}$C NMR Spectrum of compound 16H.
Figure 81A. $^1$H NMR Spectrum of compound 43A.

Figure 82A. $^{13}$C NMR Spectrum of compound 43A.
Figure 83A. $^1$H NMR Spectrum of compound 44A.

Figure 84A. $^{13}$C NMR Spectrum of compound 44A.
Figure 85A. $^1$H NMR Spectrum of compound 44B.

Figure 86A. $^{13}$C NMR Spectrum of compound 44B.
Figure 87A. $^1$H NMR Spectrum of compound 44C.

Figure 88A. $^{13}$C NMR Spectrum of compound 44C.
Figure 89A. $^1$H NMR Spectrum of compound 44D.

Figure 90A. $^{13}$C NMR Spectrum of compound 44D.
Figure 91A. $^1$H NMR Spectrum of compound 44E.

Figure 92A. $^{13}$C NMR Spectrum of compound 44E.
Figure 93A. $^1$H NMR Spectrum of compound 44F.

Figure 94A. $^{13}$C NMR Spectrum of compound 44F.
**Figure 95A.** $^1$H NMR Spectrum of compound 44G.

**Figure 96A.** $^{13}$C NMR Spectrum of compound 44G.
Figure 97A. $^1$H NMR Spectrum of compound 44H.

Figure 98A. $^{13}$C NMR Spectrum of compound 44H.