# DESIGN AND SYNTHESIS OF NOVEL $PA_N$ -TARGETING ANTI-INFLUENZA AGENTS

by

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# ABSTRACT OF THE DISSERTATION

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Pandemics and seasonal epidemics of influenza pose a major health concern worldwide. The limitation of vaccination and the emergence of influenza virus strains that are resistant to the current antivirals, have emphasized the search for a new antiviral with novel mechanisms of action. The endonuclease activity of polymerase acidic protein (PA) has been identified as an attractive target. $PA_N$ endonuclease is a highly conserved and essential viral transcription protein, which cleaves host pre-mRNA during the cap-snatching process. The cap-snatching mechanism is a unique process of the viral transcription. There are many known $PA_N$ endonuclease inhibitors, and few of them inhibited viral reproduction in the cell.

Our research efforts began with conducting a fragment screening campaign using 2009 pandemic H1N1 $PA_N$. The compound 5-chloro-3-hydroxypyridin-2(1*H*)-one was identified as a bimetal chelating ligand at the active site of the enzyme. Several scaffolds were proposed from the hit compound including 3-hydroxypyridin-2(1*H*)-ones, 3-hydroxyquinolin-2(1*H*)-ones and aza analogous of 3-hydroxypyridin-2(1*H*)-ones. Although initial SAR studies on 3-hydroxypyridin-2(1*H*)-ones led to compound **13** with a modest antiviral activity in the cellular assay ($EC_{50}$ = 11 μM), neither 3-hydroxyquinolin-2(1*H*)-ones nor aza analogous of 3-hydroxypyridin-2(1*H*)-ones displayed any *ex-vivo* activity. Our research again focused on the initial scaffold, 3-hydroxypyridin-2(1*H*)-ones. Optimization of binding interaction at the 5- and 6-positions of the pyridinone ring provided compounds having inhibitory activity that is comparative compound **13** in the enzymatic assay. Unfortunately, these compounds were not active in the cellular assay. Our research then turned to preparing noncompetitive inhibitors to validate whether irreversible or a more sustained modification of $PA_N$ could result in *ex-vivo* activity. In the meantime, 3-hydroxypyridin-2(1*H*)-one derivatives with an additional chelating moiety, which could have enhanced binding interactions with $PA_N$, were prepared. This concept, however, turned out to be unsuccessful as we could not see any *ex-vivo* activity with these compounds as well. Although our various attempts at designing $PA_N$ endonuclease inhibitor with a great *ex-vivo* activity were unsuccessful, continued efforts are being made to find a $PA_N$ endonuclease inhibitor, which could be developed into the clinic.

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# DEDICATION

To my family,

For their love and support.

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# INTRODUCTION

Influenza viruses are lipid-enveloped, negative-sense, single-strand RNA viruses, which belong to the family of Orthomyxoviridae.[1] There are three types of viruses: A, B and C. Influenza A virus is further categorized into subtypes based on their 18 hemagglutinin (HA) and 9 neuraminidase (NA) proteins. Unlike other types of influenza virus that infect only humans, influenza A infects a wide range of avian and mammalian hosts.

Influenza viruses cause upper respiratory and lung infections, and are responsible for substantial mortality and morbidity in elderly and other high-risk individuals. The World Health Organization (WHO) reported that annual epidemics of influenza A and B virus infections result in 3 to 5 million cases of severe illness with 250,000–500,000 deaths worldwide.[2] Influenza A virus, in particular, has been responsible for several sporadic pandemics such as the 1918 Spain flu, 1957 Asian flu, 1968 Hong Kong flu and 2009 Swine flu.[3-5] The pandemics of the influenza A virus infection usually cause higher mortality rates than seasonal epidemics.[3] During the 1918-1919 influenza pandemic, one third of the world's population was infected by the virus, and approximately 40 million people died from the infection.[6-7]

Vaccination with live-attenuated and/or inactivated influenza A and B viruses has been used as a prophylactic treatment to control epidemics and pandemics of influenza virus infections. Its usage, however, is limited for several reasons. Not only does the vaccine need to be re-administered annually, but also its efficacy is highly dependent on the

correct prediction of the predominant infectious strains for the given year. Furthermore, while vaccine generally effective to healthy adults, its efficacy often drops for the elderly and individuals with compromised immunity.[8-9]

Two classes of anti-influenza agents have been developed as alternative prophylactic measures and therapeutic options for influenza viral infections. These include M2 ion channel blockers such as rimantadine and amantadine (admantanes) as well as neuraminidase (NA) inhibitors such as zanamivir, oseltamivir and peramivir. The utility of admantanes are limited because of their ineffectiveness against influenza B virus and primarily because they generate resistant mutants of influenza A virus. Most of influenza A virus strains contain M2 S31N mutation. These strains are resistance to these drugs and yet maintain fitness and transmissibility similar to wild-type influenza A virus.[10-12]

The NA inhibitors have been used as the current standard of care. Oseltamivir is currently the most widely used oral anti-influenza agent. However, these inhibitors should be administered within 48 hours of infection to be effective.[13] In addition, oseltamivir-resistant seasonal influenza A virus strains are beginning to emerge. The oseltamivir-resistant strains predominantly contain the NA H274Y mutation.[14-15] With the permissive mutations, these resistant strains exhibit fitness comparable to wild-type influenza A virus.[16] Furthermore, influenza A virus and influenza B virus, which have reduced sensitivity to oseltamivir and zanamivir, have been reported.[17-18] Considering this, there is a pressing need for the development of new antiviral drugs with a different

mode of action to prevent epidemics and pandemics and to treat influenza virus infections.

Recently, the influenza viral RNA-dependent RNA polymerase (RdRp) has attracted interest as a molecular target for new antiviral agents.[8] The heterotrimer RdRp comprises polymerase acidic (PA) and polymerase basic 1 (PB1) and polymerase basic 2 (PB2) polypeptide chains, and is responsible for both transcription and replication of the viral genome.[19-20] Considering its crucial role in the viral life cycle, the protein has been recognized as a superior molecular target for the development of anti-influenza agents. Many groups are actively investigating the various processes associated with RdRp with the hope of finding new targets.[8] One target that has receiving a lot of attention is the endonuclease activity of PA, which resides in the N-terminal domain of PA ($PA_N$).[8, 21-22] The endonuclease activity of $PA_N$ is particularly attractive target for several reasons: (1) it is essential for viral transcription of influenza viruses; (2) it is highly conserved across all influenza virus types and subtypes; and (3) its analogous activity is not present in mammalian cells.[8, 21-22] Our laboratory has focused its efforts on the identifications and synthesis of novel $PA_N$-targeting anti-influenza agents that potentially could be developed into the clinic. Based on what is known about $PA_N$, molecules that inhibit the function of this essential viral transcription protein should not only be efficacious against various strains of influenza viruses, but also influenza viruses that have developed resistance to currently available antiviral agents.

## 1.1 The Viral RNA-dependent RNA Polymerase and Viral Transcription.

There are several reasons why viral RdRp is an attractive target for the development of a novel antiviral agents. The RNA polymerase complex, which consists of the PA, PB1 and PB2 polypeptides, catalyzes both transcription and replication of viral genomes. Considering its important role in the viral life cycle, an inhibitor of viral RdRp would produce antiviral activity. In addition, viral RdRp is highly conserved throughout influenza viruses, making it likely that an inhibitor of this complex could be efficacious against all members of influenza family of viruses. Presently, there are very few agents such as T705 (favipiravir) and VX-787 that actually target viral RdRp. Both of these compounds are presently in clinical trials in the United States. Therefore, an inhibitor of the viral RdRp is likely to bypass the currently observed resistance mechanisms. Viral RdRp carries out processes that are absent in human cells, including cap-snatching. An inhibitor of these specific processes would not be expected to interfere with the normal transcription and replication that occurs in human cells.[8]

The viral RdRp has been studied in great detail – primarily in influenza A virus.[19-20] It is important to understand the molecular biology of influenza A virus in depth. Influenza A virus is the most virulent human pathogens among influenza viruses. As mentioned previously, it is this virus that is responsible for epidemics and pandemics of influenza infections including the 1918 H1N1 (Spanish flu), 1957 H2N2 (Asian flu), 1968 H3N2 (Hong Kong flu) and 2009 H1N1 (swine flu).[3-5]

The influenza A virus contains eight-negative stranded RNA genomic segments, and each genomic segment encodes one or two of the 11 total viral proteins. Each of viral RNA (vRNA) segment is assembled to form a complex called viral ribonucleoprotein (vRNP) with the viral RdRp and coated with multiple nucleoproteins (NPs). The viral RdRp is responsible for transcription and replication of the viral genome, and these transformations occur in the nucleus of infected host cells. However, the molecular mechanisms by which the polymerase carries out these two different processes are not yet fully understood. Nevertheless, the extensive biochemical and virological studies along with the recent publications of several crystal structures of the polymerase have revealed the architecture and distinctive roles of the protein.[19-20]

Viral transcription is initiated by a *cis*-acting viral RdRp that is part of the vRNP structure (Figure 1). The RNA polymerase is bound to the vRNA promoter formed by the terminal 5′ and 3′ sequences of the vRNA template (Figure 1a). The conserved sequences at the 5′ and 3′ ends of each vRNA segment are found to display partially inverted complementarity, making these ends interact with each other. Although several secondary structures of the promotor have been proposed, the hairpin loop structure has gained strong support among investigators in the field.[19]

The RNA polymerase is unable to synthesize the 5′-capped mRNA, which is necessary for translation by eukaryotic host-cell translation machinery. Consequently, the transcription of viral genome is initiated by hijacking the 5′-capped RNA fragment from host pre-mRNAs in a process called ‘cap-snatching’ (Figure 1b). Cap-snatching begins

with the binding of PB2 to the cap of a host pre mRNA. A phosphodiester bond 10-13 nucleotides downstream of the cap is cleaved by the endonuclease functionality of the polymerase.[19] $PA_N$ is responsible for this cleavage.[24-25]

The cleaved host 5´-capped RNA segment, which is the product of the cap-snatching, is used as a primer to initiate transcription of the viral mRNA (Figure 1c). The 3´ end of the primer is positioned in the active site of PB1, along with 3´end of the viral genome. Usually, transcription is started by the addition of a G residue to the 3´ end of the primer using the penultimate C residue at the 3´end of the viral genome. However, initiation by the addition of a C residue to the primer with 3´-hydroxy group directed by the penultimate G residue at the 3´end of the viral genome has also been reported.[19]

The transcription elongation proceeds by using the viral genome as a template (Figure 1d). The viral RNA template is threaded through the active site of PB1 in a 3´ to 5´ direction as the elongation continues. The process keeps taking place until the RNA polymerase reaches a sequence of 5-7 U residues on the viral RNA template. The repeated U residues, usually located 16 nucleotides from the 5´ end of the viral RNA template, act as a signal for polyadenylation. Viral RdRp then catalyzes the polyadenylation of viral mRNA.[19]

The transcription cannot further be carried out once the repeated U sequence reaches the active site of the RNA polymerase (Figure 1e). The steric hindrance caused by the binding of the 5´ end of the viral RNA template leads viral RNA template slipping and

releases the synthesized viral mRNA from PB2. The viral mRNA is then bound to a cellular nuclear cap-binding complex (CBC), which triggers the recruitment of cellular factors for mRNA-protein (mRNP) assembly. The mRNP is exported to cytoplasm, and viral mRNA is then translated by the host cell.[19]

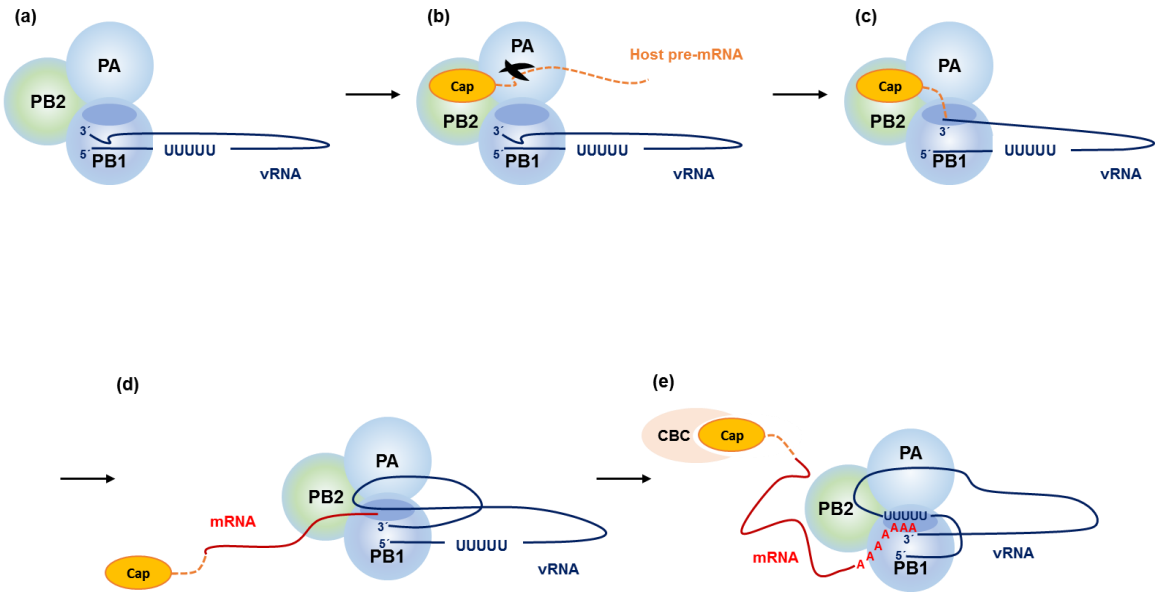



**Figure 1**. The *cis*-acting model of the viral transcription.

The RNA polymerase complex also catalyzes the viral replication mechanism. The complex first replicates vRNA into complementary RNA (cRNA), which in turn serves as a template for the production of more vRNA. The cRNA is a full-length copy of the vRNA without a 5´-cap and a 3´-poly(A) tail. Recent studies suggest *de novo* initiation of replication in a primer-independent manner; however, the exact mechanism is still controversial.[19]

## 1.2 The Cap-snatching Process.

Since transcription and replication of the viral genome by viral RdRp is essential for the viral life cycle, inhibition of these processes are viable targets for antiviral therapy.[8] Cap-snatching has attracted a lot of attention.[8, 21-22] The cap-snatching event is an essential step in the influenza virus lifecycle as the polymerase itself cannot synthesize the 5´-capped mRNA. In addition to this, it is highly conserved throughout types and subtypes of the influenza virus. Furthermore, cap-snatching is a unique property of influenza viruses. As noted previously, mammalian cells do not participate in an analogous activity.[8, 21-22]

There are two approaches available to inhibit cap-snatching and subsequent viral transcription: (1) inhibiting the host 5´-mRNA cap binding to the PB2 subunit[25-29] or (2) inhibiting N-terminal endonuclease domain of the PA subunit.[21-22] Indeed, there have been examples of inhibitors that validate each of these approaches as effective ways to inhibit cap-snatching and viral transcription. Cap mimetics would inhibit the binding of host 5´-mRNA cap binding to the PB2 subunit, and VX-787 is a promising example of this approach.[25-29] VX-787 is now in a phase II clinical trial (NCT02342249) and actively recruiting patients.[30] This approach, however, has own inherent limitation. The protein shares common features with known host cap-binding proteins like elF4E; therefore, inhibition by cap mimetics could exhibit significant cytotoxicity.[25-29]

Compared to inhibition of the host 5´-mRNA cap binding to the viral PB2 subunit, inhibitors of $PA_N$ may be selective against the viruses and may not interfere function of the host cells; mammalian cells do not have cellular counterparts of $PA_N$.[21-22] L-742,001 is the first example of this approach and selectively inhibits cap-dependent viral transcription. This inhibitor even shows no significant effects on human endonuclease RNase A or RNase H, which are involved in RNA degradation.[31-35]

### 1.3 Structure and Function of the $PA_N$.

PA is a 80-KDa subunit and can be cleaved into two independent domains: a large C-terminal domain ($PA_C$, residues 239-716) that mediates the interaction with PB1[36] and a small N-terminal domain ($PA_N$, residues 1-197) with cap-dependent endonuclease activity.[23-24] In addition to this, PA is involved in vRNA/cRNA promotor binding during replication.[37] The binding site of vRNA/cRNA promotor remains unclear.[37-38]

Crystal structures of $PA_N$ were published by several groups, although the crystal structure of $PA_N$ with ssRNA substrate is still not available yet.[21-22, 39] These structures confirmed that enzymatic activity of the RNA polymerase resides in $PA_N$, and revealed the architecture of the enzymatic domain.[21-22, 39] The N-terminal domain of PA is found to be similar to those of the PD-(D/E)XK phosphodiesterase superfamily.[21-22, 39] The large and extremely diverse superfamily has little sequence similarity, although it retains a common core fold with a few residues responsible for the cleavage. [40-41]

The single folded domain of $PA_N$ is composed of seven α-helices, a mixed and five-stranded β-sheet as shown in Figure 2a. The domain has a cation-dependent endonuclease active site core with a structural motif characteristic of the catalytic core of the family. As depicted in Figure 2b, the active site features a histidine (His41), a cluster of three acidic amino acids (Glu80, Asp108 and Glu119) and a putative catalytic lysine (Lys134). The three acidic residues along with histidine are conserved in all influenza virus types and subtypes. These residues are involved in the coordination of divalent (manganese or magnesium) metal ions; however, there are differences in opinion about number and types of metal ions that exist.[21-22]

The histidine and three acidic residues coordinate one, two or three manganese or magnesium ions.[21-22, 39, 42-45] Although the manganese has 500-fold higher binding affinity than magnesium,[46] intracellular concentration of magnesium is at least 1000-fold higher than that of manganese.[47] Therefore, magnesium may be more biologically relevant than manganese.[47]

Numerous biochemical findings support the two-metal-ion model (Figure 2b).[21-22] Based on this model, M1 is coordinated with His41, Asp108, Glu119, carbonyl oxygen of Ile120 and two water molecules (W4 and W5), and M2 is coordinated with Glu80, Asp108 and four water molecules (W1, W2, W3 and W4).[21-22] The two-metal ion model suggests that metal at site I is believed to assists nucleophilic attack of a water molecule by the formation of a hydroxide ion. Metal at site II is thought to facilitated leaving of the 3´ hydroxyl group and to stabilize the pentacovalent intermediate.[48] However, there

are data that support the existence of third metal in the active site of $PA_N$.[42-45] The three-metal catalysis model suggests that metal at site I is directly involved in catalysis whereas metal at site II provided structural support. Metal at site III is believed to stabilize the negative charge of the transition state and to provide a water needed to protonate the leaving group.[42-45] In either event, the divalent metals appear to play a crucial role in the cleavage of host mRNA.

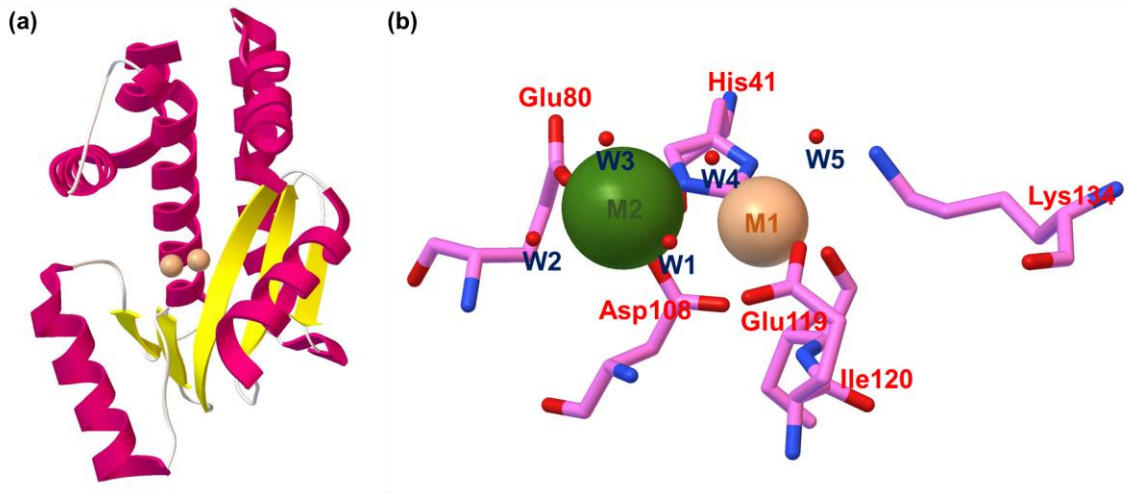



**Figure 2**. Structure of $PA_N$ and its active site. (a) Secondary structure of $PA_N$. α-Helices are colored as pink, β-sheets as yellow and two metals as orange. (b) Active site of $PA_N$. (PDB: 4AVQ)[22]

### 1.4 $PA_N$ as a Novel Target for Anti-Influenza Agents.

The viral RdRp is catalyzes cap-snatching during viral transcription.[19-20] This essential, conserved and unique cap-dependent viral transcription has been shown to be inhibited by disrupting structure and function of the viral RdRp.[8] As previously detained, this can

be accomplished in one of two ways: (1) inhibiting the host 5´-mRNA cap binding to the PB2 subunit[25-29] or (2) inhibiting endonuclease activity of $PA_N$.[21-22] The similarity between cap binding domain of PB2 ($PB2_{cap}$) and host cap-binding proteins like elF4E may pose a significant challenge for overcoming cytotoxicity of these cap mimetics.[25-29] Given this, it is not surprising that most studies targeting the inhibition of cap-snatching have been focused around finding ways to specifically inhibit endonuclease activity of $PA_N$.[21-22] A wealth of information surrounding its biochemistry and crystal structures of $PA_N$ made it a good candidate for drug screening and development.[21-22] Compounds that are inhibitors of $PA_N$ endonuclease represent a promising class of antiviral agents that could be effective to prevent or treat pandemics of influenza A viral infections that have become resistant to those presently in clinical use.

Inhibitors of $PA_N$ endonuclease activity to be effective need to disrupt the function of the protein in such a way that it blocks the cap-dependent viral transcription. This ultimately would interfere with the lifecycle of influenza viruses, and stop the replication of virus. $PA_N$ has a deep cleft with divalent ($Mg^{2+}$ or $Mn^{2+}$) metal ions in its active site.[21-22] The enzymatic activity of the protein is observed in the presence of metals.[21-22] Consequently, chelation of these metal ions is an attractive strategy to inhibit enzymatic activity.[21-22] This drug concept has been validated with HIV-1 integrase, which interestingly shares some similar controversy associated with the types and number of divalent metal ions in its catalytic site.[49] Inhibitors of HIV-1 integrase, which are under clinical trials as well as in markets, are shown in Figure 3.[49] The similar approach has also been explored in the design inhibitors of HIV RNase H or HCV polymerase.[50-51]

These studies further validate the strategy involving the potential of developing inhibitors of $PA_N$ endonuclease that incorporate chelating motifs. Several examples of these known endonuclease inhibitors, which are based on their coordination with metal cofactor(s) of influenza viral enzymes, will be discussed are provided as follows in Section 1.5 Endonuclease Inhibitors.[31-35, 52-80]

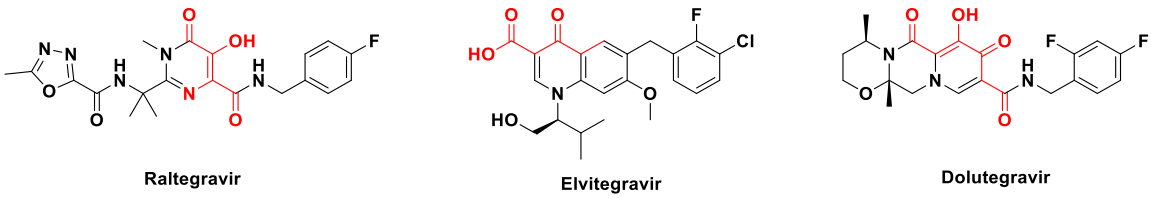



**Figure 3**. Inhibitors of HIV-1 integrase with divalent chelating motifs.

## 1.5 Endonuclease Inhibitors.

Several small molecules with ability to inhibit endonuclease activity of $PA_N$ have been identified, and representative endonuclease inhibitors are shown in Figure 4.[31-35, 52-80] Several 4-substituted 2,4-dioxobutanoic acids were initially identified as inhibitors of cap-dependent transcription through random screening using influenza A virus. One of the leads, L-742,001 showed potent and dose-dependent inhibition of the viral endonuclease activity in enzymatic assays ($IC_{50}$ = 0.43 µM) using influenza A/PR/8/34 (H1N1) strain. The inhibitor proved to be active in cell culture, specifically in Madin-Darby-Canine Kidney (MDCK), and exhibits an $IC_{50}$ of 0.35 µM in virus yield assay. Cytotoxicity of the inhibitor was not observed at concentration of up to 100 µM.[31-35]

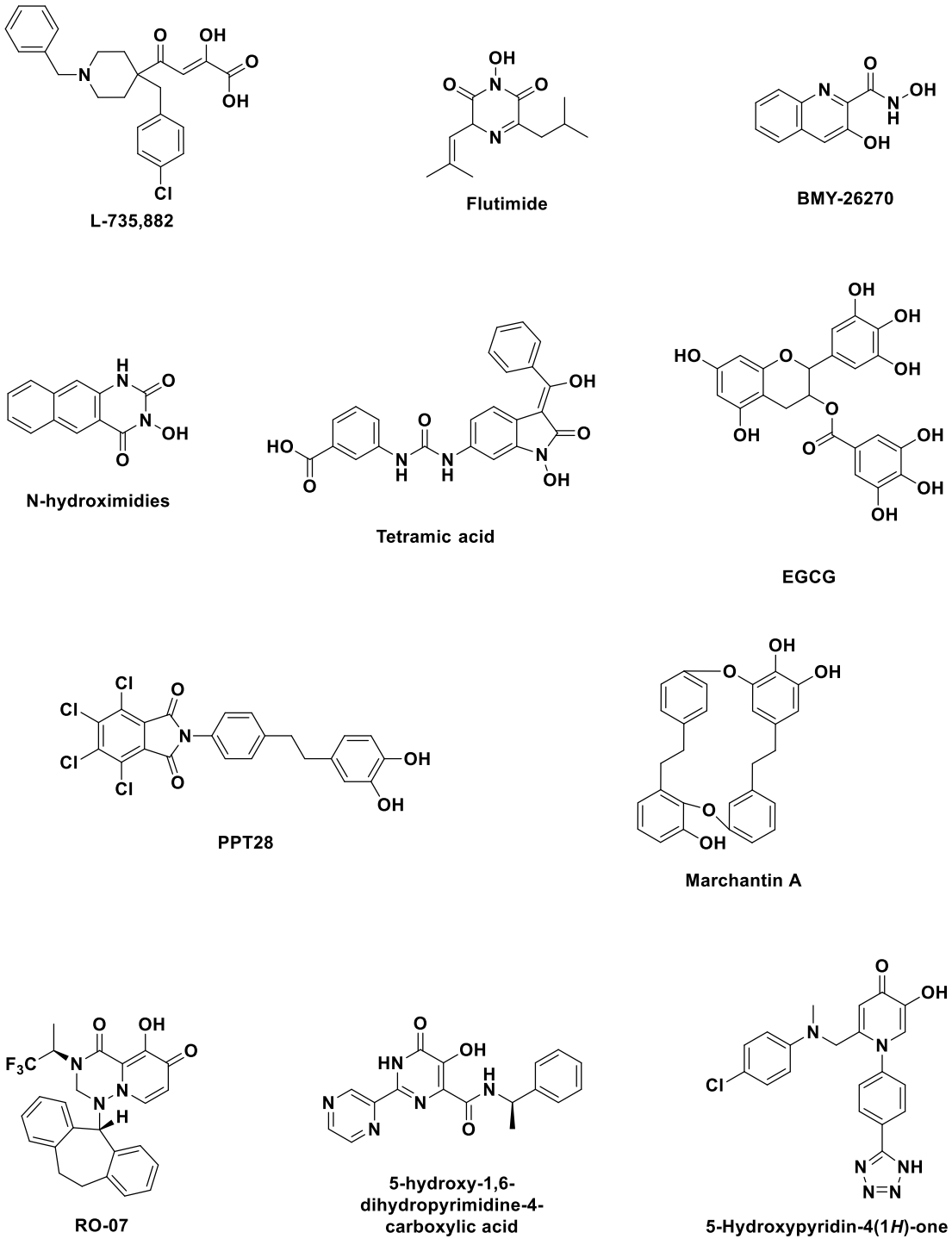



**Figure 4**. Known small molecule inhibitors of $PA_N$.

Flutimide was isolated from a fungus, *Delitschia confertaspora*, and was identified as an endonuclease inhibitor. Flutimide served as a lead compound and series of flutimide derivatives were synthesized and tested. Flutimide showed potent and dose-dependent inhibition of the viral endonuclease activity in enzymatic assays ($IC_{50}$ = 4.3 μM), which used influenza A/PR/8/34 (H1N1) strain. In a virus yield assay, flutimide inhibits influenza virus infection of MDCK cells with an $IC_{50}$ of 5.9 μM and no apparent cytotoxicity effect on MDCK cells at concentration as high as 100 μM.[52-57]

Soon after these discoveries were disclosed, several other groups begin to work on the development of endonuclease inhibitors, resulting in a wide chemical variety of endonuclease inhibitors. These include N-hydroxamic acid (BMY-26270) and N-hydroxyimide derivatives,[58] tetramic acid derivatives,[59] green tea catechins (EGCG),[60] phenethylphenylphthalimide derivatives (PPT28),[61] macrocyclic bisbenzyls (Marchantin A),[62] polycyclic carbamoyl pyridine derivatives (RO-7).[63-64] and 5-hydroxy-1,6-dihydropyrimidine-4-carboxylic acid derivatives.[65-66] During our studies on the development of endonuclease inhibitors, several other endonuclease inhibitors were also disclosed including 5-hydroxypyridin-4(1*H*)-one derivatives.[67-80] These inhibitors along with L-742,001 or flutimide bear chelating motifs and coordinate with divalent metal ions in the active sites of the $PA_N$.

Crystal structures of $PA_N$ in complexes with inhibitors revealed a deep active site cleft containing multiple subpockets, which are shown in Figure 5. As a representative example, 2,4-dioxo-4-phenylbutanoic acid (DPBA) in the binding site is depicted in

Figure 6. DPBA is a simple example of 4-substituted 2,4-dioxobutanoic acids with an $IC_{50}$ of 21 μM in enzymatic assay. Including DPBA, these inhibitors share a common chelation mode with the two active site metal ions, although they extend into different subpockets.

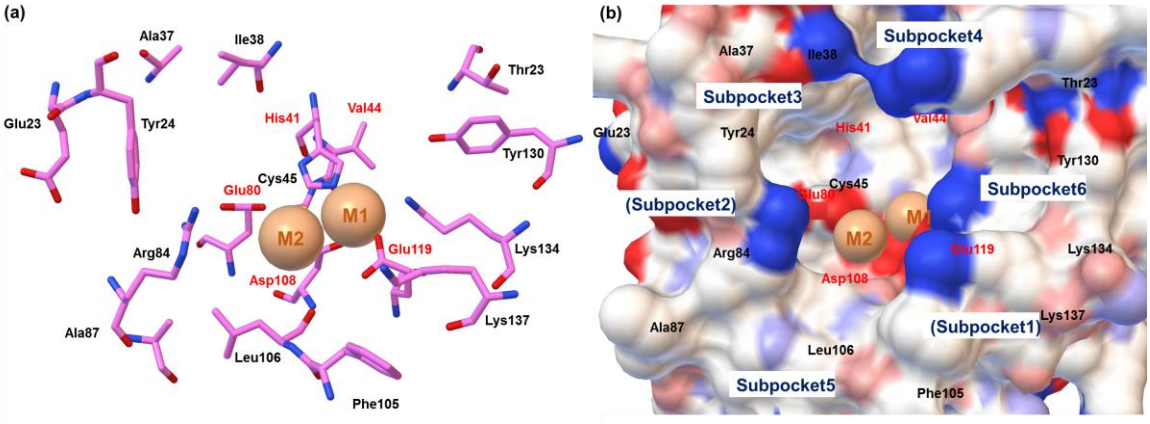



**Figure 5**. Binding site of $PA_N$. (a) Conserved amino acids in the binding site of $PA_N$. (b) Subpockets in the binding site of $PA_N$. (PDB: 4AWF)

There are two co-crystallized structures that are available.[21-22] One reported that a single molecule of DPBA is found in the active site of $PA_N$[22] whereas the other reported that two copies of DPBA are present.[21] It was assumed that the concentration of inhibitor affected the number of molecule in the binding site of the enzyme.[21-22] Although the number of molecules in binding site is different, interactions involved in chelation are shared.[21-22] As shown in Figure 6A, one molecule of DPBA engages M1 coordination.[21] Three chelating groups of DPBA forms four coordination with divalent metals in the binding site. Carboxyl moiety, which forms a salt bridge catalytic Lys134, chelates M1. The group also interacts with the hydroxyl of Tyr130 via a bridging water molecule. α-

Carbonyl moiety chelates both of M1 and M2, whereas, γ-carbonyl moiety chelates M2. The other molecule as seen with the work of Dubois et. al engages in subpocket 2 and subpocket 3 (Figure 6b).[21] Subpocket 2 consists of Leu16, Lys19, Ala20, Glu23, Gly81 and Asp83, and Subpocket 3 is surrounded by Tyr24, Glu26, Lys34 and Ile38. The carboxyl group of molecule B also forms hydrogen bonds to His41 and the bridging water molecule.

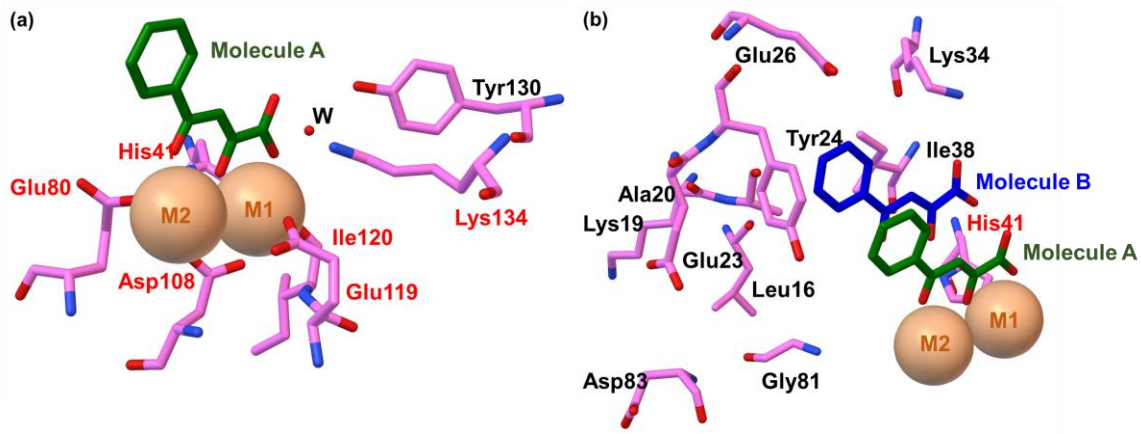



**Figure 6**. Binding site of $PA_N$ with DPBA. (a) Chelating interactions of DPBA with two metal ions in the active site of $PA_N$. (b) Binding interactions of second molecule DPBA in subpocket 2 and 3. (PDB: 4E5G)[21]

## 1.6 Rationale.

There is a considerable amount of data that supports the idea that $PA_N$ is a promising and effective target for the development of anti-influenza agents. Inhibition of $PA_N$ endonuclease activity has been shown to be associated with antiviral activity. $PA_N$ is an essential, highly conserved protein, and, thus far, an untargeted mechanism of action for

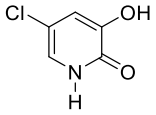
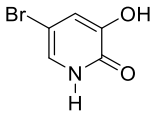
anti-influenza agents. A true understanding and realization of this will require the development of endonuclease inhibitors that have strong antiviral activity both *in vitro* and *in vivo*. In addition, inhibitors should be effective against resistant strains of influenza virus, and display no cytotoxicity in mammalian cells. Our research efforts began with conducting a fragment screening campaign using a crystal structure of 2009 pandemic H1N1 $PA_N$.[42] The compound 5-chloro-3-hydroxypyridin-2(1*H*)-one was identified as a bimetal chelating ligand at the active site of the enzyme along with other seven compounds.[42] Initial studies used 5-chloro-3-hydroxypyridin-2(1*H*)-one as a scaffold for further development.[81-83] This led to the design of several classes of endonuclease inhibitors.[81-83] These endonuclease inhibitors will enrich the chemical diversity of endonuclease inhibitors. Even though various endonuclease inhibitors are reported, very few inhibitors exhibit antiviral activity in cells. Further exploration of these novel endonuclease inhibitors, therefore, could increase the likelihood that an efficacious endonuclease inhibitor of $PA_N$ could be identified and developed into a clinically useful antiviral agent.

### 1.7 Preliminary Studies on 3-Hydroxypyridin-2(1*H*)-ones.

Fragment screening of 2009 pandemic H1N1 $PA_N$ (A/California/07/2009) by X-ray crystallography was conducted using a library of 775 compounds. Initial screening revealed eight compounds binding to the endonuclease domain including 5-chloro-3-hydroxypyridin-2(1*H*)-one, **1**. Compound **1** exhibits an $IC_{50}$ of 25 μM in a high-throughput fluorescence resonance energy transfer based inhibition assay. The inhibitory

activity of commercially-available 5-bromo-2-hydroxypyridin-2(1*H*)-one, **2**, was also evaluated. Compound **2**, which as an $IC_{50}$ of 16 μM was slightly active than compound **1**.[42]

**Table 1**. Biological activity of compounds **1** and **2**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **2** |  | 16 |

Compound **1** and **2** were soaked with $PA_N$ in an effort to have a better understanding of what structural modifications could be tolerated and potentially enhance the activity of these endonuclease inhibitors. Binding of both compound **1** and **2** revealed the presence of a third metal ion (M3) in the active site. Stronger electron density was observed for compound **2** than compound **1**. The active site of the enzyme with compound **2** bound is shown in Figure 7. Three copies of **2** were bound to the active site. Two molecules of **2** were bound to the subpockets 2 and 3, and were coordinated with M3. Compound **2** was also found coordinated with M1 and M2 at the active site, resembling the chelation mode of known endonuclease inhibitors. However, compound **2** forms three chelating interactions with two chelating groups, while the other known endonuclease inhibitors make four chelating interactions with three chelating groups. The 3-hydroxy moiety of the pyridinone ring, which forms a salt bridge with catalytic Lys134, is coordinated to

M1. The carbonyl moiety of the pyridin-2-one is involved in coordination with both M1 and M2. The pyridinone nitrogen does not directly coordinate with the metals; however, the nitrogen forms a hydrogen bond with a water molecule, which chelates M2, at a distance of 3.0 Å. The pyridinone nitrogen is also within hydrogen-bonding distance (2.8 Å) from the carboxylate of Glu80.[42]

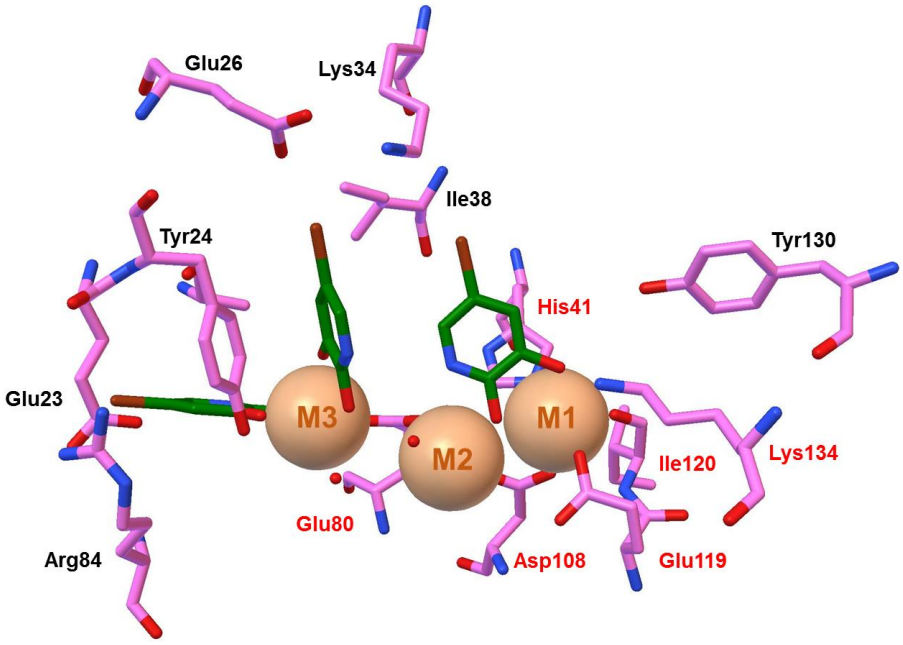
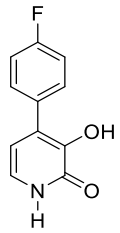
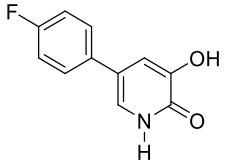
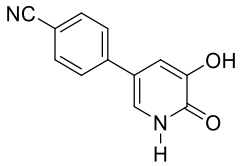
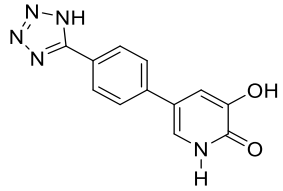
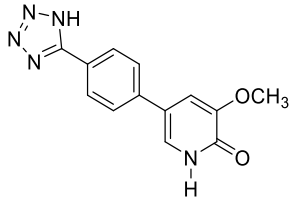



**Figure 7**. Binding site of $PA_N$ with compound **2**. (PDB: 4MK1)[42]

Dr. Ajit Parhi further developed the 3-hydroxypyridin-2(1*H*)-one series based on these initial results. The synthesis and structure-activity relationships associated with various 3-hydroxypyridin-2(1*H*)-ones was investigated using a high-throughput fluorescence resonance energy transfer based inhibition assay as a measure of their relative ability to

inhibit the endonuclease activity. The results observed with a few selected 4- and 5-phenyl substituted derivatives of 3-hydroxypyridin-2(1*H*)-one are summarized in Table 2-4.[81]

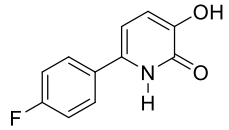
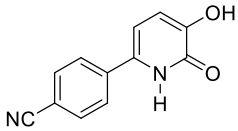
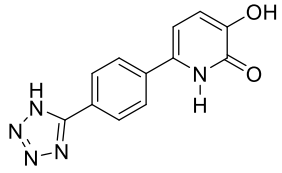
**Table 2**. Biological activity of compounds **3-7**.[81]

| | Compound Structure | [a]$IC_{50}$ (µM) | [b]$IC_{50}$ (µM) MDCK | [b]$IC_{50}$ (µM) HEK293 |
|---|---|---|---|---|
| **3** |  | >200 | >100 | >100 |
| **4** |  | 0.730 | >100 | >100 |
| **5** |  | 3.83 | >100 | >100 |
| **6** |  | 0.368 | >100 | 80 |
| **7** |  | 2.580 | >100 | 80 |

[a]$IC_{50}$ is defined as the concentration at which endonuclease activity is reduced by half in the high-throughput fluorescence resonance energy transfer based inhibition assay.
[b]MTT-microtiter plate tetrazolium cytotoxicity assays were conducted in **M**adian-**D**arby **C**anine **K**idney epithelial cells (MDCK), and in **H**uman **E**mbryonic **K**idney (HEK293) cells.

4-Fluorophenyl-3-hydroxypyridin-2(1*H*)-one, **3**, was inactive (Table 2). However, replacement of bromine at 5-postion of compound **2** with various aryl groups led to an overall increase in activity. In comparison with compound **2**, the 4-fluorophenyl (**4**), 4-cyanophenyl (**5**) and 4-(tetrazol-5-yl)phenyl (**6**) derivatives have 22-, 4- and 43-fold increase in activity, respectively. The 5-tetrazolyl moiety at *para*-position of phenyl at 5-position of the pyridinone ring was the most potent of these derivatives as a viral endonuclease inhibitor. These results are in contrast to that observed with 4-fluorophenyl-3-hydroxypyridin-2(1*H*)-one, **3**, which was inactive. In addition, the importance of hydroxyl moiety for exhibiting endonuclease inhibition activity was evaluated by preparing compound **7**. It was 7-fold less active than compound **6**, indicating that the 3-hydroxyl moiety is essential for good activity.[81]

**Table 3**. Biological activity of compounds **8-10**.[81]

| | **Compound Structure** | **$IC_{50}$ (μM)** | **$IC_{50}$ (μM) MDCK** | **$IC_{50}$ (μM) HEK293** |
|---|---|---|---|---|
| **8** |  | 0.430 | 60 | >100 |
| **9** |  | 0.802 | >100 | ≥ 28 |
| **10** |  | 0.085 | >100 | ≥ 28 |

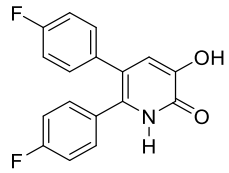
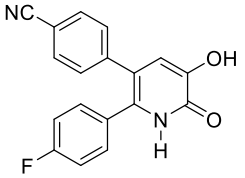
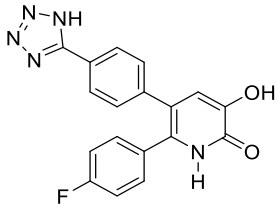
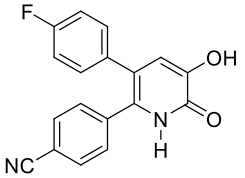
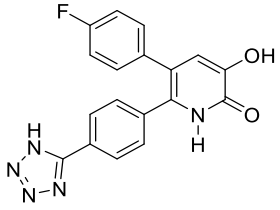
The aryl substitution at 6-position of the pyridinone ring also led to a similar overall increase in activity as was observed with aryl substitution at 5-position of the pyridinone ring. The 6-phenyl derivatives did exhibit a greater inhibitory activity than the similarly substituted 5-phenyl analogs (Table 3). As seen with 5-substituted 3-hydroxypyridin-2(1*H*)-ones, the 4-(tetrazol-5-yl)phenyl derivative, **10**, was the most active followed by the 4-fluorophenyl (**8**) and the 4-cyanophenyl (**9**) derivatives.[81]

There was significantly enhanced activity with the 5,6-diphenyl substituted 3-hydroxypyridin-2(1*H*)-one derivatives, **11-15** (Table 4). Compound **11** was 18- and 10-fold more potent than compound **4** and **8**, respectively. It is noteworthy that the presence of a 5-tetrazoyl moiety at the *para*-position of the 5-phenyl substituent of compound **13** was associated with enhanced inhibitory activity relative to the *p*-cyanophenyl derivative, **12**. Compound **13** was also more active than analogs of 5-substituted 6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-ones. A similar trend was observed in 6-phenyl substituted 5-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-ones. The *p*-(tetrazol-5-yl) derivative, **15**, was 2-fold more potent than the *p*-cyanophenyl derivative **14**.[81]

Cytotoxicity studies were performed using MDCK cells and human embryonic kidney (HEK293) cells as measured after four days of exposure. There was no correlation between the inhibitory activity and cytotoxic activity. Some of compounds showed cytotoxic activity below 100 µM but greater than 10 µM as shown in Table 2-4. As this early stage of development, these data did not pose a major concern that may interfere in

future studies directed toward the establishment of *ex-vivo* antiviral data for this series of compounds.[81]

**Table 4.** Biological activity of compounds **11-15**.[81]

| | Compound Structure | $IC_{50}$ (μM) | $IC_{50}$ (μM) MDCK | $IC_{50}$ (μM) HEK293 |
|---|---|---|---|---|
| **11** |  | 0.041 | >100 | >100 |
| **12** |  | 0.136 | 50 | ≥ 28 |
| **13** |  | 0.011 | 50 | ≥ 28 |
| **14** |  | 0.054 | 40 | ≥ 28 |
| **15** |  | 0.023 | >100 | >100 |

As part of a structure-based drug design efforts, compound **13** and **15** were soaked with $PA_N$. As shown in Figure 8, two chelating groups of compound **13** formed three

chelating interactions as seen with compound **2**. However, only one molecule of compound **13** was bound at the binding site. The 4-fluorophenyl moiety formed a cation-π interaction with M3, and this interaction might explain increased activity of 5- or 6-aryl substituted 3-hydroxypyridin-2-(1*H*)-ones. The moiety extended into subpocket 3 and involved in weak hydrophobic interaction with Tyr24. The 4-(tetrazol-5-yl)phenyl moiety, which extended into subpocket 4, formed hydrophobic interactions with the side chains of Lys34, Ala37 and Ile38. Notably, the tetrazole moiety makes bidentate hydrogen bond interactions with Arg124. This interaction might explain enhanced potency of compound **13**.[81]

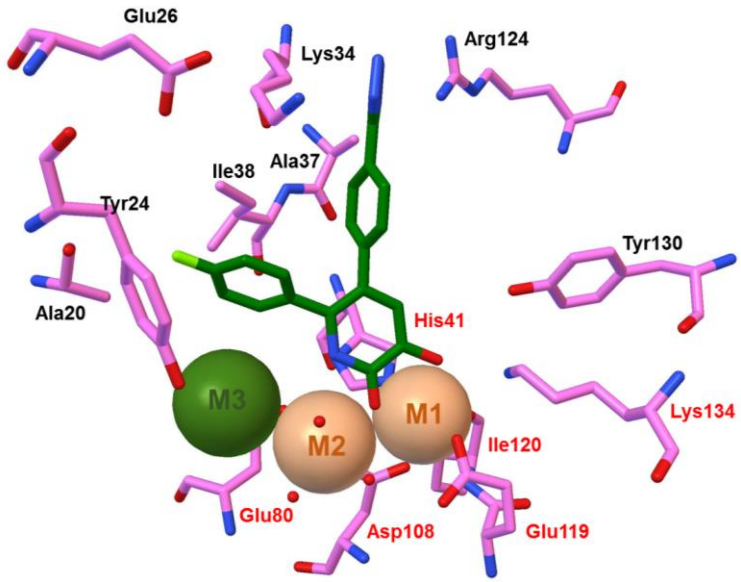



**Figure 8**. Binding site of $PA_N$ with compound **13**. (PDB: 4M4Q).[81]

The crystal structure of compound **15**, which is shown in Figure 9, revealed that compound **15** makes coordination with the metals in a flipped orientation compared what

was detected previously with **13**. The 3-hydroxy moiety of the pyridinone ring was now coordinated to both M1 and M2 whereas 2-one moiety of the pyridinone ring was involved in coordination with M1. The pyridinone nitrogen no longer interacted with the water molecule nor did it interact with the carboxylate of Glu80. However, the similar interactions between compound **15** and **13** were observed other than these interactions. The 4-fluorophenyl moiety formed a cation-π interaction with M3, and, tetrazole moiety of 4-(tetrazol-5-yl)phenyl formed bidentate hydrogen bond interactions with Arg124. The 2-fold increased potency of compound **13** compared to compound **15** may be explained by the optimal position of the pyridinone nitrogen and its favorable interactions with metal chelating atoms. What did seem to be a critical observation was that these crystal structures suggest a significant directing effect of the tetrazole group, which forms interaction with Arg124.[81]

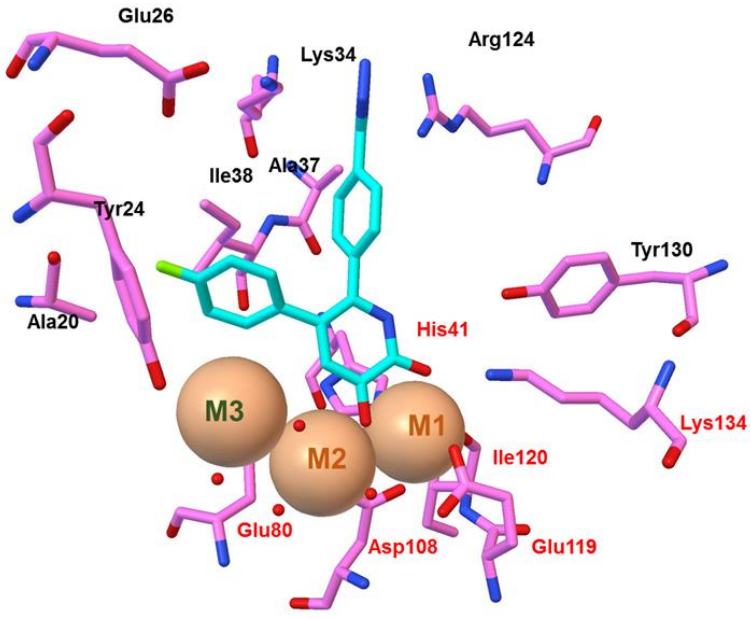



**Figure 9**. Binding site of $PA_N$ with compound **15**. (PDB: 4M4Q).[81]

Hit-to-lead optimization of 5-chloro-3-hydroxypyridin-2(1*H*)-one, **1**, identified compound **13** as an endonuclease inhibitor with an $IC_{50}$ of 11 nM activity in the enzyme assay. The antiviral activity of compound **13** against influenza A/Puerto Rico/8/1934 (H1N1) was also evaluated by a virus yield assay in MDCK cells. Virus titers in supernatants were determined by fluorescent forming unit (FFU) assays after 24h infection at the indicated concentrations of compound **13** (Figure 10). Oseltamivir and DMSO were used as the positive and negative controls, respectively. Compound **13** showed modest activity with an $EC_{50}$ of 11 µM. However, $EC_{90}$ value for compound **13** could not be determined, implying it was unable to completely suppress viral spread.[42,81] These results for the foundation upon which we continued our research on 3-hydroxypyridin-2(1*H*)-ones and related compounds as endonuclease inhibitors with the potential for possessing potent antiviral activities both *in vitro* and *ex-vivo*.

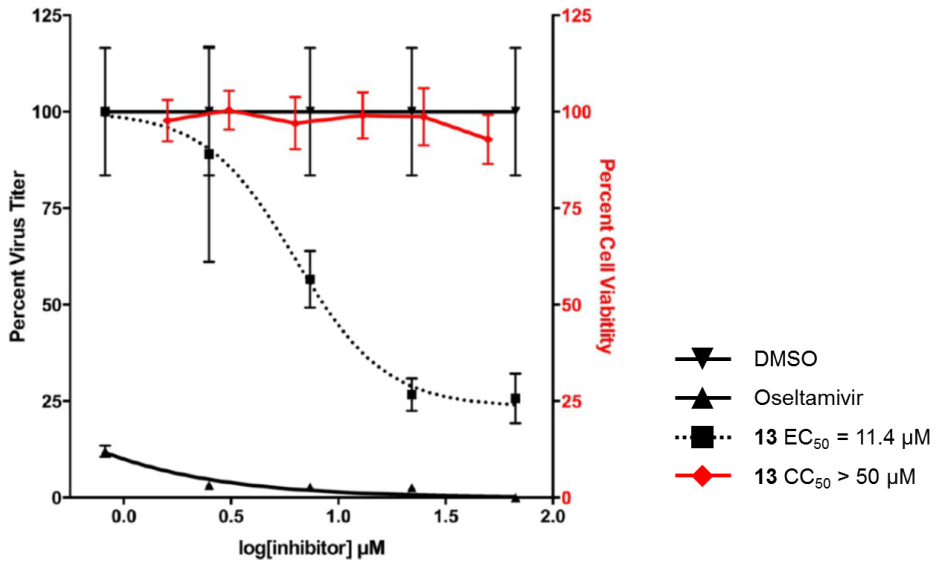



**Figure 10.** Cytotoxicity and *ex-vivo* activity of compound **13** in MDCK cells. (*modified from reference 42*)

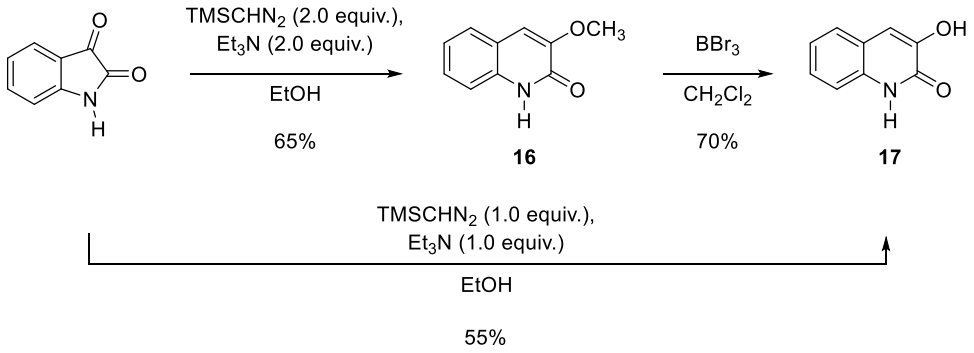
# RESULT AND DISCUSSION

## 2.1 Synthesis and Evaluation of 3-Hydroxyquinolin-2(1*H*)-one Derivatives.

The data associated with 5,6-diphenyl substituted 3-hydroxypyridin-2(1*H*)-ones prompted our lab to examine the structure activity relationships associated benzo-fused analogs of 3-hydroxypyridin-2(1*H*)-one.[82] Although there were two possible scaffolds including both 3-hydroxquinolin-2(1*H*)-one and 4-hydroxyisoquinolin-3(2*H*)-one, we decided to focus solely on 3-hydroxyquinolin-2(1*H*)-one scaffold. This decision was based upon the results from previous studies on 3-hydroxypyridin-2(1*H*)-ones that indicated aryl substitution at 4-position of pyridinone ring was detrimental to endonuclease inhibition activity whereas aryl substitution at either the 5- or 6-position of pyridinone ring was tolerated. Moreover, 5,6-bisaryl substituted 3-hydroxypyridin-2(1*H*)-ones displayed significantly increased potency. Since 3-hydroxyquinolin-2(1*H*)-one scaffold resembled 5,6-bis-substituted 3-hydroxypyridin-2(1*H*)-one, these derivatives might have enhanced potency. Additionally, the increased hydrophobicity of this novel scaffold might off-set the relatively high polarity of 3-hydroxypyridin-2(1*H*)-one. These derivatives could be expected to have increased cell permeability, and, therefore, may also exhibit increased *ex-vivo* activity.

We prepared 3-hydroxyquinolin-2(1*H*)-one, **17** as shown in Scheme 1 in order to validate 3-hydroxyquinolin-2(1*H*)-one as an alternative scaffold. Starting with commercially-available isatin, treatment with 2.0 equivalent of (trimethylsilane)diazomehane and

triethylamine in ethanol at room temperature gave 3-methoxyquinolin-2(1*H*)-one, **16**. Compound **16** was treated with excess $BBr_3$ in dichloromethane at room temperature to give the desired compound **17**. We also noted that compound **17** could be also prepared as one step reaction. The treatment of isatin with 1.0 equivalent of (trimethylsilane)diazomethane and triethylamine in ethanol at room temperature directly gave the desired product.[82]

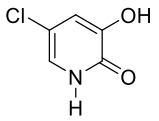
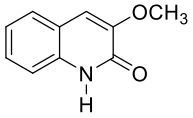
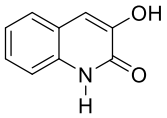



**Scheme 1**. Synthetic route for compounds **16** and **17**.

Compound **16** and **17** were evaluated in the high-throughput fluorescence resonance energy transfer based inhibition assay as performed with the 3-hydroxypyridin-2(1*H*)-one series (Table 5). All biochemical data and x-ray crystal structures presented here and in the subsequent pages were done by Dr. Joseph D. Bauman in the Department of Chemistry and Chemical Biology, unless otherwise noted. As speculated from the SAR studies of 3-hydroxypyridin-2(1*H*)-ones, compound **17** had 1.5-fold increase in activity when compared to compound **1**. These data confirmed that not only can 3-hydroxquinolin-2(1*H*)-one serve as an alternative scaffold of 3-hydroxypyridin-2(1*H*)-one, but also that it did possess increased inhibitory activity. Consistent with the SAR

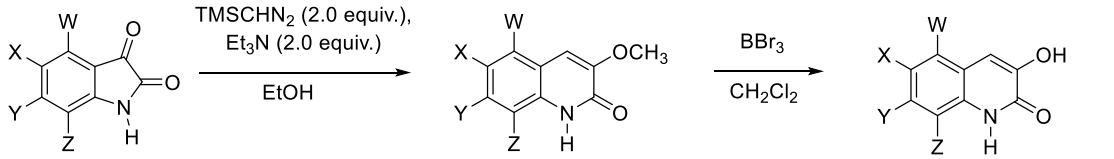
studies of 3-hydroxypyridin-2(1*H*)-ones, 3-hydroxy moiety is essential for the activity as demonstrated by the lack of activity observed for compound **16**.[82]

**Table 5**. Biological activity of **1**, **16** and **17**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **16** |  | >200 |
| **17** |  | 17 |

Studies on the substituent effect of bromine at 5, 6, 7, and 8 position of 3-hydroxyquinolin-2(1*H*)-ones were then pursued. Using the methodology developed for **16** and **17**, we prepared several bromo substituted 3-hydroxyquinolin-2(1*H*)-one derivatives, **22-25** (Scheme 2). The commercially-available and appropriately substituted bromoisatins were treated with 2.0 equivalent of (trimethylsilane)diazomethane and trimethylamine in ethanol at room temperature to give 5-, 6-, 7-, and 8-bromo-3-methoxyquinolin-2(1*H*)-one intermediates, **18-21,** which could be readily purified. Subsequent treatment of these bromo 3-methoxyquinolin-2(1*H*)-ones with excess $BBr_3$ in dichloromethane at room temperature provided the desired products, **22-25**.[82]

The relative biological activities of compound **22-25** were evaluated, and the results are summarized in Table 6. Compound **23** and **24** showed a 2-fold increase in inhibitory activity while compound **22** and **25** displayed 1.5-fold increase in inhibitory activity when compared to the unsubstituted parent compound **17**. These data suggest that the presence of a bromo substituent at either the 6- or 7-position of 3-hydroxyquinolin-2(1*H*)-one is associated with an enhancement in enzyme inhibition relative to the other positional isomers.[82]




**18**, 53%, W = Br; X, Y, Z = H
**19,** 54%, X = Br; W, Y, Z = H
**20**, 60%, Y = Br; W, X, Z = H
**21**, 41%, Z = Br; W, X, Y = H

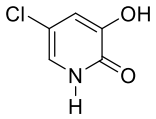
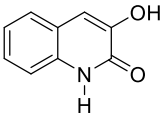
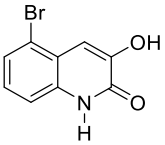
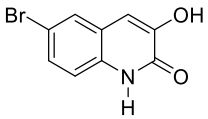
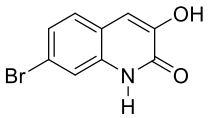
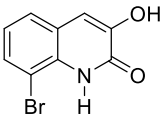
**22**, 65%, W = Br; X, Y, Z = H
**23,** 58%, X = Br; W, Y, Z = H
**24**, 50%, Y = Br; W, X, Z = H
**25**, 77%, Z = Br; W, X, Y = H

**Scheme 2**. Synthetic route for compounds **22−25**.

We had observed cytotoxic activity with some of the 3-hydroxypyridin-2(1*H*)-ones derivatives at concentrations below 100 μM. As a high level of cytotoxicity could hinder the assessment of *ex-vivo* antiviral activity, it is critical that compounds with significant cytotoxicity be avoided. Therefore, the cytotoxicity activities of compound **22-25** were evaluated at an earlier stage in the development of these series of compounds. The MTT-microtiter plate tetrazolium cytotoxicity assay was used with MDCK cells (**M**adin-**D**arby **C**anine **K**idney epithelial cells) and HEK 293 cells (**H**uman **E**mbryonic **K**idney 293 cells). As seen in Table 6, the $IC_{50}$ values for all of these compounds were >10 μM,

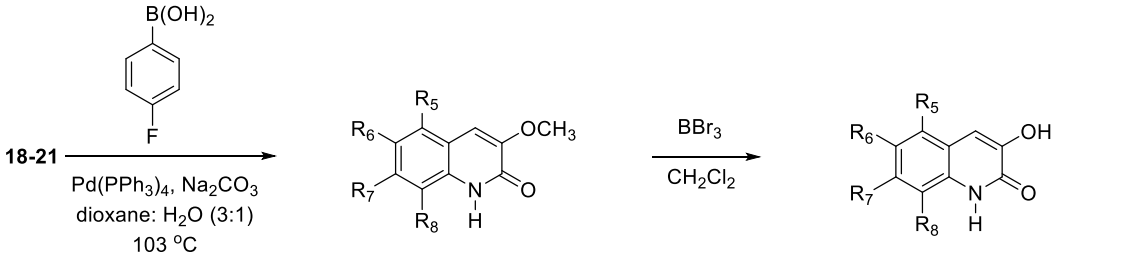
which was the highest concentration tested. The data indicated that there would be no problem in future studies directed toward the establishment of *ex-vivo* antiviral data for these 3-hydroxyquinolin-2(1*H*)-ones.[82]

**Table 6**. Biological activity of **1**, **17** and **22**-**25**.

| | Compound Structure | $IC_{50}$ (μM) | $IC_{50}$ (μM) MDCK | $IC_{50}$ (μM) HEK293 |
|---|---|---|---|---|
| **1** |  | 25 | ND | ND |
| **17** |  | 17 | ND | ND |
| **22** |  | 12 | >10 | >10 |
| **23** |  | 7.4 | >10 | >10 |
| **24** |  | 7.6 | >10 | >10 |
| **25** |  | 11 | >10 | >10 |

The SAR studies on 3-hydroxypyridin-2(1*H*)-ones indicated that aryl substitution at either the 5- or 6-position of the pyridinone ring increased activity. The structure suggested that increased activity is due to coordination of the aryl ring with M3 through cation-π interaction. Based on this, we decided to prepare aryl substituted 3-

hydroxyquinolin-2(1*H*)-ones as shown in Scheme 3. Suzuki-coupling of each of the brominated 3-methoxyquinolin-2-(1*H*)-ones, **18-21**, with 4-fluorophenylboronic acid, catalyst $Pd(PPh_3)_4$ and base $Na_2CO_3$ in solvent mixture of dioxane and water provided the 4-fluorophenyl derivatives **26-29**. Subsequent treatment with excess $BBr_3$ in dichloromethane at room temperature gave the desired compound **30-33**.[82]



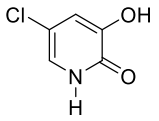
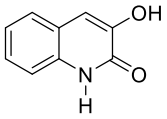
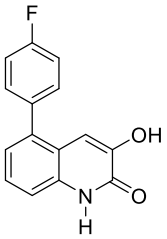
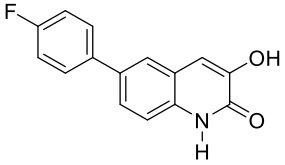
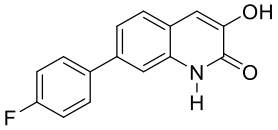
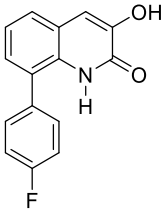

**26,** 66%, $R_5$ = p-*F*$C_6H_4$; $R_6$, $R_7$, $R_8$ = H
**27,** 85%, $R_6$ = p-*F*$C_6H_4$; $R_5$, $R_7$, $R_8$ = H
**28,** 51%, $R_7$ = p-*F*$C_6H_4$; $R_5$, $R_6$, $R_8$ = H
**29,** 75%, $R_8$ = p-*F*$C_6H_4$; $R_5$, $R_6$, $R_7$ = H

**30**, 48%, $R_5$ = p-*F*$C_6H_4$; $R_6$, $R_7$, $R_8$ = H
**31**, 60%, $R_6$ = p-*F*$C_6H_4$; $R_5$, $R_7$, $R_8$ = H
**32**, 68%, $R_7$ = p-*F*$C_6H_4$; $R_5$, $R_6$, $R_8$ = H
**33**, 46%, $R_8$ = p-*F*$C_6H_4$; $R_5$, $R_6$, $R_7$ = H

**Scheme 3**. Synthetic route for compounds **30**−**33**.

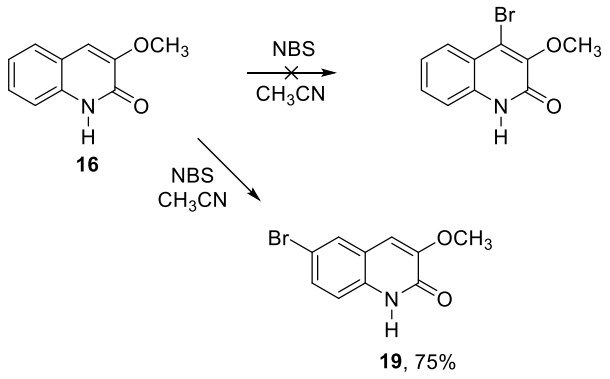
Each of these compounds were evaluated as viral endonuclease inhibitors (Table 7). As speculated from the SAR studies on 3-hydroxypyridin-2(1*H*)-ones, the 4-fluorophenyl substituted 3-hydroxyquinolin-2(1*H*)-ones, **30-33**, were more active than the bromo-substituted 3-hydroxyquinolin-2(1*H*)-ones, **22-25**, resulting in a 4 to 10-fold increase in activity. Compound **31** and **32** displayed higher inhibitory activity than compound **30** and **33** following the trend previously observed with the bromo-substituted 3-hydroxyquinolin-2(1*H*)-ones.[82]

**Table 7**. Biological activity of **1**, **17** and **30**-**33**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **17** |  | 17 |
| **30** |  | 3.3 |
| **31** |  | 0.5 |
| **32** |  | 0.5 |
| **33** |  | 4.7 |

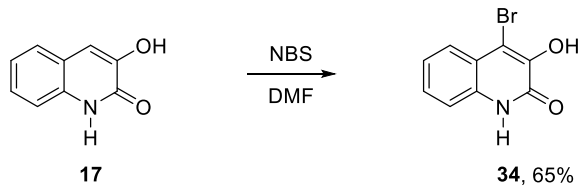
We then attempted to prepare 4-substituted derivatives to evaluate the substituent effect of various groups at the 4-position of the quinolone ring. Since the SAR studies on 3-hydroxypyridin-2(1*H*)-ones indicated that the presence of substituents at the 4-position was detrimental to the activity, these derivatives were not given high priority among the 3-hydroxyquinolin-2(1*H*)-ones synthesized as part of this study. Initially, we tried to

brominate 3-methoxyquinolin-2(1*H*)-one as shown in Scheme 4. The rationale for exploring this approach was that the presence of a 3-methoxy group on the quinolone ring would significantly simplify the purification of key intermediates. Unfortunately, bromination occurred at 6-position of 3-methoxyquinolin-2(1*H*)-one, **16**, giving instead compound **19** in 75% yield.



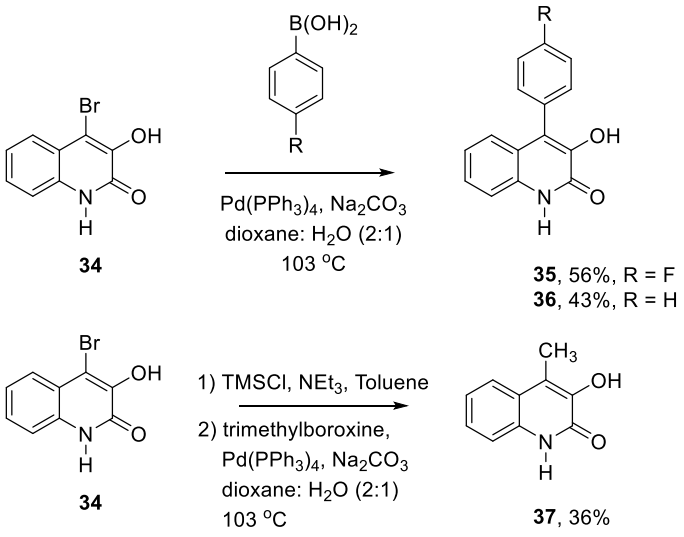

**Scheme 4.** An attempt to brominate 4-position of the quinolone ring.

In view of these results, we tried to brominate 3-hydroxyquinolin-2(1*H*)-one, **17**, hoping that strong directing effect of 3-hydroxyl group might result in the formation of the desired isomer (Scheme 5). Treatment of 3-hydroxyquinolin-2(1*H*)-one with N-bromosuccinimide in DMF at room temperature produced the desired product, **34**.[82]




**Scheme 5.** Synthetic routes for compound **34**.

Several other derivatives of 4-susbtituted 3-hydroxyquinolin-2(1*H*)-one, **35-37**, were also prepared. These analogs were selected to provide information on which substituents could be tolerated at 4-position of the quinolone ring. Compound **34** served as the key intermediate for the palladium-catalyzed cross couplings as shown in Scheme 6. Compound **34** was coupled with either 4-fluorophenylboronic acid or phenylboronic acid, catalyst $Pd(PPh_3)_4$ and base $Na_2CO_3$ in solvent mixture of dioxane and water to provide compound **35** and **36**, respectively. For the synthesis of compound **37**, the 3-hydroxyl group of **34** was temporarily protected as its trimethylsilyl ether. Together with trimethylboroxine under Suzuki-coupling condition provided the desired product, **37**.[82]

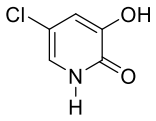
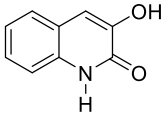
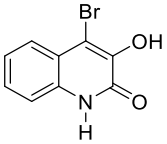
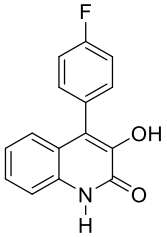
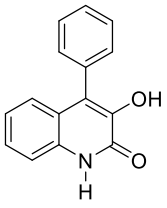
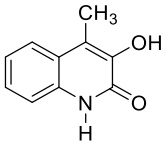



**Scheme 6.** Synthetic routes for compounds **35-37**.

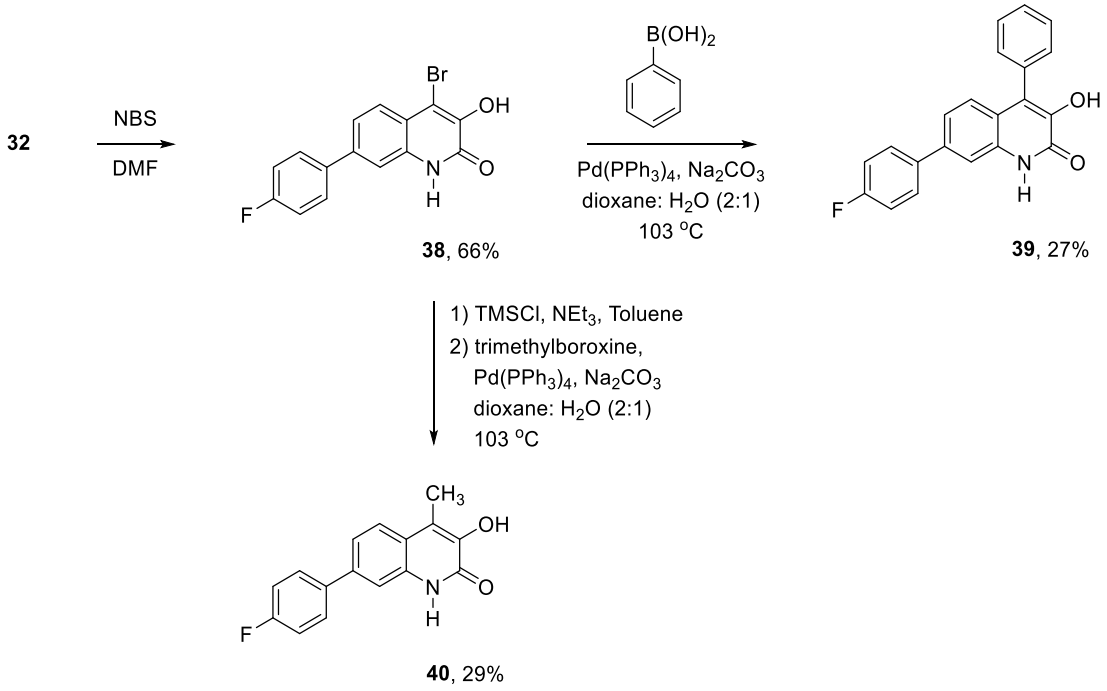
Compound **34-37** were evaluated in the enzymatic assay, and, as expected, compound **34**, **36** and **37** did not enhance enzyme inhibition relative to the unsubstituted parent compound, **17** (Table 8). However, compound **35** displayed slightly enhanced inhibitory

activity relative to compound **17**. Considering biological activities of 4-fluorophenyl substituted 3-hydroxyquinolin-2(1*H*)-one derivatives, including compound **32**, compound **35** was the least potent analog. Overall, we concluded that 4-substitution on 3-hydroxyquinolin-2(1*H*)-one, in general, is detrimental to the activity of these compounds as endonuclease inhibitors.[82]

**Table 8**. Biological activity of **1**, **17** and **34**-**37**.

| | **Compound Structure** | **$IC_{50}$ (μM)** |
|---|---|---|
| **1** |  | 25 |
| **17** |  | 17 |
| **34** |  | 53 |
| **35** |  | 11 |
| **36** |  | >20 |
| **37** |  | >100 |

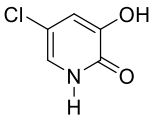
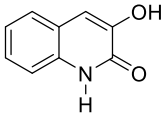
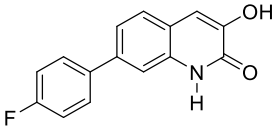
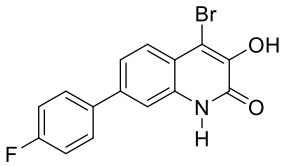
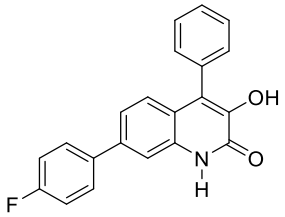
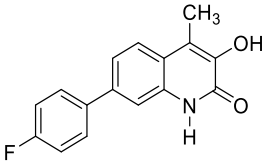
We also prepared 4-substituted 7-(4-fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one derivatives, **38**-**40,** to further assess the influence of various 4-subtituents on the inhibitory activity of 3-hydroxyquinolin-2(1*H*)-ones on viral endonuclease activity. The synthetic methodology employed for the preparation of these compounds is shown in Scheme 7. Compound **32** was treated with NBS in DMF to provide compound **38**. Using it as an intermediate, palladium-catalyzed coupling either with phenylboronic acid or trimethylboroxine provided compound **39** and **40**, respectively. For the synthesis of 4-methyl derivative, **40**, we again temporarily protected the 3-hydroxy group as its trimethylsilyl ether. Subsequent treatment with trimethylboroxine under the Suzuki-coupling condition provided the desired product, **40**.[82]




**Scheme 7.** Synthetic routes for compounds **38**-**40**.

Compound **38-40** were evaluated in enzymatic assay (Table 9). All the evaluated compounds showed decrease inhibition activity relative to compound **32**. These data further confirmed the general observation that substituents at the 4-position tend to have a detrimental effect on the inhibitory activity of 3-hydroxyquinolin-2(1*H*)-ones against viral endonuclease.[82]

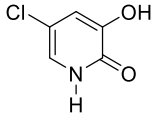
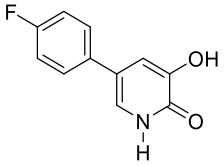
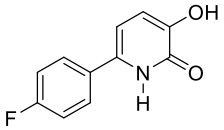
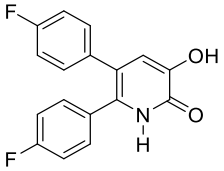
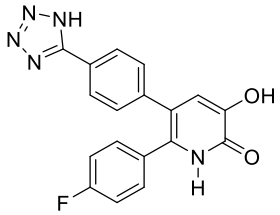
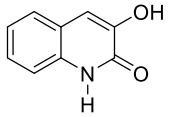
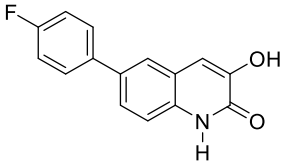
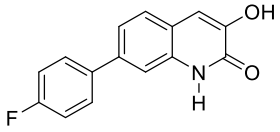
**Table 9.** Biological activity of **1**, **17**, **32** and **38**-**40**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **17** |  | 17 |
| **32** |  | 0.50 |
| **38** |  | 1.1 |
| **39** |  | 2.0 |
| **40** |  | 13 |

As our structure-based drug design effort, compound **32** was soaked with $PA_N$. As shown in Figure 11, compound **32** showed a similar binding mode to that of 3-hydroxypyridin-2(1*H*)-ones. The 3-hydroxy moiety, which interacts with Lys134, chelated metal 1, whereas the 2-one moiety chelated both metal 1 and 2 in the binding site. Like in the case of the pyridinones, the nitrogen heteroatom within the quinolone ring formed an interaction with a water molecule that coordinated with the metal 2. The 4-fluorophenyl moiety of **32** extended into a pocket formed by Ala20, Met21, Tyr24, Glu26, Lys34 and Ile38.[82]

We compared the biological activity of these 3-hydroxyquinolin-2(1*H*)-ones with that observed for 3-hydroxypyridin-2(1*H*)-ones. We specifically examined whether improved activity was observed from either our *in vitro* or *ex-vivo* assays. Compound **31** and **32** were the more potent analogs of the 3-hydroxyquinolin-2(1*H*)-ones. They had comparable to activity to some of the more active 3-hydroxypyridin-2(1*H*)-ones (Table 10). Although they displayed increased or similar activity with respect to mono-substituted 3-hydroxypyridin-2(1*H*)-ones, **4** and **8**, their activity was relatively low when compared with 5,6-bis(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one, **11**. In addition to this, compound **32** did not exhibit antiviral activity against influenza A/Puerto Rico/8/1934 (H1N1) when it was evaluated by a virus yield assay in an *ex-vivo* assay using MDCK cells. The *ex-vivo* inhibitory data presented here and in the subsequent pages were done by Dr. Luis Martinez-Sobrido in University of Rochester Medical Center, unless otherwise noted. Therefore, we concluded that 3-hydroxyquinolin-2(1*H*)-ones provide no tangible benefit over 3-hydroxypyrindin-2(1*H*)-ones.

**Table 10.** Biological activity of **1**, **4**, **8**, **11**, **13**, **17** and **31-32**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **4** |  | 0.73 |
| **8** |  | 0.43 |
| **11** |  | 0.04 |
| **13** |  | 0.01 |
| **17** |  | 17 |
| **31** |  | 0.50 |
| **32** |  | 0.50 |

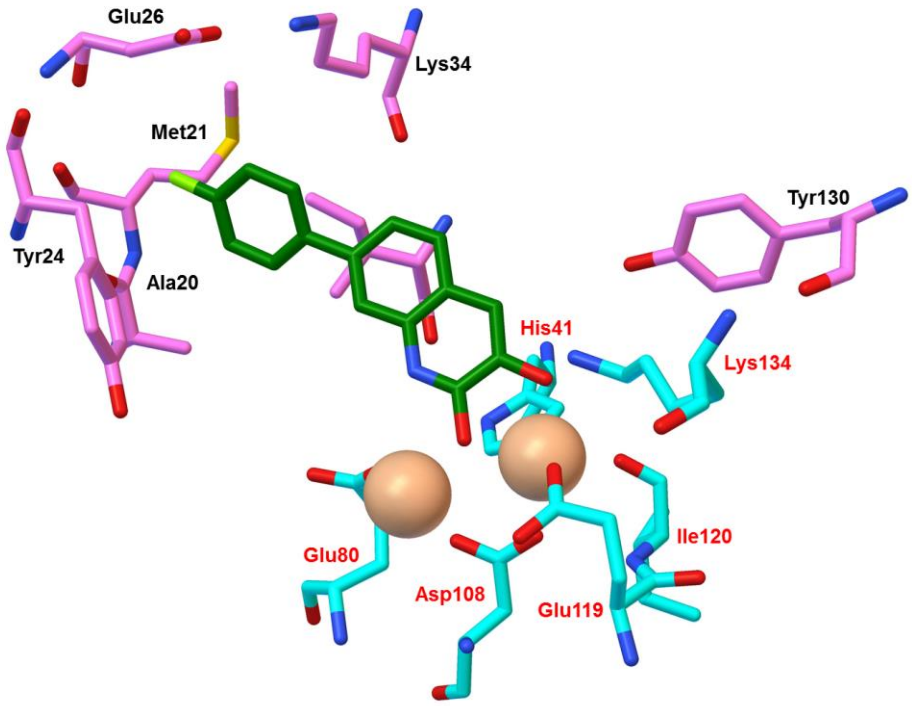


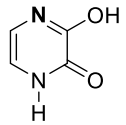

**Figure 11**. Binding of compound **32** at the endonuclease binding site (PDB 4KIL).[82]

In summary, 3-hydroxyquinolin-2(1*H*)-ones and 3-hydroxypyridin-2(1*H*)-ones were versatile scaffolds for design and synthesizing endonuclease inhibitors, and they exhibited some similarities in terms of their SAR. First of all, 3-hydroxy moiety was critical for the activity. Second, 4-substitution on either pyridinone or quinolone ring was associated with dramatically reduced activity. Despite high similarities, there were some differences present. Substitution on 5- or 8-position of 3-hydroxyquinolin-2(1*H*)-one was not optimal for the activity while substitution on 6- or 7-position of the quinolone ring was preferred. Although we were able to synthesize a collection of analogs that displayed good endonuclease inhibition activity, 3-hydroxyquinolin-2(1*H*)-ones exhibit relative low inhibitory activity when compared to 3-hydroxypyridin-2(1*H*)-ones. In addition, compound **32**, which was the most potent compound in the series along with

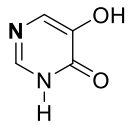
compound **31**, had no *ex-vivo* activity. This is in contrast to the 3-hydroxypyridin-2(1*H*)-ones, **13**, which had an $EC_{50}$ of 11 μM in the *ex-vivo* antiviral assay. Although our attempt of using 3-hydroxyquinolin-2(1*H*)-one as an alternative scaffold was unsuccessful, we continued to explore structurally-similar analogs to find an endonuclease inhibitor with improved *ex-vivo* activity.

## 2.2 Synthesis and Evaluation of Aza Analogs of 3-Hydroxypyridin-2(1*H*)-one.

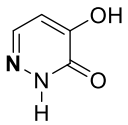
Our structure-activity studies extended into the evaluation of aza analogs of 3-hydroxypyridin-2(1*H*)-ones, which had incorporated into their structure an additional nitrogen.[83] This led to three new scaffolds that included 3-hydroxypyrazin-2(1*H*)-ones, 5-hydroxypyrimidin-4(3*H*)-ones and 4-hydroxypyridazin-3(2*H*)-ones (Figure 12). It was reasoned that the presence of the additional nitrogen heteroatom could potentially participate in an additional hydrogen bonding with the enzyme, and this interaction may lead to an enhancement in potency. We prepared several derivatives of these aza-substituted 3-hydroxypyridin-2(1*H*)-ones and evaluated these varied structural analogs on their relative inhibition of viral endonuclease activity.



3-Hydroxypyrazin-2(1*H*)-one



5-Hydroxypyrimidin-4(3*H*)-one

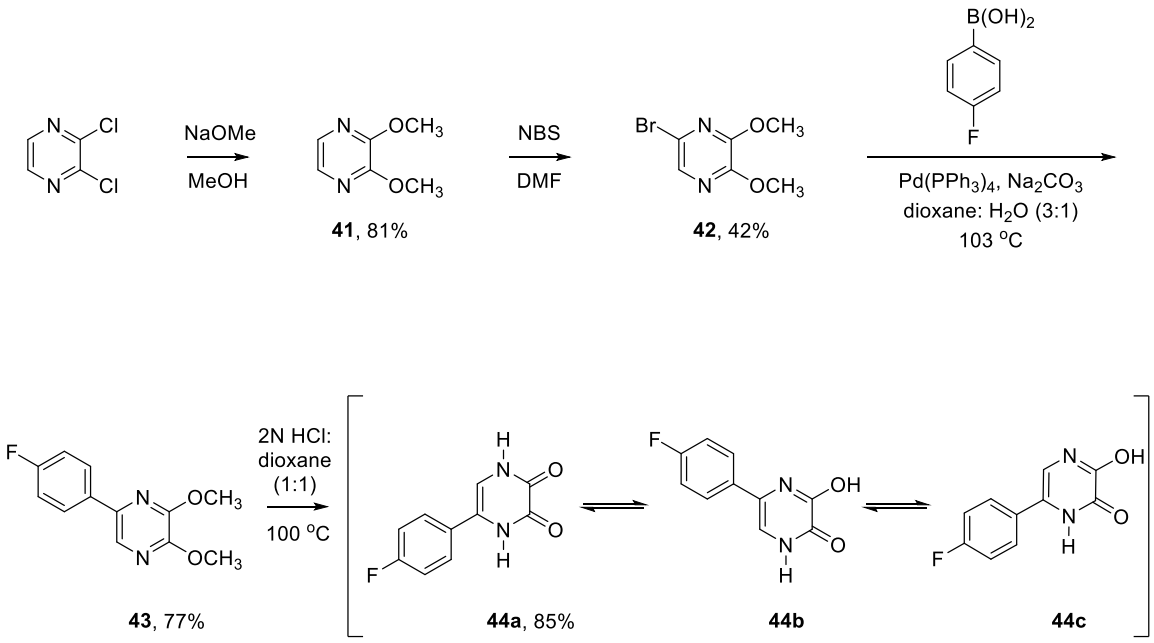


4-Hydroxypyridazin-3(2*H*)-one

**Figure 12**. Proposed new scaffolds.

Our initial emphasis was to explore the SAR of the 3-hydroxypyrazin-2(1*H*)-one series, which was a scaffold representing 3-hydroxypyridin-2(1*H*)-one with an additional nitrogen at its 4-position. To evaluate the relative effects of 4-aza substitution for both 5- and 6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one, the synthesis of 5-(4-fluorophenyl)-1,4-dihydropyrazine-2,3-dione, **44a**, was pursued as shown in Scheme 8. One of its

tautomers, **44b**, represents the 4-aza derivative of 5-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one. The other hydroxyl tautomer, **44c**, represents the 4-aza derivative of 6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one (as illustrated in Scheme 8).[83]

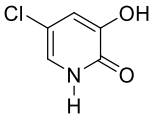
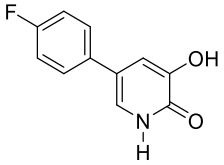
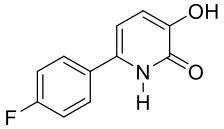
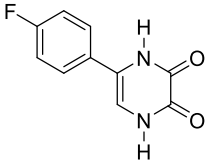



**Scheme 8.** Synthetic routes for compound **44**.

Starting with commercially-available 2,3-dichloropyrazine, treatment with sodium methoxide in methanol gave 2,3-dimethoxypyrazine, **41**. Bromination of compound **41** was achieved by using NBS in DMF. The resulting 5-bromo-2,3-dimethoxypyrazine, **42**, was coupled with 4-fluorophenylboronic acid to provide the 4-fluorophenyl derivative, **43**. The methyl ether groups were then cleaved with 2N hydrochloric acid, to provide the desired product, **44a**. Although tautomer **44b** and **44c** represent the 4-aza derivatives of 5- and 6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one, respectively, the most dominant tautomeric form of compound **44** on the basis of its NMR spectra in DMSO-$d_6$ was the

1,4-dihydropyrazine-2,3-dione, **44a**. It is possible within an aqueous environment that other tautomers may also be present to differing extents than that observed in solution in DMSO.[83]

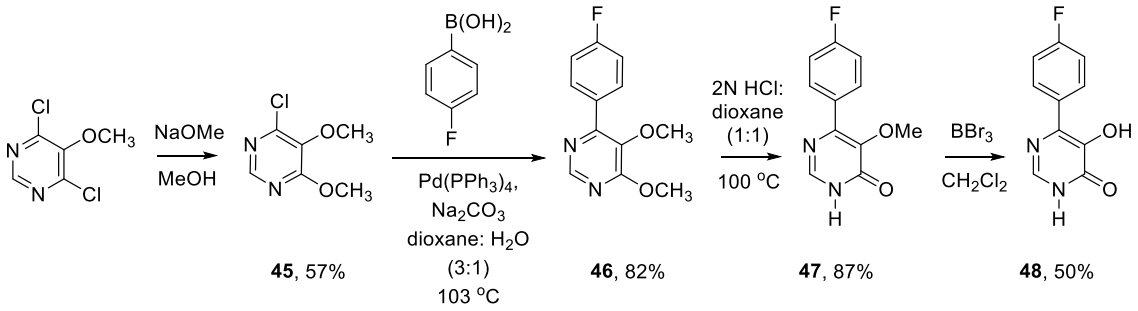
**Table 11.** Biological activity of **1**, **4**, **8** and **44**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **4** |  | 0.73 |
| **8** |  | 0.43 |
| **44** |  | 59 |

Compound **44** was evaluated and was less active as an endonuclease inhibitor when compared to 5- and 6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-ones, **4** and **8**, as well as parent compound **1** (Table 11). The reduced inhibitory activity of compound **44** might be explained by what we observed in its NMR spectra. As previously mentioned, the spectra obtained in DMSO-$d_6$ did indicate that compound **44** mainly existed as 1,4-dihydropyrazine-2,3-dione, **44a**. This tautomer might have comparatively weak inhibitory activity. Other tautomers, **44b** and **44c**, might form to an appreciable extend

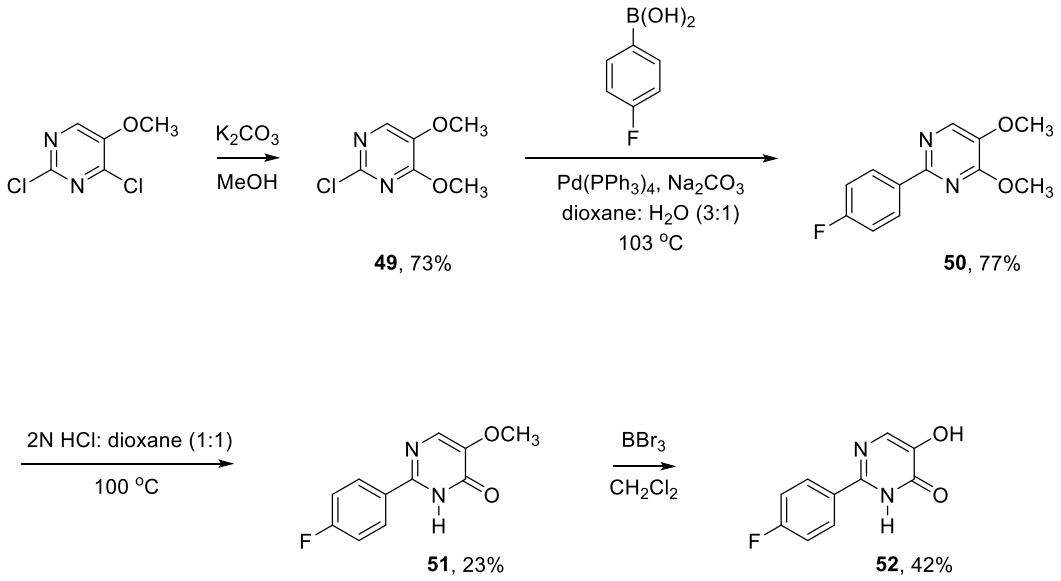
under the enzyme assay conditions. However, the presence of a 4-aza substituent adjacent to the 3-hydroxyl group of either tautomer **44b** and **44c** may also simply be associated with reduced intrinsic activity as an endonuclease inhibitor.[83]

We then explored the SAR of the 5-hydroxypyrimidin-4(3*H*)-one series, which is a scaffold representing 3-hydroxypyridin-2(1*H*)-one that has an additional nitrogen at the 5-position. We first prepared compound **48** to study the effect of 4-fluorophenyl substitution at 6-position of 5-hydroxypyrimidin-4(3*H*)-one on inhibitory activity (Scheme 9). Nucleophilic aromatic substitution of commercially-available 4,6-dichloro-5-methoxypyrimidine with sodium methoxide in methanol gave 4-chloro-5,6-dimethoxypyrimidine, **45**. Suzuki-coupling of intermediate **45** with 4-fluorophenylboronic acid gave 4-(4-fluorophenyl)-5,6-dimethoxypyrimidine, **46**. The methyl ether group at the 4-postion of compound **46** was first cleaved with 2N hydrochloric acid to provide 4-(4-fluorophenyl)-5-methoxypyrimidin-4(3*H*)-one, **47**. The remaining methyl ether group was then removed by $BBr_3$ in dichloromethane, to give the desired product, **48**.[83]




**Scheme 9.** Synthetic routes for compound **48**.

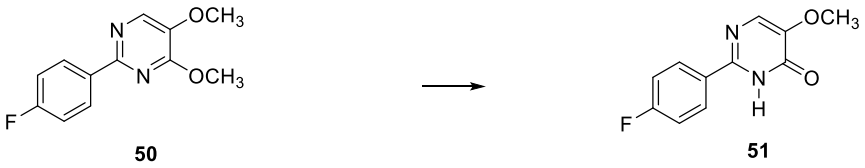
We synthesized compound **52** as outlined in Scheme 10 to study the effect of 4-fluorophenyl substitution at 2-position of 5-hydroxypyrimidin-4(3*H*)-one on inhibitory activity. The chlorine at 4-position of commercially-available 2,4-dichloro-5-methoxypyrimidine was selectively displaced under the reaction condition using potassium carbonate in methanol. The resulting 2-chloro-4,5-dimethoxypyrimidine, **49**, was used as an intermediate for coupling reaction. Suzuki-coupling of intermediate **49** with 4-fluorophenylboronic acid gave 2-(4-fluorophenyl)-5,6-dimethoxypyrimidine, **50**. Using similar reaction conditions as used previously, the methyl ether groups at 4- and 5-position of compound **50** were cleaved sequentially, to provide the desired product, **52**.[83]




**Scheme 10**. Synthetic routes for compound **52**.

Initially, we attempted to cleave both of methyl ether groups of compound **50** simultaneously using $BBr_3$ in dichloromethane as a one-step process (Scheme 11). Under these reactions condition, however, compound **51** was formed in low yield. Compound

**51** still had a methyl ether protective group at 5-position of the pyrimidine ring. Various acidic conditions including hydrochloric acid or hydrobromic acid were also tried. These conditions mainly provided once again compound **51** but in better yield than that observed using $BBr_3$ in dichloromethane (see Scheme 11)**.** Lithium iodide in DMF condition was also explored, however, only starting material, **50**, was recovered. Since we were unable to cleanly obtain the desired product, **52**, as a one-step process, we carried on reactions as a two-step process as seen in Scheme 10.




**50** **51**

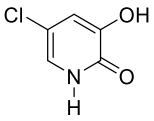
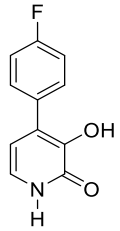
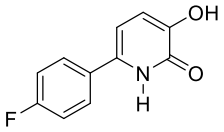
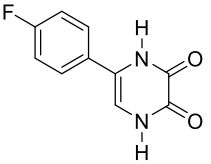
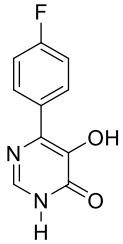
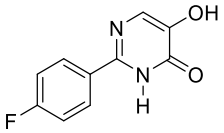
| | | Yields |
|---|---|---|
| **Reaction condition 1:** | $BBr_3$, $CH_2Cl_2$, R.T. | 5% |
| **Reaction condition 2:** | 2N HCl: dioxane (1:1), 100 $^oC$ | 66% |
| **Reaction condition 3:** | 48% HBr: dioxane (1:1), 100 $^oC$ | 38% |
| **Reaction condition 4:** | LiI, DMF, 153 $^oC$ | - |

**Scheme 11.** Attempts to deprotect two methyl ether protective groups of compound **50** as a one-step process.

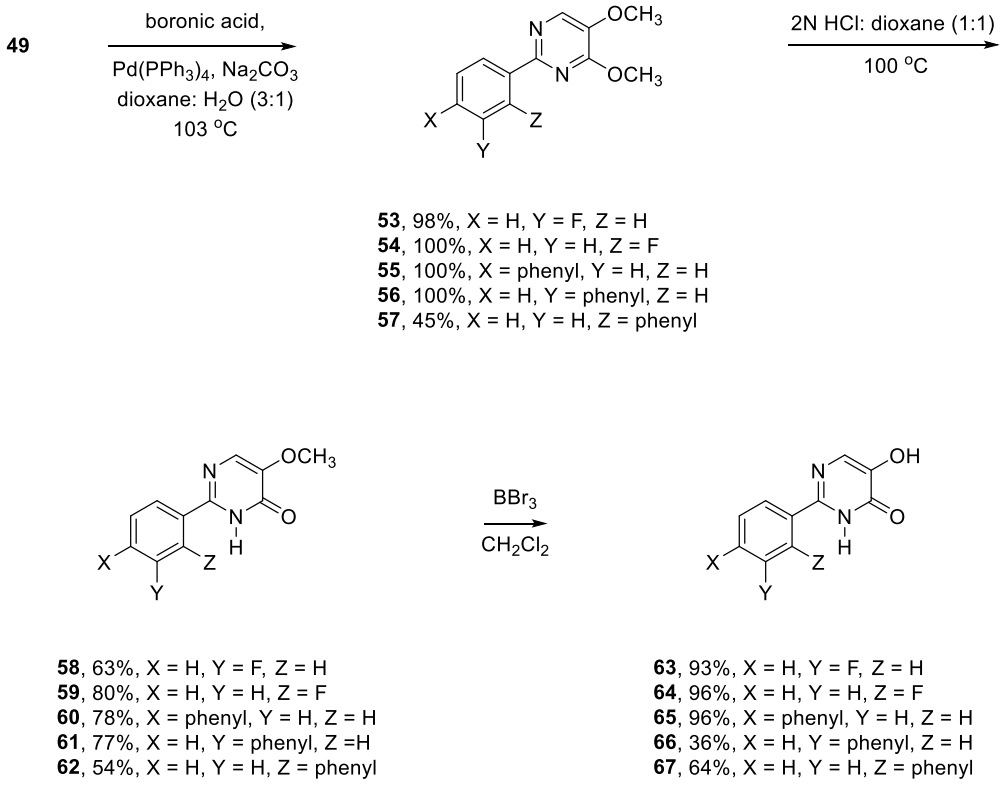
We evaluated activity of compound **48** and **52**, which represent 5-aza analogs of 4- and 6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one, respectively (Table 12). Consistent with the SAR studies of 3-hydroxypyridin-2(1*H*)-ones, compound **48** lost inhibitory activity, as had been seen with its analogous hydroxypyridin-2(1*H*)-one derivative, **3**. It is noteworthy that 4-fluorophenyl substitution at 2-position of 5-hydroxypyrimidin-4(3*H*)-

one, **52**, gave the comparable inhibitory activity to the 4-fluorophenyl substitution at 6-position of 3-hydroxypyridin-2(1*H*)-one, **8**. It has a good activity with an $IC_{50}$ of 0.58 μM. Additionally, compound **52** displayed significantly increase in activity relative to the isomeric 3-hydroxypyrazin-2(1*H*)-one, **44**.[83]

**Table 12.** Biological activity of **1**, **3**, **8**, **44**, **48** and **52**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **3** |  | >200 |
| **8** |  | 0.43 |
| **44** |  | 59 |
| **48** |  | 193 |
| **52** |  | 0.58 |

Since 2-(4-fluorophenyl)-5-hydroxypyrimidin-4(3*H*)-one, **52**, displayed inhibitory activity comparable to its 3-hydroxypyridin-2(1*H*)-one analog, **8**, several other 2-substituted 5-hydroxypyrimidin-4(3*H*)-one derivatives, **63-67**, were synthesized (Scheme 12). Palladium-catalyzed coupling of intermediate **49** with appropriate boronic acid gave compound **53-57** generally in a range of 99-100% yield except compound **57**, which gave a yield of 54%. This may due to steric hindrance of phenyl group, which produced *ortho*-substituted molecule. Following previously the established deprotection method that we adopted, the desired products, **63-67** were isolated.[83]



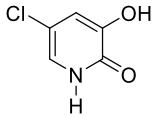
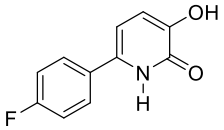
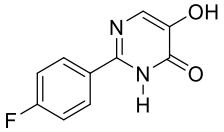
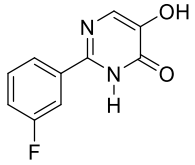
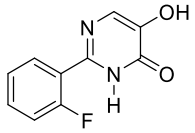
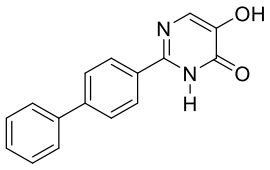
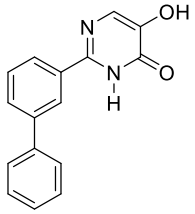
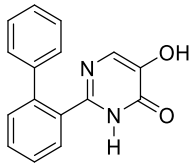

**53**, 98%, X = H, Y = F, Z = H
**54**, 100%, X = H, Y = H, Z = F
**55**, 100%, X = phenyl, Y = H, Z = H
**56**, 100%, X = H, Y = phenyl, Z = H
**57**, 45%, X = H, Y = H, Z = phenyl

**58**, 63%, X = H, Y = F, Z = H
**59**, 80%, X = H, Y = H, Z = F
**60**, 78%, X = phenyl, Y = H, Z = H
**61**, 77%, X = H, Y = phenyl, Z =H
**62**, 54%, X = H, Y = H, Z = phenyl

**63**, 93%, X = H, Y = F, Z = H
**64**, 96%, X = H, Y = H, Z = F
**65**, 96%, X = phenyl, Y = H, Z = H
**66**, 36%, X = H, Y = phenyl, Z = H
**67**, 64%, X = H, Y = H, Z = phenyl

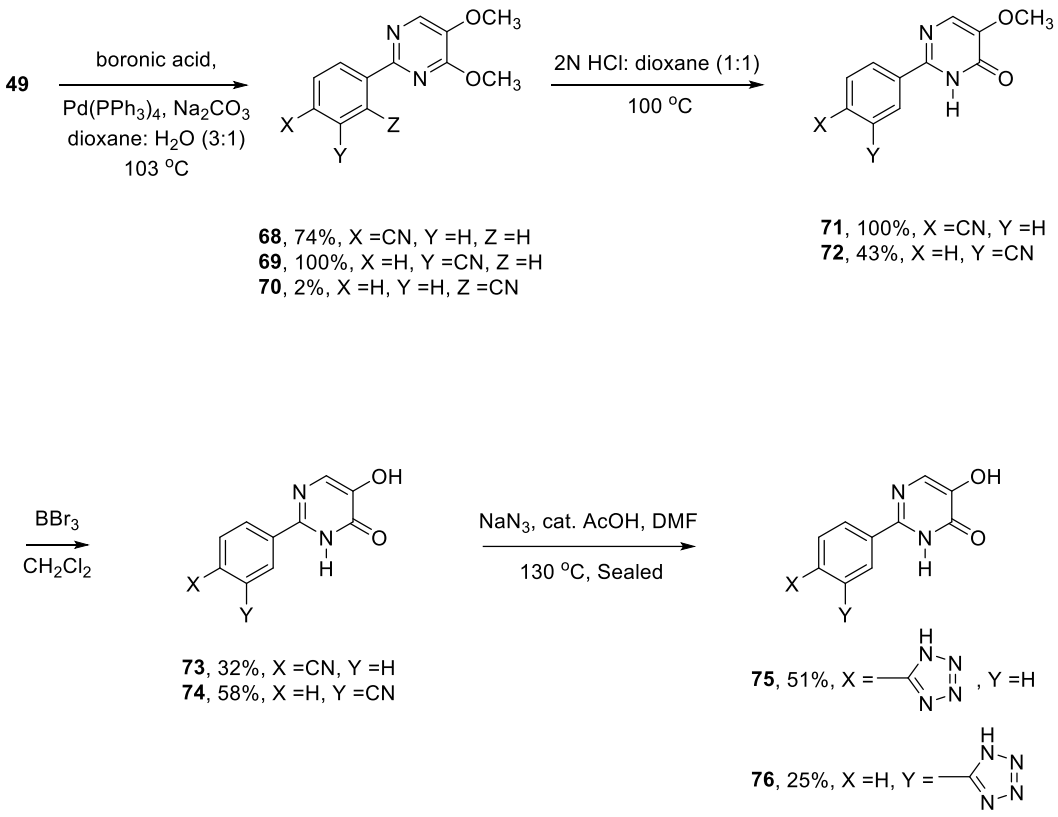
**Scheme 12**. Synthetic routes for compounds **63-67**.

**Table 13.** Biological activity of **1**, **8**, **52** and **63-67**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **8** |  | 0.43 |
| **52** |  | 0.58 |
| **63** |  | 1.6 |
| **64** |  | 1.7 |
| **65** |  | 2.24 |
| **66** |  | 0.40 |
| **67** |  | 1.1 |

The inhibitory activity of prepared compounds, **63-67**, were evaluated (Table 13). Except for compound **66**, these 2-substituted 5-hydroxypyrimidin-4(3*H*)-ones were generally less potent than compound **8** and **52**. As demonstrated with compound **64** and **67**, *ortho*-substitution was associated with the reduced activity. Additionally, the 4-fold decrease in activity observed with compound **65**, when compared to compound **52**, might be explained by steric factors that might interfere with binding to the endonuclease.[83]

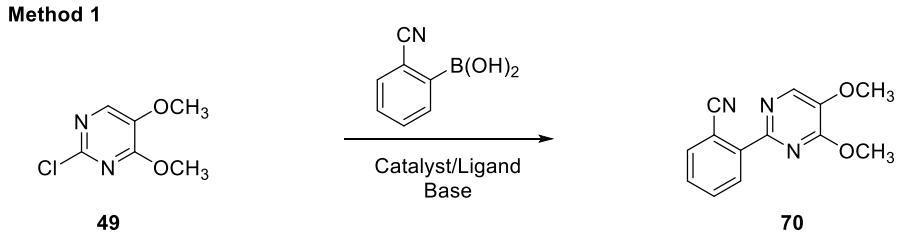
The SAR studies performed with 3-hydroxypyridin-2(1*H*)-ones indicated that 4-(tetrazol-5-yl)phenyl substitution at the 6-position of the pyridinone ring can increase potency of the compound by 5-fold. On the basis of this observation, we attempted to prepare 2-[(tetrazol-5-yl)phenyl]-5-hydroxypyrimidin-4(3*H*)-one derivatives and their 2-(cyanophenyl)-5-hydroxypyrimidin-4(3*H*)-one precursors (Scheme 13). Palladium-catalyzed coupling of intermediate **49** with appropriate boronic acid gave compounds **68-70.** Although Suzuki-coupling with 4- and 3-cyanophenylboronic acid gave product in 74% and 100% yield, respectively, Suzuki-coupling with 2-cyanophenylboronic acid gave product in low yield (2%). This may again due to steric hindrance of nitrile group. Following previously established deprotection method, 4- and 3-cyanophenyl derivatives, **73** and **74**, were synthesized in a two-step process. These 4-cyanophenyl derivatives were reacted with sodium azide in the presence of a catalytic amount of acetic acid in DMF to produce the desired compound **75** and **76**.[83]



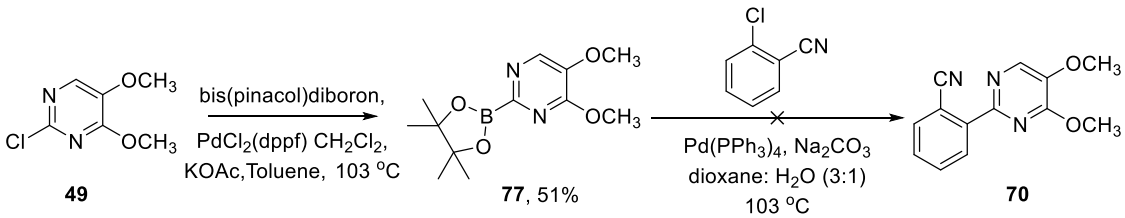

**Scheme 13.** Synthetic routes for compounds **73-76**.

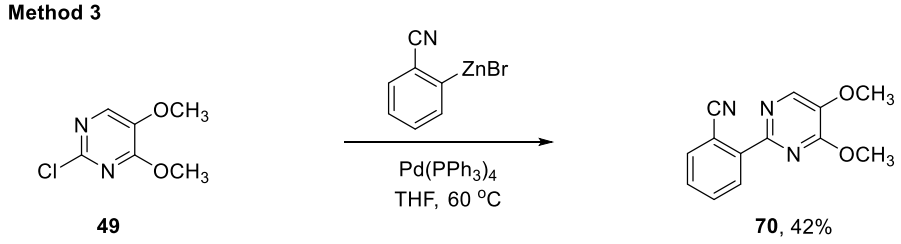
To overcome low yield observed with the Suzuki-coupling of intermediate **49** with 2-cyanophenylboronic acid using the same conditions as previously employed ($Pd(PPh_3)_4$ and $Na_2CO_3$), several catalyst/ligand systems were tried as shown in Scheme 14.[84] Changing the base or catalyst did not increase the yield dramatically. We then prepared 4,5-dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine, **77**, which was then treated with 2-chlorobenzonitrile under the Suzuki-coupling condition.[85] We only recovered starting material, **49.** This may be due to the electronic effect of chloro group. At last, we tried Negishi-coupling of intermediate **49** with commercially-available (2-

cyanophenyl)zinc(II) bromide in the presence of catalyst $Pd(PPh_3)_4$. Under these conditions, compound **70** was formed in reasonable yield (42% yield).[86]



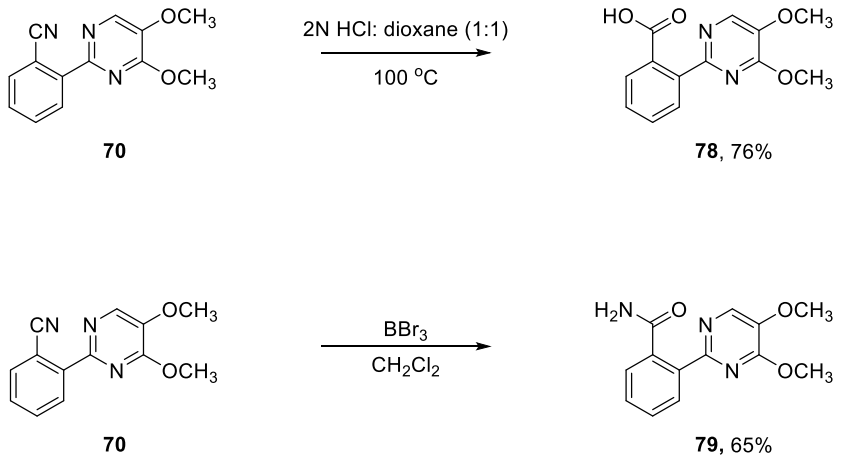

| | | Yields |
|---|---|---|
| **Reaction condition 1:** | $Pd(PPh_3)_4$, $K_2CO_3$, dioxane: $H_2O$ (3:1) 103 °C | 5% |
| **Reaction condition 2:** | $Pd(dppf)Cl_2$, $Na_2CO_3$, DMF 130 °C | 6% |
| **Reaction condition 3:** | $Pd(dppf)Cl_2$, $K_2CO_3$, DMF 130 °C | 8% |




**Scheme 14.** Suzuki- and Negishi-coupling conditions for the synthesis of compound **70**.

We then took compound **70** to the next step as outlined in Scheme 15. Initially, we attempted to use the previous two step deprotection conditions. The acidic condition using hydrochloric acid, however, hydrolyzed nitrile group to the acid without cleavage of methyl ether protective groups. Nitriles are susceptible to hydrolysis both in acidic and basic conditions. However, it is noteworthy that only compound **70**, but not compound **68** or **69** generated the carboxylic acid derivatives under these conditions. As an alternative reagent, we attempted to use $BBr_3$ in dichloromethane. This attempt surprisingly led to compound **79**. The nitrile may form the complex with boron, and, it may convert to amide during aqueous work-up process.



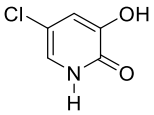
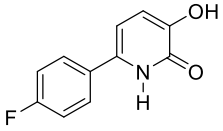
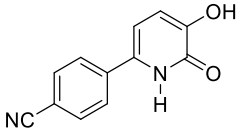
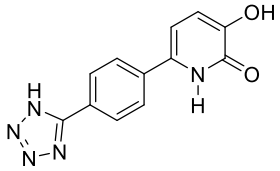
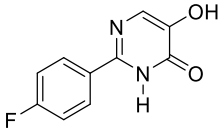
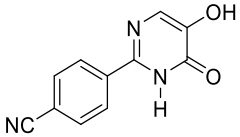
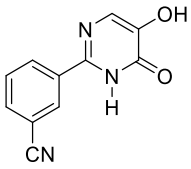
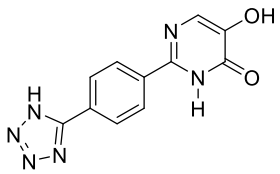
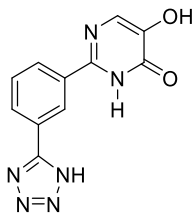

**Scheme 15.** Attempts to deprotect methyl ether protective groups.

The inhibitory activity of compound **52** and **63-67** already suggested that *ortho*-substitution on the phenyl ring at 2-position of 5-hydroxypyrimidin-3(4*H*)-one was disfavored with regards to endonuclease inhibition. The data was enough for us to predict that neither 2-(2-cyanophenyl)- nor 2-[2-(tetrazol-5-yl)phenyl]-5-

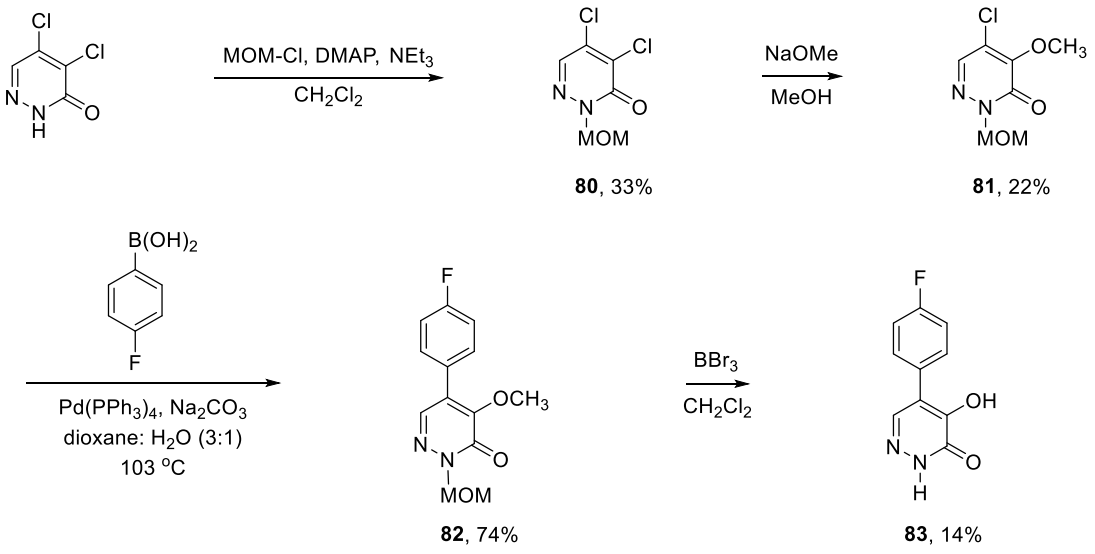
hydroxypyrimidin-3(4*H*)-one would have greater potency than compound **73-76**. As such, we dropped any further efforts to synthesize these compounds. The inhibitory activities of compounds **73-76** were evaluated (Table 14). Unlike 3-hydroxypyridin-2(1*H*)-one derivatives, the 4- and 3-cyanophenyl derivatives of 5-hydroxypyrimidin-3(4*H*)-one, **73** and **74**, displayed comparative or enhanced activity relative to the 4-fluorophenyl derivative, **52**. In addition, the 3-cyanophenyl derivative **74** was approximately twice as potent compared to the 4-cyanophenyl derivative **73**. Consistent with 3-hydroxypyridin-2(1*H*)-one derivatives, the presence of 5-tetrazoyl group at *para*-position of phenyl substituent at 2-position of 5-hydroxypyrimidin-3(4*H*)-one was associated with enhanced activity. However, conversion of nitrile group to tetrazole at the *meta*-position of phenyl substituent at 2-postion of the pyrimidinone ring led to a 2-fold reduction in activity as demonstrated for compounds **74** and **76**.[83]

Finally, we explored the SAR of the 4-hydroxypyridazin-3(2*H*)-one series, which was a scaffold representing 3-hydroxypyridin-2(1*H*)-one with an additional nitrogen at the 6-position. Compound **83**, an analog of 4-fluorophenyl-3-hydroxypyridin-2(1*H*)-one, was prepared as outlined in Scheme 16. Commercially-available 4,5-dichloropyridazin-3(2*H*)-one was treated with chloromethyl methyl ether, base triethyl amine ($NEt_3$) and catalyst 4-dimethylaminopyridine (DMAP) to provide the N-methoxymethyl protected compound, **80**. Nucleophilic aromatic substitution of **80** with sodium methoxide in methanol gave **81**. Subsequent Suzuki-coupling of intermediate **81** produced 5-(4-fluorophenyl)-4-methoxy-2-(methoxymethyl)pyridazin-3(2*H*)-one, **82**. Both the methyl

**Table 14.** Biological activity of **1**, **8-10**, **52** and **73-76**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **8** |  | 0.43 |
| **9** |  | 0.80 |
| **10** |  | 0.09 |
| **52** |  | 0.58 |
| **73** |  | 0.52 |
| **74** |  | 0.25 |
| **75** |  | 0.15 |
| **76** |  | 0.48 |

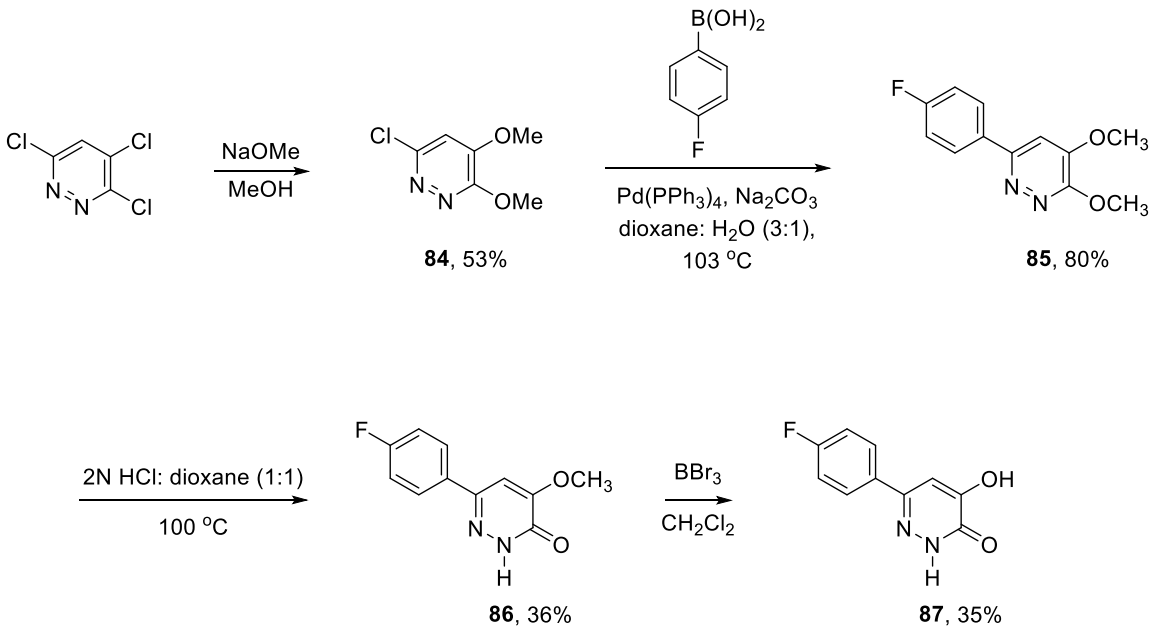
ether and the methoxymethyl ether groups were deprotected by reacting with $BBr_3$ in dichlromethane. The desired product, **83**, was obtained in poor yield. The N-methyoxymethyl group was easily cleaved and provided 5-(4-fluorophenyl)-4-methoxypyridazin-3(2*H*)-one. The methyl ether group, however, was removed using $BBr_3$ in dichloromethane in comparatively low yield (14%).[83]




**Scheme 16**. Synthetic routes for compound **83.**

The other 4-fluorophenyl derivative of 4-hydroxypyridazin-3(2*H*)-one, **87**, was prepared as outlined in Scheme 17. Starting with commercially-available 3,4,6-trichloropyridazine, treatment with 2.0 equivalent of sodium methoxide gave intermediate **84** along with 3-chloro-4,6-dimethoxypyridazine and 3,6-dichloro-4-methoxypyridazine as side-products. The intermediate was coupled with 4-fluorophenylboronic acid under Suzuki-coupling conditions to give compound **85**. It was

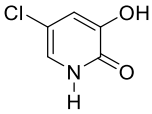
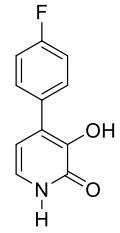
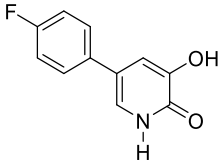
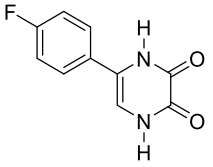
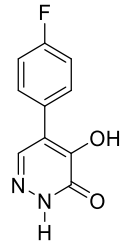
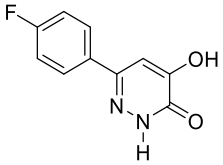
then deprotected under acidic conditions, followed by treatment with $BBr_3$ in dichloromethane to provide the desired product **87**.[83]




**Scheme 17**. Synthetic route for the preparation of compound **87.**

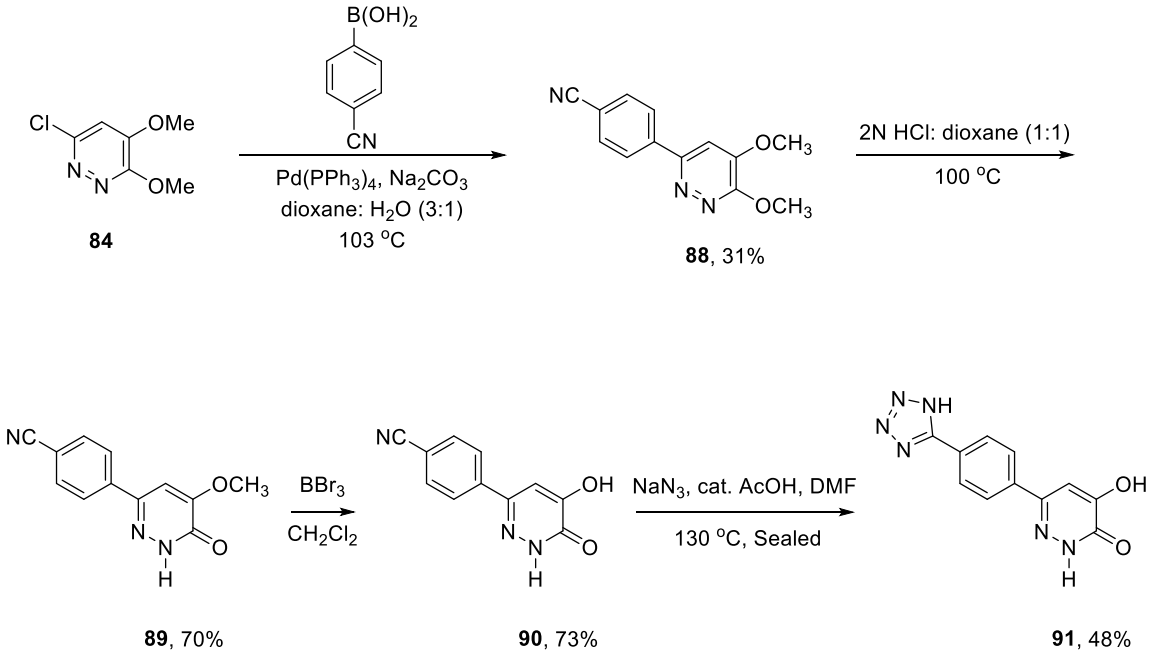
We then evaluated inhibitory activity of compound **83** and **87** (Table 15). Compound **83** and **87** represent 6-aza analogs of 4- and 5-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one, **3** and **4**, respectively. Consistent with the SAR studies of 3-hydroxypyrdin-2(1*H*)-ones, compound **83** was inactive as an endonuclease inhibitor. Compound **87** displayed modest inhibitory activity; however, it was less potent than its 3-hydroxypyridin-2(1*H*)-one analog, **4**. The presence of a 6-aza substituent as in compound **87** may be associated with reduced viral endonuclease inhibitory activity. Nonetheless, compound **87** still exhibited greater activity than its isomeric 3-hydroxypyrazin-2(1*H*)-one analog, **44**.[83]

**Table 15.** Biological activity of **1**, **3-4**, **44**, **83** and **87**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **3** |  | >200 |
| **4** |  | 0.73 |
| **44** |  | 59 |
| **83** |  | >200 |
| **87** |  | 6.0 |

We prepared the 4-(tetrazole-5-y)phenyl derivative, **91**, and its 4-cyanophenyl precursor, **90** as illustrated in Scheme 18 in order to examine whether previously established the SAR of 3-hydroxypyridin-2(1*H*)-ones also apply to the 4-hydroxypyrazin-3(2*H*)-one series. Intermediate **84** together with 4-cyanophenylboronic acid under Suzuki-coupling

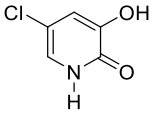
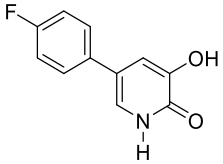
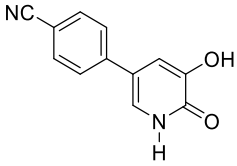
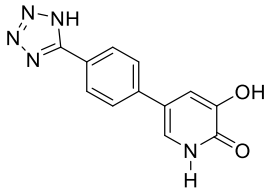
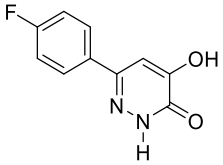
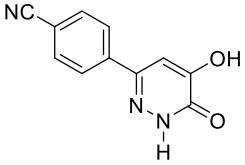
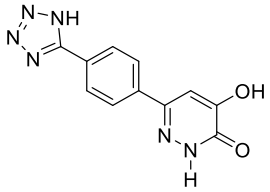
conditions provided compound **88**. Deprotection of methyl ether groups using previous reaction conditions was followed and provided 4-cyanophenyl derivative, **90**. Subsequent treatment of compound **90** with sodium azide and catalyst acetic acid in DMF provide 4-(tetrazol-5-yl)phenyl derivative, **91**.[83]




**Scheme 18**. Synthetic routes for compounds **90** and **91.**

The biological activities of compound **90** and **91** were evaluated (Table 16). In line with earlier data on 3-hydroxypyridin-2(1*H*)-one derivatives, the 4-cyanophenyl derivative, **90** was less active than the 4-fluoro derivative, **87**. Once again, transforming nitrile to a tetrazole group enhanced inhibitory activity as demonstrated with compound **91**. However, these 4-hydroxypyrazin-2(1*H*)-one derivatives as a group exhibited significantly lower inhibitory activity than 3-hydroxypyridin-2(1*H*)-one derivatives.[83]

**Table 16.** Biological activity of **1**, **4-6**, **87** and **90-91**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **4** |  | 0.73 |
| **5** |  | 3.8 |
| **6** |  | 0.37 |
| **87** |  | 6.0 |
| **90** |  | 9.3 |
| **91** |  | 3.0 |

Compound **75** was soaked with $PA_N$ in an effort to better understand the SAR associated with this series of compounds. The X-ray crystallographic results are illustrated in Figure

13. The crystal data indicated that **75** chelates to the two metal ions in a mode like the 3-hydroxypyridin-2(1*H*)-ones, but with a flipped orientation. The N1 atom of the pyrimidone ring form hydrogen bond interactions with a network of water molecules presented near the active site. The N3 atom of the pyrimidone ring interacted with Tyr130 through two bridging water molecules. Once again, 5-tetrazoyl moiety makes bidentate hydrogen bond interactions with Arg124.[83]

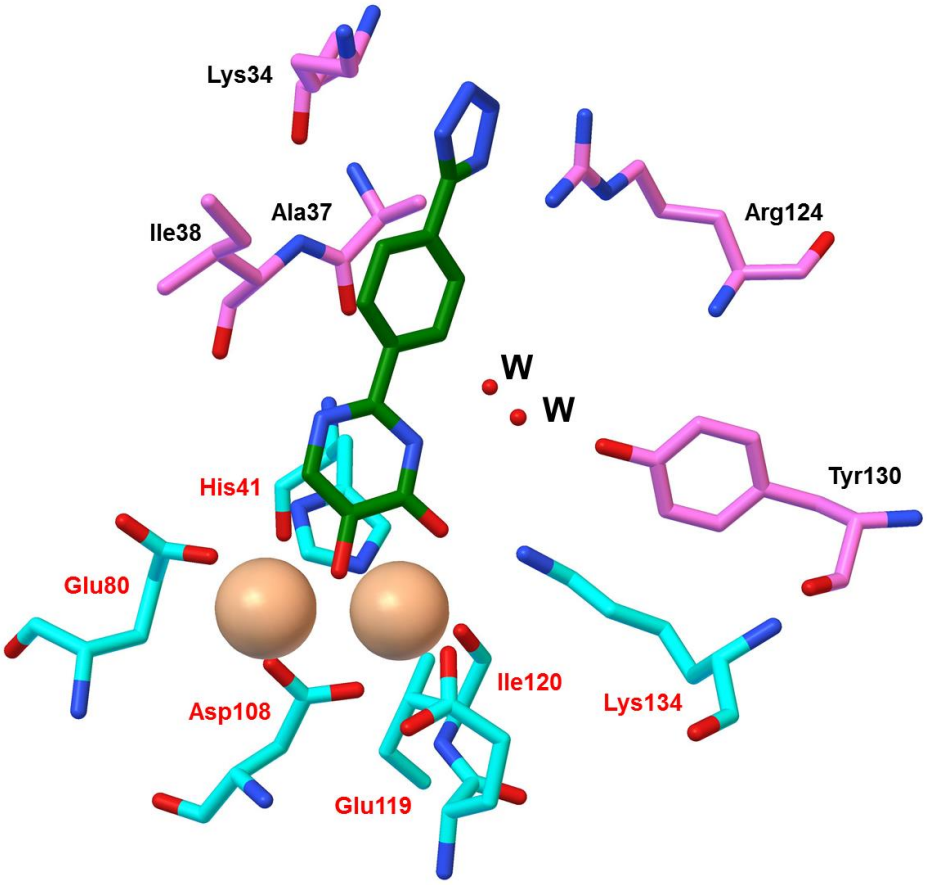



**Figure 13**. Binding of compound **75** at the endonuclease binding site (PDB: 4W9S).

Evaluation of aza-substituted 3-hydroxpyridin-2(1*H*)-ones, including 3-hydroxypyrazin-2(1*H*)-one, 5-hydroxypyrimidin-4(3*H*)-one and 4-hydroxypyridazin-3(2*H*)-one, indicated that 5-hydroxypyrimidin-4(3*H*)-one might be a good alternative scaffold to 3-hydroxypyridin-2(1*H*)-one. 2-Substituted-5-hydroxypyrimidin-4(3*H*)-ones, in particular, displayed comparable inhibitory activity to similarly substituted 6-substituted-3-hydroxypyridin-2(1*H*)-ones. However, as seen in Table 14, compound **75**, which was the most potent endonuclease inhibitor in aza-substituted 3-hydroxypyridin-2(1*H*)-ones, had relatively low inhibitory activity relative to compound **10**. Furthermore, we were not able to enhance potency of these analogs by putting an additional aryl group at 1-position of the pyrimidone ring. In any case, we evaluated antiviral activity of compound **75** against influenza A/Puerto Rico/8/1934 (H1N1) by a virus yield assay in MDCK cells. Unfortunately, the compound failed to exhibit *ex-vivo* activity.

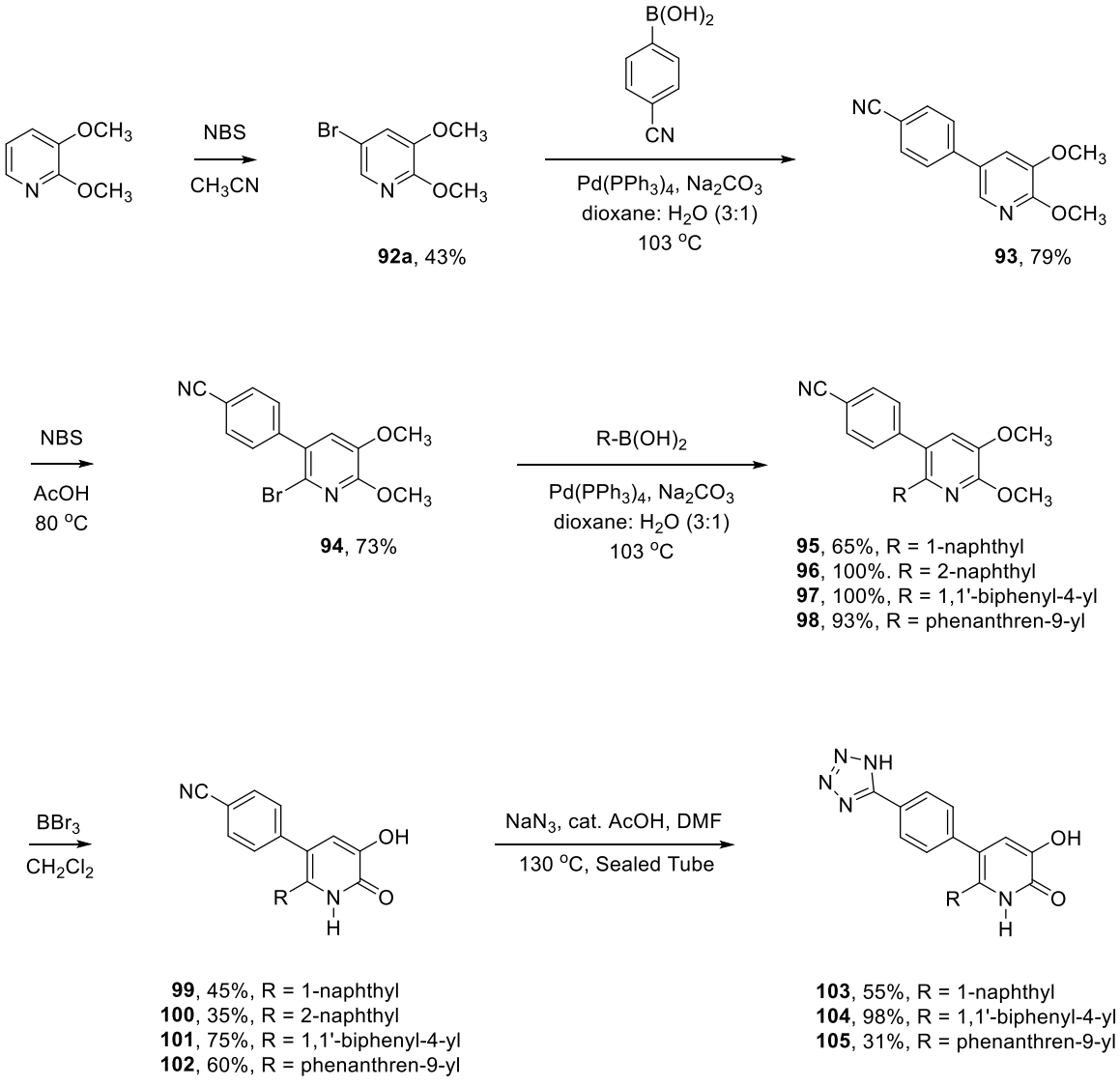
In conclusion, our efforts to design and synthesize multiple new scaffolds resulted in three novel scaffolds in addition to 3-hydroxypyridin-2(1*H*)-one and 3-hydroxyquinolin-2(1*H*)-one. Once again, there was consistency in SARs with both the pyridinone and quinolone series. For instance, when substitutions occurred at the position analog to the 4-position of 3-hydroxypyridin-2(1*H*)-ones, we observed loss of inhibitory activity. We also noticed enhanced inhibitor activity when we convert *para*-cyano derivatives to *para*-(tetrazol-5-yl) derivatives. Unfortunately, none of these derivatives has significant endonuclease inhibition activity comparable to similar analogs in the 3-hydroxypyridin-2(1*H*)-one series both in *in vitro* and *ex-vivo*. As such, our research again re-focused on the initial scaffold, 3-hydroxypyridin-2(1*H*)-one.

## 2.3 Synthesis and Evaluation of 5,6-Bis-substituted 3-Hydroxypyridin-2(1*H*)-one Derivatives.

This project once again explored new derivatives within the 3-hydroxypyridin-2(1*H*)-one series as neither 3-hydroxyquinolin-2(1*H*)-ones nor the aza-analogs of 3-hydroxypyridin-2(1*H*)-ones proved to be superior alternatives.[82-83] Previous studies on 3-hydroxypyridin-2(1*H*)-ones identified compound **13** with an $IC_{50}$ of 11 nM.[42, 81] Structural studies on compound **13** revealed that 4-(tetrazol-5-yl)phenyl group at 5-position of the pyridinone ring occupied subpocket 4 and its 5-tetrazoyl moiety was associated with bidentate hydrogen bond interactions with Arg124.[42] The study also indicated that 4-fluorophenyl group at 6-position of the pyridinone ring made a cation-π interaction with M3 and resided in hydrophobic subpocket 3.[42] Based on these observations, we decide to first optimize 6-position of the pyridinone ring with the hope of increasing potency. Various bulky hydrophobic aryl groups were evaluated during this optimization process.

During the preparation of 6-substituted 5-[4-(tetrazol-5-yl)phenyl]-3-hydroxypyridin-2(1*H*)-ones, we were also able to prepare their 6-substituted 5-(4-cyanophenyl)-3-hydroxypyridin-2(1*H*)-one precursors (Scheme 19). We slightly modified the synthetic approach previously employed to provide intermediate **94**. Commercially-available 2,3-dimethoxypyridine was treated with N-bromosuccinimide in acetonitrile to provide 5-bromo-2,3-dimethoxypyridine, **92a** along with 6-bromo-2,3-dimethoxypyridine, **92b**. Suzuki-coupling using 4-cyanophenylboronic acid provided 5-(4-cyanophenyl)-2,3-dimethoxypyridine, **93**.[81] Bromination with N-bromosuccinimide in acetic acid provided

6-bromo-5-(4-cyanophenyl)-2,3-dimethoxypyridine, **94**. The intermediate **94** was then coupled with the appropriate boronic acid to give compound **95-98**.[81] The methyl ether protective groups were then cleaved by $BBr_3$ in dichloromethane to provide compound **99-102**.[81] These 4-cyanophenyl derivatives were then converted to 4-(tetrazol-5-yl)phenyl derivatives by using sodium azide in DMF with a catalytic amount




**Scheme 19**. Synthetic routes for compounds **99-105.**

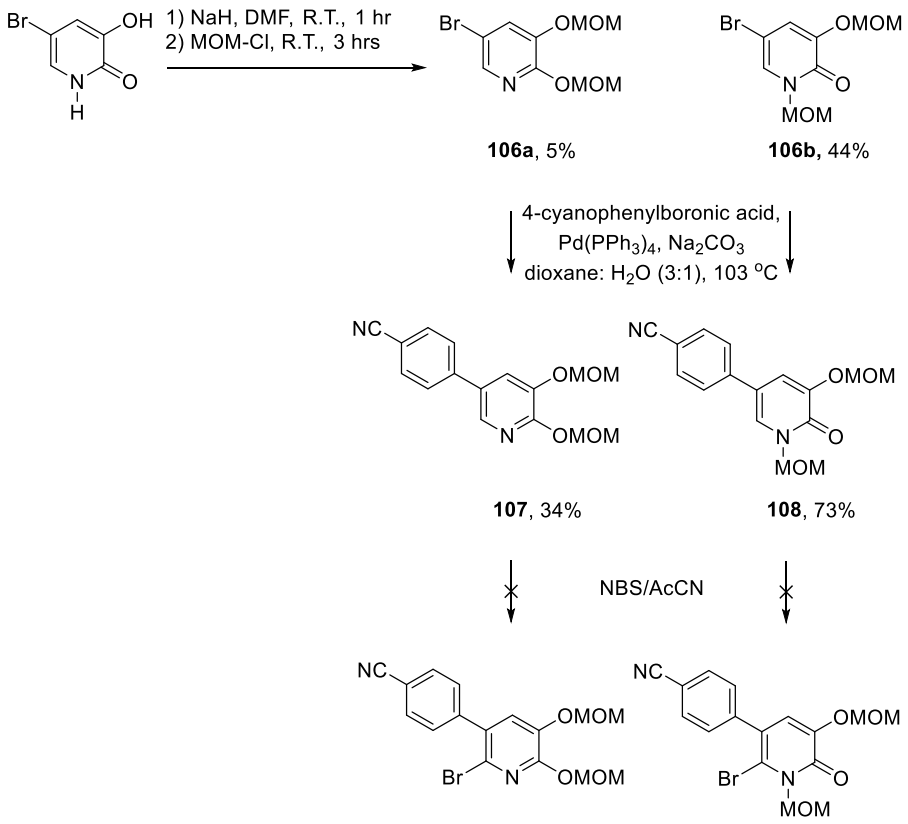
of acetic acid.[81] This modified method provided compound **103-105** with purity greater than 95%. However, when we attempted to make the tetrazole derivative of **100**, several undesired products were generated. Since these undesired products had similar chromatographic properties to the desired product on silica gel, we were not able to isolate the tetrazole derivative of **100** using this synthetic approach with purity above 95%.

In an effort to achieve our goal of preparing the tetrazole derivative of **100** with purity above 95%, we explored changing the methyl ether protective groups to other more labile protective groups. Because of stability in various reaction conditions, methyl ether protective group allowed us to try reaction conditions that used strong acid, base or heat. However, deprotection of these protective groups with $BBr_3$ in dichloromethane gave the desired product a yield ranging from 34% to 75%. Generally, the more heteroatoms in the molecule, the lower the yield. Moreover, the reaction conditions employed often require purification of the desired product using column chromatography since mono-demethylated side products were typically formed. These side protects with mono-demethylation at 2-postion of the pyridine ring often had a similar retention as the desired product on silica gel, and thus made purification difficult. As such, we attempted to synthesize a key intermediate that we could utilize that had more labile protective groups.

There are several protective groups for phenols, which can be classified into ethers, silyl ethers, ester, carbonates, carbamates, phosphinates and sulfonates.[87] The appropriate protective group for the synthesis of 3-hydroxypyridin-2(1*H*)-one derivatives should have

following properties: (i) stable to Suzuki-coupling reaction conditions, (ii) stable to N-bromosuccinimide electrophilic addition reaction, (iii) readily cleaved with mild conditions such as trifluoroacetic acid in dichloromethane. Therefore, we considered modified methyl ether groups that can be readily cleaved under mild conditions such as trifluoroacetic acid in dichloromethane.

We initially attempted to use methoxymethyl ether (MOM) protective group instead of methyl ether protective group (Scheme 20). Treatment of commercially-available 5-bromo-3-hydroxypyridin-2(1*H*)-one with sodium hydride in DMF followed by MOM-




**Scheme 20.** An attempt using MOM as a protective group.

chloride resulted in bis-O-protected **106a** and N,O-protected **106b** products.[88] Although controlling the ratio of N-alkylation and O-alkylation was difficulty, we carried reaction further just to examine the stability of MOM protective group. It was stable under the Suzuki-coupling condition,[81] but, it was cleaved during N-bromosuccinimide electrophilic addition reaction.

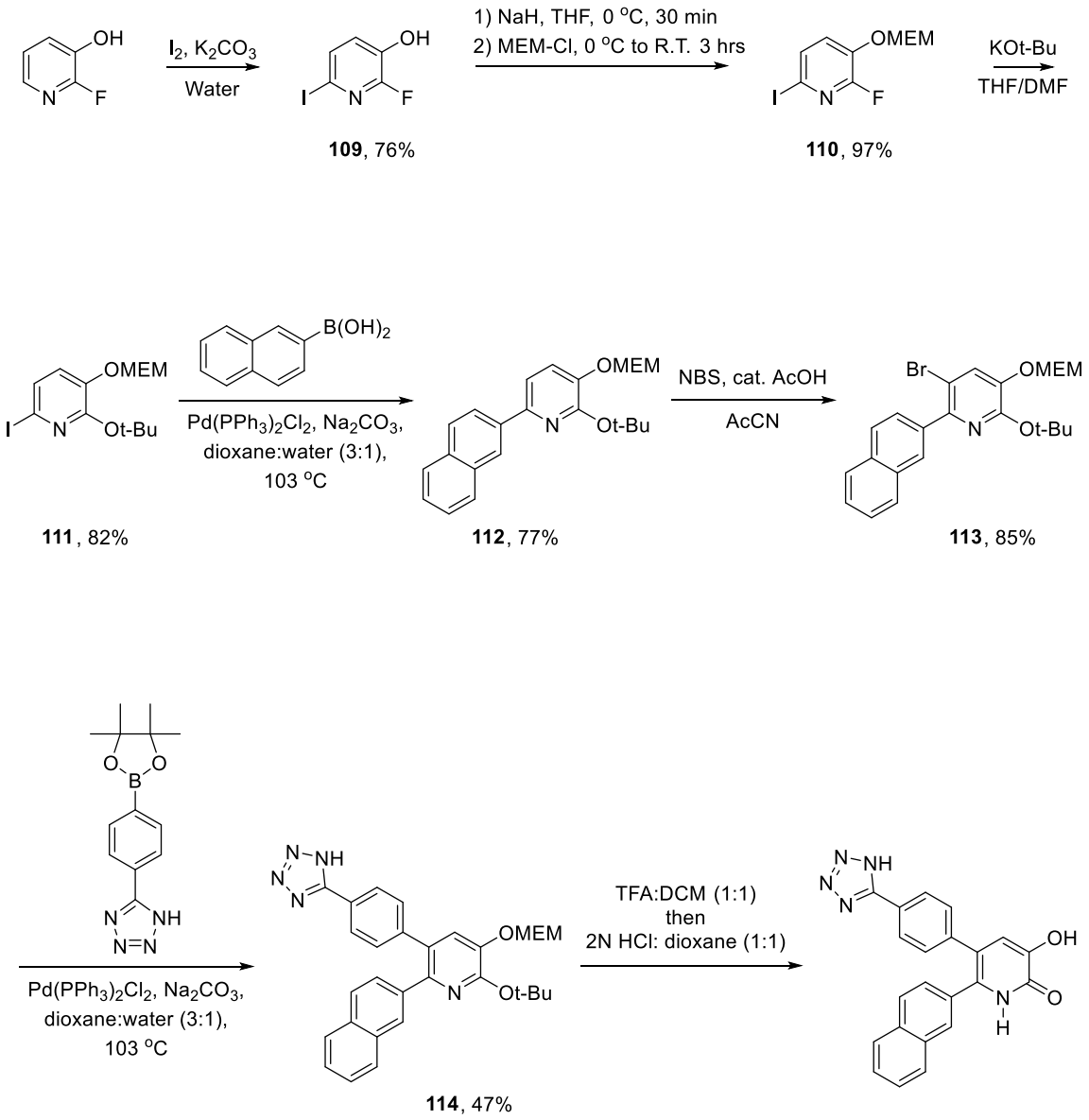
Several attempts at controlling N-alkylation verses O-alkylation of 3-hydroxypyridin-2(1*H*)-ones were unsuccessful. Consequently, we decided to switch a starting material to 2-fluoro-3-hydroxypyridine. Based on Dr. Ajit Parhi's work, fluorine or chlorine at 2-position of pyridine can be easily replaced with various nucleophiles such as sodium ethoxide.[81] Since MOM protective group was unstable in relatively mild acidic condition, we decided to use 2-methoxyethyoxymethyl (MEM) ether as the protecting group for the 3-hydroxyl substituent. The MEM protective group is stable until the condition reaches pH 1, and,[87] it may survive N-bromosuccinimide electrophilic addition reaction. We, then, chose *t*-butyl ether protective group for the 2-position of 2-fluoro-3-hydroxypyrdine. We can introduce this protective group by nucleophilic aromatic substitution reaction, and the group is stable both under basic conditions and acidic conditions (pH 2).[87] The MEM and *t*-butyl ether protective groups are known to be cleaved with trifluoroacetic acid in dichloromethane.[87] The approach, which was developed at the later stage of this research project, is shown in Scheme 21.

Starting with commercially-available 3-hydroxy-2-fluoropyridine, treatment with iodine and sodium carbonate in water gave compound **109**. Compound **109** was then reacted

with NaH and MEM chloride to give the 3-((2-methoxyethoxy)methoxy) derivative, **110**.[89] The 2-fluorosubstituent was selectively displaced with potassium *t*-butoxide in THF to form *t*-butyl ether intermediate, **111**.[90] Intermediate **111** was treated with 2-naphthylboronic acid under Suzuki-coupling condition to provide compound **112**.[81] Bromination with N-bromosuccinimide followed by palladium-catalyzed coupling with 4-(tetrazol-5-yl)phenyl boronate ester provided compound **114**.[81] An attempt to cleave MEM and *t*-butyl ether protective groups with trifluoroacetic acid in dichloromethane as described in the literature was not successful.[87] Recharging the mixture and using hydrochloric acid did provide the tetrazole derivative of **100**, but it proved to be unstable.

The biological activities of compound **99**-**105** were evaluated and are summarized in Table 17. The presence of a 5-tetrazoyl moiety at 4-position of the 5-phenyl substituent of **13** was associated with enhanced activity relative to the 4-cyanophenyl derivative **12**.[81] This trend proved consistent in comparisons of the relative inhibitory activity of 6-(1-napthyl) (**99** and **103**), 6-(1,1´-biphenyl) (**101** and **104**) and 6-(phenanthren-9-yl) (**102** and **105**). For 5-(4-cyanophenyl)-3-hydroxypyridin-2(1*H*)-one derivatives, those with either a 1-napthyl (**99**) or a phenanthren-9-yl (**102**) substituent at the 6-position displayed comparative inhibitory activity relative to compound **13**. Those with either a 2-napthyl (**100**) or a 1,1´-biphenyl (**101**), however, showed a 4-fold decrease in their inhibitory activity relative to compound **13**. A similar pattern was seen with 5-[4-(tetrazol-5-yl)phenyl]-3-hydroxypyridin-2(1*H*)-one derivatives. Of special interest was compound **105,** which had excellent potency with an $IC_{50}$ of 9 nM. Compound **105** was selected for

evaluation in the cellular assay. Unfortunately, compound **105** did not exhibit *ex-vivo* activity against influenza A/Puerto Rico/8/1934 (H1N1) in MDCK cells.




**Scheme 21**. An alternative scheme for the synthesis of the tetrazole derivative of **100**.

**Table 17.** Biological activity of **1**, **12-13** and **99-105**.

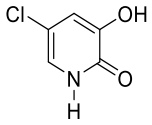
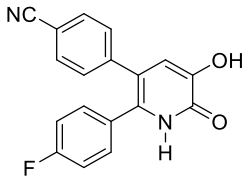
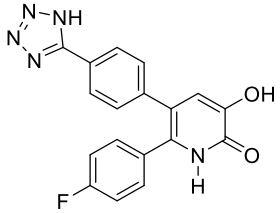
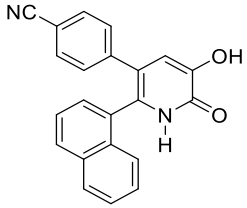
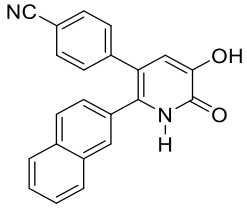
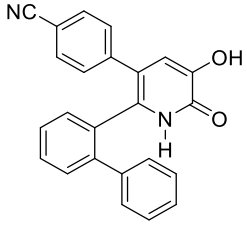
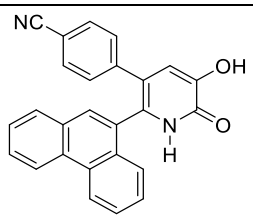
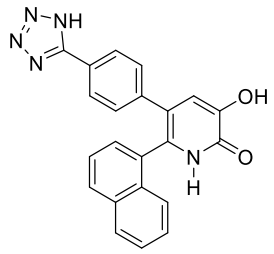
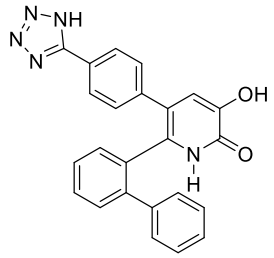
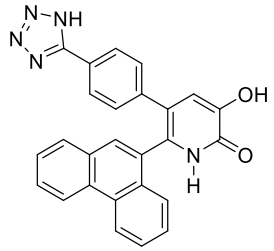
| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **12** |  | 0.14 |
| **13** |  | 0.01 |
| **99** |  | 0.22 |
| **100** |  | 0.54 |
| **101** |  | 0.56 |
| **102** |  | 0.26 |

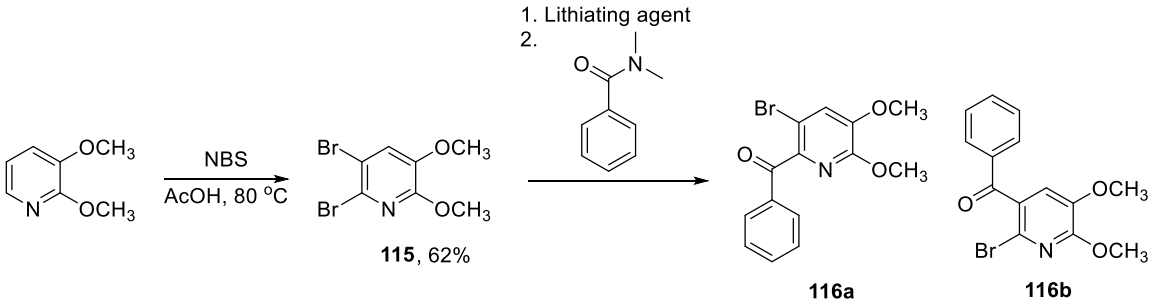
**Table 17.** Biological activity of **1**, **12-13** and **99-105 (Cont.)**.

| | | |
|---|---|---|
| **103** |  | 0.02 |
| **104** |  | 0.04 |
| **105** |  | 0.01 |

Our study on the optimization at 6-postion of 3-hydroxypyridin-2(1*H*)-one continued with 6-arylmethyl substituted 5-[4-(tetrazol-5-yl)phenyl]-3-hydroxypyridin-2(1*H*)-ones. The methyl group between the pyridinone ring and the 6-aryl ring allows these derivatives to bind deeper into the subpocket 3, thereby having the potential of enhancing their potency. The methyl linker also adds degrees of freedom to the molecules. It has been known that molecules that have flexibility generally have better solubility than those that have rigidity. Consequently, these 6-arylmethyl derivatives were viewed as having greater potential for exhibiting activity in the *ex-vivo* assay than their 6-aryl analogs.

The recent study on 2,5-dibromopyridine indicated that lithium-halogen exchange reaction can be controlled by varying lithiating agents, solvent and temperature.[91] Lithium-halogen exchange mainly occurred at 2-position of 2,5-dibromopyridine when the reaction was conducted with the lithiating agent, $TMSCH_2$-Li-LiDMAE (with LIDMAE = $Me_2N(CH_2)_2OLi$) in toluene at 0 $^oC$.[91] Addition of various electrophiles including N,N-dimethylbenzamide led to 2-substituted-5-bromopyridines.[91] On the basis of this literature procedure, we attempted to introduce an aryl ketone group at 6-position of the pyridine ring in the presence of bromine group at 5-position. The aryl ketone group could then be reduced with sodium borohydride followed by treatment with triethylsilane to provide aryl methyl group.

We initiated studies to explore whether this literature procedure would be applicable. The 5,6-dibromo derivative, **115**, was prepared by treatment of commercially-available 2,3-dimethoxypyridine with N-bromosuccinimide in acetic acid (Scheme 22). Intermediate **115** was reacted with *in situ* generated $TMSCH_2$-Li-LiDMAE. For the direct comparison with literature, N,N-dimethylbenzamide was used as an electrophile. This selective lithium-halogen exchange reaction was not successful as we obtained both **116a** and **116b**. The directing effect of LiDMAE was not sufficient for selective lithium-halogen exchange at 6-bromine of compound **115,** as we observed similar pattern when (trimethylsilyl)methyllithium or n-BuLi were employed in place of $TMSCH_2$-Li-LiDMAE.

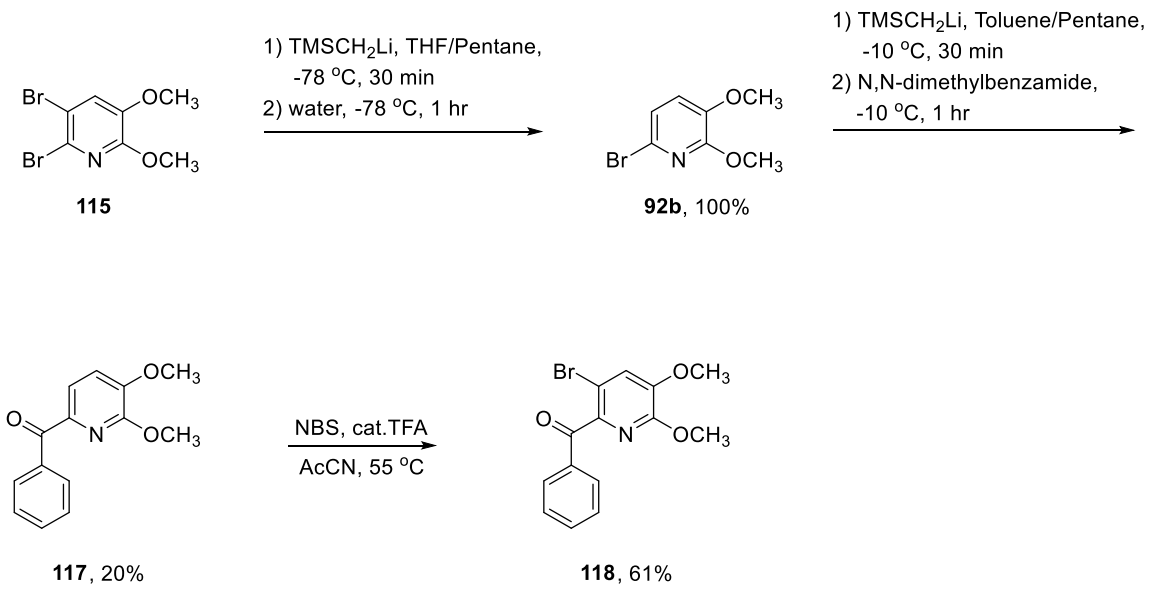



| | | Yields 116a | 116b |
|---|---|---|---|
| **Reaction condition 1:** | 1) $TMSCH_2$-Li-LiDMAE, Toluene/Pentane, 0 °C, 1 hr<br>2) N,N-dimethylbenzamide, -10 °C, 1 hr | 4% | 42% |
| **Reaction condition 2:** | 1) $TMSCH_2$,Toluene/Pentane, 0 °C, 1 hr<br>2) N,N-dimethylbenzamide, -10 °C, 1 hr | 3% | 39% |
| **Reaction condition 3:** | 1) n-BuLi. THF, -78 °C, 30 min<br>2) N,N-dimethylbenzamide, -78 °C, 1 hr | - | 9% |

**Scheme 22.** Initial approaches explored for the synthesis of 6-arylmethyl substituted 5-[4-(tetrazol-5-yl)phenyl]-3-hydroxypyridin-2(1*H*)-ones.

We attempted as an alternative approach to sequentially first add the aryl ketone group at 6-position, then brominate at the 5-position of the pyridine ring (Scheme 23). Although 6-bromo-2,3-dimethoxypyridine was obtained as a side product resulting from treatment of 2,3-dimethoxypyridine with N-bromosuccinimide as shown in Scheme 19, compound **92b** was not the major product and was difficult to purify. Therefore, compound **92b** was prepared using a different synthetic route. Since lithium-halogen exchange reaction mainly occurs at 3-bromine of compound **115** as shown in Scheme 22, quenching with water produced compound **92b** as the major product. When (trimethylsilyl)methyllithium was used as a lithiating agent, compound **92b** was obtained in a quantitative yield. Treatment of intermediate **92b** with (trimethylsilyl)methyllithium

and N,N-dimethylbenzamide gave the 6-benzoyl derivative **117**. Subsequent treatment with N-bromosuccinimide using a catalytic amount of trifluoroacetic acid in acetonitrile provided the 6-benzoyl 5-bromo derivative **118**.[92]

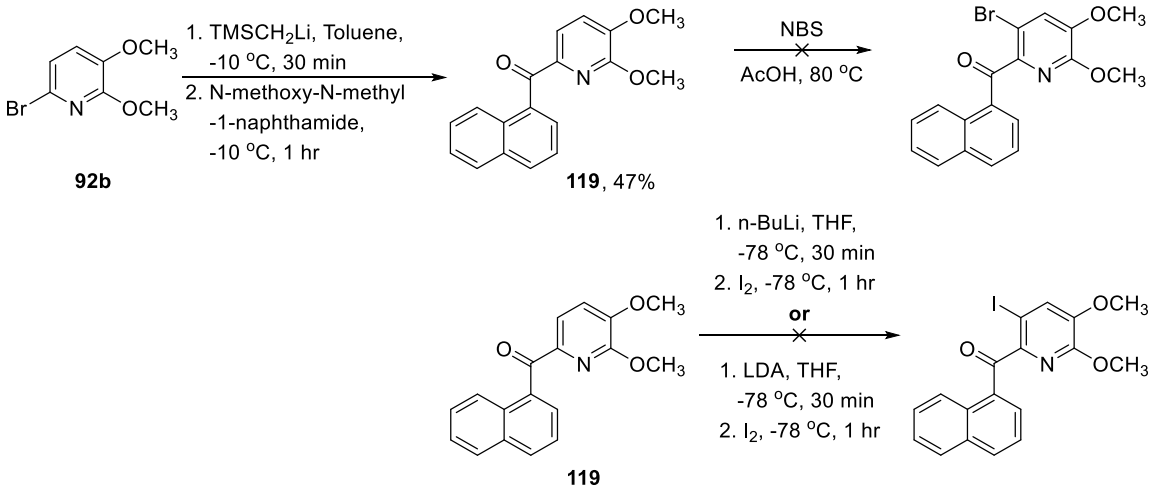



**115** **92b**, 100% **117**, 20% **118**, 61%

**Scheme 23**. Improved method developed for the synthesis of 6-arylmethyl substituted 5-[4-(tetrazol-5-yl)phenyl]-3-hydroxypyridin-2(1*H*)-ones.

The method developed for **118**, unfortunately, was not applicable for the 6-naphthyoyl derivative, **119** (Scheme 24). Treatment of intermediate **92b** with (trimethylsilyl)methyllithium followed by N-methoxy-N-methyl-1-naphthamide provided compound **119**. The reagent, N-methoxy-N-methyl-1-naphthamide, was prepared by reacting 1-naphtyl acid chloride with N,O-dimethyl hydroxylamine hydrochloride and triethylamine in dichloromethane.[93] Due to electron-rich character of naphthalene, bromine substitution occurred within the naphthalene ring during bromination.[92]

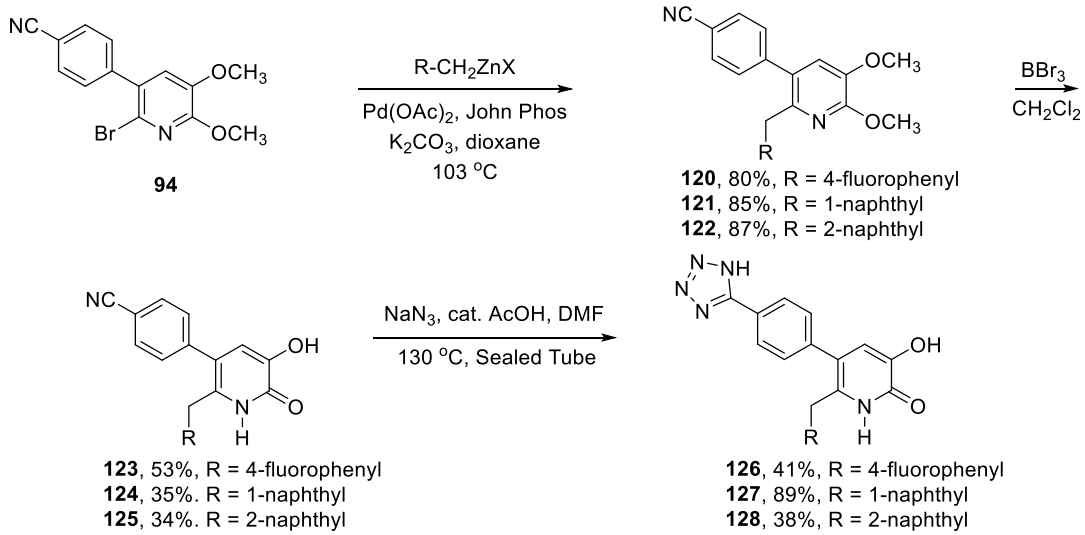
Alternatively, strong bases such as n-BuLi or LDA were used to pull the proton at 5-position of the pyridine ring. It was anticipated that the directing effect of the ketone group might lead to selective deprotonation. Unfortunately, the desired halogenated product was not detected under either of these reaction conditions. The base n-BuLi with iodine produced at least four side products along with recovered starting material. Side products were alcohol derivatives of compound **119** as n-BuLi can act as a nucleophile as well a base. A non-nucleophilic base, LDA, was then employed. Although LDA left carbonyl group intact, iodination did not occur at the 5-position of the pyridine ring. Instead, iodination occurred at the naphthalene ring.




**Scheme 24.** Application of the methodology used to prepare **118** for the synthesis of 5-bromo or 5-iodo-6-naphthoyl-2,3-dimethoxypyridine.

A general procedure that eventually proved especially useful for the preparation of several of the desired targeted compounds is outlined in Scheme 25. Intermediate **94** was coupled with appropriate organozinc halides under Negishi-coupling conditions to

provide the 6-arylmethyl substituted derivatives, **120-122**, in excellent yields (80-87%).[94] Deprotection using $BBr_3$ in dichloromethane provided the 6-arylmethyl substituted 5-(4-cyanophenyl)-3-hydroxypyridin-2(1*H*)-one precursors, **123-125**.[81] Subsequent tetrazole formation by reaction with sodium azide led to the 6-arylmethyl substituted 5-[4-(tetrazol-5-yl)phenyl]-3-hydroxypyridin-2(1*H*)-ones, **126-128**.[81]




**Scheme 25**. Synthetic routes for compounds **123-128.**

The inhibitory activity of these compounds was evaluated and the results are summarized in Table 18. For these 5-(4-cyanophenyl)- or 5-[4-(5-tetrazoyl)phenyl]-3-hydroxypyridin(1*H*)-2-ones, the presence of a 1-naphthylmethyl substituent at the 6-position (**124** and **127**) was associated with greater potency than the similarly substituted 4-fluorobenzyl derivatives, **123** and **126,** or the 2-naphthylmethyl derivative, **125** and **128**. As previously observed for **12** and **13**, the tetrazole derivatives were again consistently more active than the cyano derivatives. Although the 1-naphthylmethyl derivatives were slightly more active than 1-naphthyl derivatives, the 4-fluorobenzyl

derivatives or the 2-napthylmethyl derivatives were less active then 4-fluorophenyl derivatives or the 2-napthyl derivative. Unlike the tetrazole derivative of compound **100**, we could prepare its aryl methyl analog, compound **128**, with purity above 95%. The antiviral activity of compound **127** was examined using the virus yield assay. Once again, there was no *ex-vivo* activity observed with compound **127** in this assay. These 6-arylmethyl substituted 3-hydroxypyridin-2(1*H*)-one derivatives unfortunately did not offer any significant advantage over the previously studied 6-aryl 3-hydroxypyrindin-2(1*H*)-ones.

**Table 18.** Biological activity of **1**, **12-13** and **123-128**.

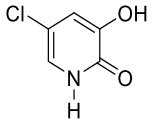
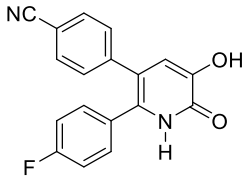
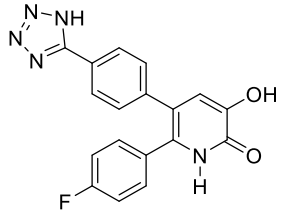
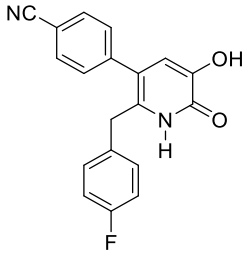
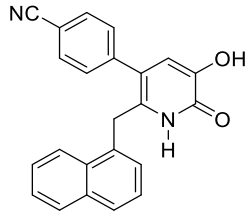
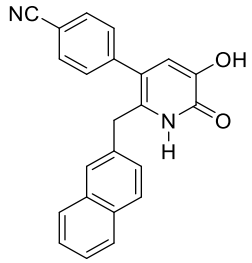
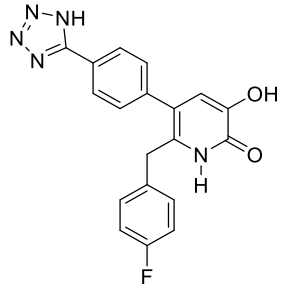
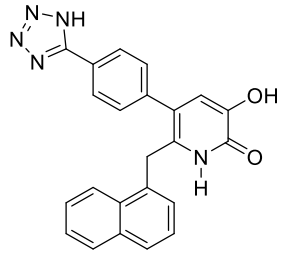
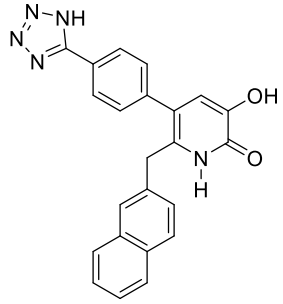
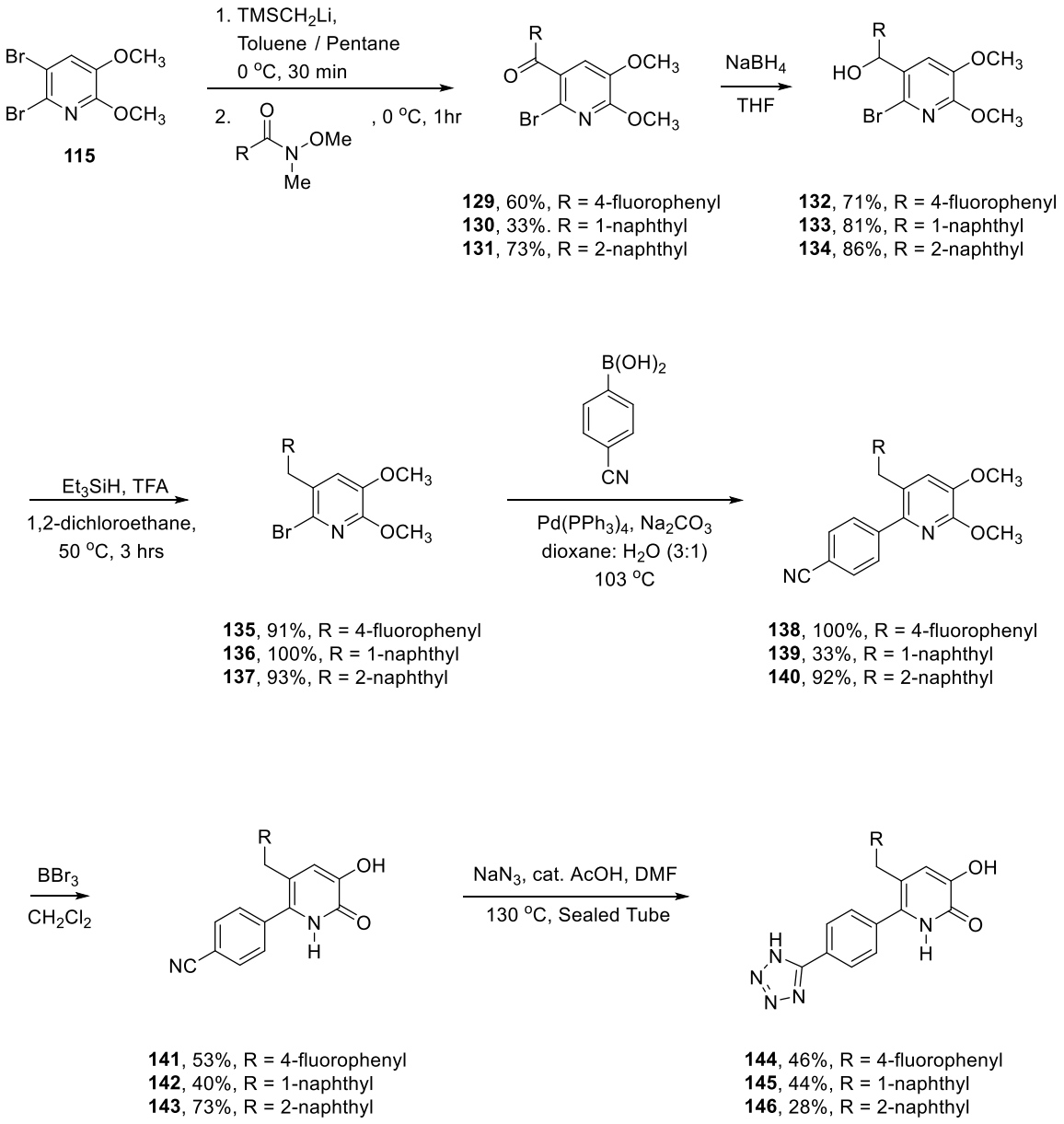
| | **Compound Structure** | **$IC_{50}$ (μM)** |
|---|---|---|
| **1** |  | 25 |
| **12** |  | 0.14 |
| **13** |  | 0.01 |
| **123** |  | 0.51 |

**Table 18.** Biological activity of **1**, **12-13** and **123-128 (Cont.)**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **124** |  | 0.11 |
| **125** |  | 0.66 |
| **126** |  | 0.03 |
| **127** |  | 0.02 |
| **128** |  | 0.07 |

During the process of developing a synthetic pathway for compound **123-128**, we found a useful synthetic procedure for making 5-arylmethyl substituted 6-[(tetrazol-5-yl)phenyl]-3-hydroxypyridin-2(1*H*)-ones, **144-146**, and their cyano precursors, **141-143**. They were prepared employing the lengthy synthetic pathway outlined in Scheme 26. Using the synthetic methodology that we developed, we initiated studies to explore the effect of 5-arylmethyl substitutions on either 6-[(tetrazol-5-yl)]- or 6-(cyanophenyl)-3-hydroxypyridin-2(1*H*)-ones. The aryl ketone group was introduced at 5-position of intermediate **115** in the presence of bromine at the 6-position using the procedure shown in Scheme 22. Lithiation of intermediate **115** with (trimethylsilyl)methyllithium, and subsequent reaction with the appropriate Weinreb amide provided the 5-(aryloyl)-6-bromo-2,3-dimethoxypyridines, **129-131** in yields ranging from 60% to 73%, with the exception of compound **130**, which was prepared in 33% yield. The relative low yield for compound **130** maybe due to steric hindrance N-methoxy-N-methyl-1-naphthamide. These aryloyl derivatives were then converted to 5-(arylmethyl)-6-bromo-2,3-dimethoxypyridines, **135-137**, using a two-step reduction using $NaBH_4$ to form the secondary alcohol[95] with subsequent treatment with triethylsilane and trifluoroacetic acid to form the arylmethyl derivatives.[96] These intermediates together with 4-cyanophenylboronic acid under Suzuki-coupling condition provided compound **138-140**.[81] Deprotection using $BBr_3$ in dichloromethane provided 5-arylmethyl substituted 6-(4-cyanophenyl)-3-hydroxypyridin-2(1*H*)-one precursors, **141-143**.[81] Subsequent tetrazole formation reaction led to 6-arylmethyl substituted 5-[4-(tetrazol-5-yl)phenyl]-3-hydroxypyridin-2(1*H*)-ones, **144-146**.[81]




**Scheme 26.** Synthetic pathway for compounds **141-146.**

Those 6-(4-cyanophenyl)- or 6-[4-(5-tetrazoyl)phenyl]-3-hydroxypyridin(1*H*)-ones were evaluated, and their results are summarized in Table 19. For these derivatives, the presence of a 1-naphthylmethyl substituent at the 5-position (**142** and **145**) was again associated with greater potency than the similarly substituted 4-fluorobenzyl derivatives

(**141** and **144**) or the 2-naphthylmethyl derivatives (**143** and **146**). As previously observed for compound **14** and **15**, the tetrazole derivatives were again consistently more active than the cyano derivatives. The antiviral activity of compound **144-146** was examined by the virus yield assay. Once again, no *ex-vivo* activity was observed with these compounds under these assay conditions. These 5-arylmethyl substituted 3-hydroxypyridin-2(1*H*)-one derivatives again failed to display any benefit over 5, 6-bisaryl or 6-arylmethyl 3-hydroxypyridin-2(1*H*)-ones.

**Table 19.** Biological activity of **1**, **14-15** and **141-146**.

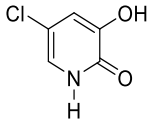
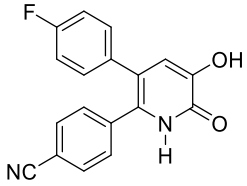
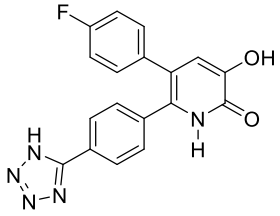
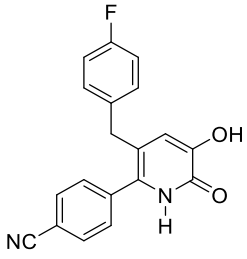
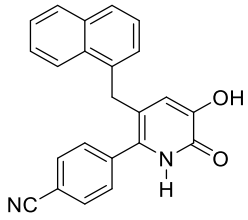
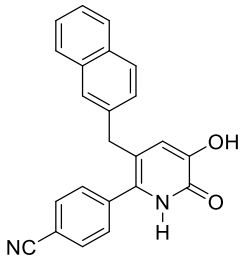
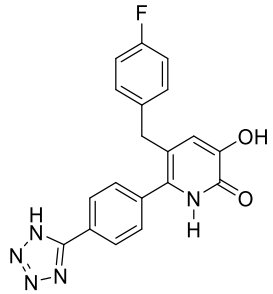
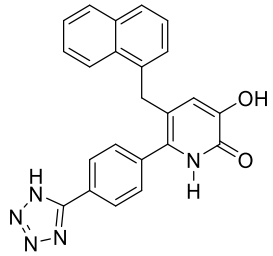
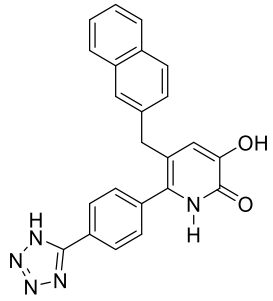
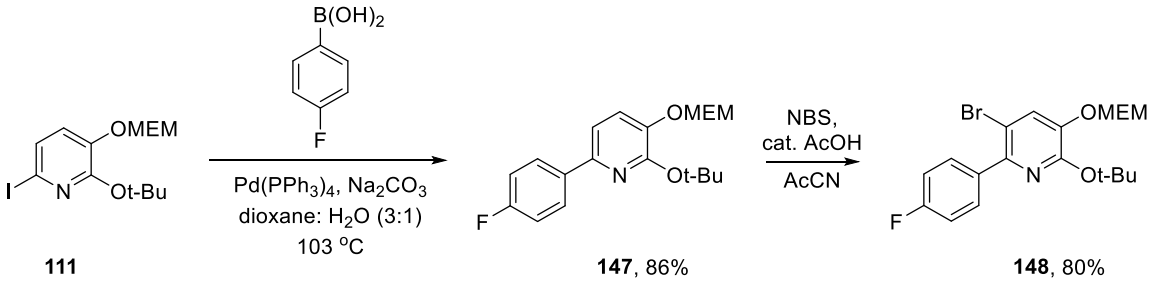
| | **Compound Structure** | **$IC_{50}$ (μM)** |
|---|---|---|
| **1** |  | 25 |
| **14** |  | 0.05 |
| **15** |  | 0.02 |
| **141** |  | 0.48 |

**Table 19.** Biological activity of **1**, **14-15** and **141-146 (Cont.)**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **142** |  | 0.17 |
| **143** |  | 0.25 |
| **144** |  | 0.05 |
| **145** |  | 0.01 |
| **146** |  | 0.08 |

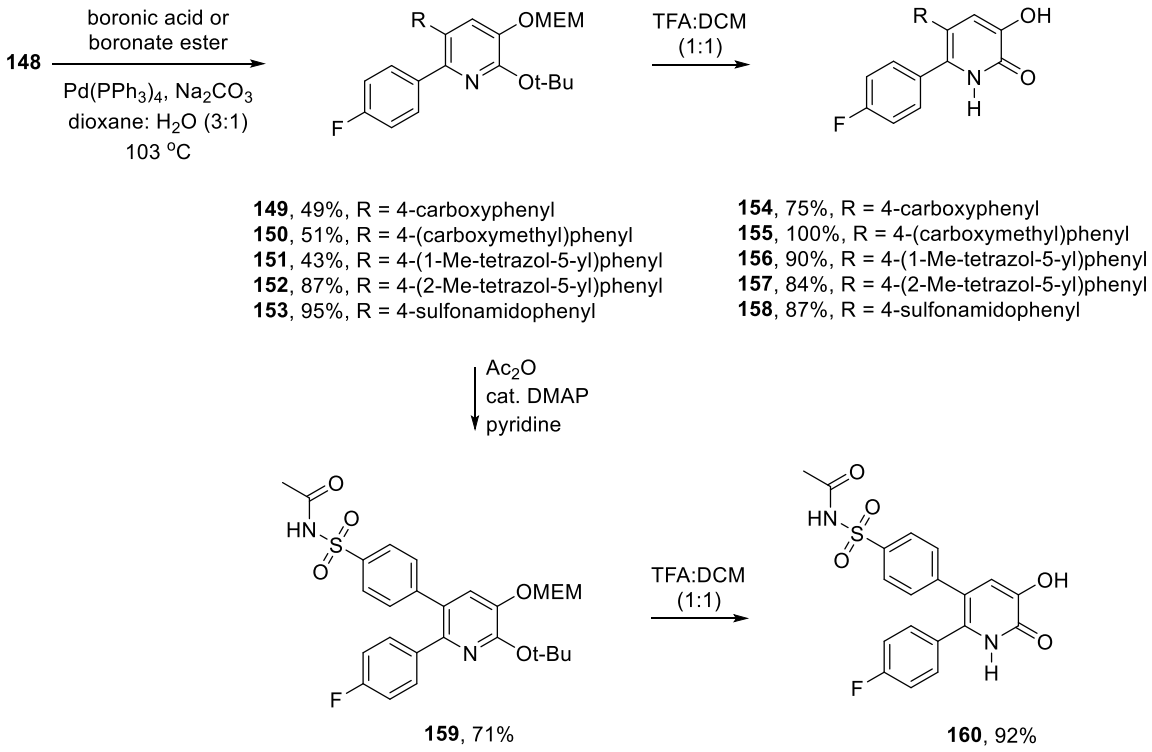
Efforts were then made to examine whether we could further optimize activity by making the appropriate modification to the 5-position of these 3-hydroxpyridin-2(1*H*)-ones. Structural studies on compound **13** revealed that a 5-tetrazolyl at 4-position of the 5-phenyl substituent of **13** interacts with Arg124 through bidentate hydrogen bond interactions.[81] This interaction appeared to be the primary determinant of the binding mode. Considering its crucial interaction with $PA_N$, we decided to search groups that can be used in place of the tetrazole moiety.

Intermediate **111**, which was prepared from Scheme 21, was coupled with 4-fluorophenylboronic acid to provide compound **147**,[81] which could be efficiently brominated using NBS to provide intermediate **148** (Scheme 27). Because compound **13** showed *ex-vivo* activity, we prepared intermediate **148** with a 4-fluorophenyl substituent at 6-position of the pyridine ring. The bromo group at the 5-position of the pyridine ring allowed us to place phenyl groups with varied functionalities through coupling reactions at this site.



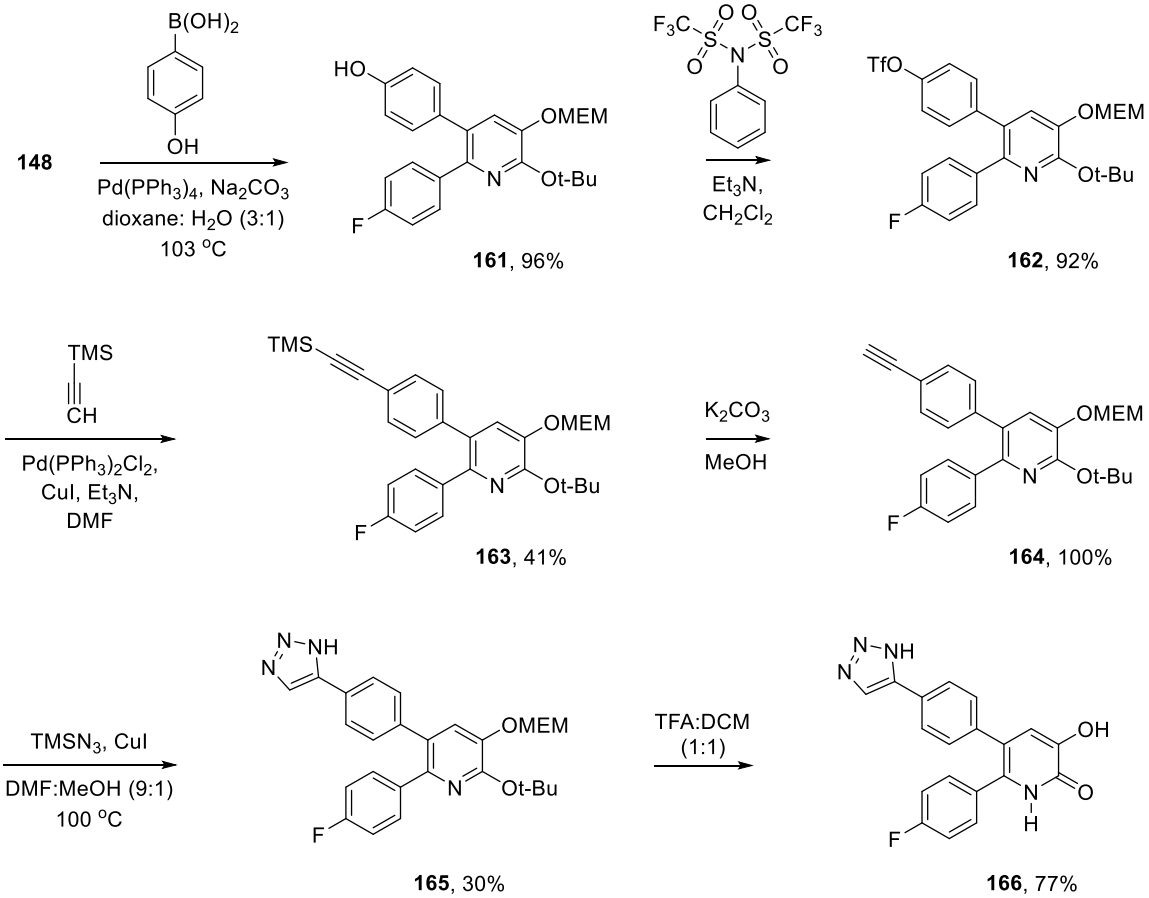

**Scheme 27.** An attempt to using MEM and *t*-butyl ether as protective groups for the preparation of 5-bromo-6-(4-fluorophenyl) intermediate, **148**.

Intermediate **148** together with the appropriate boronic acid or boronate ester under Suzuki coupling conditions provided the desired 5-phenyl derivatives of 6-(4-fluorophenyl)-2-(*t*-butoxy)-3-((2-methoxyethoxy)methoxy)pyridine, **149-153** (Scheme 28).[81] Treatment with trifluoroacetic acid in dichloromethane at room temperature provided the desired products, **154-158**, in yields ranging from 75% to 100%.[87] Generally, this deprotection reaction condition did not require column purification to obtain products with purity above 95%. Acetylation of the compound **153** with acetic anhydride in pyridine followed by the removal of the protective groups gave compound **160** in 92% yield.[87, 97]




**Scheme 28**. Synthetic routes for compounds **154-158** and **160**.

The preparation of compound **166** was accomplished as outlined in Scheme 29. Intermediate **148** was coupled with 4-hydroxyphenylboronic acid under Suzuki-coupling condition to give compound **161**.[81] This phenol derivative was reacted with N-phenyl-bis(trifluoromethanesulfonimide) and triethylamine, providing the triflate derivative, **162**.[98] Sonogashira coupling of compound **163** with (trimethylsilyl)acetylene followed by removal of the TMS-protective group provided the acetylene intermediate, **164**.[99] The intermediate was converted to the triazole derivative, **165**, by using $TMSN_3$ and CuI in solvent mixture of DMF and methanol.[100] Once again, removal of protective groups under trifluoroacetic acid in dichloromethane provided compound **166** in 77% yield.[87]




**Scheme 29.** Synthetic routes for compound **166**.

These 5-substituted 6-fluorophenyl-3-hydroxypyridin-2(1*H*)-one derivatives were evaluated for their relative biological activities, and they are summarized in Table 20-21. The observation of identical activity between compound **13** and **154** indicated the importance of having an acidic functional group at *para*-position on the 5-phenyl substituent of the pyridinone ring. The carboxyl functional group would have negative charge in physiological condition and might interact with Arg124 through ionic interaction. Replacement of the carboxylic acid of **154** to the methyl ester, **155**, resulted in a dramatic loss in inhibitory activity. Similarly, loss of the acidic proton on the tetrazole moiety by methylation at either the 1- or 2-position of compound **13,** as in the case of compound **156** and **157**, respectively, also resulted in a drop in inhibitory activity. These dramatic losses in inhibitory activity reaffirmed the significance of either bidentate hydrogen bond interaction or ionic interaction between acidic functionalities and Arg124.

Replacing the carboxylate with a sulfonamide, as in compound **158**, or with an acylsulfonamide, as in compound **160**, did not result in compounds with similar potency to either of **13** or **154**. The reduced inhibitory activities observed with compound **158** and **160** might indicate steric factors also affect their inhibitory activities. In the case of the 5-[4-(triazol-5-yl)phenyl] derivative, **166,** significant potency was restored relative to either compound **13** or **154**. 1,2,3-Triazole is less acidic than tetrazole, but it maintains a similar size to tetrazole. Compound **154**, which has the same inhibitory activity to compound **13**, was evaluated in the virus yield assay using MDCK cells. Unlike compound **13**, which has an $EC_{50}$ of 11 μM, compound **154** did not display any *ex-vivo* activity when screened against influenza A/Puerto Rico/8/1934 (H1N1).

**Table 20.** Biological activity of **1**, **12-13** and **154-157.**

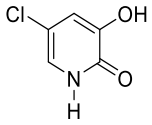
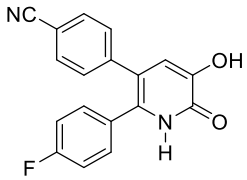
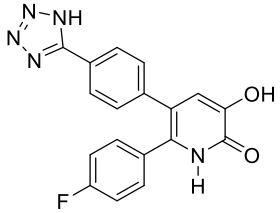
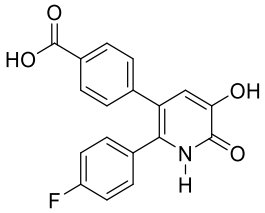
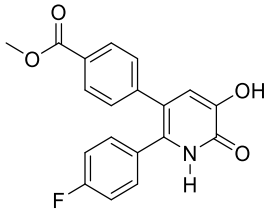
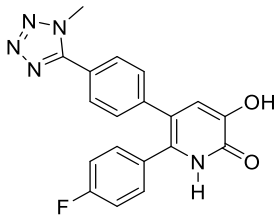
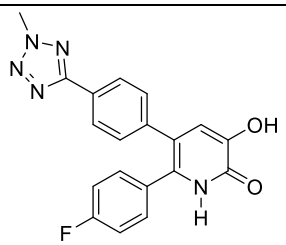
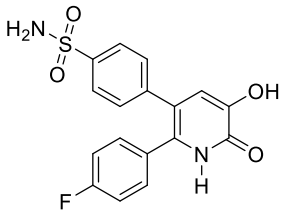
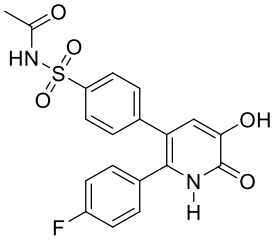
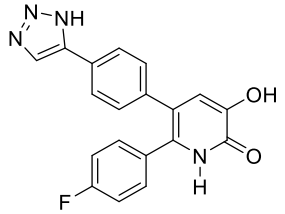
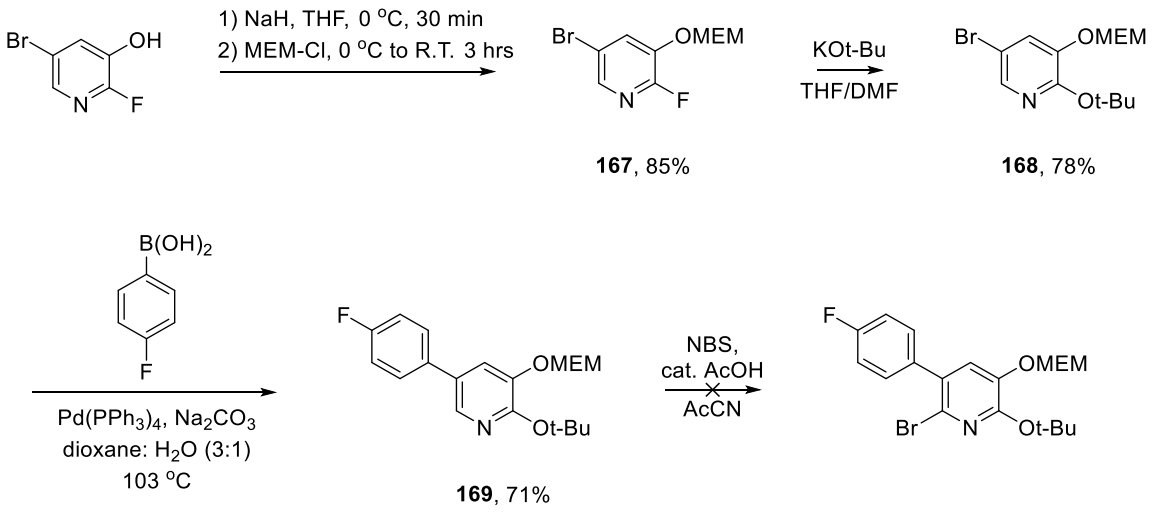
| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **12** |  | 0.14 |
| **13** |  | 0.01 |
| **154** |  | 0.01 |
| **155** |  | 0.13 |
| **156** |  | 0.30 |
| **157** |  | 0.14 |

**Table 21.** Biological activity of **158**, **160**, **166**.

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **158** |  | 0.35 |
| **160** |  | 0.15 |
| **166** |  | 0.03 |

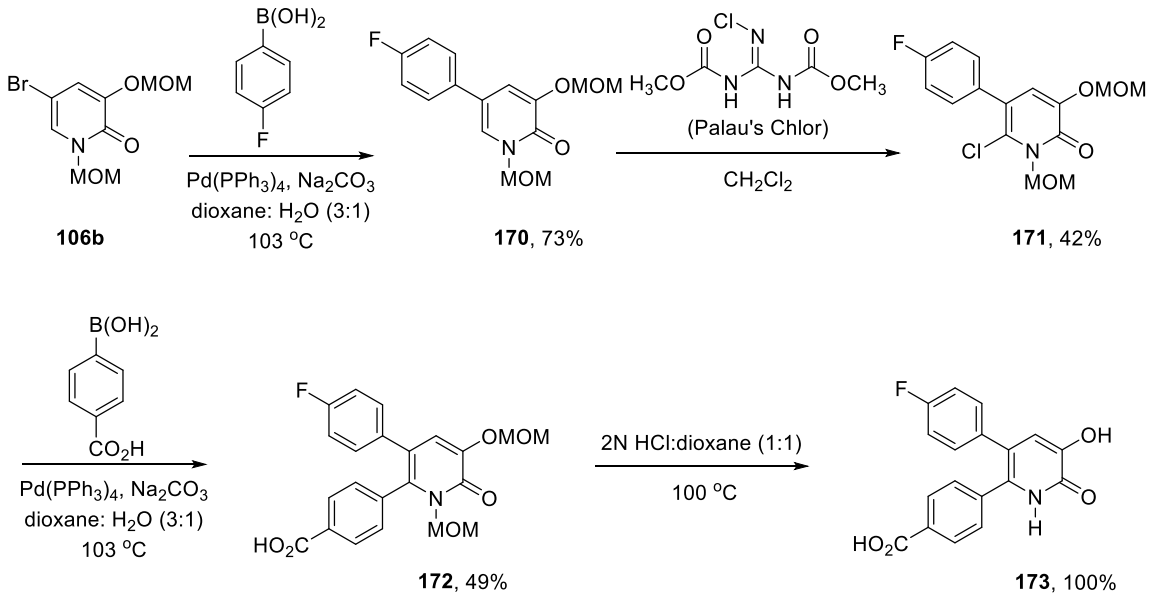
Previous studies have demonstrated that there are two distinct metal binding modes associated with inhibition of $PA_N$. It was believed that the tetrazole moiety at the *para*-position of either a 5- or 6-phenyl substituent of a 3-hydroxypyridin-2(1*H*)-one can determine the binding mode since the moiety interacted with Arg124 through bidentate hydrogen bond interactions. Compound **15** has a 4-(tetrazol-5-yl)phenyl substituent at 6-position of the pyridinone ring, and it binds to the enzyme in a flipped orientation compared to that of compound **13**. Compound **15** displayed an $IC_{50}$ of 23 nM as it maintained binding interaction with Arg124.[81] We, therefore, prepared 6-(4-carboxyphenyl)-5-fluorophenyl-3-hydroxypyridin-2(1*H*)-one, **173**, to see whether the carboxylate functionality behaves similarly.

For the preparation of 5-bromo-5-(4-fluorophenyl) intermediate with labile protective group, we used our recently developed synthetic method that employed MEM and *t*-butyl as protective groups (Scheme 30). Starting with commercially-available 5-bromo-3-hydroxy-2-fluoropyridine, treatment with NaH and MEM chloride gave 3-((2-methoxyethoxy)methoxy) derivative, **167**.[89] The 2-fluorosubstituent was selectively displaced with potassium *t*-butoxide in THF to form *t*-butyl ether intermediate, **168**.[90] Palladium-catalyzed coupling of compound **168** with 4-fluorophenylboronic acid provided compound **169**.[81] Unfortunately, the bromination of compound **169** with N-bromosuccinimide in acetonitrile was unsuccessful. Starting material, **169**, was recovered. This might be due to lower activation of 6-position of pyridine in relative to 5-position of pyridine. Alternatively, directing effect of MEM protected hydroxyl group is weaker than that of a *t*-butyl ether protected hydroxyl group.




**Scheme 30.** An attempt to using MEM and *t*-butyl ether as protective groups for the preparation of 6-bromo-5-(4-fluorophenyl) intermediate

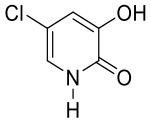
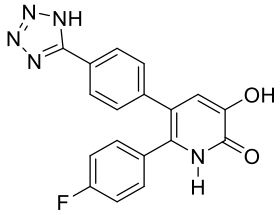
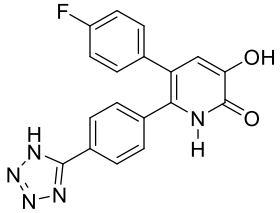
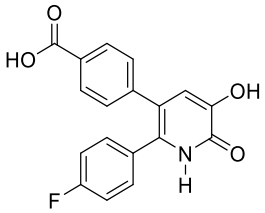
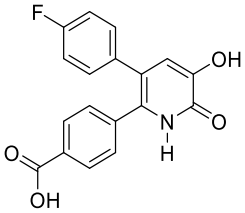
To introduce halides at 6-position of the pyridine ring, we need to use either a stronger directing group such as hydroxyl group or *ortho*-located directing group. A previous attempt using the MOM protective group provided compound **106b**, which had a MOM group on the nitrogen of the pyridine ring (Scheme 20). Starting from compound **106b**, palladium-catalyzed coupling with 4-fluorophenylboronic acid under the Suzuki-Coupling condition provided intermediate **170** (Scheme 31).[81] Treatment of compound **170** with Palau's chlor provided intermediate **171**.[101] This recently available reagent can be used for chlorination under relatively mild reaction conditions.[101] Suzuki-coupling condition using this intermediate together with 4-carboxyphenylboronic acid provided compound **172**.[81] Unlike having a chloro group at the 5-position of pyridine, a 6-chloro substituent can undergo palladium-catalyzed coupling reaction. Subsequent deprotection of **172** under acidic conditions gave the desired product, **173**, in 100% yield.[102]




**Scheme 31.** Synthetic routes for compound **173**.

Based on our enzymatic assay, compound **173** displayed modest inhibitory activity with an $IC_{50}$ of 55 nM (Table 22). However, unlike compound **15**, which was 2-fold less active than compound **13**, it was 5-fold less active than compound **154**.

**Table 22.** Biological activity of **1**, **13**, **15**, **154** and **173.**

| | **Compound Structure** | **$IC_{50}$ (µM)** |
|---|---|---|
| **1** |  | 25 |
| **13** |  | 0.01 |
| **15** |  | 0.02 |
| **154** |  | 0.01 |
| **173** |  | 0.06 |

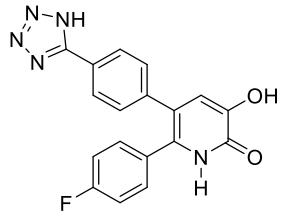
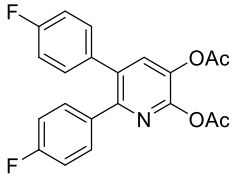
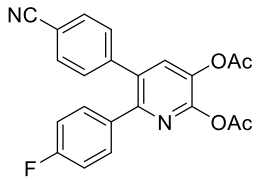
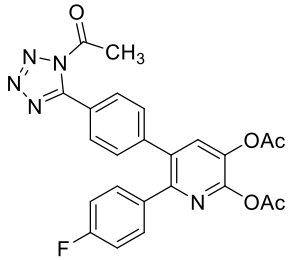
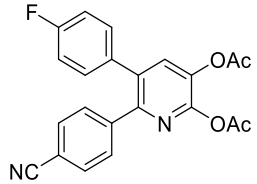
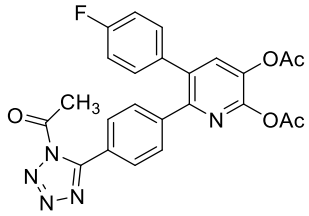
In summary, we once more turned our attention to 3-hydroxypyridin-2(1*H*)-one series as data from 3-hydroxyquinolin-2(1*H*)-ones and various aza-substituted 3-hydroxypyridin-2(1*H*)-ones failed to resolve the concern associated with a lack of *ex-vivo* activity for these related compound. Initially, we sought alternative groups for 6-position of compound **13**, which had an $EC_{50}$ of 11 μM in the cell-based assay. The resulted inhibitor **105** had an $IC_{50}$ of 9 nM, which was the most potent of all. Unfortunately, the compound was not active in an *ex-vivo* assay. We then made efforts to prepare 6-arylmethyl derivatives of compound **13**, hoping flexibility can increase inhibitory activity in *ex-vivo*. The resulted inhibitor **127** exhibited no antiviral activity in the *ex-vivo* assay using mammalian cells. Along the way, 5-arylmethyl derivatives of compound **15** were prepared, and, representative inhibitors again did not show any activity in the virus yield assay. Continuing our work, we attempted to find alternative groups for the 5-tetrazoyl moiety of compound **13**. The carboxyl derivative **154** had the same activity in the enzymatic assay, emphasizing the importance of acidic functionality at *para*-position of 5-phenyl substituted 6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one. Our endeavor once more was not successful as one of our more potent enzyme inhibitors, compound **154**, had no activity in an *ex-vivo* antiviral assay. Our research continued in an effort to identify an endonuclease inhibitor structurally-related to 3-hydroxypyridin-2(1*H*)-ones with improved *ex-vivo* activity.

## 2.4 Synthesis and Evaluation of Noncompetitive Inhibitors.

Our attempts at discovering an endonuclease inhibitor with reasonable activity in *ex-vivo* were unsuccessful despite having examined several differing derivatives with varied scaffolds. Low cell permeability of our test compounds was thought to be one possible explanation for the absence of antiviral activity in the cellular assay. For the validation of the assumption, Dr. Ajit Parhi prepared acetylated derivatives, **174-178**. Compound **11-15** were heated in a neat acetic anhydride solution to provide prodrug compound **174-178**.[103]

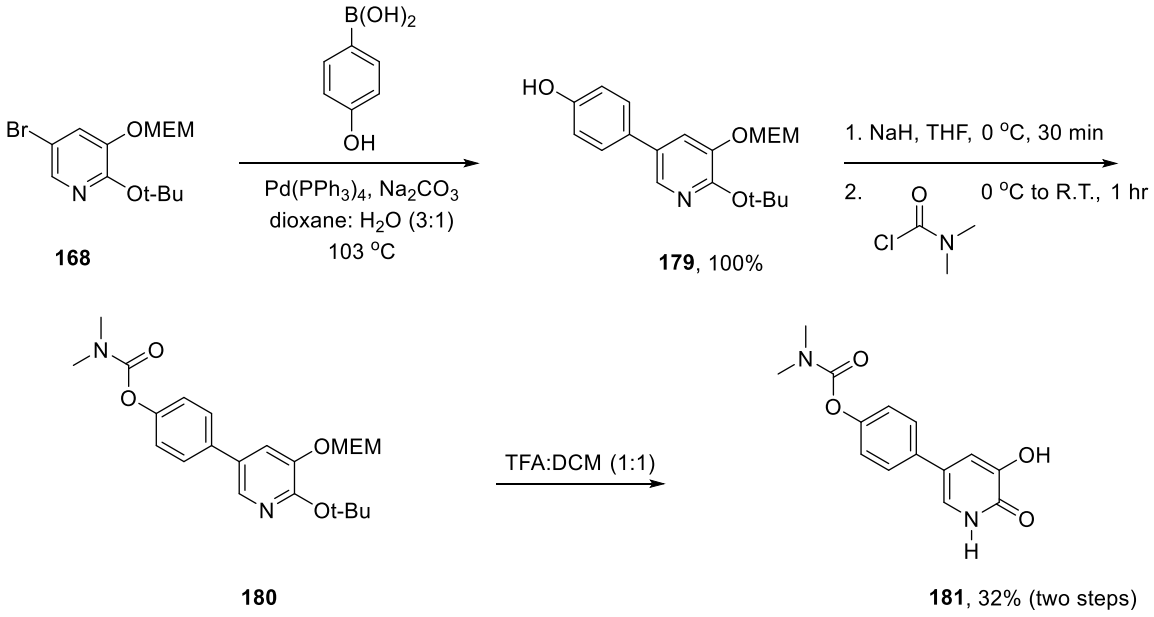
These prodrugs, **174-178**, were evaluated against influenza A/Puerto Rico/8/1934 (H1N1) using the virus yield assay in MDCK cells (Table 23). Surprisingly, only compound **178** displayed inhibitory activity with an $EC_{50}$ of 2.5 µM. This result implies that low cell permeability might not be a reason for the loss of activity in the cellular assay. To find an explanation for the *ex-vivo* activity of compound **178**, soaking of compound **178** with $PA_N$ was undertaken. The structure suggested that Arg124, which forms bidentate hydrogen bond interaction with tetrazole moiety, was being modified. Although we were able to model acetyl group onto Arg124, as an evidence that acetylation had taken place on Arg124, follow-study is needed to verify it. Despite this unclarity, we speculated that acetylation on Arg124 may be responsible for the *ex-vivo* activity of compound **178**. Modification on Arg124 could inhibit the endonuclease activity of the enzyme long enough to hinder virus reproduction.

**Table 23.** Biological activity of **13** and **174-178.**

| | Compound Structure | *Ex-vivo* activity (μM) |
|---|---|---|
| **13** |  | 11 |
| **174** |  | Non detected |
| **175** |  | Non detected |
| **176** |  | Non detected |
| **177** |  | Non detected |
| **178** |  | 2.5 |

We prepared compounds bearing various electrophiles to see whether irreversible or a more sustained modification of the $PA_N$ would result in *ex-vivo* activity. Initially, 5-

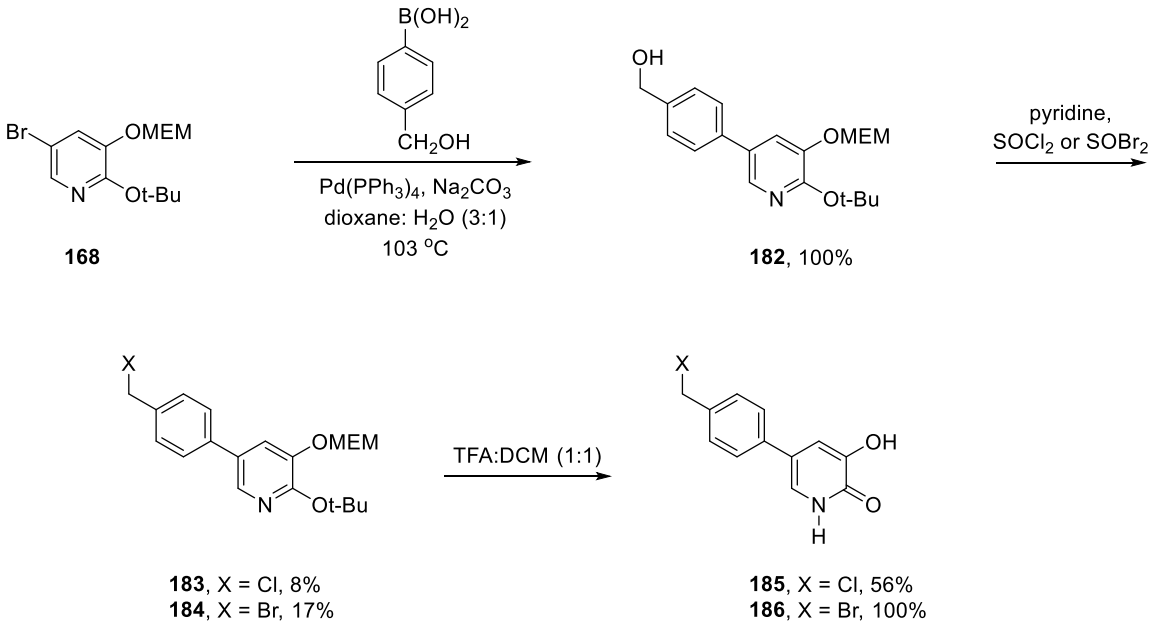
substituted 3-hydroxypyridin-2(1*H*)-ones were prepared. These derivatives were selected as an efficient means of exploring the validity of the concept that noncompetitive inhibitors could improve *ex-vivo* efficacy. The carbamoyl derivative, **181**, which has mild electrophile, was prepared as shown in the Scheme 32. Intermediate **168**, which was prepared as in Scheme 30, was coupled with 4-hydroxyphenylboronic acid under Suzuki-coupling conditions to give compound **179**.[81] Its phenol was then converted to N,N-dimethyl carbamate derivative, **180**, by forming the phenoxide with sodium hydride followed by treatment with dimethylcarbamyl chloride.[104] Cleavage of protective groups with trifluoroacetic acid in dichloromethane provided the desired product, **181**.[87]




**Scheme 32.** Synthetic routes for compound **181**.

Compounds bearing strong electrophiles including alkyl chloride and alkyl bromide were also prepared as shown in Scheme 33. Intermediate **168** was coupled with 4-

(hydroxymethyl)phenylboronic acid under Suzuki-coupling conditions to give compound **182**.[81] The primary alcohol was then converted to either the chloromethyl derivative (**183**) or bromomethyl derivative (**184**) by reacting either with thionyl chloride or thionyl bromide in the presence of pyridine.[105-106] Cleavage of protective groups with trifluoroacetic acid in dichloromethane provided the desired products, **185** and **186**.[87]

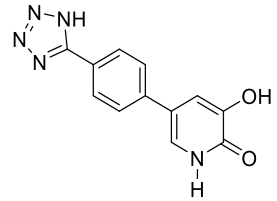
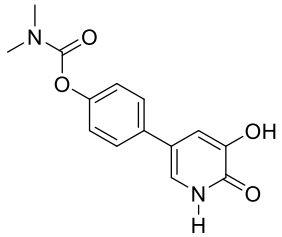
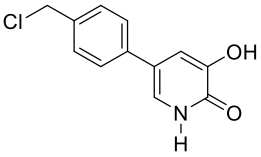
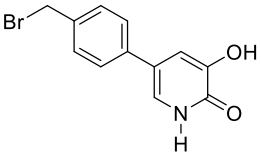



**Scheme 33.** Synthetic routes for compounds **185-186**.

The inhibitory activity of **181**, **185** and **186** was evaluated. These data revealed that these noncompetitive inhibitors were much less active than compound **6** as shown in Table 24. One explanation of the loss of inhibitory activity shown with these derivatives is the absence of critical interaction with Arg124. As they no longer can sustain neither hydrogen bond nor ionic interaction with Arg124, they might exhibit significantly lower activity than compound **6**. Another explanation is susceptibility or instability of

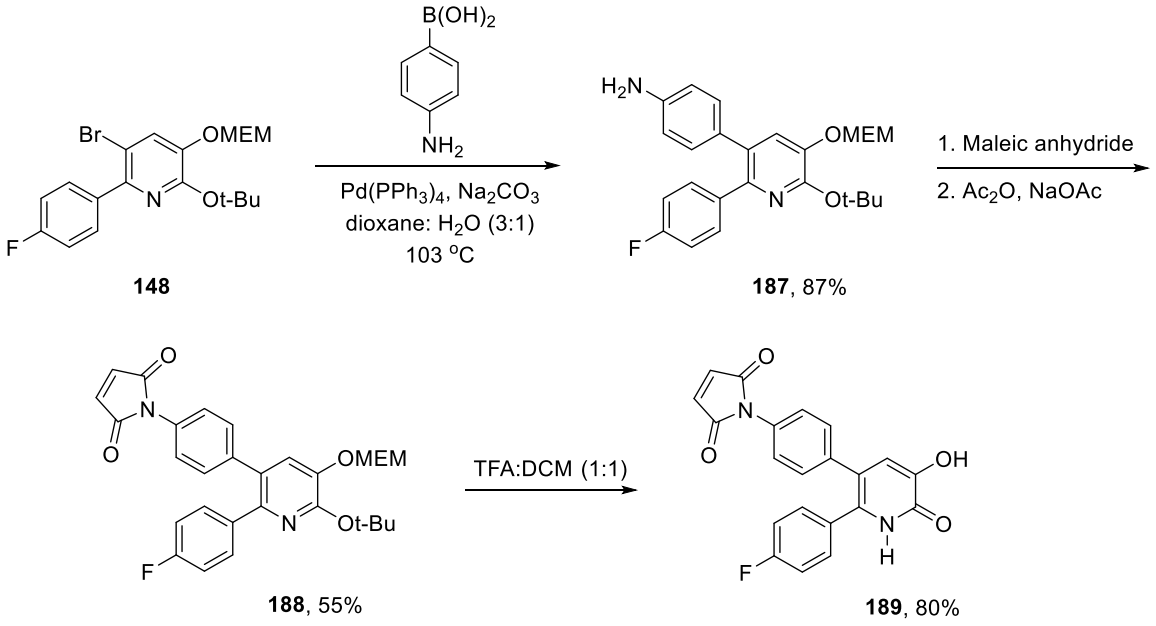
electrophiles under the aqueous assay conditions. Since these inhibitors are good electrophiles, especially, compound **185** and **186**, they could be attacked by various nucleophiles such as water.

**Table 24.** Biological activity of **6**, **181** and **185-186.**

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **6** |  | 0.37 |
| **181** |  | 6.3 |
| **185** |  | 7.8 |
| **186** |  | >2 |

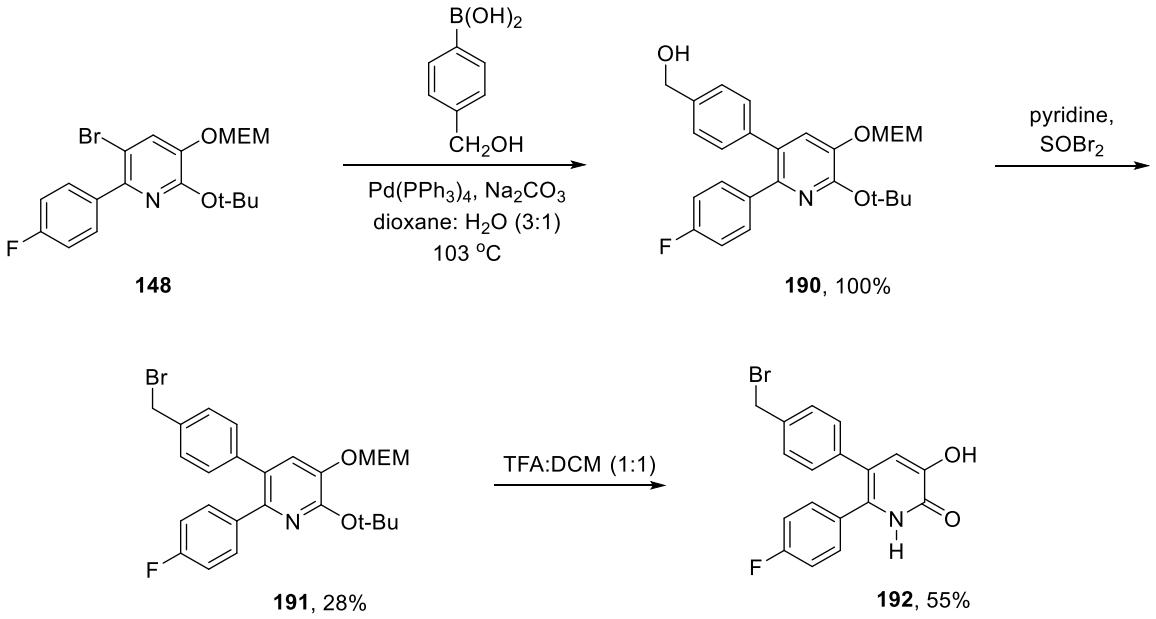
We could not conclude from these data whether or not 5-substituted 3-hydroxypyridin-2(1*H*)-one derivatives with electrophilic moieties might exhibit *ex-vivo* activity. Consequently, 5-substituted 6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-ones bearing electrophiles were designed with hope of restoring activity. The malimide derivative, **189**, were prepared as shown in Scheme 34. Intermediate **148**, which was prepared as in

Scheme 27, was coupled with 4-aminophenylboronic acid under Suzuki-coupling condition to give compound **187**.[81] The amine was then reacted with maleic anhydride followed by acetic anhydride and sodium acetate to give malimide derivative, **188**.[107] Cleavage of protective groups with trifluoroacetic acid in dichloromethane provided the desired product, **189**.[87]




**Scheme 34.** Synthetic routes for compound **189**.

For compounds bearing strong electrophiles, we prepared bromomethyl derivative, **192** as outlined in Scheme 35. Using previously methodology, palladium-catalyzed coupling of intermediate **148** with 4-(hydroxymethyl)phenylboronic acid under Suzuki-coupling condition resulted in compound **190**,[81] which was then converted to methyl bromide derivative, **191**.[106] Cleavage of protective groups with trifluoroacetic acid in dichloromethane provided the desired product, **192**.[87]



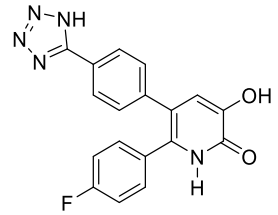
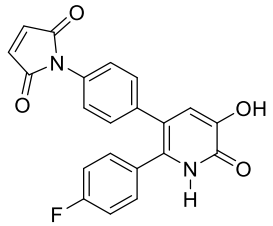
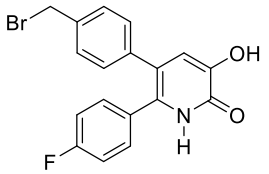

**Scheme 35.** Synthetic routes for compound **192**.

These 5-phenyl substituted 6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-ones were evaluated in the enzymatic assay (Table 25). By adding 4-fluorophenyl group at 6-position of the pyridinone ring, significant inhibitory activity was restored. However, compound **189** and **192** were less active than compound **13**.

During the preparation of compounds, we evaluated N-acetylated derivatives, **176** and **178**, in a plasmid-based minigenome assay. The assay is used to validate whether a compound inhibits viral transcription/replication process in a cell, by measuring released light from a reporter protein, Firefly luciferase (FFluc). The assay also measured released light from the second reporter protein, Renilla luciferase (Rluc), to make sure the reduced light from the FFluc was not originated from interfering with cellular transcription/replication process. The expression of the FFluc is dependent on the Rluc.

Both of compounds displayed dose-dependent FFluc inhibition. However, as these compounds also exhibited dose-dependent Rluc inhibition, it was not certain whether these compounds were indeed inhibitors of viral transcription/replication process. Since cell viability was reduced upon the treatment of these compounds, we concluded that their off-target effects are likely responsible for their inhibition of viral transcription/replication process. Therefore, the *ex-vivo* activity we observed with compound **178** is more likely due to its off-target effects, which reduce cell viability.

**Table 25.** Biological activity of **13**, **189** and **192.**

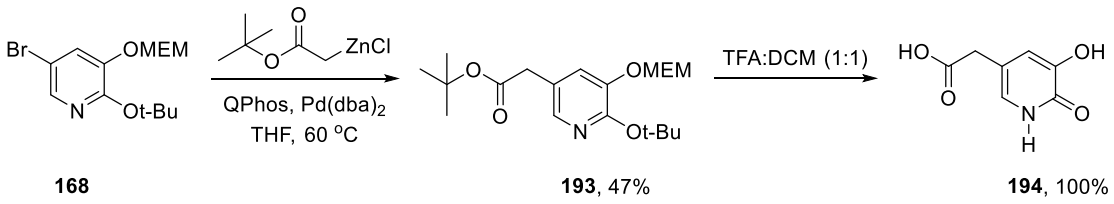
| | **Compound Structure** | **$IC_{50}$ (μM)** |
|---|---|---|
| **13** |  | 0.01 |
| **189** |  | 0.16 |
| **192** |  | 0.04 |

In summary, we speculated that the antiviral activity of N-acetylated derivative, **178**, was due to modification of Arg124 in the binding site of the enzyme. This assumption led 3-hydroxypyridin-2(1*H*)-one derivatives with various electrophiles at *para*-position of 5-

phenyl substituent. Through the addition of the 4-fluorophenyl moiety at the 6-position, we were able to restore the inhibitory activity of these derivatives in the enzymatic assay. However, the evaluation of compound **178** in the plasmid-based minigenome assay indicated that it had off-target effects, and its off-target effects seems to be responsible for the observed *ex-vivo* activity. Therefore, the idea of irreversible or a more sustained modification of $PA_N$ seems to be an invalid approach to achieve *ex-vivo* activity.

## 2.5 Synthesis and Evaluation of 3-Hydroxypyridin-2(1*H*)-ones with an Additional Chelating Group.

Crystallization of several compounds have indicated the presence of a third metal in the binding site. At the same time as we were examining possible noncompetitive inhibitors for viral endonuclease, we attempted to make compounds that incorporated an additional chelating group. It was anticipated that such derivatives might form chelation with third metal, and, therefore, they could exhibit enhanced potency. Based on docking experiment conducted by Dr. Joseph D. Bauman, 5- and 6-carboxymethyl-3-hydroxypyridin-2(1*H*)-one, **194** and **196**, was viewed as candidate compounds that had the potential to chelate the third metal. For the preparation of compound **194**, intermediate **168**, which was prepared as in Scheme 30, was coupled with (2-(*t*-butoxy)-2-oxoethyl)zinc(II) chloride under Negishi-coupling condition to give compound **193** (Scheme 36).[108] Subsequent deprotection provided the desired product, **194**.[87]

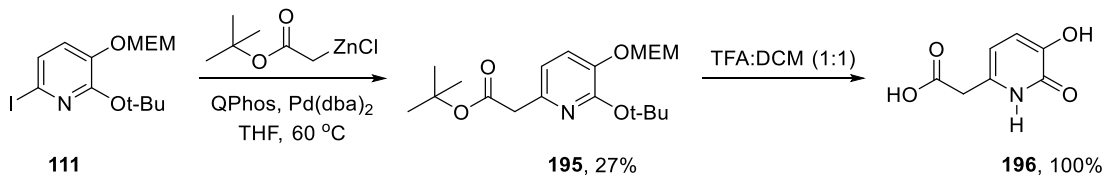



**168** **193**, 47% **194**, 100%

**Scheme 36.** Synthetic routes for compound **194**.

Following the method developed previous for **194** (Scheme 36), compound **196** was prepared as shown in Scheme 37. Intermediate **111**, which was prepared as in Scheme 21, was coupled with (2-(*t*-butoxy)-2-oxoethyl)zinc(II) chloride under Negishi-coupling

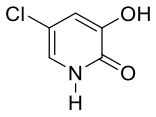
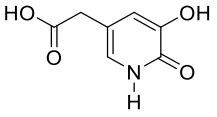
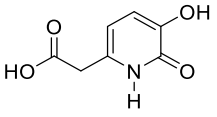
condition to give compound **195**.[108] Cleavage of protective groups provided the desired product, **196**.[87]



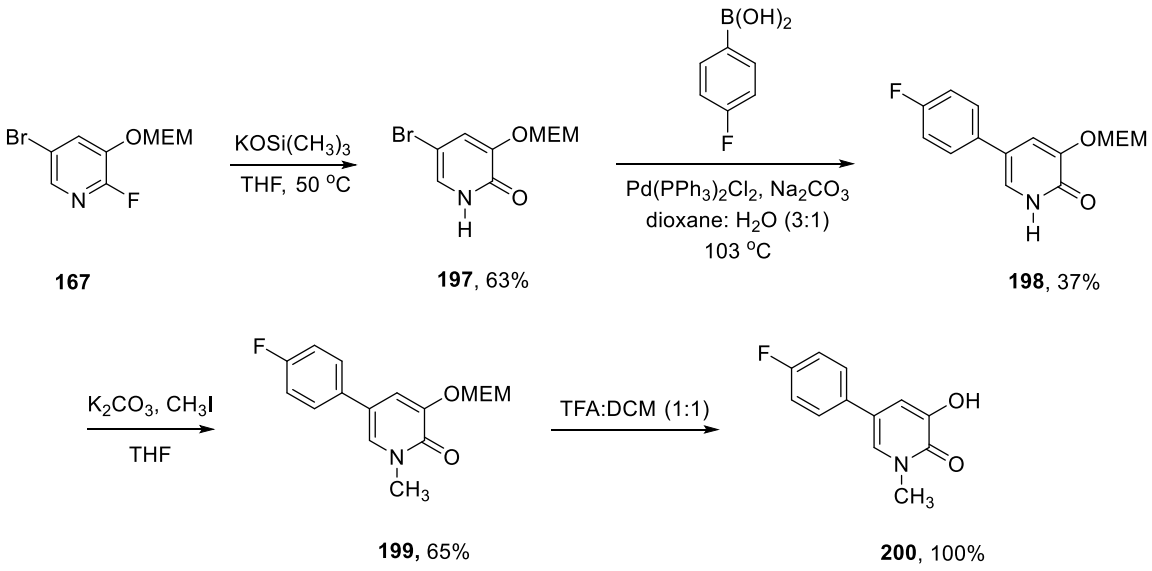

**Scheme 37**. Synthetic routes for compound **196**.

The activity of compound **194** and **196** were evaluated (Table 26). The 5-carboxymethyl derivative, **194**, was more potent than compound **1** while the 6-carboxymethyl derivative, **196**, was less potent. Further efforts to synthesize and evaluate other substituted 5-carboxymethyl 3-hydroxypyridin-2-ones were not undertaken in view of the fact that compound **194** had only marginally enhanced activity.

**Table 26.** Biological activity of **1**, **194** and **196.**

| | **Compound Structure** | **$IC_{50}$ (μM)** |
|---|---|---|
| **1** |  | 25 |
| **194** |  | 17 |
| **196** |  | 41 |

3-Hydroxypyridin-2(1*H*)-one derivatives that had aryl groups at the 5-, 6- or both 5 and 6-positions were among the more potent inhibitors of viral endonuclease activity. We explored adding a chelating group at nitrogen of the pyridinone ring as a means of examining whether this would allow for enhanced activity among this derivatives. We prepared 5-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one derivatives with a third metal chelating group on the pyridyl nitrogen to examine the potential benefits of such a modification on inhibition of viral endonuclease. For a negative control, we first prepared N-methyl 5-(4-fluorophenyl)-3-hydroxypyrdin-2(1*H*)-one, **200** as shown in Scheme 38. Starting from intermediate **167**, prepared as shown in Scheme 30, treatment with potassium trimethylsilanolate provided compound **197**. Subsequent palladium-catalyzed coupling with 4-fluorophenylboronic acid gave compound **198**,[81] which was methylated with methyl iodide and base potassium carbonate.[109] Compound **200** was obtained by the cleavage of protective groups in acidic condition.[87]




**167**

**197**, 63%

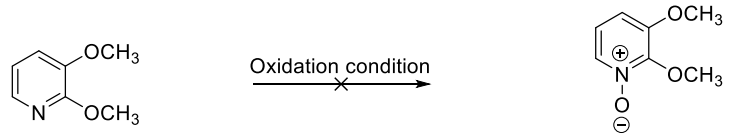
**198**, 37%

**199,** 65%

**200**, 100%

**Scheme 38.** Synthetic routes for compound **200**.

The hydroxyl group was added at nitrogen of the pyridinone ring as an extra chelating group, giving N-hydroxy-3-hydroxypyridin-2(1*H*)-one derivatives. Initially, oxidation of 2,3-dimethoxypyrdine was attempted under various conditions as shown in Scheme 39.[110] None of these methods proved to be useful.

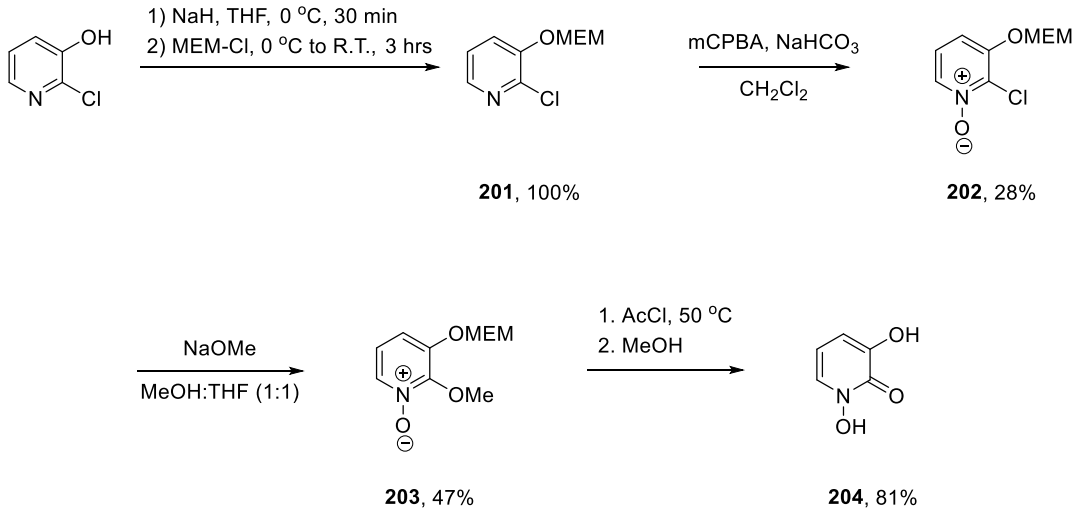



**Reaction condition 1:** mCPBA, $CH_2Cl_2$, R.T., overnight then, 50 °C, 1 hr

**Reaction condition 2:** 30% $H_2O_2$ in acetic acid, 50 °C, overnight

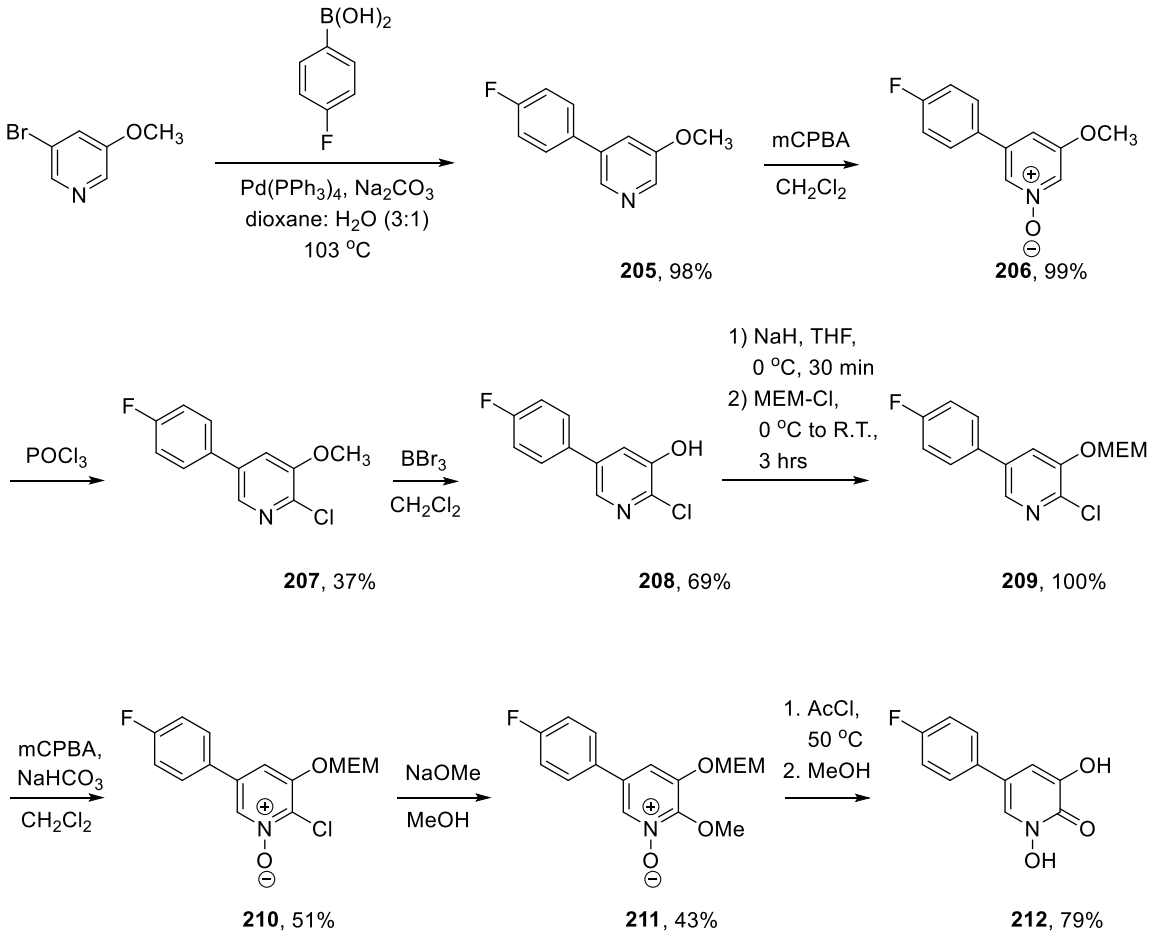
**Scheme 39.** Attempts to oxidize 2,3-dimethoxypyridine.

The procedure that eventually led to the desired N-hydroxy-3-hydroxypyridin-2(1*H*)-ones are outlined in Scheme 40 and 41. This synthetic approach was initially explored with commercially available 3-hydroxy-2-chloropyridine as shown in Scheme 40. The hydroxyl group was protected using sodium hydride and MEM-chloride, giving compound **201**.[95] It was oxidized by *meta*-chloroperoxybenzoic acid (mCPBA) in dichloromethane to give the N-oxide derivative **202**.[110] Nucleophilic aromatic substitution of 2-chloro group with sodium methoxide provided compound **203**,[110] which was then converted to N-hydroxy-3-hydroxypyridin-2(1*H*)-one, **204**, by reacting with acetyl chloride followed by methanol.[111-112]




**Scheme 40.** Synthetic routes for compound **204**.

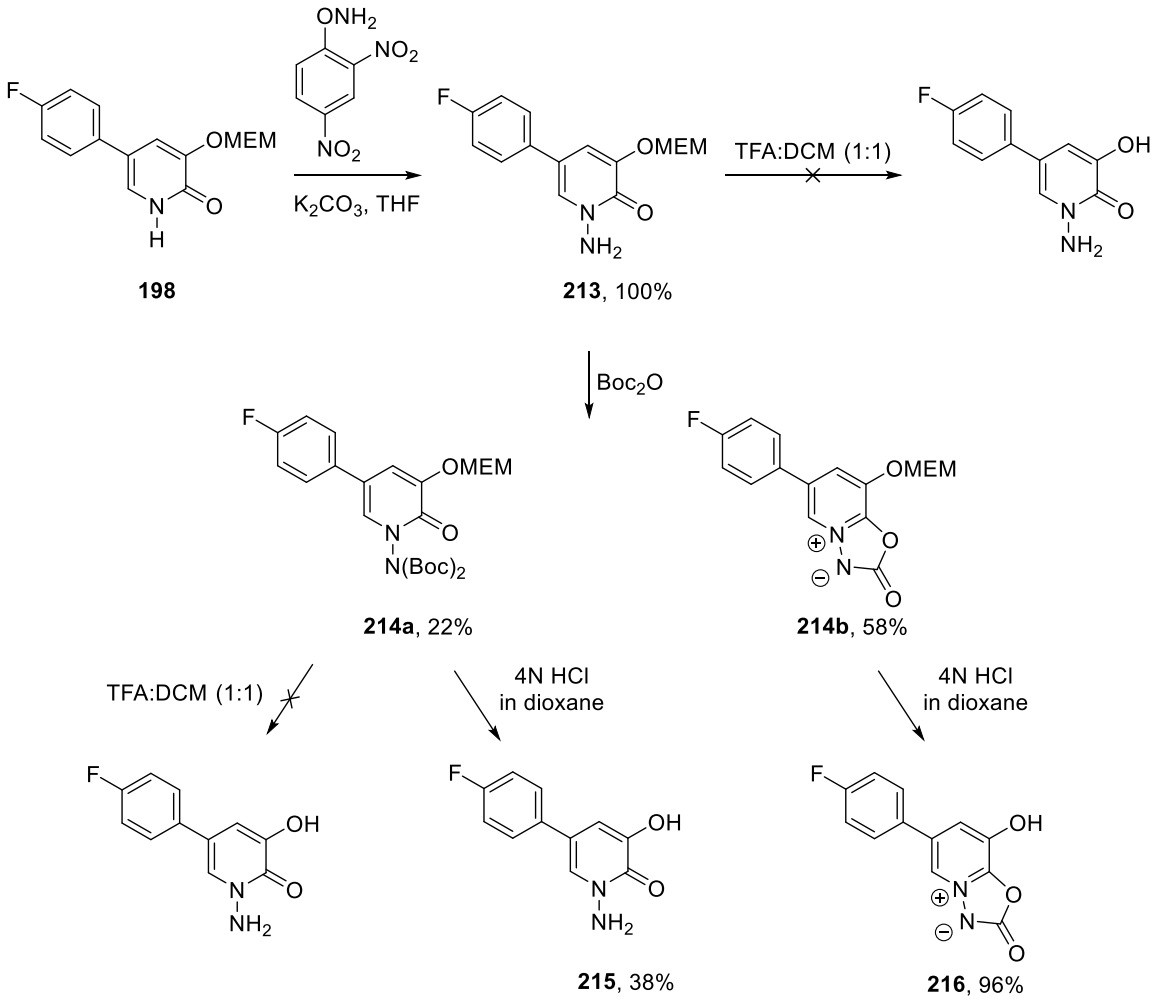
Based on developed method, 5-(4-fluorophenyl) derivative **212** was prepared (Scheme 41). Commercially-available 3-bromo-5-methoxypyridine together with 4-fluorophenylboronic acid under Suzuki-coupling coupling resulted in compound **205**.[81] 2-Chlorine was introduced as a two-step process: mCPBA oxidation and subsequent treatment with phosphoryl chloride.[81] Methyl ether protective group of intermediate **207** was then switched to a MEM protective group as this protective group can be readily cleaved during the formation of the N-hydroxy pyridin-2(1*H*)-one.[81, 89] Oxidation of the MEM protected intermediate **209** with mCPBA resulted in the formation of the N-oxide derivative **210**.[110] Subsequent nucleophilic aromatic substitution of 2-chloro group with sodium methoxide gave compound **211**, which was reacted with acetyl chloride followed by methanol to give the desired product, **212**.[110-112]




**Scheme 41.** Synthetic routes for compound **212**.

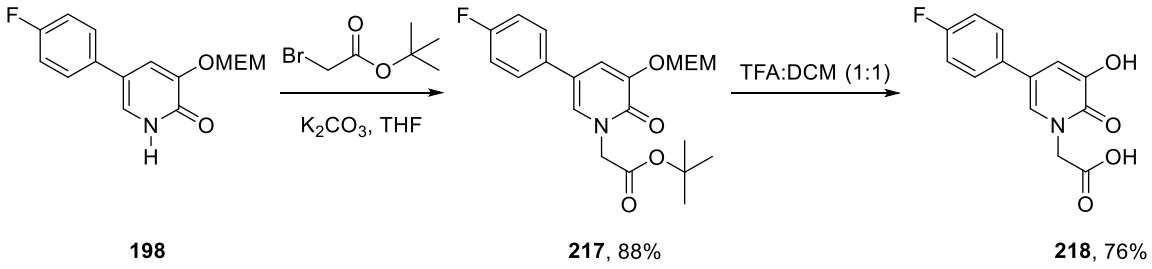
In addition, the amine group was added at nitrogen of the pyridinone ring as an extra chelating group, giving the N-amino substituted 3-hydroxypyridin-2(1*H*)-one, **215**, which was prepared as shown in Scheme 42. Intermediate **198** was reacted with O-(2,4-dinitrophenyl)hydroxylamine to give the N-amino derivative, **213**.[113] Cleavage of MEM protective group with trifluoroacetic acid in dichloromethane was initially attempted.[87] Under these reaction conditions, however, two products were formed: 1-amino-5-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one and 1-(2,2,2-trifluoroacetamide)-5-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one. These two compounds were unable to

separate through purification using column chromatography. We then attempted to protect the amine group with neat Boc anhydride, yielding two products: N-diBoc protected compound (**214a**) and cyclized N-Boc protected intermediate (**214b**). The attempt of using trifluoroacetic acid in dichloromethane again was not successful.[87] As an alternative reagent, 4N hydrochloric acid in dioxane was used.[114] Treatment of intermediate **214a** and **214b** with 4N hydrochloric acid provided compound **215** and **216**, respectively.[114]




**Scheme 42.** Synthetic routes for compounds **215** and **216**.

The N-carboxymethyl substituted 3-hydroxypyridin-2(1*H*)-one, **218**, was also prepared as outlined in Scheme 43. The rationale for targeting this compound was that the carboxyl group would be ionized at physiological pH (pH = 7.4). Under these conditions, it would be expected that the resulting carboxylate ion could participate in metal chelation. Intermediate **197** was alkylated with *t*-butyl 2-bromoacetate and base potassium carbonate,[115] and, subsequent cleavage of protective groups with trifluoroacetic acid in dichloromethane provided the desired product, **218**.[87]

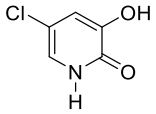
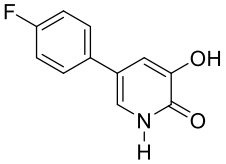
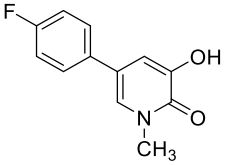
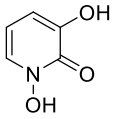
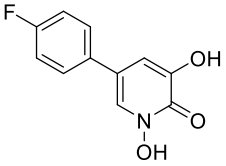
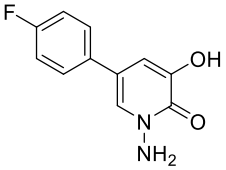
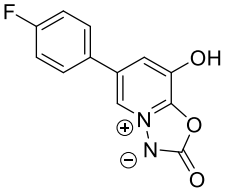
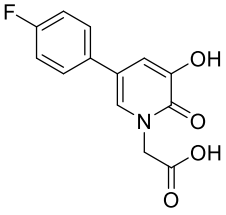



**198** **217**, 88% **218**, 76%

**Scheme 43**. Synthetic route for the preparation of compound **218**.

These 5-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one derivatives, each with an additional functional group that could contribute as a chelating substituent, as well as the negative control, **200**, were evaluated for their ability to inhibit viral endonuclease as shown in Table 27. Not only compound **200**, which is a negative control of compound **4**, but also the N-amino and N-carboxymethyl derivatives, **215** and **218**, displayed reduced inhibitory activity against viral endonuclease. It is noteworthy that N-hydroxy derivatives, **204** and **212**, exhibited enhanced activity relative to their analogous, **1** and **4**.

**Table 27.** Biological activity of **1**, **4**, **200**, **204**, **212**, **215-216** and **218.**

| | Compound Structure | $IC_{50}$ (μM) |
|---|---|---|
| **1** |  | 25 |
| **4** |  | 0.73 |
| **200** |  | >2 |
| **204** |  | 0.18 |
| **212** |  | 0.02 |
| **215** |  | 1.76 |
| **216** |  | 2.4 |
| **218** |  | >2 |

Compound **212** was especially potent, being 33-fold active than compound **4**. Therefore, the antiviral activity of compound **212** was evaluated in an *ex-vivo* antiviral assay. The result was not promising, as there was no antiviral activity observed with compound **212** in the cellular assay.

In addition to noncompetitive inhibitors, we prepared 3-hydroxypyridin-2(1*H*)-one derivatives with additional chelating groups at either 5- or 6-position or the nitrogen of the 5-(*p*-fluorophenyl)-3-hydroxypyridin-2-ones. Although 5-carboxymethyl-3-hydroxypyridin-2(1*H*)-one, **194**, displayed enhanced activity relative to the parent compound, **1**, we did not put further efforts in this series considering its marginally enhanced activity. Several 3-hydroxypyridin-2-ones with additional chelating groups at the nitrogen were also prepared, however, only N-hydroxy derivatives, **204** and **212**, exhibited enhanced inhibitory activity in relative to compound **1** and **4**, respectively. Compound **212** was especially potent with $IC_{50}$ of 22 nM, and therefore it was evaluated in virus yield assay; but, the compound was inactive. Once more, the concept of adding additional chelating group did not address the principal concern that these compounds failed to exhibit antiviral activity in an *ex-vivo* assay.

# SUMMARY

Pandemics and annual epidemics of influenza and the emerging prevalence of drug-resistant strains of influenza viruses have intensified the search for new antivirals with a novel mechanism of action. $PA_N$ endonuclease is an essential and highly conserved protein, which represents a novel and promising therapeutic target. It is a subunit of viral RdRp and is involved in the cap-snatching mechanism during early transcription process. $PA_N$ endonuclease therefore plays a crucial role in transcription, making it a key target for inhibiting viral reproduction.

Our research efforts in this field began with conducting a fragment screening campaign using a crystal structure of 2009 pandemic H1N1 $PA_N$, which identified 5-chloro-3-hydroxypyridin-2(1*H*)-one, **1**. Several novel scaffolds were proposed from the hit, **1**, including 3-hydroxypyridin-2(1*H*)-one, 3-hydroxyquinolin-2(1*H*)-one and aza analogs of 3-hydroxypyridin-2(1*H*)-one. Initial SAR studies on 3-hydroxypyridin-2-ones identified compound **13**, which has a modest *ex-vivo* activity ($EC_{50}$ = 11.4 μM).[81] Since neither 3-hydroxyquinolin-2(1*H*)-ones nor the aza-analogs of 3-hydroxypyridin-2(1*H*)-ones proved to be superior alternatives, the project once again explored new derivatives within the 3-hydroxypyridin-2(1*H*)-one series. Several 3-hydroxypyridin-2(1*H*)-one derivatives displayed the comparative inhibitory activity with compound **13**. However, none of them exhibited any *ex-vivo* activity.

Our research on the 3-hydroxypyridin-2(1*H*)-one derivatives revealed that there was a clear absence of a correlation between the activity we observed *in vitro* and with the activity we observed *ex-vivo*. Extended studies to determine if the absence of *ex-vivo* activity was associated with physiochemical properties failed to identify derivatives with *ex-vivo* activity. It is our current hypothesis that using an *in vitro* assay, which uses a truncated endonuclease and is not comprised of the entire ribonucleoprotein complex, is responsible for misleading the SAR data.

Our group undertook the synthesis of compound **240**, one of the more potent endonuclease inhibitor reported by Shionogi, Inc (Figure 14) in preparation for challenging this hypothesis. It is also noteworthy that recently one of compounds from Shionogi, Inc. has been selected for a phase II clinical trial (NCT02954354).[116] The exact structure of compound, S-033188, has not yet been disclosed. The Shionogi compound that was synthesized in our laboratory, as shown in Figure 14, displayed very high potency in our high-throughput fluorescence resonance energy transfer based inhibition assay with $IC_{50}$ of 1.4 nM. It also was very potent in our *ex-vivo* assay, the fluorescent forming unit (FFU) assay, with an $EC_{50}$ value below 50 nM. We propose to use this compound in an assay designed to determine if an *in vitro* assay using the entire ribonucleoprotein complex is capable of distinguishing between compounds that in our earlier studies exhibited activity only *in vitro* from compounds that exhibit activity both *in vitro* and *ex-vivo*.

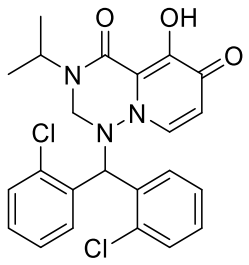



**Figure 14**. Structure of **240** (Shionogi, Inc.).

Our current hypothesis will be challenged by accessing the *in vitro* activity of compound **13** and **127** together with L-742,001 (Merck & Co., Inc.) and **240** (Shionogi, Inc.) using the entire ribonucleoprotein complex. If our current hypothesis is correct, the assay would be capable of discerning compounds with *ex-vivo* activity from compounds without *ex-vivo* activity. We expect to see inhibitory activity with L-742,001 (Merck & Co., Inc.) and **240** (Shionogi, Inc.), and absence of inhibitory activity with compound **13** and **127** using this more sophisticated *in vitro* assay that incorporates the entire ribonucleoprotein complex.

Overall, the work in this dissertation describe the synthesis, SAR and biological evaluation of numerous, novel scaffolds of $PA_N$ endonuclease inhibitors with good inhibitory activity. Despite the lack of activity in the cellular assay, ongoing studies are continuing with 3-hydroxypyridin-2(1*H*)-one series to uncover a lead compound among these derivatives with potent *ex-vivo* activity that can be developed into the clinic.

# EXPERIMENTAL

## General

All reactions, unless otherwise stated, were done under nitrogen atmosphere. Reaction monitoring and follow-up were done using aluminum baked Silica G TLC plates with UV254 (Sorbent Technologies), visualizing with ultraviolet light. Flash column chromatography was done using a 230-400 mesh silica gel columns (Teledyne ISCO) with a Combi Flash Rf Teledyne ISCO using hexane, ethyl acetate, dichloromethane, methanol or 2-propanol as indicated. The proton, $^{1}H$ (400 MHz), and carbon, $^{13}C$ (100 MHz) NMR spectra were done in $CDCl_3$, methanol-$d_4$, or DMSO-$d_6$ as indicated and recorded on a Bruker Avance III (400 MHz) Multinuclear NMR Spectrometer. Deuterated solvents were purchased from Cambridge Isotopes Laboratory (Cambridge, MA). Data are expressed in parts per million (δ) relative to the residual nondeuterated solvent signals, spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), dt (doublet of triplets), td (triplet of doublets), q (quartet), m (multiplet), brs (broad singlet), and bt (broad triplet), and coupling constants (*J*) are reported in Hertz (Hz). Melting points were determined using Mel-temp II apparatus and are uncorrected. HRMS experiments were conducted by Washington University Resource for Biomedical and Bioorganic Mass Spectrometry Department of Chemistry.

## 3-Methoxyquinolin-2(1*H*)-one (16)

1*H*-Indole-2,3-dione (147 mg, 1.0 mmol), (trimethylsilyl)diazomethane (1.0 mL of 2M in toluene, 2.0 mmol), and triethylamine (0.28 mL, 2.0 mmol) were dissolved in ethanol (10 mL). The reaction mixture was stirred at room temperature for 18 hours. The resulting suspension was filtered to give the product as a beige solid (113 mg, 65%); mp 188-190 $^{o}$C (mp 197-198 $^{o}$C)[117]; $^{1}$H NMR (400 MHz) (MeOD) δ 7.60-7.57 (m, 1H), 7.39-7.35 (m, 1H), 7.30-7.28 (m, 1H), 7.25-7.19 (m, 2H), 3.92 (s, 3H); $^{13}$C NMR (100 MHz) (MeOD) δ 160.5, 149.8, 134.8, 128.6, 127.7, 124.1, 122.0, 116.1, 113.4, 56.5.

**3-Hydroxyquinolin-2(1*H*)-one (17).**

3-Methoxyquinolin-2(1*H*)-one, **16**, (66 mg, 0.38 mmol) was dissolved in anhydrous dichloromethane (5 mL). A solution of 1M $BBr_3$ in dichloromethane (3.0 mL, 3.0 mmol) was added at 0 $^{o}$C. The reaction mixture was stirred for 39 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in dichloromethane, and it was filtered to give the desired product as a beige solid (42 mg, 70 %); mp 248-250 $^{o}$C (mp 260 $^{o}$C)[118]; $^{1}$H NMR (400MHz) (DMSO-$d_6$) δ 11.98 (brs, 1H), 9.42 (brs, 1H), 7.48 (d, *J* = 8 Hz, 1H), 7.31-7.24 (m, 2H), 7.12 (t, *J* = 8 Hz, 1H) 7.08 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.5, 146.2, 133.5, 126.2, 125.8, 122.0, 120.7, 114.7, 112.4.

**3-Hydroxyquinolin-2(1*H*)-one (17).**

1*H*-Indole-2,3-dione (147 mg, 1.0 mmol), (trimethylsilyl)diazomethane (0.5 mL of 2M in toluene, 1.0 mmol), and triethylamine (0.14 mL, 1.0 mmol) were dissolved in ethanol (5 mL). The reaction mixture was stirred at room temperature for 15 hours. A yellow colored suspension was formed. The mixture was filtered to give the desired product as a beige solid (89.2 mg, 55 %); mp 248-250 $^{o}$C (mp 260 $^{o}$C)[118]; $^{1}$H NMR (400MHz) (DMSO-$d_6$) δ 11.98 (brs, 1H), 9.42 (brs, 1H), 7.48 (d, *J* = 8 Hz, 1H), 7.31-7.24 (m, 2H), 7.12 (t, *J* = 8 Hz, 1H) 7.08 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.5, 146.2, 133.5, 126.2, 125.8, 122.0, 120.7, 114.7, 112.4.

**5-Bromo-3-methoxyquinolin-2(1*H*)-one (18).**

1*H*-4-Bromoindole-2,3-dione (452 mg, 2.0 mmol), (trimethylsilyl)diazomethane (2.0 mL of 2M in toluene, 4.0 mmol), and triethylamine (0.56 mL, 4.0 mmol) were dissolved in ethanol (10 mL). The reaction mixture was stirred at room temperature for 18 hours. The resulting suspension was filtered to give the product as a white solid (267 mg, 53 %); mp 286-288 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.97 (brs, 1H), 7.31 (dd, *J* = 8 Hz, , *J* = 2 Hz, 1H), 7.15-7.09 (m, 2H), 7.02 (s, 1H), 3.73 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 156.9, 150.0, 135.0, 128.0, 125.8, 119.7, 118.6, 114.6, 109.0, 55.7; HRMS (ESI) calculated for $C_{10}H_9BrNO_2$ $(M+H)^+$ 253.9811, found 253.9811.

**6-Bromo-3-methoxyquinolin-2(1*H*)-one (19).**

1*H*-5-Bromoindole-2,3-dione (452 mg, 2.0 mmol), (trimethylsilyl)diazomethane (2.0 mL of 2M in toluene, 4.0 mmol), and triethylamine (0.56 mL, 4.0 mmol) were dissolved in ethanol (10 mL). The reaction mixture was stirred at room temperature for 18 hours. The resulting suspension was filtered to give the desired product as a white solid (273.6 mg, 54 %); mp 265-267 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.92 (brs, 1H), 7.73 (s, 1H), 7.40 (d, *J* = 8 Hz, 1H), 7.15-7.12 (m, 2H), 3.74 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 157.0, 149.5, 133.0, 129.4, 128.1, 121.8, 116.6, 113.6, 110.1, 55.7; HRMS (ESI) calculated for $C_{10}H_9BrNO_2$ $(M+H)^+$ 253.9811, found 253.9811.

**7-Bromo-3-methoxyquinolin-2(1*H*)-one (20).**

1*H*-6-Bromoindole-2,3-dione (904 mg, 4 mmol), (trimethylsilyl)diazomethane (4.0 mL of 2M in toluene, 8.0 mmol), and triethylamine (1.12 mL, 8.0 mmol) were dissolved in ethanol (15 mL) and placed under argon. The reaction mixture was stirred at room temperature for 33 hours. The resulting suspension was filtered to afford the product as a beige solid (553 mg). The filtrate was concentrated under the reduced pressure. Chromatography of the residue using an ISCO chromatograph and a gradient of 0-100% ethyl acetate/hexane gave additional product as a beige solid (53 mg). The solids were combined (606 mg, 60 %); mp 265-267 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.80 (brs, 1H), 7.39 (d, *J* = 8 Hz, 1H), 7.29 (d, *J* = 2 Hz, 1 H), 7.16 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 7.09 (s, 1 Hz), 3.67 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 157.0, 149.0, 135.0, 128.1, 124.7, 119.4, 119.0, 116.8, 110.7, 55.6; HRMS (ESI) calculated for $C_{10}H_9BrNO_2$ $(M+H)^+$ 253.9811, found 253.9811.

**8-Bromo-3-methoxyquinolin-2(1*H*)-one (21).**

1*H*-7-Bromoindole-2,3-dione (226 mg, 1.0 mmol), (trimethylsilyl)diazomethane (1.0 mL of 2M in toluene, 2.0 mmol), and triethylamine (0.28 mL, 2.0 mmol) were dissolved in ethanol (5 mL). The reaction mixture was stirred at room temperature for 27 hours. The solvent was then removed under reduced pressure. The residue was purified on an ISCO chromatograph (50-100% ethyl acetate/hexane) to give the product as a white solid (96 mg, 41 %); mp 175-177 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 9.16 (brs, 1H), 7.58 (dd, *J* = 8 Hz, *J* = 2 Hz, *1H*), 7.45 (d, *J* = 8 Hz, 1H), 7.09 (t, *J* = 8 Hz, 1H), 6.90 (s, 1H), 3.96 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 157.9, 149.0, 130.9, 130.5, 126.0, 123.7, 121.6, 110.9, 106.7, 56.3; HRMS (ESI) calculated for $C_{10}H_9BrNO_2$ $(M+H)^+$ 253.9811, found 253.9812.

**5-Bromo-3-hydroxyquinolin-2(1*H*)-one (22).**

5-Bromo-3-methoxyquinolin-2(1*H*)-one, **18**, (70 mg, 0.28 mmol) was dissolved in anhydrous dichloromethane (5 mL) under the nitrogen. A solution of 1M $BBr_3$ in dichloromethane (3.0 mL, 3.0 mmol) was added at 0 $^{o}$C. The reaction mixture was stirred for 42 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in dichloromethane, and it was filtered to give the desired product as a white solid (43 mg, 65%); mp 308-310 $^{o}$C; $^{1}$H NMR (400MHz) (DMSO-$d_6$) δ 12.21 (brs, 1H), 10.04 (brs, 1H), 7.44 (d, *J* = 8 Hz, 1H), 7.29 (d,

*J* = 8 Hz, 1H), 7.24-7.20 (m, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.1, 147.9, 134.5, 127.2, 125.8, 119.6, 119.1, 114.7, 110.7; HRMS (ESI) calculated for $C_9H_5BrNO_2$ $(M-H)^-$ 237.9498, found 237.9507.

**6-Bromo-3-hydroxyquinolin-2(1*H*)-one (23).**

6-Bromo-3-methoxyquinolin-2(1*H*)-one, **19**, (70 mg, 0.28 mmol) was dissolved in anhydrous dichloromethane (5 mL). A solution of 1M $BBr_3$ in dichloromethane (3.0 mL, 3.0 mmol) was added at 0 °C. The reaction mixture was stirred for 42 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in dichloromethane, and was filtered to give the desired product as a beige solid (38.2 mg, 58 %); mp 272-274 °C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 12.11 (brs, 1H), 9.73 (brs, 1H), 7.75 (d, *J* = 2 Hz, 1H), 7.43 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 7.20 (d, *J* = 8 Hz, 1H), 7.08 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.3, 147.1, 132.6, 128.7, 127.6, 122.8, 116.7, 113.8, 111.3; HRMS (ESI) calculated for $C_9H_5BrNO_2$ $(M-H)^-$ 237.9498, found 237.9505.

**7-Bromo-3-hydroxyquinolin-2(1*H*)-one (24).**

7-Bromo-3-methoxyquinolin-2(1*H*)-one, **20**, (53 mg, 0.21 mmol) was dissolved in anhydrous dichloromethane (5 mL). A solution of 1M $BBr_3$ in dichloromethane (2 mL, 2 mmol) was added at 0 °C. The reaction mixture was stirred for 24 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue

was suspended in dichloromethane, and it was filtered to give the product a gray solid (25 mg, 50 %); mp 273-275 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.07 (brs, 1H), 7.46 (d, *J* = 8 Hz, 1H), 7.43 (d, *J* = 2 Hz, 1 H), 7.28 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 7.10 (s, 1 Hz); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.3, 146.6, 134.6, 127.6, 124.8, 119.9, 118.6, 116.9, 112.0; HRMS (ESI) calculated for $C_9H_5BrNO_2$ $(M-H)^-$ 237.9498, found 237.9507.

**8-Bromo-3-hydroxyquinolin-2(1*H*)-one (25).**

8-Bromo-3-methoxyquinolin-2(1*H*)-one, **21**, (47 mg, 0.19 mmol) was dissolved in anhydrous dichloromethane (5 mL). A solution of 1M $BBr_3$ in dichloromethane (3.7 mL, 3.7 mmol) was added at 0 $^{o}$C. The reaction mixture was stirred for 48 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in dichloromethane, and it was filtered to give the product as a white solid (34.5 mg, 77 %); mp 210-212 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 7.49 (d, *J* = 8 Hz, 1H), 7.44 (d, *J* = 8 Hz, 1H), 7.02 (t, *J* = 8 Hz, 1H), 6.97 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 160.2, 149.1, 130.7, 128.3, 124.9, 123.7, 122.9, 110.8, 108.1; HRMS (ESI) calculated for $C_9H_5BrNO_2$ $(M-H)^-$ 237.9498, found 237.9493.

**5-(4-Fluorophenyl)-3-methoxyquinolin-2(1*H*)-one (26).**

5-Bromo-3-methoxyquinolin-2(1*H*)-one, **18**, (100 mg, 0.39 mmol), (4-fluorophenyl)boronic acid (83 mg, 0.59 mmol), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and $Na_2CO_3$(125 mg, 1.18 mmol) were dissolved in a mixture of dioxane (6 mL) and water (3

mL). The air in the reaction flask was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for 8 hours. Reaction was monitored by TLC and stopped once the starting material was consumed. It was diluted with ethyl acetate, and washed with sat. $NaHCO_3$ followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a white solid (70 mg, 66%); mp 233-235 ºC; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 12.03 (brs, 1H), 7.54-7.50 (m, 2H), 7.43-7.31 (m, 4H), 7.09 (dd, $J$ = 7 Hz, $J$ = 1 Hz, 1H), 6.92 (s, 1H), 3.66 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 161.7 ($J_{C,F}$ = 243 Hz), 156.9, 148.8, 137.5, 135.5 ($J_{C,F}$ = 3 Hz), 134.6, 131.4 ($J_{C,F}$ = 8 Hz), 126.9, 123.3, 117.1, 115.5 ($J_{C,F}$ = 21 Hz) 114.3, 108.4, 55.2; HRMS (ESI) calculated for $C_{16}H_{13}FNO_2$ $(M+H)^+$ 270.0925, found 270.0925.

**6-(4-Fluorophenyl)-3-methoxyquinolin-2(1*H*)-one (27).**

6-Bromo-3-methoxyquinolin-2(1*H*)-one, **19**, (100 mg, 0.39 mmol), (4-fluorophenyl)boronic acid (83 mg, 0.59 mmol), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and $Na_2CO_3$(125 mg, 1.18 mmol) were dissolved in a mixture of dioxane (6 mL) and water (3 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for 8 hours. Reaction was monitored by TLC and stopped once the starting material was consumed. The reaction mixture was diluted with ethyl acetate, and it was washed with sat. $NaHCO_3$ followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was

purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a beige solid (90 mg, 85%); mp 240-242 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.94 (brs, 1H), 7.88 (d, *J* = 2 Hz, 1H), 7.74-7.70 (m, 2H), 7.64 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 7.35-7.28 (m, 4H), 3.84 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 161.6 ($J_{C,F}$ = 242 Hz), 157.2, 149.0, 136.2 ($J_{C,F}$ = 3 Hz), 133.4, 132.9, 128.3 ($J_{C,F}$ = 8 Hz), 125.6, 124.1, 121.2, 115.7 ($J_{C,F}$ = 22 Hz), 115.1, 111.3, 55.6; HRMS (ESI) calculated for $C_{16}H_{13}FNO_2$ $(M+H)^+$ 270.0925, found 270.0925.

**7-(4-Fluorophenyl)-3-methoxyquinolin-2(1*H*)-one (28).**

7-Bromo-3-methoxyquinolin-2(1*H*)-one, **20**, (200 mg, 0.79 mmol), (4-fluorophenyl)boronic acid (166 mg, 1.19 mmol), $Pd(PPh_3)_4$ (91 mg, 0.08 mmol) and $Na_2CO_3$(251 mg, 2.37 mmol) were dissolved in a mixture of dioxane (6 mL) and water (3 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for 8 hours. Reaction was monitored by TLC and stopped once the starting material was consumed. The reaction mixture was diluted with ethyl acetate, and was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the desired product as a beige solid (108 mg, 51%): mp. 252-254 $^{o}$C**;** $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.76 (brs, 1H), 7.55-7.49 (m, 3H), 7.32 (s, 1H), 7.28 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 7.19-7.15 (m, 2H), 7.11 (s, 1H), 3.68 (s, 3H)**;** $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 162.0 ($J_{C,F}$ = 244 Hz), 157.3, 148.8, 137.8, 136.2 ($J_{C,F}$ = 3 Hz), 134.4, 128.6 ($J_{C,F}$ = 8 Hz),

126.9, 120.7, 119.1, 115.9 ($J_{C,F}$ = 21 Hz), 112.2, 110.9, 55.6**;** HRMS (ESI) calculated for $C_{16}H_{13}FNO_2$ $(M+H)^+$ 270.0925, found 270.0925.

**8-(4-Fluorophenyl)-3-methoxyquinolin-2(1*H*)-one (29).**

8-Bromo-3-methoxyquinolin-2(1*H*)-one, **21**, (55 mg, 0.22 mmol), (4-fluorophenyl)boronic acid (40 mg, 0.28 mmol), $Pd(PPh_3)_4$ (25 mg, 0.02 mmol) and $Na_2CO_3$ (92 mg, 0.87 mmol) were dissolved in a mixture of dioxane (6 mL) and water (3 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 4 hours. The reaction mixture was diluted with ethyl acetate, and was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the desired product as a white solid (43 mg, 75%); mp 183-185 $^oC$; $^1H$ NMR (400MHz) ($CDCl_3$) δ 8.76 (brs, 1H), 7.52-7.50 (m, 1H), 7.39-7.36 (m, 2H), 7.27-7.19 (m, 4H), 7.00 (s, 1H) ,3.95 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 162.7 ($J_{C,F}$ = 247 Hz), 157.9, 149.0, 132.2 ($J_{C,F}$ = 3 Hz), 130.6 ($J_{C,F}$ = 8 Hz), 130.5, 128.5, 127.2, 126.2, 122.8, 120.6, 116.6 ($J_{C,F}$ = 21 Hz) 111.6, 56.0; HRMS (ESI) calculated for $C_{16}H_{13}FNO_2$ $(M+H)^+$ 270.0925, found 270.0925.

**5-(4-Fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one (30).**

5-(4-Fluorophenyl)-3-methoxyquinolin-2(1*H*)-one, **26**, (66 mg, 0.24 mmol) was dissolved in anhydrous dichloromethane (5 mL). A solution of 1M $BBr_3$ in dichloromethane (3.0 mL, 3.0 mmol) was added at 0 $^oC$, and the mixture was stirred for 28 hours at room temperature. Then, additional 1M $BBr_3$ in dichloromethane (3.0 mL, 3.0 mmol) was added, and the reaction mixture was stirred for additional 44 hours at room temperature. The solvent was removed under reduced pressure, and the resulting residue was suspended in dichloromethane. The suspension was filtered, and it was washed with methanol to give the desired product as a white solid (30 mg, 48%); mp 278-280 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 12.11 (brs, 1H), 9.58 (brs, 1H), 7.46-7.43 (m, 2H), 7.38-7.31 (m, 4H), 7.06 (d, $J$ = 8 Hz, 1H), 6.89 (s, 1H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 161.6 ($J_{C,F}$ = 243 Hz), 158.1, 146.6, 137.0, 135.7, 134.1, 131.3 ($J_{C,F}$ = 8 Hz), 126.1, 123.2, 118.2, 115.4 ($J_{C,F}$ = 22 Hz), 114.4, 109.9; HRMS (ESI) calculated for $C_{15}H_9FNO_2$ $(M-H)^-$ 254.0612, found 254.0622.

**6-(4-Fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one (31).**

6-(4-Fluorophenyl)-3-methoxyquinolin-2(1*H*)-one, **27**, (81 mg, 0.30 mmol) was dissolved in anhydrous dichloromethane (5 mL). A solution of 1M $BBr_3$ in dichloromethane (3.0 mL, 3.0 mmol) was added at 0 $^oC$. The reaction mixture was stirred for 16 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in dichloromethane. The suspension was filtered to give the desired product as a white solid (47 mg, 60%); mp 291-293 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 12.08 (brs, 1H), 9.56 (brs, 1H) 7.80 (d, $J$ = 2 Hz, 1H),

7.73-7.70 (m, 2H), 7.60 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 7.35-7.27 (m, 3H), 7.17 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 161.6 ($J_{C,F}$ = 243 Hz), 158.5, 146.5, 136.3 ($J_{C,F}$ = 3 Hz), 133.0, 132.9, 128.4 ($J_{C,F}$ = 8 Hz), 124.9, 123.6, 121.1, 115.6 ($J_{C,F}$ = 21 Hz), 115.3, 112.5; HRMS (ESI) calculated for $C_{15}H_9FNO_2$ $(M-H)^-$ 254.0612, found 254.0622.

**7-(4-Fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one (32).**

7-(4-Fluorophenyl)-3-methoxyquinolin-2(1*H*)-one, **28**, (106 mg, 0.40 mmol) was dissolved in anhydrous dichloromethane (5 mL). A solution of 1M $BBr_3$ in dichloromethane (4.0 mL, 4.0 mmol) was added at 0 ºC. The reaction mixture was then stirred for 18 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in dichloromethane. The suspension was filtered, and it was washed with methanol to give the product as a white solid (68 mg, 68%): mp 283-285 ºC; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 12.06 (brs, 1H), 9.54 (brs, 1H), 7.70-7.66 (m, 2H), 7.59 (d, *J* = 8Hz, 1H), 7.48 (d, *J* = 2Hz, 1H), 7.42 (dd, *J* = 8Hz, *J* = 2Hz, 1H), 7.36-7.30 (m, 2H), 7.13 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 161.8 ($J_{C,F}$ = 243 Hz), 159.0, 147.3, 136.7, 136.4, 133.8, 128.5 ($J_{C,F}$ = 8 Hz), 126.1, 120.7, 120.4, 115.8 ($J_{C,F}$ = 21 Hz), 112.3, 111.7; HRMS (ESI) calculated for $C_{15}H_9FNO_2$ $(M-H)^-$ 254.0612, found 254.0620.

**8-(4-Fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one (33).**

8-(4-Fluorophenyl)-3-methoxyquinolin-2(1*H*)-one, **29**, (43 mg, 0.16 mmol) was dissolved in anhydrous dichloromethane (5 mL). A solution of 1M $BBr_3$ in dichloromethane (1.60 mL, 1.60 mmol) was added at 0 ºC. The reaction mixture was stirred for 54 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in dichloromethane. The suspension was filtered, and it was washed with methanol to give the desired product as a white solid (19 mg, 46%); mp. 209-211 ºC; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 7.45 (dd, $J$ = 8 Hz, $J$ = 2 Hz, 1H), 7.41-7.37 (m, 2H), 7.28-7.23 (m, 2H), 7.15-7.10 (m, 2H), 7.08 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 162.0 ($J_{C,F}$ = 243 Hz), 158.7, 146.5, 133.5 ($J_{C,F}$ = 3 Hz), 131.3 ($J_{C,F}$ = 8 Hz), 130.4, 127.6, 127.2, 125.5, 122.1, 121.5, 115.8 ($J_{C,F}$ = 21 Hz) 112.7; HRMS (ESI) calculated for $C_{15}H_9FNO_2$ $(M-H)^-$ 254.0612, found 254.0621.

**4-Bromo-3-hydroxyquinolin-2(1*H*)-one (34).**

3-Hydroxyquinolin-2(1*H*)-one, **17**, (120.6 mg, 0.748 mmol) and N-bromosuccinimide (139.7 mg, 0.785 mmol) were dissolved in anhydrous DMF (5 mL). The reaction mixture was stirred for 15 hours at room temperature. The solvent was removed under reduced pressure, and the resulting residue was suspended in dichloromethane. The suspension was filtered, and it was washed with methanol to give the product as an orange solid (100 mg, 56%); mp 243-245 ºC; $^1$H NMR (400MHz) (DMSO-$d_6$) δ 12.31 (brs, 1H), 10.40 (brs, 1H), 7.73 (d, $J$ = 8 Hz, 1H), 7.41 (t, $J$ = 8 Hz, 1H), 7.33 (d, $J$ = 8 Hz, 1H), 7.28 (t, $J$ = 8 Hz, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 156.6, 145.0, 132.5, 127.4, 125.1, 122.9, 119.7, 115.3, 109.2.

**4-(4-Fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one (35).**

4-Bromo-3-hydroxyquinolin-2(1*H*)-one, **34**, (61 mg, 0.25 mmol), (4-fluorophenyl)boronic acid (53 mg, 0.38 mmol), $Pd(PPh_3)_4$ (29 mg, 0.03 mmol) and $Na_2CO_3$(92 mg, 0.87 mmol) were dissolved in a mixture of dioxane (6 mL) and water (3 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 4 hours. The reaction mixture was diluted with ethyl acetate, and was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane + 1% acetic acid) to give the desired product as a brown solid (37 mg, 56%): mp 236-238 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) 12.23 (brs, 1H), 9.26 (brs, 1H), 7.41-7.32 (m, 6H), 7.11-7.05 (m, 2H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 161.6 ($J_{C,F}$ = 244 Hz), 158.2, 142.7, 133.2, 132.0 ($J_{C,F}$ = 8 Hz), 129.4, 126.5, 124.1, 122.9, 122.2, 120.8, 115.3 ($J_{C,F}$ = 21 Hz), 115.2; HRMS (ESI) calculated for $C_{15}H_9FNO_2$ $(M-H)^-$ 254.0612, found 254.0614.

**4-Phenyl-3-hydroxyquinolin-2(1*H*)-one (36).**

4-Bromo-3-hydroxyquinolin-2(1*H*)-one, **34**, (100 mg, 0.42 mmol), phenylboronic acid (76 mg, 0.63 mmol), $Pd(PPh_3)_4$ (49 mg, 0.04 mmol) and $Na_2CO_3$(133 mg, 1.25 mmol) were dissolved in a mixture of dioxane (6 mL) and water (3 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for

4 hours. The reaction mixture was diluted with ethyl acetate, and was washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-5% methanol/dichloromethane) to give the desired product as a white solid (42 mg, 43%); mp 239-241 $^oC$ (mp 268-269 $^oC$)[119]; $^1H$ NMR (400 MHz) (DMSO-$d_6$) 12.24 (brs, 1H), 9.22 (brs, 1H), 7.52 (t, *J* = 7 Hz, 2H), 7.44 (t, *J* = 7 Hz, 1H), 7.37-7. 42 (m, 4H), 7.12-7. 02 (m, 2H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 158.3, 142.4, 133.7, 133.2, 129.8, 128.3, 127.6, 126.4, 124.3, 123.9, 122.1, 120.9, 115.2.

**4-Methyl-3-hydroxyquinolin-2(1*H*)-one (37).**

4-Bromo-3-hydroxyquinolin-2(1*H*)-one, **34**, (50 mg, 0.21 mmol), TMSCl (0.08 mL, 0.63 mmol) and triethylamine (0.06 mL, 0.43 mmol) were dissolved in toluene (5 mL). The reaction mixture was stirred for 4 hours at room temperature. After starting material was no longer present, the reaction mixture was concentrated under reduced pressure. Along with the resulting residue, trimethylboroxine (0.05 mL, 0.36 mmol), $Pd(PPh_3)_4$ (24 mg, 0.02 mmol) and $Na_2CO_3$ (66 mg, 0.62 mmol) were dissolved in a mixture of dioxane (6 mL) and water (3 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 10 hours. A solution of 3N HCl (5 mL) was then added, and the mixture was stirred for 15 minutes. The mixture was diluted with ethyl acetate, and was washed with brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-80% ethyl acetate/hexane + 1% acetic acid) to give the desired product

as a white solid (13 mg, 36%); mp 234-236 °C (mp 249-250 °C)[119]; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.98 (brs, 1H), 9.09 (brs, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.34-7.26 (m, 2H), 7.18 (t, *J* = 7 Hz, 1H), 2.27 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 157.8, 142.8, 133.0, 126.3, 123.1, 122.0, 121.3, 119.3, 115.1, 10.5.

**4-Bromo-7-(4-fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one (38).**

7-(4-Fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one, **32**, (68 mg, 0.26 mmol) and N-bromosuccinimide (49 mg, 0.28 mmol) were dissolved in anhydrous DMF. It was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure. The resulting residue was suspended in dichloromethane. The suspension was filtered, and it was washed with methanol to give the desired product as a beige solid (59 mg, 66%): mp 263-265 °C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.39 (brs, 1H), 10.53 (brs, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.73-7.69 (m, 2H), 7.58 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 7.54 (d, *J* = 2 Hz, 1H), 7.38-7.33 (m, 2H);$^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 162.1 ($J_{C,F}$ = 243 Hz), 156.7, 145.0, 138.2, 135.6 ($J_{C,F}$ = 3 Hz), 132.9, 128.7 ($J_{C,F}$ = 8 Hz), 125.9, 121.7, 119.1, 116.0 ($J_{C,F}$ = 22 Hz), 112.9, 109.0; HRMS (ESI) calculated for $C_{15}H_8BrFNO_2$ $(M-H)^-$ 331.9717, found 331.9712.

**4-Phenyl-7-(4-fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one (39).**

4-Bromo-7-(4-fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one, **38**, (42 mg, 0.13 mmol), (4-fluorophenyl)boronic acid (23 mg, 0.19 mmol), $Pd(PPh_3)_4$ (15 mg, 0.013mmol) and

$Na_2CO_3$(40 mg, 0.38 mmol) were dissolved in a mixture of dioxane (6 mL) and water (3 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for 16 hours. The reaction mixture was diluted with ethyl acetate, and washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane + 1% acetic acid) to give the desired product as a white solid (11 mg, 27%): mp. 234-236 $^oC$; $^1H$ NMR (400MHz) (DMSO-$d_6$) 12.29 (brs, 1H), 9.31 (brs, 1H), 7.69-7.65 (m, 2H), 7.57-7.52 (m, 3H), 7.46 (t, 1H, $J$ = 7 Hz), 7.39-7.31 (m, 5H), 7.13 (d, $J$ = 8 Hz, 1H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 162.0 ($J_{C,F}$ = 243 Hz), 158.4, 142.6, 137.2, 136.03 ($J_{C,F}$ = 3 Hz), 133.7, 133.6, 129.9, 128.6 ($J_{C,F}$ = 8 Hz), 128.4, 127.7, 125.0, 123.7, 120.9, 120.3, 115.9 ($J_{C,F}$ = 21 Hz), 112.9; HRMS (ESI) calculated for $C_{21}H_{15}FNO2$ $(M+H)^+$ 332.1081, found 332.1082.

**4-Methyl-7-(4-fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one (40).**

4-Bromo-7-(4-fluorophenyl)-3-hydroxyquinolin-2(1*H*)-one, **38**, (51 mg, 0.15 mmol), TMSCl (0.06 mL, 0.48 mmol) and triethylamine (0.04 mL, 0.29 mmol) were dissolved in toluene (5 mL). The reaction mixture was stirred for 4 hours at room temperature. Then, additional TMSCl (0.10 mL, 0.79 mmol) was added and stirred for 2 hours at room temperature. After starting material was no longer present, the reaction mixture was concentrated under reduced pressure. Along with the resulting residue, trimethylboroxine (0.03 mL, 0.22 mmol), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) and $Na_2CO_3$ (49 mg, 0.46 mmol)

were dissolved in a mixture of dioxane (6 mL) and water (3 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 10 hours. A solution of 3N HCl (5 mL) was added, and the mixture was stirred for 15 minutes. The reaction mixture was then diluted with ethyl acetate, was washed with brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-40% ethyl acetate/hexane + 1% acetic acid) to give the desired product as a white solid (12 mg, 29%); mp. 162-164 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 12.04 (brs, 1H), 9.19 (brs, 1H), 7.70-7.67 (m, 3H), 7.49-7.47 (m, 2H), 7.35-7.31 (m, 2H), 2.30 (s, 3H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) 161.9 ($J_{C,F}$ = 244 Hz), 157.9, 142.9, 137.1, 136.1, 133.4, 128.5 ($J_{C,F}$ = 8 Hz), 123.9, 120.8, 120.7, 119.2, 115.9 ($J_{C,F}$ = 21 Hz), 112.7, 10.5; HRMS (ESI) calculated for $C_{16}H_{13}FNO_2$ $(M+H)^+$ 270.0925, found 270.0922.

**2,3-Dimethoxypyrazine (41).**

2,3-Dichloropyrazine (1.04 mL, 10 mmol) was added to methanol (10 mL). The reaction mixture was treated with sodium methoxide (5.4 g, 100 mmol) at 0 $^oC$. The mixture was then stirred for 22 hours at room temperature. The resulting white suspension was filtered, and it was washed with dichloromethane. The filtrate was concentrated under reduced pressure. The residue was diluted with dichloromethane, and washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure to give the desired product as a colorless oil (1.13 g, 81%); $^1H$ NMR

(400 MHz) ($CDCl_3$) δ 7.47 (s, 2H), 3.88 (s, 6H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 150.3, 131.7, 53.4.

**5-Bromo-2,3-dimethoxypyrazine (42).**

2,3-Dimethoxypyrazine, **41**, (565 mg, 4.03 mmol) and N-bromosuccinimde (754 mg, 4.23 mmol) were dissolved in anhydrous DMF (5mL). The reaction mixture was stirred for 29 hours at room temperature. DMF was then removed by **kugelrohr** distillation. The resulting residue was diluted with dichloromethane, and it was washed with sat. $NaHCO_3$ followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure to give the product as a white solid (384 mg, 43%); mp 54-56 $^oC$ (mp 65 $^oC$)[120]; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.86 (s, 1H), 4.03 (s, 3H), 3.88 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 161.2, 150.0, 141.7, 138.1, 56.6, 55.1.

**5-(4-Fluorophenyl)-2,3-dimethoxypyrazine (43).**

5-Bromo-2,3-dimethoxypyrazine, **42**, (150 mg, 0.69 mmol), (4-fluorophenyl)boronic acid (144 mg, 1.03 mmol), $Pd(PPh_3)_4$ (80 mg, 0.069 mmol) and $Na_2CO_3$(218 mg, 2.06 mmol) were dissolved in a mixture of dioxane (6 mL) and water (2 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for 5 hours. Since the reaction was not completed as indicated by TLC, additional (4-fluorophenyl)boronic acid (48 mg, 0.34 mmol) was added. It was then again refluxed for 16 hours. It was allowed to cool to room temperature, and it was diluted with ethyl

acetate. The organic layer was washed with sat. $NH_4Cl$ followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the desired product as a white solid (123 mg, 77%); mp.108-110 $^oC$; $^1H$ NMR (400MHz) ($CDCl_3$) δ 8.03 (s, 1H), 7.90 (dd, *J* = 9 Hz, *J* = 5 Hz, 2H), 7.15-7.10 (m, 2H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 163.1 ($J_{C,F}$ = 247 Hz), 149.43, 149.41, 140.3, 132.7 ($J_{C,F}$ = 3 Hz), 127.8, 127.7, 127.7 ($J_{C,F}$ = 8 Hz), 115. 7 ($J_{C,F}$ = 21 Hz), 54.1, 53.8; HRMS (ESI) calculated for $C_{12}H_{12}FN_2O_2$ $(M+H)^+$ 235.0877, found 235.0880.

**5-(4-Fluorophenyl)pyrazine-2,3(1*H*,4*H*)-dione (44).**

5-(4-Fluorophenyl)-2,3-dimethoxypyrazine, **43**, (100 mg, 0.43 mmol) was dissolved in a mixture of dioxane (5 mL) and 2N HCl (5 mL). The reaction mixture was refluxed for 21 hours. The reaction mixture was then allowed to cool to room temperature. The solvent was removed under reduced pressure. The resulting white solid was suspended in sat. $NaHCO_3$. The white suspension was filtered to give the desired product as a white solid (75 mg, 85%); mp. 285-287 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 11.55 (sbr, 1H), 11.46 (brs, 1H), 7.57, (dd, *J* = 9 Hz, *J* = 5 Hz, 2H), 7.23-7.19 (m, 2H), 6.59 (d, *J* = 3 Hz, 1H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 161.8 ($J_{C,F}$ = 243 Hz), 156.9, 155.7, 128.1, 127. 6 ($J_{C,F}$ = 9 Hz), 121.0, 115.5 ($J_{C,F}$ =21 Hz), 107.1; HRMS (ESI) calculated for $C_{10}H_7FN_2O_2$ $(M+Na)^+$ 229.0384, found 229.0382.

**4-Chloro-5,6-dimethoxypyrimidine (45).**

4,6-Dichloro-5-methoxypyrimidine (300 mg, 1.68 mmol) was added to methanol (10 mL). The reaction mixture was treated with sodium methoxide (99 mg, 1.85 mmol) at 0 $^{o}$C. The reaction mixture was stirred for 19 hours at room temperature. The reaction mixture was then put under reduced pressure to remove methanol. The resulting residue was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the desired product as a white solid (168 mg, 57%); mp 53-55 $^{o}$C (mp 53-55 $^{o}$C)[121]; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.27 (s, 1H), 4.03 (s, 3H), 3.88 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 163.6, 151.6, 151.3, 138.2, 60.7, 54.8.

**4-(4-Fluorophenyl)-5,6-dimethoxypyrimidine (46).**

4-Chloro-4,5-dimethoxypyrimidine, **45**, (165 mg, 0.95 mmol), (4-fluorophenyl)boronic acid (99 mg, 1.42 mmol), $Pd(PPh_3)_4$ (110 mg, 0.095 mmol) and $Na_2CO_3$(300 mg, 2.84 mmol) were dissolved in a mixture of dioxane (9 mL) and water (3 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 19 hours. The reaction mixture was then allowed to cool to room temperature. It was diluted with ethyl acetate, and was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the desired product as a white solid (181 mg, 82%); mp 62-64 $^{o}$C;

$^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.53 (s, 1H), 8.07 (dd, *J* = 9 Hz, *J* = 6 Hz, 2H), 7.15-7.11 (m, 2H), 4.07 (s, 3H), 3.73 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 163.7 ($J_{C,F}$ = 249 Hz), 164.0, 154.3, 152.0,139.4, 131.4 ($J_{C,F}$ = 8 Hz), 131.3, 115.3 ($J_{C,F}$ = 21 Hz), 60.2, 54.2; HRMS (ESI) calculated for $C_{12}H_{12}FN_2O_2$ $(M+H)^+$ 235.0877, found 235.0882.

**6-(4-Fluorophenyl)-5-methoxypyrimidin-4(3*H*)-one (47).**

4-(4-Fluorophenyl)-5,6-dimethoxypyrimidine, **46**, (134 mg 0.57 mmol) was dissolved in a mixture of 2N HCl (5 mL) and dioxane (5 mL). The reaction mixture was refluxed for 12 hours. It was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The residue was suspended in water, and it was filtered to give the desired product as a white solid (109 mg, 87%); mp 204-206 ºC; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.76 (brs, 1H), 8.07 (s, 1H), 8.04 (dd, *J* = 9 Hz, *J* = 6 Hz, 2H), 7.33-7.28 (m, 2H), 3.34 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 162.5 ($J_{C,F}$ =246 Hz), 158.8, 147.4, 143.7, 142.9, 131.7, 131.2 ($J_{C,F}$ = 8 Hz), 115.0 ($J_{C,F}$ = 21 Hz), 58.8; HRMS (ESI) calculated for $C_{11}H_{10}FN_2O_2$ $(M+H)^+$ 221.0721, found 221.0721.

**6-(4-Fluorophenyl)-5-hydroxypyrimidin-4(3*H*)-one (48)**

6-(4-Fluorophenyl)-5-methoxypyrimidin-4(3*H*)-one, **47**, (107 mg, 0.49 mmol) was dissolve in anhydrous dichloromethane (5mL). A solution of 1M $BBr_3$ in dichloromethane (5.0 mL, 5.0 mmol) was then added at 0 ºC. The reaction mixture was stirred for 24 hours at room temperature. The solvent was removed under reduced

pressure, and the resulting residue was diluted with ethyl acetate. It was washed with sat. $NaHCO_3$ followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the desired product as a white solid (50 mg, 50%); mp 285-287 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 12.67 (brs, 1H), 9.83 (brs, 1H), 8.20 (dd, $J$ = 9 Hz, $J$ = 6 Hz, 2H), 7.87 (s, 1H), 7.29-7.25 (m, 2H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 161.9 ($J_{C,F}$ = 245 Hz), 158.7, 141.1, 138.5, 136.0, 132.3, 130.7 ($J_{C,F}$ = 8 Hz), 114.8 ($J_{C,F}$ = 21 Hz); HRMS (ESI) calculated for $C_{10}H_8FN_2O_2$ $(M+H)^+$ 207.0564, found 207.0568.

**2-Chloro-4,5-dimethoxypyrimidine (49).**

2,4-Dichloro-5-methoxypyrimidine (2.37 g, 13.20 mmol) and $K_2CO_3$ (1.8 g, 13.20 mmol) were dissolved in methanol (50 mL), and was stirred for 19 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was dissolved in ethyl acetate, and was washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give the desired product as a white solid (1.70 g, 73%); mp 65-67 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.84 (s, 1H), 4.03 (s, 3H), 3.88 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 161.2, 150.0, 141.7, 138.2, 56.6, 55.0.

**2-(4-Fluorophenyl)-4,5-dimethoxypyrimidine (50).**

2-Chloro-4,5-dimethoxypyrimidine, **49**, (500 mg, 2.86 mmol), (4-fluorophenyl)boronic acid (601 mg, 4.30 mmol), $Pd(PPh_3)_4$ (330 mg, 0.29 mmol) and $Na_2CO_3$(910 mg, 8.59 mmol) were dissolved in a mixture of dioxane (12 mL) and water (4 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 5 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, and the organic layer was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the desired product as a white solid (123 mg, 77%); mp 114-116 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.37 (dd, $J$ = 9 Hz, $J$ = 6 Hz, 2H), 8.12 (s, 1H), 7.16-7. 12 (m, 2H), 4.17 (s, 3H), 3.98 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 163.1 ($J_{C,F}$ = 248 Hz), 159.7, 155.3, 141.0, 137.2, 133.6 ($J_{C,F}$ = 3 Hz), 129.6 ($J_{C,F}$ = 8 Hz), 115.3 ($J_{C,F}$ = 22 Hz), 56.4, 54.0; HRMS (ESI) calculated for $C_{12}H_{12}FN_2O_2$ $(M+H)^+$ 235.0877, found 235.0878.

**2-(4-Fluorophenyl)-5-methoxypyrimidin-4(3*H*)-one (51).**

2-(4-Fluorophenyl)-4,5-dimethoxypyrimidine, **50**, (187 mg, 0.80 mmol) was dissolved in a mixture of 2N HCl (5 mL) and dioxane (5 mL). The reaction mixture was refluxed for 12 hours. It was then allowed to cool to room temperature. The reaction mixture was diluted with ethyl acetate, which was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduce pressure. The

residue was purified on an ISCO chromatograph (50-100% ethyl acetate/hexane) to give the desired product as a white solid (41 mg, 23%); mp 229-231 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.79 (brs, 1H), 7.68 (brs, 1H), 8.08 (dd, *J* = 9 Hz, *J* = 5 Hz, 2H), 7.35-7.30 (m, 2H), 3.79 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 163.6 ($J_{C,F}$ =247 Hz), 158.1, 148.4, 145.4, 130.4, 129.6 ($J_{C,F}$ =9Hz), 129.1, 115.5 ($J_{C,F}$ =22Hz), 56.0; HRMS (ESI) calculated for $C_{11}H_9FN_2O_2Na$ $(M+Na)^+$ 243.0540, found 243.0546.

**2-(4-Fluorophenyl)-5-hydroxypyrimidin-4(3*H*)-one (52).**

2-(4-Fluorophenyl)-5-methoxypyrimidin-4(3*H*)-one, **51**, (58 mg, 0.26 mmol) was dissolved in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0 $^{o}$C, and a solution of 1M $BBr_3$ in dichloromethane (3.0 mL, 3.0 mmol) was added. The reaction mixture was stirred for 24 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in water, and the suspension was filtered to give the desired product as a white solid (23 mg, 42%); mp 252-254 $^{o}$C ; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.88 (brs, 1H), 9.64 (brs, 1H), 8.05 (dd, *J* = 9 Hz, *J* = 5 Hz, 2H), 7.54 (s, 1H), 7.33-7.29 (m,2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 163.4 ($J_{C,F}$ = 246 Hz), 159.0, 146.9, 143.4, 131.7, 129.4 ($J_{C,F}$ = 9 Hz), 129.1, 115.5 ($J_{C,F}$ = 22 Hz); HRMS (ESI) calculated for $C_{10}H_8FN_2O_2$ $(M+H)^+$ 207.0564, found 207.0566.

**2-(3-Fluorophenyl)-4,5-dimethoxypyrimidine (53).**

2-Chloro-4,5-dimethoxypyrimidine, **49**, (300 mg, 1.72 mmol), (3-fluorophenyl)boronic acid (343 mg, 2.58 mmol), $Pd(PPh_3)_4$ (199 mg, 0.17 mmol), and $Na_2CO_3$ (546 mg, 5.15 mmol) were dissolved in a mixture of dioxane (12 mL) and water (4 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for 8 hours. After the reaction was complete as indicated by TLC, it was allowed to cool to room temperature. The mixture was diluted with ethyl acetate, which was washed with sat $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the desired product as a white solid (393 mg, 98%); mp 83-85 °C; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.09 (dt, *J* = 8 Hz, *J* = 1 Hz, 1H), 8.03 (s, 1H), 8.01-7.98 (m, 1H), 7.38-7.33 (m, 1H), 7.07 (tdd, *J* = 8 Hz, *J* = 3 Hz, *J* = 1 Hz, 1H), 4.09 (s, 3H), 3.90 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 163.1 ($J_{C,F}$ = 242 Hz), 159.5, 154.6 ($J_{C,F}$ =3 Hz), 141.3, 139.8 ($J_{C,F}$ = 8 Hz), 136.9, 129.7 ($J_{C,F}$ = 8 Hz), 123.1 ($J_{C,F}$ = 3 Hz), 116.4 ($J_{C,F}$ = 22 Hz), 114.3 ($J_{C,F}$ = 23 Hz), 56.2, 53.9; HRMS (ESI) calculated for $C_{12}H_{12}FN_2O_2$ $(M + H)^+$ 235.0877, found 235.0879.

**2-(2-Fluorophenyl)-4,5-dimethoxypyrimidine (54).**

2-Chloro-4,5-dimethoxypyrimidine, **49**, (300 mg, 1.72 mmol), (2-fluorophenyl)boronic acid (343 mg, 2.58 mmol), $Pd(PPh_3)_4$ (199 mg, 0.17 mmol), and $Na_2CO_3$ (546 mg, 5.15 mmol) were dissolved in a mixture of dioxane (12 mL) and water (4 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature, and

was diluted with ethyl acetate, which was then washed with sat $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a white solid (402 mg, 100%); mp 72-74 °C; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.11 (s, 1H), 7.97 (td, *J* = 8 Hz, *J* = 2 Hz, 1H), 7.34-7.29 (m, 1H), 7.15 (td, *J* = 8 Hz, *J* = 1 Hz, 1H), 7.11-7.06 (m, 1H), 4.06 (s, 3H), 3.90 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 161.0 ($J_{C,F}$ = 253 Hz), 159.5, 154.2 ($J_{C,F}$ = 4 Hz), 140.9, 137.0, 131.4 ($J_{C,F}$ = 2 Hz), 130.9 ($J_{C,F}$ = 8 Hz), 126. 0 ($J_{C,F}$ = 9 Hz), 123.8 ($J_{C,F}$ = 4 Hz), 116.7 ($J_{C,F}$ = 22 Hz), 56.2, 54.1; HRMS (ESI) calculated for $C_{12}H_{12}FN_2O_2$ $(M+H)^+$ 235.0877, found 235.0877.

**2-(4-Biphenyl)-4,5-dimethoxypyrimidine (55).**

2-Chloro-4,5-dimethoxypyrimidine, **49**, (400 mg, 2.29 mmol), 4-biphenylboronic acid (681 mg, 3.44 mmol), $Pd(PPh_3)_4$ (264 mg, 0.23 mmol), and $Na_2CO_3$ (728 mg, 6.87 mmol) were dissolved in a mixture of dioxane (12 mL) and water (4 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for 8 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, and it was washed with sat $NH_4Cl$ followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give product as a white solid (670 mg, 100%); mp 115-117 °C; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.43 (d, *J* = 8 Hz, 2H), 8.15 (s, 1H), 7.70 (d, *J* = 8 Hz, 2H),

7.67 (d, *J* = 7 Hz, 2H), 7.47 (t, *J* = 8 Hz, 2H), 7.37 (t, *J* = 7 Hz, 1H), 4.19 (s, 3H), 3.98 (s, 3H); $^{13}$C NMR (100 MHz), ($CDCl_3$) δ 159.7, 156.0. 142.5, 141.1, 140.7, 137.3, 136.4, 128.8, 128.1, 127.5, 126.1, 56.4, 54.0; HRMS (ESI) calculated for $C_{18}H_{17}N_2O_2$ $(M+H)^+$ 293.1285, found 293.1286.

**2-(3-Biphenyl)-4,5-dimethoxypyrimidine (56).**

2-Chloro-4,5-dimethoxypyrimidine, **49**, (400 mg, 2.29 mmol), 3-biphenylboronic acid (681 mg, 3.44 mmol), $Pd(PPh_3)_4$ (264 mg, 0.23 mmol), and $Na_2CO_3$ (728 mg, 6.87 mmol) were dissolved in a mixture of dioxane (12 mL) and water (4 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 8 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, and then washed with sat $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a white solid (670 mg, 100%); mp 72-74 °C; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.62 (s, 1H), 8.36 (d, *J* = 8 Hz, 1H), 8.15 (s, 1H), 7.71 (d, *J* = 7 Hz, 2H), 7.67 (d, *J* = 8 Hz, 1H), 7.54 (t, *J* = 8 Hz, 2H), 7.49-7.45 (m, 3H), 7.37 (t, *J* = 7 Hz, 1H), 4.18 (s, 3H), 3.97 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 159.7, 156.1, 141.4, 141.17, 141.15, 137.9, 137.2, 128.9, 128.8, 128.6, 127.4, 127.3, 126.6, 126.4, 56.4, 54.0; HRMS (ESI) calculated for $C_{18}H_{17}N_2O_2$ $(M+H)^+$ 293.1285, found 293.1286.

**2-(2-Biphenyl)-4,5-dimethoxypyrimidine (57).**

2-Chloro-4,5-dimethoxypyrimidine, **49**, (500 mg, 2.86 mmol), 2-biphenylboronic acid (851 mg, 4.30 mmol), $Pd(PPh_3)_4$ (266 mg, 0.29 mmol), and $Na_2CO_3$ (909 mg, 8.58 mmol) were dissolved in a mixture of dioxane (21 mL) and water (7 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 8 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat $NH_4Cl$ followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a colorless oil (377 mg, 45%); $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 8.26 (s, 1H), 7.84 (dd, *J* = 7 Hz, *J* = 1 Hz, 1H), 7.54-7.45 (m, 2H), 7.40 (dd, *J* = 7 Hz, *J* = 1 Hz, 1H), 7.30-7.24 (m, 3H), 7.08 (d, *J* = 7 Hz, 2H), 3.85 (s, 3H), 3.30 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) 158.1, 157.2, 142.2, 141.1, 140.0, 137.7, 137.3, 130.4, 130.2, 128.9, 128.6, 127.8, 127.2, 126.2, 56.0, 52.9; HRMS (ESI) calculated for $C_{18}H_{17}N_2O_2$ $(M+H)^+$ 293.1285, found 293.1290.

**2-(3-Fluorophenyl)-5-methoxypyrimidin-4(3*H*)-one (58).**

2-(3-Fluorophenyl)-4,5-dimethoxypyrimidine, **53**, (390 mg, 1.67 mmol) was dissolved in a mixture of 2N HCl (10 mL) and dioxane (10 mL). The reaction mixture was refluxed for 18 hours. It was then allowed to cool to room temperature. The reaction mixture was diluted with ethyl acetate, which was then washed with water, followed by brine. The

organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the desired product as a white solid (237 mg, 63%); mp 122-124 °C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 12.86 (brs, 1H), 7.91 (d, $J$ = 8 Hz, 1H), 7.87-7.83 (m, 1H), 7.71 (s, 1H), 7.58-7.53 (m, 1H), 7.37 (td, $J$ = 8 Hz, $J$ = 2 Hz, 1H), 3.81 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 162.1 ($J_{C,F}$ = 242 Hz), 157.9, 147.8, 145.5, 134.7, 130.7 ($J_{C,F}$ = 9 Hz), 130.1, 123.2 ($J_{C,F}$ = 9 Hz), 117.5 ($J_{C,F}$ = 22 Hz), 113.8 ($J_{C,F}$ = 24 Hz), 56.1; HRMS (ESI) calculated for $C_{11}H_{10}FN_2O_2$ $(M+H)^+$ 221.0721, found 227.0722.

**2-(2-Fluorophenyl)-5-methoxypyrimidin-4(3*H*)-one (59).**

2-(2-Fluorophenyl)-4,5-dimethoxypyrimidine, **54**, (400 mg, 1.71 mmol) was dissolved in a mixture of 2N HCl (10 mL) and dioxane (10 mL). The reaction mixture was refluxed for 18 hours. It was then allowed to cool to room temperature. The mixture was diluted with ethyl acetate, which was washed with water followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethanone) to give the product as a white solid (300 mg, 80%); mp 159-161 °C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 12.81 (brs, 1H), 7.70 (s, 1H), 7.66 (t, J = 8 Hz, 1H), 7.60-7.55 (m, 1H), 7.37-7.31 (m, 1H), 3.80 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 159.3 ($J_{C,F}$ = 248 Hz), 157.3, 145.9, 132.4 ($J_{C,F}$ = 9 Hz), 130.8 ($J_{C,F}$ = 8 Hz), 130.2, 124.5 ($J_{C,F}$ = 3 Hz), 121.8, 121.6, 116.1 ($J_{C,F}$ = 22 Hz), 56.0; HRMS (ESI) calculated for $C_{11}H_{10}FN_2O_2$ $(M+H)^+$ 221.0721, found 221.0721.

**2-(4-Biphenyl)-5-methoxypyrimidin-4(3*H*)-one (60).**

2-(4-Biphenyl)-4,5-dimethoxypyrimidine, **55**, (343 mg, 1.73 mmol) was dissolved in a mixture of 2N HCl (15 mL) and dioxane (15 mL). The reaction mixture was refluxed for 18 hours, and then became a white suspension. It was allowed to cool to room temperature. The suspension was filtered to give the desired product as a white solid (256 mg, 78%); mp 292-294 °C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.83 (brs, 1H), 8.14 (d, *J* = 8 Hz, 2H), 7.81 (d, *J* = 8 Hz, 2H), 7.77-7.72 (m, 3H), 7.50 (t, *J* = 8 Hz, 2H), 7.42 (t, *J* = 7 Hz, 1H), 3.81 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.0, 148.8, 145.6, 142.1, 139.0, 131.2, 130.4, 129.0, 128.0, 127.7, 126.74, 126.70, 56.1; HRMS (ESI) calculated for $C_{17}H_{15}N_2O_2$ $(M+H)^+$ 279.1128, found 279.1129.

**2-(3-Biphenyl)-5-methoxypyrimidin-4(3*H*)-one (61).**

2-(3-Biphenyl)-4,5-dimethoxypyrimidine, **56**, (670 mg, 2.29 mmol) was dissolved in a mixture of 2N HCl (15 mL) and dioxane (15 mL). The reaction mixture was refluxed for 18 hours. It was then allowed to cool to room temperature. The mixture was diluted with ethyl acetate, which was then washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The resulting residue was suspended in hot chloroform, and the suspension was filtered to give the desired product as a white solid (493 mg, 77%); mp 209−211 °C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.97 (brs, 1H), 8.34 (s, 1H), 8.04 (d, *J* = 8 Hz, 1H), 7.83-7.80 (m, 3H),

7.73 (s, 1H), 7.59 (t, *J* = 8 Hz, 1H), 7.51 (t, *J* = 8 Hz, 2H), 7.41 (t, *J* = 7 Hz, 1H), 3.82 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 157.9, 148.9, 145.8, 140.4, 139.4, 132.9, 130.5, 129.3, 128.9, 128.8, 127.8, 126.9, 126.2, 125.2, 56.1. HRMS (ESI) calculated for $C_{17}H_{15}N_2O_2$ $(M+H)^+$ 279.1128, found 279.1129.

**2-(2-Biphenyl)-5-methoxypyrimidin-4(3*H*)-one (62).**

2-(2-Biphenyl)-4,5-dimethoxypyrimidine, **57**, (309 mg, 1.06 mmol) was dissolved in a mixture of 2N HCl (15 mL) and dioxane (15 mL). The reaction mixture was refluexed for 18 hours. It was then allowed to cool to room temperature. The mixture was diluted with ethyl acetate, and was washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethanone) to give the desired product as a colorless oil (158 mg, 54%); $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 12.51 (brs, 1H), 7.59 (t, *J* = 8 Hz, 1H), 7.55-7.47 (m, 4H), 7.36 (t, *J* = 7 Hz, 2H), 7.30 (t, *J* = 7 Hz, 1H), 7.23 (d, *J* = 7 Hz, 2H), 3.72 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 157.1, 151.0, 145.4, 140.3, 139.8, 133.0, 131.5, 131.4, 130.03, 130.01, 129.8, 128.6, 128.2, 127.2, 55.8. HRMS (ESI) calculated for $C_{17}H_{15}N_2O_2$ $(M+H)^+$ 279.1128, found 279.1129.

**2-(3-Fluorophenyl)-5-hydroxypyrimidin-4(3*H*)-one (63).**

2-(3-Fluorophenyl)-5-methoxypyrimidin-4(3*H*)-one, **58**, (100 mg, 0.45 mmol) was dissolved in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0 °C, and then a solution of 1M $BBr_3$ in dichloromethane (4.54 mL, 4.54 mmol) was added. The reaction mixture was stirred for 18 hours at room temperature. The solvent was then removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethanone) to give the desired product as a white solid (87 mg, 93%); mp 210-212 °C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 7.89 (d, *J* = 8 Hz, 1H), 7.84 (dd, *J* = 10 Hz, *J* = 2 Hz, 1H), 7.61 (s, 1H), 7.57-7.52 (m, 1H), 7.36 (td, *J* = 8 Hz, *J* = 2 Hz, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 162.1 ($J_{C,F}$ = 243 Hz), 158.9, 146.5, 143.8, 134.7, 131.5, 130.6 ($J_{C,F}$ = 8 Hz), 123.0, 117.2 ($J_{C,F}$ = 20 Hz), 113.6 ($J_{C,F}$ = 24 Hz); HRMS (ESI) calculated for $C_{10}H_8FN_2O_2$ $(M+H)^+$ 207.0564, found 207.0565.

**2-(2-Fluorophenyl)-5-hydroxypyrimidin-4(3*H*)-one (64).**

2-(2-Fluorophenyl)-5-methoxypyrimidin-4(3*H*)-one, **59**, (100 mg, 0.45 mmol) was dissolved in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0 °C, and 1M $BBr_3$ in dichloromethane (4.54 mL, 4.54 mmol) was added. The reaction mixture was stirred for 18 hours at room temperature. The solvent was then removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and

was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethanone) to give the desired product as a white solid (89 mg, 96%); mp 187-189 °C. $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.80 (brs, 1H), 9.73 (brs, 1H), 7.65 (t, *J* = 7 Hz, 1H), 7.59 (s, 1H), 7.55 (t, *J* = 7 Hz, 1H), 7.36-7.30 (m, 2H). $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 159.3 ($J_{C,F}$ = 248 Hz), 158.2, 144.6, 143.9, 132.2 ($J_{C,F}$ = 8 Hz), 132.1, 130.8, 124.5 ($J_{C,F}$ = 3 Hz), 121.8 ($J_{C,F}$ = 12 Hz), 116.1 ($J_{C,F}$ = 21 Hz); HRMS (ESI) calculated for $C_{10}H_8FN_2O_2$ $(M+H)^+$ 207.0564, found 207.0565.

**2-(4-Biphenyl)-5-hydroxypyrimidin-4(3*H*)-one (65).**

2-(4-Biphenyl)-5-methoxypyrimidin-4(3*H*)-one, **60**, (50 mg, 0.18 mmol) was dissolved in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0 °C, and 1M $BBr_3$ in dichloromethane (1.80 mL, 1.80 mmol) was added. The reaction mixture was stirred for 18 hours. The solvent was removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was washed with 2N HCl followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethanone) to give the desired product as a white solid (46 mg, 96%); dec 259-261 °C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.85 (brs, 1H), 9.68 (brs, 1H), 8.13 (d, *J* = 8 Hz, 2H), 7.80 (d, *J* = 8 Hz, 2H), 7.75 (d, *J* = 7 Hz, 2H), 7.62 (s, 1H), 7.50 (t, *J* =8 Hz, 2H), 7.41 (t, *J* = 7 Hz, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 159.1, 147.5, 143.5, 141.9, 139.0, 131.7, 131.3, 129.0, 128.0, 128.5, 126.7, 126.7; HRMS (ESI) calculated for $C_{16}H_{13}N_2O_2$ $(M+H)^+$ 265.0972, found 265.0973.

**2-(3-Biphenyl)-5-hydroxypyrimidin-4(3*H*)-one (66).**

2-(3-Biphenyl)-5-methoxypyrimidin-4(3*H*)-one, **61**, (100 mg, 0.36 mmol) was dissolved in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0 °C, and the 1M $BBr_3$ in dichloromethane (3.60 mL, 3.60 mmol) was added. The reaction mixture was stirred for 6 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was then washed with 2N HCl followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethanone) to give the desired product as a white solid (34 mg, 36%); dec 221-223 °C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 8.30 (s, 1H), 7.99 (d, *J* = 7 Hz, 1H), 7.88 (d, *J* = 8 Hz, 1H), 7.81 (d, *J* = 8 Hz, 2H), 7.66 (s, 1H), 7.63 (t, *J* = 8 Hz, 1H), 7.52 (t, *J* = 8 Hz, 2H), 7.43 (t, *J* = 7 Hz, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.9, 147.5, 143.7, 140.4, 139.5, 133.1, 132.3, 129.2, 128.9, 128.5, 127.7, 126.8, 126.0, 125.0; HRMS (ESI) calculated for $C_{16}H_{13}N_2O_2$ $(M+H)^+$ 265.0972, found 265.0973.

**2-(2-Biphenyl)-5-hydroxypyrimidin-4(3*H*)-one (67).**

2-(2-Biphenyl)-5-methoxypyrimidin-4(3*H*)-one, **62**, (50 mg, 0.18 mmol) was dissolved in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0 °C, and 1M $BBr_3$ in dichloromethane (1.80 mL, 1.80 mmol) was added. The reaction mixture was

stirred for 18 hours at room temperature. The solvent was then removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was then washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$, followed by concentration under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethanone) to give the desired product as a white solid (31 mg, 64%); mp 271-273 °C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 7.70-7.65 (m, 2H), 7.56 (t, *J* = 8 Hz, 2H), 7.48 (s, 1H), 7.39 (t, *J* = 7 Hz, 2H), 7.33 (t, *J* = 7 Hz, 1H), 7.23 (d, *J* = 7 Hz, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.6, 156.9, 148.3, 140.8, 140.5, 139.4, 131.9, 130.4, 130.1, 129.9, 128.6, 128.2, 127.2. HRMS (ESI) calculated for $C_{16}H_{13}N_2O_2$ $(M+H)^+$ 265.0972, found 265.0974.

**4-(4,5-Dimethoxypyrimidin-2-yl)benzonitrile (68).**

2-Chloro-4,5-dimethoxypyrimidine, **49**, (100 mg, 0.57 mmol), (4-cyanophenyl)boronic acid (126 mg, 0.86 mmol), $Pd(PPh_3)_4$ (66 mg, 0.06 mmol) and $Na_2CO_3$(182 mg, 1.72 mmol) were dissolved in a mixture of dioxane (9 mL) and water (3 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for 4 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. The mixture was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give the desired product as a white solid (69 mg, 74%); mp 170-172 $^o$C; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.49 (d, *J* = 9 Hz,

2H), 8.18 (s, 1H), 7.76 (d, *J* = 9 Hz, *J* = 2H), 4.20 (s, 3H), 4.02 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 159.8, 154.0, 141.8, 141.5, 137.0, 132.3, 128.0, 119.0, 113.0, 56.4, 54.2; HRMS (ESI) calculated for $C_{13}H_{12}N_3O_2$ $(M+H)^+$ 242.0924, found 242.0929.

**3-(4,5-Dimethoxypyrimidin-2-yl)benzonitrile (69).**

2-Chloro-4,5-dimethoxypyrimidine, **49**, (100 mg, 0.57 mmol), (3-cyanophenyl)boronic acid (126 mg, 0.86 mmol), $Pd(PPh_3)_4$ (66 mg, 0.06 mmol) and $Na_2CO_3$(182 mg, 1.72 mmol) were dissolved in a mixture of dioxane (9 mL) and water (3 mL). The air was evacuated and replaced with $N_2$. The reaction mixture was refluxed for 5 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. The mixture was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give the desired product as a white solid (138 mg, 100%); mp.134-136 $^oC$; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.61 (s, 1H), 8.54 (d, *J* = 8 Hz, 1H), 8.09 (s, 1H), 7.65 (d, *J* = 8 Hz, 1H), 7.51 (t, *J* = 8 Hz, 1H), 4.13 (s, 3H), 3.95 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 159.8, 153.6, 141.7, 138.5, 137.0, 132.8, 131.6, 131.3, 129.2, 118.9, 112.6, 56.4, 54.2; HRMS (ESI) calculated for $C_{13}H_{12}N_3O_2$ $(M+H)^+$ 242.0924, found 242.0928.

**2-(4,5-Dimethoxypyrimidin-2-yl)benzonitrile (70).**

2-Chloro-4,5-dimethoxypyrimidine, **49**, (500 mg, 2.90 mmol), 0.5 M (2-cyanophenyl)zinc bromide in tetrahydrofuran (5.80 mmol, 2.90 mmol) and $Pd(PPh_3)_4$ (335 mg, 0.29 mmol) were dissolved in tetrahydrofuran (10 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for overnight. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give product as a white solid (291 mg, 42%).

**4-(5-Methoxy-6-oxo-1,6-dihydropyrimidin-2-yl)benzonitrile (71).**

4-(4,5-Dimethoxypyrimidin-2-yl)benzonitrile, **68**, (53 mg, 0.22 mmol) was dissolved in a mixture of 2N HCl (5 mL) and dioxane (5 mL). The reaction mixture was refluxed for 5 hours. Reaction was monitored by TLC and stopped once the starting material was consumed. It was then allowed to cool to room temperature. The mixture was diluted with ethyl acetate, which was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-5% methanol/dichloromethane) to give the desired product as a white solid (50 mg, 100%); mp 297-299 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 12.99 (brs, 1H), 8.19 (d, $J$ = 8 Hz, 2H), 7.96 (d, $J$ = 8 Hz, 2H), 7.75 (s, 1H), 3.81 (s, 3H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) 157.8, 147.4, 146.2, 136.5, 132.5, 130.0,

127.8, 118.4, 112.8, 56.1; HRMS (ESI) calculated for $C_{12}H_{10}N_3O_2$ $(M+H)^+$ 228.0768, found 228.0770.

**3-(5-Methoxy-6-oxo-1,6-dihydropyrimidin-2-yl)benzonitrile (72).**

3-(4,5-Dimethoxypyrimidin-2-yl)benzonitrile, **69**, (138 mg, 0.57 mmol) was dissolved in a mixture of 2N HCl (5 mL) and dioxane (5 mL). The reaction mixture was refluxed for 6 hours. Reaction was monitored by TLC and stopped once the starting material was consumed. It was then allowed to cool to room temperature. The mixture was diluted with ethyl acetate, which was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the desired product as a white solid (56 mg, 43%); mp 255-257 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 12.93 (brs, 1H), 8.44 (s, 1H), 8.34 (d, $J$ = 8 Hz, 1H), 7.99 (d, $J$ = 8 Hz, 1H), 7.74 – 7.70 (m, 2H), 3.82 (s, 3H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 157.9, 147.5, 145.9, 133.9, 133.7, 131.7, 130.7, 130.4, 129.9, 118.3, 111.7, 56.1; HRMS (ESI) calculated for $C_{12}H_{10}N_3O_2$ $(M+H)^+$ 228.0768, found 228.0767.

**4-(5-Hydroxy-6-oxo-1,6-dihydropyrimidin-2-yl)benzonitrile (73).**

4-(5-Methoxy-6-oxo-1,6-dihydropyrimidin-2-yl)benzonitrile, **71**, (50 mg, 0.22 mmol) was dissolved in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0 $^oC$ and 1M $BBr_3$ in dichloromethane (2.2 mL, 2.2 mmol) was added. The reaction

mixture was stirred for 18 hours at room temperature. The solvent was removed under reduced pressure, and the resulting residue was suspended in water. It was filtered to give the desired product as a white solid (15 mg, 32%); mp 324-326 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 13.05 (brs, 1H), 9.91 (brs, 1H), 8.18 (d, *J* = 8 Hz, 2H), 7.95 (d, *J* = 8 Hz, 2H), 7.64 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.8, 132.5, 129.4, 127.6, 127.2, 127.1, 126.7, 118.4, 112.5; HRMS (ESI) calculated for $C_{11}H_8N_3O_2$ $(M+H)^+$ 214.0611, found 214.0618.

**3-(5-Hydroxy-6-oxo-1,6-dihydropyrimidin-2-yl)benzonitrile (74).**

3-(5-Methoxy-6-oxo-1,6-dihydropyrimidin-2-yl)benzonitrile, **72**, (50 mg, 0.22 mmol) was dissolved in anhydrous dichloromethane (5mL). The reaction mixture was cooled to 0 $^{o}$C and the 1M $BBr_3$ in dichloromethane (2.2 mL, 2.2 mmol) was added. The reaction mixture was stirred for 18 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in water. It was filtered to give the desired product as a white solid (27 mg, 58%); mp 294-296 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 8.44 (s, 1H), 8.35 (d, *J* = 8 Hz, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.68 (t, *J* = 8 Hz, 1H), 7.61 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 159.3, 146.4, 143.9, 134.3, 133.4, 131.9, 131.5, 130.4, 129.8, 118.4, 111.7; HRMS (ESI) calculated for $C_{11}H_8N_3O_2$ $(M+H)^+$ 214.0611, found 214.0613.

**2-(4-(1*H*-Tetrazol-5-yl)phenyl)-5-hydroxypyrimidin-4(3*H*)-one (75).**

4-(5-Hydroxy-6-oxo-1,6-dihydropyrimidin-2-yl)benzonitrile, **73**, (68 mg, 0.32 mmol) and $NaN_3$ (79 mg, 1.21 mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with 1-2 drops of acetic acid. It was sealed, and it was heated at 130 $^oC$ for 17 hours. It was allowed to cool to room temperature, which gave a brownish suspension. DMF was removed by kugelrohr distillation. The resulting residue was suspended in water and filtered to give the desired product as a dark brown solid (42 mg, 51%); dec 290-292 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 8.08 (d, *J* = 9 Hz, 2H), 8.03 (d, *J* = 8 Hz, 2H), 7.55 (s, 1H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 161.0, 160.2, 148.9, 143.3, 133.8, 132.4, 131.6, 126.9, 125.5; HRMS (ESI) calculated for $C_{11}H_9N_6O_2$ $(M+H)^+$ 257.0781, found 257.0791.

**2-(3-(1*H*-Tetrazol-5-yl)phenyl)-5-hydroxypyrimidin-4(3*H*)-one (76).**

3-(5-Hydroxy-6-oxo-1,6-dihydropyrimidin-2-yl)benzonitrile, **74**, (108 mg, 0.50 mmol) and $NaN_3$ (131 mg, 2.02 mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with 1-2 drops of acetic acid. It was sealed, and it was heated at 130 $^oC$ for 18 hours. It was allowed to cool to room temperature, which gave brownish suspension. It was filtered, and the collected solid was suspended in 2N HCl. The suspension was filtered to give the desired product as a beige solid (32 mg, 25%); dec. 295-297$^oC$; $^1H$ NMR (400MHz) (DMSO-$d_6$) δ 8.67 (s, 1H), 8.11 (d, *J* = 8 Hz, 1H), 7.97 (d, *J* = 8 Hz, 1H), 7.63 (s, 1H), 7.56 (t, *J* = 8 Hz, 1H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ162.3, 159.1, 158.7, 148.0, 143.4, 133.1, 130.4, 128.9, 127.9, 126.5, 125.1; HRMS (ESI) calculated for $C_{11}H_9N_6O_2$ $(M+H)^+$ 257.0781, found 257.0785.

**4,5-Dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (77).**

2-Chloro-4,5-dimethoxypyrimidine, **49**, (150 mg, 0.86 mmol), bis(pinacol)diboron (240 mg, 0.95 mmol), Pd(dppf)$Cl_2$ (66 mg, 0.09 mmol) and KOAc (327 mg, 2.58 mmol) were dissolved in a toluene (20 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 4 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$ followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the desired product as a colorless oil (118 mg, 51%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.82 (s, 1H), 4.01 (s, 3H), 3.85 (s, 3H), 1.20 (s, 12 H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 161.2, 150.1, 141.8, 138.2, 83.1, 56.7, 55.1, 24.5.

**2-(4,5-Dimethoxypyrimidin-2-yl)benzoic acid (78).**

2-(4,5-Dimethoxypyrimidin-2-yl)benzonitrile, **70**, (20 mg, 0.08 mmol) was dissolved in a mixture of 2N HCl (1 mL) and dioxane (1 mL). The reaction mixture was refluxed for 5 hours. The mixture was then allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with water and brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the desired product

as a white solid (2 mg, 10%); mp 183-185 ºC; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.67 (brs, 1H), 8.32 (s, 1H), 7.96 (d, *J* = 8 Hz, 1H), 7.58-7.48 (m, 3 H), 3.96 (s, 3H), 3.90 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 170.6, 158.7, 155.3, 140.7, 137.8, 136.3, 134.4, 129.8, 129.1, 129.0, 128.0, 56.2, 53.8.

**2-(4,5-Dimethoxypyrimidin-2-yl)benzamide (79).**

To a solution of 2-(4,5-dimethoxypyrimidin-2-yl)benzonitrile, **70**, (100 mg, 0.42 mmol) in anhydrous dichloromethane (3 mL), a solution of 1M $BBr_3$ in dichloromethane (2.1 mL, 2.10 mmol) was added. The mixture was stirred for overnight at room temperature. The reaction was stopped by removing excess $BBr_3$ and dichloromethane under reduced pressure. It was diluted with ethyl acetate, and was then washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was recharged with additional 1M $BBr_3$ in dichloromethane (4.2 mL, 4.20 mmol). The reaction mixture was stirred for overnight at room temperature. The reaction was again stopped by removing excess $BBr_3$ and dichloromethane under reduced pressure. It was again diluted with ethyl acetate, which was then washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the desired product as a white solid (70 mg, 65%); mp 193-195 ºC; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.11 (s, 1H), (d, J = Hz, 1H), 7.57-7.43 (m, 3H), 6.20 (brs, 1H), 6.02 (brs, 1H), 4.11 (s, 3H), 3.96 (s,

3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 173.6, 159.6, 156.1, 141.1, 136.7, 136.2, 136.0, 129.86, 129.85, 129.2, 127.9, 56.3, 54.4.

**4,5-Dichloro-2-(methoxymethyl)pyridazin-3(2*H*)-one (80).**

4,5-Dichloropyridazin-3(2*H*)-one (200 mg, 1.21 mmol) and 4-dimethylaminopyridine (15 mg, 0.12 mmol) were dissolved in anhydrous dichloromethane (20 mL). The reaction mixture was cooled to 0 $^{o}$C, and was treated with triethylamine (0.29 mL, 1.70 mmol), followed by MOM-Cl (0.11 mL, 1.45 mmol). The reaction mixture was stirred for 17 hours at room temperature. It was then poured into dichloromethane, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$, which was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a white solid (84 mg, 33%); mp 65-67 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.78 (s, 1H), 5.41 (s, 2H), 3.43 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 156.9, 137.0, 136.0, 134.9, 82.4, 58.1.

**5-Chloro-4-methoxy-2-(methoxymethyl)pyridazin-3(2*H*)-one (81).**

4,5-Dichloro-2-(methoxymethyl)pyridazin-3(2*H*)-one, **80**, (84 mg, 0.40 mmol) was added to methanol (10 mL). Then the reaction mixture was cooled to 0 $^{o}$C. It was treated with NaOMe (24 mg, 0.44 mmol), and the mixture was stirred for 18 hours at room temperature. The reaction mixture was put under reduced pressure to remove methanol. The resulting residue was diluted with ethyl acetate, which was then washed with sat.

$NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (59 mg, 72%); mp 101-103 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.85 (s, 1H), 5.45 (s, 2H), 4.08 (s, 3H), 3.44 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 159.1, 155.1, 127.1, 116.9, 81.9, 57.9, 57.8. HRMS (ESI) calculated for $C_7H_{10}ClN_2O_3$ $(M+H)^+$ 205.0374, found 205.0384.

**5-(4-Fluorophenyl)-4-methoxy-2-(methoxymethyl)pyridazin-3(2*H*)-one (82).**

5-Chloro-4-methoxy-2-(methoxymethyl)pyridazin-3(2*H*)-one, **81**, (58 mg, 0.28 mmol), (4-fluorophenyl)boronic acid (140 mg, 0.43 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol) and $Na_2CO_3$ (90 mg, 0.85 mmol) were dissolved in a mixture of dioxane (9 mL) and water (3 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for 14 hours. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a white solid (56 mg, 74%); mp 123-125 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.95 (s, 1H), 7.53 (dd, $J$ = 9 Hz, $J$ = 6 Hz, 2H), 7.11 – 7. 07 (m, 2H), 5.48 (s, 2H), 3.93 (s, 3H), 3.49 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 162.6 ($J_{C,F}$ = 247 Hz), 161.6, 154.8, 132.3 ($J_{C,F}$ = 8 Hz), 128.5, 125.7, 120.7, 112.9 ($J_{C,F}$ = 22 Hz), 81.6, 57.9, 57.3; HRMS (ESI) calculated for $C_{13}H_{14}FN_2O_3$ $(M+H)^+$ 265.0983, found 265.0992.

**5-(4-Fluorophenyl)-4-hydroxypyridazin-3(2*H*)-one (83).**

5-(4-Fluorophenyl)-4-methoxy-2-(methoxymethyl)pyridazin-3(2*H*)-one, **82**, (55 mg, 0.21 mmol) was dissolve in anhydrous dichloromethane (10 mL). The mixture was cooled to 0 $^{o}$C and the 1M in $BBr_3$ in dichloromethane (2.1 mL, 2.1 mmol) was added. The reaction mixture was stirred for 24 hours at room temperature. The solvent was removed under reduced pressure. This gave 5-(4-fluorophenyl)-4-methoxypyridazin-3(2*H*)-one, which was again recharged with 1M $BBr_3$ in dichloromethane (2.1 mL, 2.1 mmol). The reaction mixture was stirred for 24 hours at room temperature. The solvent was again removed under reduced pressure. The resulting residue was suspended in water, and was filtered. The solid was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the desired product as a white solid (6.2 mg, 14%); mp 274-276 $^{o}$C ; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.70 (brs, 1H), 7.76 (s, 1H), 7.58 (*J* = 8 Hz, *J* = 5 Hz, 2H), 7.21-7.17 (m, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 161.2 ($J_{C,F}$ = 243 Hz), 161.9, 154.6, 132.7, 132.4 ($J_{C,F}$ = 8 Hz), 127.2 ($J_{C,F}$ = 4 Hz), 115.8, 114.2 ($J_{C,F}$ = 21 Hz); HRMS (ESI) calculated for $C_{10}H_8FN_2O_2$ $(M+H)^+$ 207.0564, found 207.0575.

**6-Chloro-3,4-dimethoxypyridazine (84).**

3,4,6-Trichloropyridazine (200 mg, 1.09 mmol) was dissolved in methanol (15 mL). The reaction mixture was cooled to 0 $^{o}$C, and it was treated with NaOMe (117 mg, 2.17

mmol). The reaction mixture was stirred for 10 hours at room temperature. The reaction mixture was put under reduced pressure to remove methanol. The resulting residue was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The resulting residue was suspended in water, and it was filtered solid was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a white solid (101 mg, 53%); mp 117-119 $^oC$ (mp 128-129 $^oC$)[122]; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 6.71 (s, 1H), 4.08 (s, 3H), 3.88 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 156.9, 151.1, 149.8, 108.4, 56.2, 55.3.

**6-(4-Fluorophenyl)-3,4-dimethoxypyridazine (85).**

6-Chloro-3,4-dimethoxypyridazine, **84**, (101 mg, 0.58 mmol), (4-fluorophenyl)boronic acid (122 mg, 0.87 mmol), $Pd(PPh_3)_4$ (67 mg, 0.06 mmol) and $Na_2CO_3$(184 mg, 1.74 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for 3 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was suspended in water, and was filtered. The solid was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give the product as a white solid (109 mg, 80%); mp 103-105 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.88 (dd, $J$ = 9 Hz, $J$ = 5 Hz, 2H), 7.10-7. 06 (m, 2H), 7.00

(s, 1H), 4.14 (s, 3H), 3.93 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 163.7 ($J_{C,F}$ = 247 Hz), 156.5, 155.7, 148.9, 132.9 ($J_{C,F}$ = 3 Hz), 128.5 ($J_{C,F}$ = 9 Hz), 115.8 ($J_{C,F}$ = 21 Hz), 104.7, 55.7, 55.2; HRMS (ESI) calculated for $C_{12}H_{12}FN_2O_2$ $(M+H)^+$ 235.0877, found 235.0885.

**6-(4-Fluorophenyl)-4-methoxypyridazin-3(2*H*)-one (86).**

6-(4-Fluorophenyl)-3,4-dimethoxypyridazine, **85**, (122 mg 0.52 mmol) was dissolved in a mixture of 2N HCl (5 mL) and dioxane (5 mL). The reacion mixture was then refluxed for 11 hours. It was then allowed to cool to room temperature. The mixture was diluted with ethyl acetate, which then was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The resulting residue was suspended in water, and was filtered. The solid was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the desired product as a white solid (41 mg, 36%); mp 211-213 $^o$C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 13.05 (brs, 1H), 7.96 (dd, $J$ = 9 Hz, $J$ = 6 Hz, 2H), 7.34-7.29 (m, 2H), 7.28 (s, 1H), 3.92 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 162.7 ($J_{C,F}$ =245 Hz), 156.2, 155.7, 144.3, 132.0 ($J_{C,F}$ = 3 Hz), 128.2 ($J_{C,F}$ =8 Hz), 115.6 ($J_{C,F}$ = 22 Hz), 104.4, 56.2; HRMS (ESI) calculated for $C_{11}H_{10}FN_2O_2$ $(M+H)^+$ 221.0721, found 221.0727.

**6-(4-Fluorophenyl)-4-hydroxypyridazin-3(2*H*)-one (87).**

6-(4-Fluorophenyl)-4-methoxypyridazin-3(2*H*)-one, **86**, (16 mg, 0.074 mmol) was dissolve in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0$^o$C,

and 1M $BBr_3$ in dichloromethane (0.74 mL, 0.74 mmol) was added. The reaction mixture was stirred for 36 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in water, and the suspension was filtered to give the product as a white solid (5 mg, 35%); mp 281-283 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 13.10 (brs, 1H), 11.02 (brs, 1H), 7.87 (dd, $J$ = 9 Hz, $J$ = 5 Hz, 2H), 7.30-7.26 (m,2H), 7.19 (s, 1H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 162.6 ($J_{C,F}$ = 245 Hz), 157.6, 155.4, 145.2, 132.0 ($J_{C,F}$ = 3 Hz), 128.0 ($J_{C,F}$ = 9 Hz), 115.6 ($J_{C,F}$ = 22 Hz), 106.0; HRMS (ESI) calculated for $C_{10}H_8FN_2O_2$ $(M+H)^+$ 207.0564, found 207.0567.

**4-(5,6-Dimethoxypyridazin-3-yl)benzonitrile (88).**

6-Chloro-3,4-dimethoxypyridazine, **84**, (298 mg, 1.71 mmol), (4-cyanophenyl)boronic acid (376 mg, 2.56 mmol), $Pd(PPh_3)_4$ (198 mg, 0.17 mmol) and $Na_2CO_3$(543 mg, 5.12 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for 15 hours. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a white solid (130 mg, 31%); mp 187-189 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.10 (d, $J$ = 8 Hz, 2H), 7.77 (d, $J$ = 8 Hz, 2H), 7.14 (s, 1H), 4.23 (s, 3H), 4.03 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 157.1, 154.7, 149.1,

140.9, 132.6, 127.3, 118.5, 113.0, 104.9, 55.9, 55.3; HRMS (ESI) calculated for $C_{13}H_{12}N_3O_2$ $(M+H)^+$ 242.0924, found 242.0931.

**4-(5-Methoxy-6-oxo-1,6-dihydropyridazin-3-yl)benzonitrile (89)**

4-(5,6-Dimethoxypyridazin-3-yl)benzonitrile, **88**, (125 mg, 0.52 mmol) was dissolved in a mixture of 2N HCl (5 mL) and dioxane (5 mL). The reaction mixture was refluxed for 4 hours. Reaction was monitored by TLC and stopped once the starting material was consumed. The reaction mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in water, and the suspension was filtered to give the desired product as a white solid (82 mg, 70%); mp 271-273 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 13.97 (brs, 1H), 8.02 (d, $J$ = 8 Hz, 2H), 7.94 (d, $J$ = 8 Hz, 2H), 6.62 (s, 1H), 3.96 (s, 3H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 156.3, 155.9, 143.5, 139.7, 132.7, 126.7, 118.6, 111.4, 104.3, 56.3; HRMS (ESI) calculated for $C_{12}H_{10}N_3O_2$ $(M+H)^+$ 228.0768, found 228.0774.

**4-(5-Hydroxy-6-oxo-1,6-dihydropyridazin-3-yl)benzonitrile (90).**

4-(5-Methoxy-6-oxo-1,6-dihydropyridazin-3-yl)benzonitrile, **89**, (109 mg, 0.48 mmol) was dissolved in anhydrous dichloromethane (5mL). The reaction mixture was cooled to 0 $^oC$, and 1M in $BBr_3$ in dichloromethane (4.8 mL, 4.8 mmol) was added. The reaction mixture was then stirred for 20 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was suspended in water. The suspension

was filtered, and the solid was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a white solid (75 mg, 73%); mp 305-307 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 13.29 (brs, 1H), 11.15 (brs, 1H), 8.03 (d, *J* = 9 Hz, 2H), 7.92 (d, *J* = 9 Hz, *J* = 2H), 7.29 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 157.7, 154.6, 144.4, 139.8, 132.7, 126.5, 118.6, 111.4, 106.0; HRMS (ESI) calculated for $C_{11}H_8N_3O_2$ $(M+H)^+$ 214.0611, found 214.0615.

**6-(4-(1*H*-Tetrazol-5-yl)phenyl)-4-hydroxypyridazin-3(2*H*)-one (91).**

4-(5-Methoxy-6-oxo-1,6-dihydropyridazin-3-yl)benzonitrile, **90**, (56 mg, 0.26 mmol) and $NaN_3$ (69 mg, 1.06 mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with 1-2 drops of acetic acid. It was sealed and heated at 130 $^{o}$C for 21 hours. It was allowed to cool to room temperature, which resulted in the formation of a brownish suspension. The solid residue was suspended in 2N HCl, and it was filtered to give the desired product as a white solid (33 mg, 48%); dec 273-275 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.13 (brs, 1H), 8.09 (d, *J* = 8 Hz, *J* = 2H), 7.95 (d, *J* = 7 Hz, 2H), 7.25 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.0, 157.7, 154.9, 145.7, 135.8, 128.9, 126.6, 126.2, 105.9; HRMS (ESI) calculated for $C_{11}H_9N_6O_2$ $(M+H)^+$ 257.0781, found 257.0791.

**5-Bromo-2,3-dimethoxypyridine (92a).**

2,3-Dimethoxypyridine (2 g, 14.37 mmol) and N-bromosuccinimide (3.84 g, 21.56 mmol) were dissolved in acetonitrile (100 mL). It was then stirred for 48 hours at room temperature. The reaction mixture was diluted with ethyl acetate, which was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% dichloromethane/hexane) to give the desired product as a colorless oil (1.36 g, 43%);$^1$H NMR (400 MHz) ($CDCl_3$) δ 7.77 (d, *J* = 2 Hz, 1H), 7.13 (d, *J* = 2 Hz, 1H), 3.99 (s, 3H), 3.87 (s, 3H);$^{13}$C NMR (100 MHz) ($CDCl_3$) δ 153.5, 144.6, 137.4, 120.2, 111.1, 56.0, 53.9.

**6-Bromo-2,3-dimethoxypyridine (92b).**

A solution of 1M (trimethylsilyl)methyllithium in pentane (6.74 mL, 6.74 mmol) was added slowly at -78 $^o$C to a solution of 2,3-dibromo-5,6-dimethoxypyridin, **115**, (1.0 g, 3.37 mmol) in anhydrous tetrahydrofuran (20 mL). The reaction mixture was stirred for 30 min at -78 $^o$C. The reaction was stopped by adding 10 mL water, and, it was extracted with ethyl acetate. The organic layer was washed with brine and dried over $Na_2SO_4$. The organic layer was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a colorless oil (735 mg, 100%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.00 (d, *J* = 8 Hz, 1H), 6.93 (d, *J* = 8 Hz, 1H), 4.02 (s, 3H), 3.85 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 153.9, 143.6, 126.7, 119.9, 56.1, 54.4.

**4-(5,6-Dimethoxypyridin-3-yl)benzonitrile (93).**

5-Bromo-2,3-dimethoxypyridine, **92a**, (692 mg, 3.17mmol), 4-cyanophenyl boronic acid (699 mg, 4.76 mmol), $Pd(PPh_3)_4$ (370 mg, 0.32 mmol) and $Na_2CO_3$ (1.01 g, 9.51mmol) were dissolved in a mixture of dioxane (60 mL) and water (20 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (603 mg, 79%); mp 109-111 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.97 (d, *J* = 2 Hz, 1H), 7.73 (d, *J* = 8 Hz, *J* = 2H), 7.64 (d, *J* = 9 Hz, 2H), 7.22 (d, *J* = 2 Hz, 1H), 4.07 (s, 3H), 3.96 (s, 3H);$^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 154.8, 144.3, 142.6, 135.5, 132.7, 128.7, 127.3, 118.7, 115.8, 111.0, 55.8, 54.0.

**4-(2-Bromo-5,6-dimethoxypyridin-3-yl)benzonitrile (94).**

To a solution of 4-(5,6-dimethoxypyridin-3-yl)benzonitrile, **93**, (603 mg, 2.51 mmol) in AcOH (20 mL) under nitrogen, N-bromosuccinimde (893 mg, 5.02 mmol) was added. The reaction mixture was then stirred overnight at 80 $^oC$. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, and it was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was

concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as a white solid (588 mg, 73%); mp 151-153 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.72 (dd, *J* = 9 Hz, 2H), 7.54 (d, *J* = 8 Hz, 2H), 6.96 (s, 1H), 4.06 (s, 3H), 3.88 (s, 3H);$^{13}$C NMR (100 MHz) ($CDCl_3$) δ 153.4, 143.8, 143.7, 132.1, 130.4, 129.9, 125.9, 120.4, 118.6, 111.8, 56.3, 54.7.

**4-(5,6-Dimethoxy-2-(naphthalen-1-yl)pyridin-3-yl)benzonitrile (95).**

4-(2-Bromo-5,6-dimethoxypyridin-3-yl)benzonitrile, **94**, (293 mg, 0.92 mmol), naphthalene-1-boronic acid (190 mg, 1.10 mmol), $Pd(PPh_3)_4$ (106 mg, 0.092 mmol) and $Na_2CO_3$ (292 mg, 2.75 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a white solid (220 mg, 65%); mp 226-228 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.87 (dd, *J* = 8 Hz, *J* = 1 Hz, 1H), 7.81 (d, *J* = 8 Hz, 2H), 7.48 (td, *J* = 7 Hz, *J* = 1 Hz, 1H), 7.42-7.39 (m, 1H), 7.37-7.32 (m, 3H), 7.21 (s, 1H), 7.17-7.14 (m, 3H), 4.06 (s, 3H), 4.03 (s, 3H);$^{13}$C NMR (100 MHz) ($CDCl_3$) δ 153.3, 144.6, 143.4, 136.9, 133.7, 132.9, 132.1, 131.8, 129.7, 129.2, 128.6, 128.4, 127.9, 126.1, 125.82, 125.77, 125.0, 119.1, 118.7, 110.3, 56.0, 54.2; HRMS (ESI) calculated for $C_{24}H_{19}N_2O_2$ $(M+H)^+$ 367.1441, found 367.1450.

**4-(5,6-Dimethoxy-2-(naphthalen-2-yl)pyridin-3-yl)benzonitrile (96)**

4-(2-Bromo-5,6-dimethoxypyridin-3-yl)benzonitrile, **94**, (300 mg, 0.97 mmol), naphthalene-2-boronic acid (251 mg, 1.46 mmol), $Pd(PPh_3)_4$ (112 mg, 0.10 mmol) and $Na_2CO_3$ (310 mg, 2.92 mmol) were dissolved in a mixture of dioxane (30 mL) and water (10 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a white solid (357 mg, 100%); mp 182-184$^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.84 (d, *J* = 1 Hz, 1H), 7.82-7.80 (m, 1H), 7.73-7.70 (m, 2H), 7.55 (d, *J* = 8 Hz, 2H), 7.49-7.46 (m, 2H), 7.41 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.35 (d, *J* = 8 Hz, 2H), 7.11 (s, 1H), 4.18 (s, 3H), 3.99 (s, 3H);$^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 153.6, 145.2, 144.4, 143.3, 136.5, 133.1, 132.7, 132.2, 129.5, 128.3, 127.7, 127.6, 127.5, 127.4, 126.4, 126.2, 119.8, 118.8, 110.6, 56.1, 54.0; HRMS (ESI) calculated for $C_{24}H_{19}N_2O_2$ $(M+H)^+$ 367.1441, found 367.1449.

**4-(2-([1,1'-Biphenyl]-2-yl)-5,6-dimethoxypyridin-3-yl)benzonitrile (97).**

4-(2-Bromo-5,6-dimethoxypyridin-3-yl)benzonitrile, **94**, (300 mg, 0.97 mmol), 2-biphenyl boronic acid (289 mg, 1.46 mmol), $Pd(PPh_3)_4$ (113 mg, 0.10 mmol) and $Na_2CO_3$

(310 mg, 2.92 mmol) were dissolved in a mixture of dioxane (30 mL) and water (10 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a white solid (311 mg, 100%); mp 213-215 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.51 (dd, *J* = 7 Hz, *J* = 2 Hz, 1H), 7.37-7.29 (m, 2H), 7.20 (d, *J* = 9 Hz, 2H), 7.10 (dd, *J* = 7 Hz, *J* = 2 Hz, 1H), 7.03 (t, *J* = 7 Hz, 1H), 6.95 (t, *J* = 7 Hz, 2H), 6.70 (s, 1H), 6.54 (dd, *J* = 7 Hz, *J* = 2 Hz, 2H), 6.51 (d, *J* = 7 Hz, 2H), 3.98 (s, 3H), 3.81 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 153.5, 145.0, 144.1, 143.2, 140.9, 140.8, 137.9, 131.7, 131.4, 129.9, 129.6, 128.9, 128.5, 128.3, 127.8, 127.4, 126.2, 119.0, 118.7, 109.7, 59.9, 54.1; HRMS (ESI) calculated for $C_{26}H_{20}N_2O_2Na$ $(M+Na)^+$ 415.1417, found 415.1423.

**4-(5,6-Dimethoxy-2-(phenanthren-9-yl)pyridin-3-yl)benzonitrile (98).**

4-(2-Bromo-5,6-dimethoxypyridin-3-yl)benzonitrile, **94**, (200 mg, 0.63 mmol), phenantherene-9-boronic acid (209 mg, 0.941 mmol), $Pd(PPh_3)_4$ (73 mg, 0.063 mmol) and $Na_2CO_3$ (126 mg, 1.88 mmol) were dissolved in a mixture of dioxane (30 mL) and water (10 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat.

$NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (243 mg, 93%); mp 111-113 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.74 (d, *J* = 8 Hz, 1H), 8.69 (d, *J* = 8 Hz, 1H), 7.83 (d, *J* = 8 Hz, 1H), 7.72 (d, *J* = 8 Hz, 1H), 7.68-7.64 (m, 2H), 7.57 (t, *J* = 7 Hz, 1H), 7.52 (t, *J* = 8 Hz, 1H), 7.47 (s, 1H), 7.33 (d, *J* = 8 Hz, 2H), 7.26-7.24 (m, 3H), 4.06 (s, 3H), 4.04 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 153.5, 144.49, 144.47, 143.5, 135.6, 131.9, 131.17, 131.16, 130.6, 130.2, 129.60, 129.56, 129.3, 128.71, 127.0, 126.8, 126.7, 126.52, 126.49, 123.0, 122.5, 119.1, 118.7, 110.4, 56.1, 54.2; HRMS (ESI) calculated for $C_{28}H_{20}N_2O_2Na$ $(M+Na)^+$ 439.1417, found 439.1422.

**4-(5-Hydroxy-2-(naphthalen-1-yl)-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile (99).**

4-(5,6-Dimethoxy-2-(naphthalen-1-yl)pyridin-3-yl)benzonitrile, **95**, (80 mg, 0.22 mmol) was dissolved in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0 $^oC$ and the 1M $BBr_3$ in dichloromethane (2.2 mL, 2.2 mmol) was added. The reaction mixture was stirred for 24 hours at room temperature. The solvent was removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was then washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a white solid (32 mg, 45%); mp 288-290 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 12.11 (brs, 1H), 9.47 (brs, 1H), 7.96-7.93 (m, 2H), 7.60 (d, *J* = 8Hz, 1H), 7.52-7.47 (m, 5H), 7.42 (d, *J* = 7 Hz,

1H), 7.13 (d, *J* = 8 Hz, 2H), 6.97 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.0, 146.9, 143.2, 132.9, 132.6, 131.7, 131.5, 131.2, 129.31, 129.25, 129.2, 128.3, 126.8, 126.1, 125.2, 124.8, 118.5, 117.5, 117.2, 108.8; HRMS (ESI) calculated for $C_{22}H_{15}N_2O_2$ $(M+H)^+$339.1128, found 339.1136.

**4-(5-Hydroxy-2-(naphthalen-2-yl)-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile (100).**

4-(5,6-Dimethoxy-2-(naphthalen-2-yl)pyridin-3-yl)benzonitrile, **96**, (100 mg, 0.27mmol) was dissolved in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0 $^o$C, and 1M $BBr_3$ in dichloromethane (2.7 mL, 2.7 mmol) was added. The reaction mixture was stirred for 24 hours at room temperature. The solvent was then removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was then washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$, followed by concentration under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a white solid (32 mg, 35%); mp 262-264 $^o$C;$^1$H NMR (400 MHz) (DMSO-$d_6$) δ 12.13 (brs, 1H), 9.49 (brs, 1H), 7.88-7.85 (m, 3H), 7.77 (d, *J* = 8 Hz, 1H), 7.64-7.62 (m, 2H), 7.55-7.54 (m, 2H), 7.25 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 1H), 6.92 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.2, 146.6, 143.5, 132.4, 132.0, 131.5, 131.4, 130.4, 129.5, 128.8, 128.7, 128.2, 127.5, 127.43, 127.37, 126.9, 126.5, 118.7, 117.9, 109.0; HRMS (ESI) calculated for $C_{22}H_{15}N_2O_2$ $(M+H)^+$ 339.1128, found 339.1139.

**4-(2-([1,1'-Biphenyl]-2-yl)-5-hydroxy-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile (101).**

4-(2-([1,1'-Biphenyl]-2-yl)-5,6-dimethoxypyridin-3-yl)benzonitrile, **97**, (150 mg, 0.38 mmol) was dissolved in anhydrous dichloromethane (10 mL). The reaction mixture was cooled to 0 $^{o}$C, and 1M $BBr_3$ in dichloromethane (3.82 mL, 3.82 mmol) was added. The reaction mixture was stirred for 24 hours at room temperature. The solvent was then removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was then washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$, followed by concentration under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a white solid (104 mg, 75%); mp 286-288 $^{o}$C ; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.16 (brs, 1H), 9.38 (brs, 1H), 7.56-7.54 (m, 1H), 7.49-7.47 (m, 2H), 7.42 (d, *J* = 8 Hz, 2H), 7.23-7.13 (m, 4H), 6.65 (dd, *J* = 8 Hz, *J* = 1 Hz, 2H), 6.60-6.55 (m, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ158.2, 158.1, 146.7, 142.7, 141.1, 139.6, 133.5, 131.9, 131.8, 131.4, 129.7, 129.6, 129.2, 128.0, 127.8, 127.4, 126.7, 118.8, 117.0, 108.3; HRMS (ESI) calculated for $C_{24}H_{16}N_2O_2Na$ $(M+Na)^+$ 387.1104, found 387.1109.

**4-(5-Hydroxy-6-oxo-2-(phenanthren-9-yl)-1,6-dihydropyridin-3-yl)benzonitrile (102).**

4-(5,6-Dimethoxy-2-(phenanthren-9-yl)pyridin-3-yl)benzonitrile, **98**, (226 mg, 0.54 mmol) was dissolved in anhydrous dichloromethane (20 mL). The reaction mixture was

cooled to 0 $^{o}$C, and 1M $BBr_3$ in dichloromethane (5.43 mL, 5.43 mmol) was added. The reaction mixture was stirred for 24 hours at room temperature. The solvent was then removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ followed by concentration under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane + 0.1% TFA) to give the product as a white solid (126 mg, 60%)**;** mp 309-311 $^{o}$C ; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.17 (brs, 1H), 9.54 (brs, 1H), 8.85 (t, *J* = 9Hz, 2H), 7.95 (d, *J* = 7 Hz, 1H), 7.84 (s, 1H), 7.76-7.64 (m , 4H), 7.58 (t, *J* = 7 Hz, 1H), 7.47 (d, *J* = 8Hz, 2H), 7.24 (d, *J* = 8Hz, 2H), 7.01 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.0, 147.0, 143.2, 132.3, 131.8, 130.5, 130.3, 130.2, 130.0, 129.7, 128.9, 127.7, 127.2, 127.1, 127.0, 125.7, 123.3, 122.8, 119.5, 117.5, 117.2, 108.9; HRMS (ESI) calculated for $C_{26}H_{16}N_2O_2Na$ $(M+Na)^+$ 411.1104, found 411.1104.

**5-(4-(1*H*-Tetrazol-5-yl)phenyl)-3-hydroxy-6-(naphthalen-1-yl)pyridin-2(1*H*)-one (103).**

4-(5-Hydroxy-2-(naphthalen-1-yl)-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile, **99**, (60 mg, 0.18 mmol) and $NaN_3$ (46 mg, 0.71 mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with catalytic amount of acetic acid. It was sealed and then heated at 130$^{o}$C for overnight. The reaction was allowed to cool to room temperature, which resulted in the formation of a brownish suspension. The solvent was removed under reduced pressure. The solid residue was suspended in 2N HCl, and the

suspension filtered to give the product as a white solid (37 mg, 55%); mp 223-225 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.07 (brs, 1H), 9.43 (brs, 1H), 7.95-7.92 (m, 2H), 7.65 (d, *J* = 8 Hz, 2H), 7.62 (d, *J* = 2Hz, 1H), 7.5-7.45 (m, 4H), 7.18 (d, *J* = 8 Hz, 2H), 7.01 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.0, 146.7, 141.2, 132.9, 132.2, 131.6, 129.4, 129.2, 129.1, 128.3, 126.8, 126.4, 126.1, 125.2, 124.9, 121.8, 118.1, 117.6; HRMS (ESI) calculated for $C_{22}H_{16}N_5O_2$ $(M+H)^+$ 382.1299, found 382.1300.

**5-(4-(1*H*-Tetrazol-5-yl)phenyl)-6-([1,1'-biphenyl]-2-yl)-3-hydroxypyridin-2(1*H*)-one (104).**

4-(2-([1,1'-Biphenyl]-2-yl)-5-hydroxy-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile, **101**, (100 mg, 0.27 mmol) and $NaN_3$ (71 mg, 1.10 mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with catalytic amount of acetic acid. It was sealed and then heated at 130 $^{o}$C for overnight. The reaction was allowed to cool to room temperature, which resulted in the formation of a brownish suspension. It was diluted with ethyl acetate, which was then washed with 6N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$, followed by concentration under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% TFA) to give the desired product as an orange solid (110 mg, 98%); dec. 189-191$^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.08 (brs, 1H), 9.28 (brs, 1H), 7.64 (d, *J* = 8 Hz, 2H), 7.55 (t, *J* = 4 Hz, 1H), 7.47 (t, *J* = 4 Hz, 2H), 7.22-7.19 (m, 2H), 7.15 (t, *J* = 7 Hz, 2H), 6.70 (d, *J* = 7 Hz, 2H), 6.65-6.53 (m, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 157.9, 146.4, 141.2, 140.5, 139.7, 133.4, 132.2, 131.8, 129.7, 129.4, 129.3, 128.1, 127.8,

127.3, 126.6, 126.2, 121.4, 117.5, 117.4; HRMS (ESI) calculated for $C_{24}H_{18}N_5O_2$ $(M+H)^+$ 408.1455, found 408.1457.

**5-(4-(1*H*-Tetrazol-5-yl)phenyl)-3-hydroxy-6-(phenanthren-9-yl)pyridin-2(1*H*)-one (105).**

4-(5-Hydroxy-6-oxo-2-(phenanthren-9-yl)-1,6-dihydropyridin-3-yl)benzonitrile, **102**, (80 mg, 0.21 mmol) and $NaN_3$ (54 mg, 0.82 mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with catalytic amount of acetic acid. It was sealed and heated at 130 $^oC$ for overnight. The reaction was allowed to cool to room temperature, which resulted in the formation of a brownish suspension. It was diluted with ethyl acetate, which was washed with 6N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$, followed by concentration under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% TFA) to give the desired product as a white solid (28 mg, 31%); dec. 284-286 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 12.13 (brs, 1H), 9.49 (brs, 1H), 8.84 (t, *J* = 8 Hz, 2H), 7.97 (d, *J* = 8 Hz, 1H), 7.87 (s, 1H), 7.73-7.58 (m, 7H), 7.29 (d, *J* = 8 Hz, 2H), 7.05 (s, 1H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 158.0, 154.6, 146.8, 141.1, 132.1, 130.5, 130.3, 130.1, 129.9, 129.7, 129.3, 128.9, 127.7, 127.2, 127.1, 126.9, 126.5, 125.8, 123.3, 122.8, 121.9, 118.3, 117.6; HRMS (ESI) calculated for $C_{24}H_{18}N_5O_2$ $(M+H)^+$ 432.1455, found 432.1441.

**5-Bromo-2,3-bis(methoxymethoxy)pyridine (106a) and 5-bromo-3-(methoxymethoxy)-1-(methoxymethyl)pyridin-2(1*H*)-one (106b).**

NaH, 60% dispersion in mineral oil (1.05 g, 26.3 mmol) was added at 0 $^{o}$C to a solution of 5-bromopyridin-2,3-diol (500 mg, 2.63 mmol) in DMF (25 mL) under nitrogen. The reaction mixture was then stirred for an hour at room temperature. Chloromethyl methyl ether (1.0 mL, 13.2 mmol) was added to the mixture and was stirred for 3 hours at at 0 $^{o}$C. After the reaction was completed as determined by TLC, it was diluted with ethyl acetate. The organic layer was washed with water, followed by brine. The organic layer was then dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give 5-bromo-2,3-bis(methoxymethoxy)pyridine as a colorless oil (36 mg, 5%). $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.83 (d, *J* = 2Hz, 1H), 7.49 (d, *J* = 2Hz, 1H), 5.52 (s, 2H), 5.20 (s, 2H), 3.49 (s, 3H), 3.47 (s, 3H); $^{13}$C NMR (100 MHz) (CDCl3) δ 152.4, 141.9, 139.3, 126.2, 111.9, 95.3, 92.1, 57.2, 56.4. along with 5-bromo-3-(methoxymethoxy)-1-(methoxymethyl)pyridin-2(1*H*)-one as a colorless oil (321 mg, 44%). $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.19 (d, *J* = 2Hz, 1H), 7.04 (d, *J* = 2Hz, 1H), 5.30 (s, 2H), 5.20 (s, 2H), 3.47 (s, 3H), 3.38 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 157.3, 147.6, 127.9, 121.8, 97.6, 95.3, 78.5, 57.2, 56.4.

**4-(5,6-Bis(methoxymethoxy)pyridin-3-yl)benzonitrile (107).**

5-Bromo-2,3-bis(methoxymethoxy)pyridine, **106a**, (296 mg, 1.06 mmol), 4-cyanophenylboronic acid (234 mg, 1.60 mmol), $Pd(PPh_3)_4$ (122 mg, 0.10 mmol) and $Na_2CO_3$ (338 mg, 3.19 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for overnight. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a colorless oil (108 mg, 34%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.09 (d, *J* = 2Hz, 1H), 7.75 (d, *J* = 8Hz, 2H), 7.66-7.63 (m, 3H), 5.68 (s, 2H), 5.34 (s, 3H), 3.60 (s, 3H), 3.57 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ. 153.7, 142.2, 141.7, 137.3, 132.8, 129.7, 127.4, 122.1, 118.7, 111.2, 95.4, 92.2, 57.3, 56.5.

**4-(5-(Methoxymethoxy)-1-(methoxymethyl)-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile (108).**

5-Bromo-3-(methoxymethoxy)-1-(methoxymethyl)pyridin-2(1*H*)-one, **106b**, (259 mg, 0.93 mmol), 4-cyanophenylboronic acid (205 mg, 1.40 mmol), $Pd(PPh_3)_4$ (107 mg, 0.09 mmol) and $Na_2CO_3$ (296 mg, 2.79 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for overnight. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed

with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a white solid (262 mg, 93%); mp 82- 84 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.72 (d, $J$ = 9 Hz, 2H), 7.57 (d, $J$ = 9 Hz, 2H), 7.42 (d, $J$ = 2 Hz, 1H), 7.33 (d, $J$ = 2 Hz, 1H), 5.46 (s, 2H), 5.33 (s, 2H), 3.56 (s, 3H), 3.47 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ. 157.9, 147.7, 141.2, 134.5, 132.8, 126.5, 126.4, 118.6, 117.7, 111.0, 95.3, 78.8, 57.5, 56.7.

**2-Fluoro-6-iodopyridin-3-ol (109).**

To a solution of 2-fluoro-3-hydroxypyridine (2.5 g, 22.1 mmol) in water (125 mL), $I_2$ (5.61g, 44.20 mmol) followed by $K_2CO_3$ (6.11 g, 44.2 mmol) were added. The reaction mixture was then stirred for 3 hours at room temperature. After the reaction was completed as determined y TLC, it was diluted with ethyl acetate, which was then washed with 2N HCl, 10% sodium thiosulfate, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a white solid (4.01 g, 76%); mp 117-119 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.27 (d, $J$ = 8 Hz, 1H), 7.01 (dd, $J$ = 10 Hz, $J$ = 8 Hz, 1H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 151.7 ($J_{C,F}$ = 239 Hz), 139.9 ($J_{C,F}$ = 27 Hz), 133.2 ($J_{C,F}$ = 5 Hz), 128.6 ($J_{C,F}$ = 5 Hz), 96.7 ($J_{C,F}$ =12 Hz); HRMS (ESI) calculated for $C_5H_4FINO$ $(M+H)^+$ 239.9316, found 239.9316.

**2-Fluoro-6-iodo-3-((2-methoxyethoxy)methoxy)pyridine (110).**

NaH, 60% dispersion in mineral oil (1.34 g, 33.56 mmol) was added at -15 $^{o}$C (ice/acetone) to a solution of 2-fluoro-6-iodopyridin-3-ol, **109**, (4.01 g, 16.78 mmol) in anhydrous THF (170 mL) under nitrogen. The reaction mixture was then stirred for 30 minutes at 0 $^{o}$C. 2-Methoxyethoxymethyl chloride (3.83 mL, 33.56 mmol) was added and the reaction mixture was stirred for 3 hours at room temperature. After the reaction was completed as determined by TLC, it was diluted with ethyl acetate, which was washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a colorless oil (5.31 g, 97%);$^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.11 (d, $J$ = 8 Hz, 1H), 6.90 (dd, $J$ = 10 Hz, $J$ = 8 Hz, 1H), 4.90 (s, 2H), 3.46 – 3.44 (m, 2H), 3.15-3.13 (m 2H), 2.96 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 152.7 ($J_{C,F}$ = 244 Hz), 140.4 ($J_{C,F}$ = 24 Hz), 132.9 ($J_{C,F}$ = 5 Hz), 128.3 ($J_{C,F}$ = 4 Hz), 100.1 ($J_{C,F}$ = 12 Hz), 94.5, 71.4, 68.4, 59.0; HRMS (ESI) calculated for $C_9H_{12}IFNO_3$ $(M+H)^+$ 327.9840, found 327.9833.

**2-(*t*-Butoxy)-6-iodo-3-((2-methoxyethoxy)methoxy)pyridine (111).**

Potassium *t*-butoxide (3.64 g, 32.46 mmol) in DMF (10 mL) was added over 30 min to a solution of 2-fluoro-6-iodo-3-((2-methoxyethoxy)methoxy)pyridine, **110**, (5.31 g, 16.23 mmol) in anhydrous THF (160 mL) under nitrogen.. The reaction mixture was then stirred for 15 minutes at room temperature. After the reaction was complete, it was diluted with ethyl acetate, which was then washed with water, followed by brine. The

organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a white solid as a colorless oil (5.10 g, 82%);$^1$H NMR (400 MHz) ($CDCl_3$) δ 7.13 (d, *J* = 8 Hz, 1H), 6.99 (d, *J* = 8 Hz, 1H), 5.20 (s, 2H), 3.84-3.81 (m, 2H), 3.54-3.52 (m, 2H), 3.36 (s, 3H), 1.58 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 154.1, 142.2, 126.74, 126.68, 101.6, 94.6, 81.5, 71.5, 68.0, 59.0, 28.3; HRMS (ESI) calculated for $C_{13}H_{21}INO_4$ $(M+H)^+$ 382.0510, found 382.0510.

**2-(*t*-Butoxy)-3-((2-methoxyethoxy)methoxy)-6-(naphthalen-2-yl)pyridine (112).**

A mixture of 2-(*t*-butoxy)-6-iodo-3-((2-methoxyethoxy)methoxy)pyridine, **111**, (500 mg, 1.31 mmol), naphthalene-2-boronic acid (339 mg, 1.97 mmol), $Pd(PPh_3)_2Cl_2$ (91 mg, 0.13 mmol) and $Na_2CO_3$ (417 mg, 3.93 mmol) was dissolved in a solution of dioxane (45 mL) and water (15 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 2 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$, and was concentrated under the reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give the product as a brown oil (384 mg, 77%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.30 (s, 1H), 8.11 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.93-7.84 (m, 3H), 7.51-7.40 (m, 4H), 5.32 (s, 2H), 3.93-3.91 (m, 2H), 3.61-3.59 (m, 2H), 3.40 (s, 3H), 1.75 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ

154.6, 147.2, 141.5, 136.6, 133.6, 133.2, 128.5, 128.2, 127.6, 126.1, 126.0, 125.4, 125.2, 124.5, 112.9, 94.8, 80.3, 71.6, 68.0, 59.0, 28.9.

**3-Bromo-6-(*t*-butoxy)-5-((2-methoxyethoxy)methoxy)-2-(naphthalen-2-yl)pyridine (113).**

N-Bromosuccinimide (327 mg, 1.84 mmol) in AcCN (20 mL) was added slowly to a mixture of 2-(*t*-butoxy)-3-((2-methoxyethoxy)methoxy)-6-(naphthalen-2-yl)pyridine, **112**, (350 mg, 0.92 mmol) in acetonitrile (10 mL). The reaction mixture was stirred for 3 hours at room temperature. After the reaction was completed as indicated by TLC, it was diluted with ethyl acetate. It was washed with sat. $NaHCO_3$ followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give the product as a beige solid (362 mg, 85%); mp 63-65 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.12 (s, 1H), 7.84-7.79 (m, 3H), 7.73 (dd, $J$ = 9 Hz, $J$ = 2 Hz, 1H), 7.59 (s, 1H), 7.43-7.41 (m, 2H), 5.23 (s, 2H), 3.84-3.82 (m, 2H), 3.54-3.51 (m, 2H), 3.34 (s, 3H), 1.55 (s, 9H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 153.4, 146.8, 141.4, 136.9, 132.9, 132.8, 129.6, 128.9, 128.5, 127.7, 127.4, 127.2, 126.4, 126.1, 108.8, 94.8, 81.1, 71.5, 68.2, 59.1, 28.8.

**3-(4-(1*H*-Tetrazol-5-yl)phenyl)-6-(*t*-butoxy)-5-((2-methoxyethoxy)methoxy)-2-(naphthalen-2-yl)pyridine (114).**

3-Bromo-6-(*t*-butoxy)-5-((2-methoxyethoxy)methoxy)-2-(naphthalen-2-yl)pyridine, **113**, (100 mg, 0.22 mmol), 4-(2*H*-tetrazol-5-yl)phenylboronic acid (63 mg, 0.33 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol) and $Na_2CO_3$ (70 mg, 0.66 mmol) were dissolved in a mixture of DMF (3 mL) and water (1 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Then, the reaction mixture was refluxed for overnight. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, and it was washed with 1N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the desired product as a colorless oil (55 mg, 47%); $^1$H NMR (400 MHz) ($CDCl_3$) δ; 7.99 (d, *J* = 8 Hz, 2H), 7.82 (s, 1H), 7.74-7.72 (m, 1H), 7.66-7.62 (m, 2H), 7.45 (s, 1H), 7.42-7.37 (m, 3H), 7.32 (d, *J* = 8 Hz, 2H), 5.34 (s, 2H), 3.94-3.91 (m, 2H), 3.60-3.58 (m, 2H), 3.35 (s, 3H), 1.70 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 177.8, 154.0, 146.3, 143.1, 141.0, 137.3, 133.0, 132.5, 130.6, 129.4, 128.3, 127.9, 127.8, 127.5, 127.3, 127.2, 126.1, 125.9, 94.8, 80.9, 71.6, 68.0, 59.0, 28.9.

**2,3-Dibromo-5,6-dimethoxypyridine (115).**

N-Bromosuccinimide (6.2 g, 34.76 mmol) was added to a mixture of 2,3-dimethoxypyridine (2.2 g, 15.80 mmol) in acetic acid (15 mL). The reaction mixture was stirred for 48 hours at 50 $^o$C. The reaction mixture was allowed to cool to room temperature, and it was diluted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$, followed by brine. The organic layer was then dried over $Na_2SO_4$ and was

concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a white solid (2.89 g, 62%); mp 115-117 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.11 (s, 1H), 3.91 (s, 3H), 3.78 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 152.5, 143.7, 127.7, 122.8, 112.9, 56.4, 54.6.

**(2-Bromo-5,6-dimethoxypyridin-3-yl)(phenyl)methanone (116a) and (3-bromo-5,6-dimethoxypyridin-2-yl)(phenyl)methanone (116b).**

A solution of 1M (trimethylsilyl)methyllithium in pentane (5.52 mL, 5.52 mmol) was added slowly at 0 $^{o}$C to a solution of 2-dimethylamino ethanol (0.19 mL, 1.84 mmol) in toluene (6 mL). The reaction mixture was stirred for 30 min at 0 $^{o}$C. Then, 2,3-dibromo-5,6-dimethoxypyridine, **115**, (546 mg, 1.84 mmol) in toluene (2 mL) was added to the mixture at 0 $^{o}$C. The reaction mixture was stirred for an hour at 0 $^{o}$C. N,N-Dimethylbenzamide (412 mg, 2.76 mmol) in toluene (2 mL) was then added to the mixture at -10 $^{o}$C. The reaction mixture was stirred for an hour at -10 $^{o}$C. The reaction was stopped by addition of water (10 mL) and extracted with ethyl acetate. The organic layer was washed with brine and dried over $Na_2SO_4$. The reaction mixture was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give 2-bromo-5,6-dimethoxypyridin-3-yl)(phenyl)methanone as a yello oil (250 mg, 42%). $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.82 (dd, *J* = 8 Hz, *J* = 1 Hz, 2H), 7.63-7.58 (m, 1H), 7.44 (t, *J* = 8 Hz, 2H), 7.07 (s, 1H), 4.07 (s, 3H), 3.85 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ.194.2, 154.5, 143.4, 136.4, 133.7,

130.2, 129.7, 128.7, 124.5, 119.3, 56.3, 54.9. along with (3-bromo-5,6-dimethoxypyridin-2-yl)(phenyl)methanone as a yello oil (25 mg, 4%). $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.87 (d, *J* = 8 Hz, 2H), 7.58 (t, *J* = 8 Hz, 1H), 7.46 (t, *J* = 8 Hz, 2H), 7.27 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 192.6, 152.4, 145.6, 142.1, 136.0, 133.4, 130.5, 128.4, 121.8, 109.5, 56.3, 54.3.

**(5,6-Dimethoxypyridin-2-yl)(phenyl)methanone (117).**

A solution of 1M (trimethylsilyl)methyllithium in pentane (1.39 mL, 1.39 mmol) was added slowly at -10 $^{o}$C to a mixture of 6-bromo-2,3-dimethoxypyridine, **92b**, (254 mg, 1.16 mmol) in toluene (10 mL). The reaction mixture was stirred for 30 min at -10 $^{o}$C. Then, N,N-dimethylbenzamide (260 mg, 1.74 mmol) in toluene (3 mL) was added, and it was stirred for an hour at -10 $^{o}$C. The reaction was stopped by adding 10 mL water, and it was extracted with ethyl acetate. The organic layer was washed with brine and dried over $Na_2SO_4$. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (54 mg, 20%); mp 63-65 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.15 (dd, *J* = 8 Hz, *J* = 1 Hz, 2H), 7.83 (d, *J* = 8 Hz, *J* = 1H), 7.60-7.56 (m, 1H), 7.48 (t, *J* = 8 Hz, 2H), 7.20 (d, *J* = 8 Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 192.2, 152.6, 147.1, 142.7, 137.3, 133.1, 130.8, 127.7, 120.2, 116.7, 56.0, 54.0.

**(3-Bromo-5,6-dimethoxypyridin-2-yl)(phenyl)methanone (118).**

N-Bromosuccinimide (45 mg, 0.25 mmol) and (5,6-dimethoxypyridin-2-yl)(phenyl)methanone, **117**, (41 mg, 0.17 mmol) were dissolved in acetonitrile (10 mL). After the addition of catalytic amount of trifluoroacetic acid to the reaction mixture, it was stirred for overnight at 55 $^{o}$C. The reaction mixture was allowed to cool to room temperature, and it was diluted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ and brine, and it was dried over $Na_2SO_4$. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a yellow oil (33 mg, 61%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.87 (d, *J* = 8 Hz, 2H), 7.58 (t, *J* = 8 Hz, 1H), 7.46 (t, *J* = 8 Hz, 2H), 7.27 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 192.6, 152.4, 145.6, 142.1, 136.0, 133.4, 130.5, 128.4, 121.8, 109.5, 56.3, 54.3.

**(5,6-Dimethoxypyridin-2-yl)(naphthalen-1-yl)methanone (119).**

A solution of 1M (trimethylsilyl)methyllithium in pentane (3.81 mL, 3.81 mmol) was added at -10 $^{o}$C to a mixture of 6-bromo-2,3-dimethoxypyridine, **92b**, (756 mg, 3.47 mmol) in toluene (5 mL). The reaction mixture was stirred for 30 min at -10 $^{o}$C. Then, N-methoxy-N-methyl-1-naphthamide (1.49 mg, 6.93 mmol) in toluene (5 mL) was added, and was allowed to stir for an hour at -10 $^{o}$C. The reaction was stopped by adding 10 mL water, and it was extracted with ethyl acetate. The organic layer was washed with brine and dried over $Na_2SO_4$. The solvent was removed under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a colorless oil (477 mg, 47%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.07 (d, *J* = 7

Hz, 1H), 7.98 (d, *J* = 8 Hz, 1H), 7.91-7.89 (m, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.75-7.73 (m, 1H), 7.53-7.46 (m, 3H), 7.15 (d, *J* = 8Hz, 1H), 3.95 (s, 3H), 3.74 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 195.2, 153.0, 147.5, 143.0, 136.3, 133.6, 131.3, 131.0, 128.4, 128.3, 126.8, 126.0, 126.0, 124.2, 120.4, 116.4, 56.0, 53.8.

**4-(2-(4-Fluorobenzyl)-5,6-dimethoxypyridin-3-yl)benzonitrile (120).**

4-(2-Bromo-5,6-dimethoxypyridin-3-yl)benzonitrile, **94**, (300 mg, 0.94 mmol), 0.5 M in THF (4-fluorophenyl)zinc(II) chloride (4.7 mL, 2.35 mmol), Johnphos (56 mg, 0.19 mmol), $Pd(OAc)_2$ (60 mg, 0.09 mmol) and $K_2CO_3$ (325 mg, 2.35 mmol)were dissolved in dioxane (20 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Then, reaction mixture was refluxed for 8 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the desired product as a white solid (263 mg, 80%); mp 112-114 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.69 (d, *J* = 8 Hz, 2H), 7.34 (d, *J* = 8 Hz, 2H), 7.02 (dd, *J* = 9 Hz, *J* = 6 Hz, 2H), 6.89 (t, *J* = 9 Hz, 2H), 6.87 (s, 1H), 4.03 (s, 3H), 3.88 (s, 2H), 3.86 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 161.4 ($J_{C,F}$ = 243 Hz), 153.5, 144.7, 144.4, 142.3, 135.8 ($J_{C,F}$ = 3 Hz), 132.2, 130.2, 130.0 ($J_{C,F}$ = 8 Hz), 128.1, 119.1, 118.6, 114.9 ($J_{C,F}$ = 21 Hz), 111.3, 55.9, 53.9, 39.4; HRMS (ESI) calculated for $C_{21}H_{18}FN_2O_2$ $(M+H)^+$ 349.1437, found 349.1347.

**4-(5,6-Dimethoxy-2-(naphthalen-1-ylmethyl)pyridin-3-yl)benzonitrile (121).**

4-(2-Bromo-5,6-dimethoxypyridin-3-yl)benzonitrile, **94**, (200 mg, 0.63 mmol), 0.25 M in THF (naphthalen-1-ylmethyl)zinc(II) chloride (6.27 mL, 1.57 mmol), Johnphos (37 mg, 0.13 mmol), $Pd(OAc)_2$ (42 mg, 0.06 mmol) and $K_2CO_3$(217mg, 1.57 mmol) were dissolved in dioxane (20 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Then, reaction mixture was refluxed for 2 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (202 mg, 85%); mp 173-175 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.80 (d, *J* = 8 Hz, 1H), 7.84 (d, *J* = 8 Hz, 1H), *7*.71 (d, *J* = 8 Hz, 1H), 7.65 (dd, *J* = 7 Hz, *J* = 2 Hz, 2H), 7.49-7.43 (m, 2H), 7.40 (dd, *J* = 7 Hz, *J* = 2 Hz, 2H), 7.32 (dd, *J* = 8 Hz, *J* = 7 Hz, 1H), 6.98 (dd, *J* = 7 Hz, *J* = 1Hz, 1H), 6.94 (s, 1H), 4.43 (s, 2H), 3.94 (s, 3H), 3.90 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 153.4, 144.8, 144.3, 142.3, 136.4, 133.8, 132.2, 132.0, 130.1, 128.6, 128.5, 126.8, 126.6, 125.7, 125.5, 125.3, 124.2, 119.1, 118.7, 111.2, 55.9, 53.9, 37.6; HRMS (ESI) calculated for $C_{25}H_{20}N_2O_2Na$ $(M+Na)^+$ 403.1417, found 403.1423.

**4-(5,6-Dimethoxy-2-(naphthalen-2-ylmethyl)pyridin-3-yl)benzonitrile (122).**

4-(2-Bromo-5,6-dimethoxypyridin-3-yl)benzonitrile, **94**, (200 mg, 0.63 mmol), 0.5 M in THF (naphthalen-2-ylmethyl)zinc(II) bromide (3.14 mL, 1.57 mmol), Johnphos (37 mg, 0.13 mmol), $Pd(OAc)_2$ (42 mg, 0.06 mmol) and $K_2CO_3$ (217mg, 1.57 mmol) were dissolved in dioxane (20 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for 8 hours. After the reaction was completed as determined by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (207 mg, 87%); mp 151-153 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.81 (dd, *J* = 7 Hz, *J* = 2 Hz, 1H), 7.75-7.68 (m, 4H), 7.48-7.44 (m, 3H), 7.39 (dd, *J* = 7 Hz, *J* = 2 Hz, 2H), 7.33 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 6.93 (s, 1H), 4.12 (s, 2H), 4.09 (s, 3H), 3.90 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 153.5, 144.8, 144.5, 142.3, 138.0, 133.5, 132.1, 132.0, 130.3, 128.3, 127.8, 127.6, 127.5, 127.4, 126.8, 126.0, 125.4, 119.1, 118.7, 111.2, 55.9, 53.9, 40.5; HRMS (ESI) calculated for $C_{25}H_{21}N_2O_2$ $(M+H)^+$ 381.1598, found 381.1596.

**4-(2-(4-Fluorobenzyl)-5-hydroxy-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile (123).**

4-(2-(4-Fluorobenzyl)-5,6-dimethoxypyridin-3-yl)benzonitrile, **120**, (146 mg, 0.42 mmol) was dissolved in anhydrous dichloromethane (10 mL). The reaction mixture was cooled to 0 $^oC$, and 1M $BBr_3$ in dichloromethane (4.2 mL, 4.2mmol) was added. It was then allowed to warm to room temperature and stirred for 18 hours. The solvent was then

removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a white solid (63 mg, 53%); mp 191-193 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 11.95 (brs, 1H), 9.26 (brs, 1H), 7.83 (d, *J* = 8 Hz, 2H), 7.44 (d, *J* = 8 Hz, 2H), 7.06 (t, *J* = 9 Hz, 2H), 6.96 (dd, *J* = 8 Hz, *J* = 6 Hz, 2H), 6.70 (s, 1H), 3.79 (s, 2H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 160.8 ($J_{C,F}$ = 241 Hz), 158.4, 145.7, 143.2, 134.7, 132.7, 132.4, 130.0, 129.6 ($J_{C,F}$ = 8 Hz), 118.7, 117.7, 116.8, 115.1 ($J_{C,F}$ = 21 Hz), 109.7, 34.1; HRMS (ESI) calculated for $C_{19}H_{14}FN_2O_2$ $(M+H)^+$ 321.1034, found 321.1019.

**4-(5-Hydroxy-2-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile (124).**

4-(5,6-Dimethoxy-2-(naphthalen-1-ylmethyl)pyridin-3-yl)benzonitrile, **121**, (116 mg, 0.31 mmol) was dissolved in anhydrous dichloromethane (10 mL). The reaction mixture was cooled to 0 $^oC$, and 1M $BBr_3$ in dichloromethane (3.05 mL, 3.05mmol) was added. It was then allowed to warm to room temperature and stirred for 18 hours. The solvent was removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a white solid (37 mg, 35%)**;** mp 133-135 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 11.89 (brs,

1H), 9.29 (brs, 1H), 7.94-7.89 (m, 2H), 7.80 (d, *J* = 8 Hz, 1H), 7.71 (d, *J* = 8 Hz, 2H), 7.55-7.49 (m, 2H), 7.44 (d, *J* = 8 Hz, 1H), 7.40 (d, *J* = 8 Hz, 2H), 6.98 (d, *J* = 7 Hz, 1H), 6.81 (s, 1H), 4.23 (s, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ158.5, 145.9, 143.1, 135.0, 133.2, 132.3, 132.0, 131.0, 129.4, 128.5, 126.9, 126.2, 125.9, 125.6, 124.7, 123.2, 118.6, 117.6, 109.6, 32.5; HRMS (ESI) calculated for $C_{23}H_{16}N_2O_2Na$ $(M+Na)^+$ 375.1104, found 375.1107.

**4-(5-Hydroxy-2-(naphthalen-2-ylmethyl)-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile (125).**

4-(5,6-Dimethoxy-2-(naphthalen-2-ylmethyl)pyridin-3-yl)benzonitrile, **122**, (139 mg, 0.37 mmol) was dissolved in anhydrous dichloromethane (10 mL). The reaction mixture was cooled to 0 ºC, and the 1M in dichloromethane $BBr_3$ (3.65 mL, 3.65mmol) was added. It was then allowed to warm to room temperature and stirred for 18 hours. The solvent was removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a white solid (44 mg, 34%); mp 167-169 ºC;$^1$H NMR (400 MHz) (DMSO-$d_6$) δ 12.00 (brs, 1H), 9.26 (brs, 1H), 7.86-7.78 (m, 5H), 7.48-7.44 (m, 4H), 7.41 (s, 1H), 7.14 (d, *J* = 8 Hz, 1H), 6.76 (s, 1H), 3.98 (s, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.4, 145.8, 143.3, 136.3, 132.9, 132.6, 132.4, 131.6, 129.9, 128.0, 127.4, 126.5, 126.2, 125.9,

125.6, 118.7, 117.7, 117.1, 109.7, 35.1;HRMS (ESI) calculated for $C_{23}H_{16}N_2O_2Na$ $(M+Na)^+$ 375.1104, found 375.1106.

**5-(4-(1*H*-Tetrazol-5-yl)phenyl)-6-(4-fluorobenzyl)-3-hydroxypyridin-2(1*H*)-one (126).**

4-(2-(4-Fluorobenzyl)-5-hydroxy-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile, **123**, (70 mg, 0.22 mmol) and $NaN_3$ (57 mg, 0.88 mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with catalytic amount of acetic acid. It was sealed and heated at 130$^o$C for overnight. The reaction was allowed to cool to room temperature, which resulted in the formation of a brownish suspension. The solvent was removed under reduced pressure, and the residue was suspended in 2N HCl. The suspension was filtered to give the desired product as a white solid (33 mg, 41%)**;** dec. 154-156 $^o$C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 11.91 (brs, 1H), 9.26 (brs, 1H), 8.03 (d, *J* = 8 Hz, 2H), 7.49 (d, *J* = 8 Hz, 2H), 7.07 (t, *J* = 9 Hz, 2H), 7.01-6.97 (m 2H), 6.74 (s, 1H), 3.83 (s, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 160.8 ($J_{C,F}$ = 241 Hz), 158.4, 145.6, 141.1, 134.9, 132.4, 130.0, 129.6 ($J_{C,F}$ = 8 Hz), 127.1, 118.0, 117.3, 115.1 ($J_{C,F}$ = 21 Hz), 34.1; HRMS (ESI) calculated for $C_{19}H_{15}FN_5O_2$ $(M+H)^+$ 364.1204, found 364.1182.

**5-(4-(1*H*-Tetrazol-5-yl)phenyl)-3-hydroxy-6-(naphthalen-1-ylmethyl)pyridin-2(1*H*)-one (127).**

4-(5-Hydroxy-2-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile, **124**, (25 mg, 0.07 mmol) and $NaN_3$ (18 mg, 0.28 mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with catalytic amount of acetic acid. It was sealed and heated at 130 $^oC$ for overnight. The reaction was allowed to cool to room temperature, which resulted in a brownish suspension. The solvent was removed under reduced pressure, and the residue was suspended in 2N HCl. The suspension was filtered to give the product as a white solid (25 mg, 89%)**;** dec. 156-158 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 11.87 (brs, 1H), 9.27 (brs, 1H), 7.96-7.90 (m, 4H), 7.82 (d, *J* = 8 Hz, 1H), 7.56-7.50 (m, 2H), 7.48-7.44 (m, 3H), 7.04 (d, *J* = 8 Hz, 1H), 6.87 (s, 1H), 4.29 (s, 2H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 158.5, 145.8, 141.0, 135.1, 133.2, 131.7, 131.0, 129.4, 128.5, 127.0, 126.9, 126.2, 125.9, 125.6, 124.8, 123.2, 118.0, 117.9, 32.6; HRMS (ESI) calculated for $C_{23}H_{18}FN_5O_2$ $(M+H)^+$ 396.1455, found 396.1455.

**5-(4-(1*H*-Tetrazol-5-yl)phenyl)-3-hydroxy-6-(naphthalen-2-ylmethyl)pyridin-2(1*H*)-one (128).**

4-(5-Hydroxy-2-(naphthalen-2-ylmethyl)-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile, **125**, (35 mg, 0.10mmol) and $NaN_3$ (26 mg, 0.40mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with a catalytic amount of acetic acid. It was sealed and heated at 130$^oC$ for overnight. The reaction was allowed to cool to room temperature, which resulted in a brownish suspension. The solvent was removed under reduced pressure, and the residue suspended in 2N HCl. The suspension was filtered to give the desired product as a white solid (15 mg, 38%)**;** dec. 64-66 $^oC$; $^1H$ NMR (400

MHz) (DMSO-$d_6$) δ 11.97 (brs ,1H), 9.25 (brs, 1H), 8.01 (d, *J* = 8 Hz, 2H), 7.96 (s, 1H), 7.86-7.84 (m, 1H), 7.82-7.77 (m, 2H), 7.52 (d, *J* = 8 Hz, 2H), 7.47-7.45 (m, 2H), 7.18-7.16 (m, 1H), 6.73 (s, 1H), 4.02 (s, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 158.4, 145.6, 141.2, 136.5, 132.9, 132.3, 131.6, 130.0, 127.9, 127.42, 127.40, 127.1, 126.5, 126.2, 125.9, 125.6, 118.1, 117.6, 35.1; HRMS (ESI) calculated for $C_{23}H_{18}FN_5O_2$ $(M+H)^+$ 396.1455, found 396.1463.

**(2-Bromo-5,6-dimethoxypyridin-3-yl)(4-fluorophenyl)methanone (129).**

2,3-Dibromo-5,6-dimethoxypyridine, **115**, (546 mg, 1.84 mmol) was dissolved in toluene (5 mL), and was cooled to -10 $^o$C (acetone/ice). This solution was treated with 1M trimethylsilylmethylithium in pentane (2.02 mL, 2.02mmol). After reaction mixture was stirred for 30 minutes at -10 $^o$C, 4-fluoro-N-methoxy-N-methylbenzamide (674 mg, 3.68 mmol) in toluene (5 mL) was added slowly. The mixture was stirred an hour at -10 $^o$C, which was then stopped by adding 10 mL of water. The mixture was then diluted with ethyl acetate. The organic solution was washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$, which was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the desired product as a white solid (379 mg, 60%); mp 131-133 $^o$C; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.86 (dd, *J* = 9 Hz, *J* = 5 Hz, 2H), 7.16 (t, *J* = 9 Hz, 2H), 7.06 (s, 1H), 4.09 (s, 3H), 3.87 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 192.8, 166.2 ($J_{C,F}$ = 255 Hz), 154.6, 143.6, 132.8 ($J_{C,F}$ = 9 Hz), 129.4, 119.1, 116.0 ($J_{C,F}$ = 22 Hz), 56.3, 55.0; HRMS (ESI) calculated for $C_{14}H_{12}BrFNO_3$ $(M+H)^+$ 339.9979, found 339.9984.

**(2-Bromo-5,6-dimethoxypyridin-3-yl)(naphthalen-1-yl)methanone (130).**

2,3-Dibromo-5,6-dimethoxypyridine, **115**, (546 mg, 1.84 mmol) was dissolved in toluene (5 mL) and it was cooled to -10 $^{o}$C (acetone/ice). The reaction mixture was treated with 1M trimethylsilylmethylithium in pentane (2.02 mL, 2.02 mmol). After it was stirred for 30 minutes at -10 $^{o}$C, N-methoxy-N-methyl-1-naphthamide (792 mg, 3.68 mmol) in toluene (5 mL) was slowly added. The reaction mixture was stirred an hour at -10 $^{o}$C and then stopped by adding 10 mL of water. The mixture was diluted with ethyl acetate, which was washed with water, followed by brine. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give the product as a white solid (226 mg, 33%); mp 115-117 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.77 (d, *J* = 8 Hz, 1H), 8.12 (d, *J* = 8 Hz, 1H), 8.00 (d, *J* = 8 Hz, 1H), 7.75-7.64 (m, 4H), 7.34 (s, 1H), 7.53 (t, *J* = 8 Hz, 1H), 4.17 (s, 3H), 3.95 (s, 3H);$^{13}$C NMR (100 MHz) ($CDCl_3$) δ 196.0, 154.7, 143.5, 134.6, 134.0, 133.6, 131.1, 131.0, 128.5, 128.3, 126.7, 126.0, 125.8, 124.4, 124.2, 120.1, 56.3, 55.0; HRMS (ESI) calculated for $C_{18}H_{15}BrNO_3$ $(M+H)^+$ 372.0230, found 372.0233.

**(2-Bromo-5,6-dimethoxypyridin-3-yl)(naphthalen-2-yl)methanone (131).**

2,3-Dibromo-5,6-dimethoxypyridine, **115**, (1.64g, 5.52 mmol) was dissolved in toluene (10 mL) and was cooled to 0 $^{o}$C. This solution was treated with 1M trimethylsilylmethylithium in pentane (6.07 mL, 6.07 mmol). After it was stirred for 30

minutes at 0 $^{o}$C, N-methoxy-N-methyl-2-naphthamide (2.38 g, 11.04 mmol) in toluene (10 mL) was slowly added. The mixture was stirred an hour at 0 $^{o}$C, which was stopped by adding 10 mL of water. The mixture was diluted with ethyl acetate, which was then washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a white solid (1.51 g, 73%); mp 152-154 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.15 (s, 1H), 7.90 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.84-7.79 (m, 3H), 7.52 (t, *J* = 7 Hz, 1H), 7.45 (t, *J* = 8 Hz, 1H), 7.05 (s, 1H), 4.02 (s, 3H), 3.78 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 194.2, 154.5, 143.5, 135.9, 133.7, 132.9, 132.5, 129.9, 129.8, 129.0, 128.7, 127.9, 127.0, 124.9, 119.3, 56.3, 54.9; HRMS (ESI) calculated for $C_{18}H_{15}BrNO_3$ $(M+H)^+$ 372.0230, found 372.0239.

**(2-Bromo-5,6-dimethoxypyridin-3-yl)(4-fluorophenyl)methanol (132).**

(2-Bromo-5,6-dimethoxypyridin-3-yl)(4-fluorophenyl)methanone, **129**, (378 mg, 1.11 mmol) was dissolved in THF (10 mL).and cooled to 0 $^{o}$C. The reaction mixture was then treated with $NaBH_4$ (63 mg, 1.67 mmol), which was then allowed to slowly warm to room temperature. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, which was then washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a colorless oil (269 mg, 71%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.35 (dd, *J* = 9 Hz, *J* = 5 Hz, 2H), 7.19 (s, 1H), 7.01 (t, *J* = 9 Hz, 2H), 6.04 (s,

1H), 3.99 (s, 3H), 3.81 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 162.3 ($J_{C,F}$ = 245 Hz), 153.0, 144.0, 137.8 ($J_{C,F}$ = 3 Hz), 131.9, 128.3 ($J_{C,F}$ = 9 Hz), 126.1, 118.1, 115.4 ($J_{C,F}$ = 21 Hz), 73.0, 56.1, 54.5; HRMS (ESI) calculated for $C_{14}H_{14}BrFNO_3$ $(M+H)^+$ 342.0136, found 342.0143.

**(2-Bromo-5,6-dimethoxypyridin-3-yl)(naphthalen-1-yl)methanol (133).**

(2-Bromo-5,6-dimethoxypyridin-3-yl)(naphthalen-1-yl)methanone, **130**, (927 mg, 2.49 mmol) was dissolved in anhydrous THF (10 mL) and was cooled to 0ºC. The reaction mixture was treated with $NaBH_4$ (188 mg, 4.88 mmol), which was then allowed to warm to room temperature. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, which was then washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a colorless oil (752 mg, 81%); $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 8.24 (d, *J* = 8 Hz, 1H), 7.96 (d, *J* = 8 Hz, 1H), 7.87 (d, *J* = 8 Hz, 1H), 7.60 (t, *J* = 7 Hz, 1H), 7.54 (t, *J* = 7 Hz, 1H), 7.46 (t, *J* = 8 Hz, 1H), 7.40 (s, 1H), 7.28 (d, *J* = 7 Hz, 1H), 6.52 (d, *J* = 6 Hz, 1H), 6.25 (d, *J* = 6 Hz, 1H), 3.89 (s, 3H), 3.74 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 152.4, 143.5, 138.5, 133.4, 132.6, 130.9, 128.6, 128.0, 126.2, 125.7, 125.6, 125.3, 124.3, 123.7, 119.9, 69.4, 55.8, 53.9; HRMS (ESI) calculated for $C_{18}H_{17}BrNO_3$ $(M+H)^+$ 374.0386, found 374.0388.

**(2-Bromo-5,6-dimethoxypyridin-3-yl)(naphthalen-2-yl)methanol (134).**

(2-Bromo-5,6-dimethoxypyridin-3-yl)(naphthalen-2-yl)methanone , **131**, (1.0 g, 2.69 mmol) was dissolved in anhydrous THF (10 mL), and was cooled to 0 $^{o}$C. The reaction mixture was treated with $NaBH_4$ (203 mg, 5.37 mmol), which was then allowed to warm to room temperature. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, which was then washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a colorless oil (869 mg, 86%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.90 (s, 1H), 7.85-7.80 (m, 3H), 7.50-7.46 (m, 2H), 7.44 (d, *J* = 2 Hz, 1H), 7.24 (s, 1H), 6.27 (s, 1H), 4.02 (s, 3H), 3.80 (s, 3H), 2.57 (brs, 1H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 153.0, 144,0, 139.4, 133.2, 132.9, 132.0, 128.4, 128.2, 127.7, 126.4, 126.3, 126.2, 125.2, 124.5, 118.5, 73.7, 56.1, 54.6; HRMS (ESI) calculated for $C_{18}H_{17}BrNO_3$ $(M+H)^+$ 374.0386, found 374.0389.

**2-Bromo-3-(4-fluorobenzyl)-5,6-dimethoxypyridine (135).**

(2-Bromo-5,6-dimethoxypyridin-3-yl)(4-fluorophenyl)-methanol, **132**, (221 mg, 0.65 mmol) was dissolved in 1,2-dichloroethane (5 mL). The reaction mixture was treated with TFA (0.2 mL, 2.91 mmol) followed by triethylsilane (0.3 mL, 1.94 mmol). It was heated to 50 $^{o}$C and stirred for 3 hours. It was allowed to cool to room temperature and was diluted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$, followed by brine. It was dried over $Na_2SO_4$ and was concentrated under reduced

pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a colorless oil (211 mg, 91%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.13 (dd, *J* = 9 Hz, *J* = 5 Hz, 2H), 6.97 (t, *J* = 9 Hz, 2H), 6.77 (s, 1H), 3.99 (s, 3H), 3.96 (s, 2H), 3.76 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 161.6 ($J_{C,F}$ = 243 Hz), 152.3, 143.6, 134.8 ($J_{C,F}$ = 3 Hz), 130.1 ($J_{C,F}$ = 8 Hz), 129.2, 128.1, 120.8, 115.4 ($J_{C,F}$ = 21 Hz), 56.1, 54.4, 39.4; HRMS (ESI) calculated for $C_{14}H_{14}BrFNO_2$ $(M+H)^+$ 326.0186, found 326.0194.

**2-Bromo-5,6-dimethoxy-3-(naphthalen-1-ylmethyl)pyridine (136).**

(2-Bromo-5,6-dimethoxypyridin-3-yl)(naphthalen-1-yl)methanol, **133**, (752 mg, 2.01 mmol) was dissolved in 1,2-dichloroethane (20 mL). The reaction mixture was treated with TFA (0.69 mL, 9.04 mmol) followed by triethylsilane (0.96 mL, 6.03 mmol). It was then heated to 50 $^{o}$C and stirred for 3 hours. It was allowed to cool to room temperature and was diluted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$, and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a colorless oil (720 mg, 100%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.93-7.87 (m, 2H), 7.79 (d, *J* = 8 Hz, 1H), 7.51-7.48 (m, 2H), 7.43 (t, *J* = 8 Hz, 1H), 7.22 (d, *J* = 7 Hz, 1H), 6.59 (s, 1H), 4.43 (s, 2H), 4.03 (s, 3H), 3.55 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 152.3, 143.6, 134.8, 134.0, 132.0, 128.9, 128.8, 128.1, 127.6, 127.0, 126.3, 125.8, 125.5, 123.9, 120.7, 55.9, 54.4, 37.6; HRMS (ESI) calculated for $C_{18}H_{17}BrNO_2$ $(M+H)^+$ 358.0437, found 358.0438.

**2-Bromo-5,6-dimethoxy-3-(naphthalen-2-ylmethyl)pyridine (137).**

(2-Bromo-5,6-dimethoxypyridin-3-yl)(naphthalen-2-yl)methanol, **134**, (153 mg, 0.41 mmol) was dissolved in 1,2-dichloroethane (5 mL). The reaction mixture was treated with TFA (0.20 mL, 1.23 mmol) followed by triethylsilane (0.14 mL, 1.84 mmol). It was then heated to 50 $^{o}$C and stirred for 3 hours. The reaction mixture was allowed to cool to room temperature and was diluted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$, and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a colorless oil (137 mg, 93%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.83-7.77 (m, 4H), 7.60 (s, 1H), 7.48-7.45 (m, 2H), 7.34 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 4.18 (s, 2H), 4.03 (s, 3H), 3.73 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 152.3, 143.7, 136.7, 133.6, 132.3, 129.3, 128.34, 128.29, 127.7, 127.6, 127.2, 127.1, 126.2, 125.6, 121.0, 56.1, 54.4, 40.4; HRMS (ESI) calculated for $C_{18}H_{17}BrNO_2$ $(M+H)^+$ 358.0437, found 358.0347.

**4-(3-(4-Fluorobenzyl)-5,6-dimethoxypyridin-2-yl)benzonitrile (138).**

2-Bromo-3-(4-fluorobenzyl)-5,6-dimethoxypyridine, **135**, (190 mg, 0.58 mmol), 4-cyanophenylboronic acid (129 mg, 0.88 mmol), $Pd(PPh_3)_4$ (67 mg, 0.058 mmol) and $Na_2CO_3$ (185 mg, 1.75 mmol) were dissolved in a mixture of dioxane (12 mL) and water (4 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The

reaction mixture was then refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the desired product as a white solid (203 mg, 100%); mp 141-143 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.68 (d, $J$ = 8 Hz, 2H), 7.61 (d, $J$ = 8 Hz, 2H), 7.01-6.99 (m, 4H), 6.88 (s, 1H), 4.05 (s, 3H), 3.99 (s, 2H), 3.86 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 160.5 ($J_{C,F}$ = 243 Hz), 152.6, 144.4, 144.0, 143.5, 136.1 ($J_{C,F}$ = 4 Hz), 131.9, 129.8 ($J_{C,F}$ = 7 Hz), 136.4, 120.0, 118.9, 115.5 ($J_{C,F}$ = 22 Hz), 111.2, 55.9, 53.8, 39.1; HRMS (ESI) calculated for $C_{21}H_{18}FN_2O_2$ $(M+H)^+$ 349.1347, found 349.1356.

**4-(5,6-Dimethoxy-3-(naphthalen-1-ylmethyl)pyridin-2-yl)benzonitrile (139).**

2-Bromo-5,6-dimethoxy-3-(naphthalen-1-ylmethyl)pyridine, **136**, (720 mg, 2.01 mmol), 4-cyanophenylboronic acid (443 mg, 3.01 mmol), $Pd(PPh_3)_4$ (232 mg, 0.20 mmol) and $Na_2CO_3$ (639 mg, 6.03 mmol) were dissolved in a mixture of dioxane (30 mL) and water (10 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for overnight. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give the product as a white solid (250 mg, 33%); mp 172-174 $^oC$;

$^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 7.93 (d, *J* = 8 Hz, 1H), 7.86 (d, *J* = 8 Hz, 1H), 7.80 (d, *J* = 8 Hz, 2H), 7.71 (d, *J* = 8 Hz, 2H), 7.53-7.46 (m, 2H), 7.42 (t, *J* = 8 Hz, 1H), 7.14 (s, 1H), 7.09 (d, J = 7 Hz, 1H), 4.43 (s, 2H), 3.92 (s, 3H), 3.68 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ152.1, 144.1, 143.6, 142.7, 136.5, 133.3, 312.0, 131.2, 129.6, 128.6, 126.9, 126.3, 126.2, 126.0, 125.8, 125.6, 123.3, 121.1, 118.7, 110.1, 55.6, 53.0, 34.5; HRMS (ESI) calculated for $C_{25}H_{21}N_2O_2$ $(M+H)^+$ 381.1598, found 381.1597.

**4-(5,6-Dimethoxy-3-(naphthalen-2-ylmethyl)pyridin-2-yl)benzonitrile (140).**

2-Bromo-5,6-dimethoxy-3-(naphthalen-2-ylmethyl)pyridine, **137**, (137 mg, 0.38 mmol), 4-cyanophenylboronic acid (84 mg, 0.57 mmol), $Pd(PPh_3)_4$ (44 mg, 0.04 mmol) and $Na_2CO_3$ (121 mg, 1.15 mmol) were dissolved in a mixture of dioxane (12 mL) and water (4 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for overnight. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (133 mg, 92%); mp 61-63 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.86-7.76 (m, 4H), 7.68-7.67 (m, 3H), 7.50-7.48 (m, 3H), 7.24 (dd, *J* = 8 Hz, *J* = 1 Hz, 1H), 6.98 (s, 1H), 4.20 (s, 2H), 4.11 (s, 3H), 3.84 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 152.6, 144.5, 144.1, 143.6, 138.1, 133.6, 132.9, 132.2, 131.9, 129.9, 128.5, 127.9, 127.7, 127.6, 127.0, 126.8, 126.3,

125.7, 120.3, 119.0, 111.1, 55.9, 53.8, 38.1; HRMS (ESI) calculated for $C_{25}H_{21}BrN_2O_2$ $(M+H)^+$ 381.1598, found 381.1606.

**4-(3-(4-Fluorobenzyl)-5-hydroxy-6-oxo-1,6-dihydropyridin-2-yl)benzonitrile (141).**

4-(3-(4-Fluorobenzyl)-5,6-dimethoxypyridin-2-yl)benzonitrile, **138**, (145 mg, 0.42 mmol) was dissolved in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0 $^oC$ and1M $BBr_3$in dichloromethane (4.2 mL, 4.2 mmol) was added. It was then allowed to warm to room temperature and stirred for overnight. Theolvent was then removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was then washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a white solid (70 mg, 53%); mp 225-227 $^oC$; $^1H$ NMR (400 MHz) (MeOD) δ 7.81 (d, $J$ = 8 Hz, 2H), 7.55 (d, $J$ = 8 Hz, 2H), 7.02 (dd, $J$ = 8 Hz, $J$ = 6 Hz, 2H), 6.96 (t, $J$ = 9 Hz, 2H), 6.75 (s, 1H), 3.66 (s, 2H); $^{13}C$ NMR (100 MHz) (MeOD) δ 162.9 ($J_{C,F}$ = 242 Hz), 159.9, 148.4, 139.8, 137.4, ($J_{C,F}$ = 3 Hz), 133.8, 133.5, 131.6, 131.1 ($J_{C,F}$ = 8 Hz), 120.9, 119.3, 119.1, 116.2 ($J_{C,F}$ = 21 Hz), 113.8, 36.2; HRMS (ESI) calculated for $C_{19}H_{14}FN_2O_2$ $(M+H)^+$ 321.1034, found 321.1046.

**4-(5-Hydroxy-3-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyridin-2-yl)benzonitrile (142).**

4-(5,6-Dimethoxy-3-(naphthalen-1-ylmethyl)pyridin-2-yl)benzonitrile, **139**, (250 mg, 0.66 mmol) was dissolve in anhydrous dichloromethane (10 mL). The reaction mixture was cooled to 0 $^{o}$C, and 1M $BBr_3$in dichloromethane (6.57 mL, 6.57 mmol) was added. The reaction mixture was then allowed to warm to room temperature and was stirred for overnight. Then, solvent was removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was then washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$, and concentrated under reduce pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dochloromethane) to give the product as a white solid (92 mg, 40%); mp 289-291 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.91 (brs, 1H), 9.29 (brs, 1H), 7.93-7.89 (m, 3H), 7.91 (d, *J* = 8 Hz, 1H), 7.73 (d, *J* = 8 Hz, 1H), 7.64 (d, *J* = 7 Hz, 2H), 7.52-7.44 (m, 3H), 7.24 (d, *J* = 7 Hz, 1H), 6.49 (s, 1H), 4.07 (s, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 157.7, 146.8, 138.4, 136.1, 133.4, 132.2, 131.3, 130.2, 128.5, 126.9, 126.3, 126.1, 125.7, 125.6, 123.4, 118.5, 118.0, 115.2, 111.1, 33.0; HRMS (ESI) calculated for $C_{23}H_{17}N_2O_2$ $(M+H)^+$ 353.1285, found 353.1284.

**4-(5-Hydroxy-3-(naphthalen-2-ylmethyl)-6-oxo-1,6-dihydropyridin-2-yl)benzonitrile (143).**

4-(5,6-Dimethoxy-3-(naphthalen-2-ylmethyl)pyridin-2-yl)benzonitrile, **140**, (133 mg, 0.35 mmol) was dissolve in anhydrous dichloromethane (5 mL). The reaction mixture was cooled to 0 $^{o}$C, and 1M $BBr_3$ in dichloromethane (3.5 mL, 3.5mmol) was added. It was then allowed to warm to room temperature and stirred for overnight. Then, solvent

was then removed under reduced pressure. The resulting residue was diluted with ethyl acetate, which was washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a white solid (89 mg, 73%); mp 194-196 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 7.91 (d, *J* = 7 Hz, 2H), 7.86-7.80 (m, 3H), 7.61 (d, *J* = 7 Hz, 2H), 7.52 (s, 1H), 7.50-7.44 (m, 2H), 7.18 (d, *J* = 8 Hz, 1H), 6.64 (s, 1H), 3.77 (s, 2H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 157.6, 146.8, 138.5, 138.1, 133.1, 132.4, 132.2, 131.6, 130.5, 128.0, 127.41, 127.40, 127.03, 126.3, 126.1, 125.5, 118.5, 118.4, 115.6, 111.1, 35.6; HRMS (ESI) calculated for $C_{23}H_{17}N_2O_2$ $(M+H)^+$ 353.1285, found 353.1295.

**6-(4-(1*H*-Tetrazol-5-yl)phenyl)-5-(4-fluorobenzyl)-3-hydroxypyridin-2(1*H*)-one (144).**

4-(3-(4-Fluorobenzyl)-5-hydroxy-6-oxo-1,6-dihydropyridin-2-yl)benzonitrile, **141**, (140 mg, 0.44 mmol) and $NaN_3$ (114 mg, 1.76 mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with catalytic amount of acetic acid. It was sealed and heated at 130 $^oC$ for overnight. It was allowed to cool to room temperature, which resulted in the formation of a brownish suspension. Solvent was removed under reduced pressure, and the residue was suspended in 2N HCl. The suspension was filtered to give the desired product as a white solid (73 mg, 46%)**;** dec. 181-183 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 11.83 (brs ,1H), 9.23 (brs, 1H), 8.09 (d, *J* = 7 Hz, 2H), 7.60 (d, *J* = 7 Hz, 2H), 7.08-7.06 (m 4H), 6.60 (s, 1H), 3.64 (s, 2H); $^{13}C$ NMR (100 MHz)

(DMSO-$d_6$) δ 160.7 ($J_{C,F}$ = 241 Hz), 157.7, 146.6, 136.7 ($J_{C,F}$ = 3 Hz), 136.4, 132.7, 130.5, 130.0 ($J_{C,F}$ = 8 Hz), 126.8, 124.2, 118.1, 115.1 ($J_{C,F}$ = 21 Hz), 34.6; HRMS (ESI) calculated for $C_{19}H_{15}FN_5O_2$ $(M+H)^+$ 364.1204, found 364.1202.

**6-(4-(1*H*-Tetrazol-5-yl)phenyl)-3-hydroxy-5-(naphthalen-1-ylmethyl)pyridin-2(1*H*)-one (145).**

4-(5-Hydroxy-3-(naphthalen-1-ylmethyl)-6-oxo-1,6-dihydropyridin-2-yl)benzonitrile, **142**, (40 mg, 0.11 mmol) and $NaN_3$ (30 mg, 0.46 mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with catalytic amount of acetic acid. It was sealed, and it was heated at 130 $^oC$ for overnight. It was allowed to cool to room temperature, which result in the formation of a brownish suspension. Solvent was removed under reduced pressure, and the residue was suspended in 2N HCl. The suspension was filtered to give the product as a white solid (20 mg, 44%)**;** dec. 179-181 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 11.93 (brs, 1H), 8.08 (d, *J* = 7 Hz, 2H), 7.92 (d, *J* = 8 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 7.69 (d, *J* = 7 Hz, 2H), 7.51 – 7.43 (m, 3H), 7.28 (d, *J* = 7 Hz, 1H), 6.50 (s, 1H), 4.11 (s, 2H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 158.3, 157.9, 157.8, 146.5, 136.5, 136.3, 133.4, 132.7, 131.3, 130.3, 128.5, 126.89, 126.85, 126.4, 126.1, 125.7, 125.6, 123.4, 118.0, 114.7, 33.1; HRMS (ESI) calculated for $C_{23}H_{18}FN_5O_2$ $(M+H)^+$ 396.1455, found 396.1456.

**6-(4-(1*H*-Tetrazol-5-yl)phenyl)-3-hydroxy-5-(naphthalen-2-ylmethyl)pyridin-2(1*H*)-one (146).**

4-(5-Hydroxy-3-(naphthalen-2-ylmethyl)-6-oxo-1,6-dihydropyridin-2-yl)benzonitrile, **143**, (50 mg, 0.14 mmol) and $NaN_3$ (37 mg, 0.57mmol) were dissolved in anhydrous DMF (1 mL). The reaction mixture was treated with a catalytic amount of acetic acid. It was sealed, and heated at 130 $^oC$ for overnight. It was allowed to cool to room temperature, which resulted in the formation of a brownish suspension. Solvent was removed under reduced pressure, and the residue was suspended in 2N HCl. The suspension was filtered to give the desired product as a white solid (16 mg, 28%)**;** dec. 197-199 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 11.85 (brs, 1H), 9.20 (brs, 1H), 8.09 (d, *J* = 8 Hz, 2H), 7.86-7.80 (m, 3H), 7.65 (d, *J* = 8 Hz, 2H), 7.56 (s, 1H), 7.47-7.45 (m, 2H), 7.21 (d, *J* = 9 Hz, 2H), 6.64 (s, 1H), 3.82 (brs, 1H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 157.8, 146.6, 138.3, 136.5, 133.1, 131.6, 130.5, 128.0, 127.42, 127.39, 127.1, 126.8, 126.3, 126.1, 125.4, 124.2, 118.3, 35.7; HRMS (ESI) calculated for $C_{23}H_{18}FN_5O_2$ $(M+H)^+$ 396.1455, found 396.1462.

**2-(*t*-Butoxy)-6-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridine (147).**

2-(*t*-Butoxy)-6-iodo-3-((2-methoxyethoxy)methoxy)pyridine, **111**, (5.10 g, 13.38 mmol), 4-fluorophenyl boronic acid (2.81 g, 20.07 mmol), $Pd(PPh_3)_4$ (1.55 g, 1.34 mmol) and $Na_2CO_3$ (4.25 g, 40.14 mmol) were dissolved in a mixture of dioxane (45 mL) and water (15 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Then, reaction mixture was refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$,

followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a yellow oil (4.00 g, 86%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.92-7.89 (m, 2H), 7.38 (d, *J* = 8 Hz, 1H), 7.19 (d, *J* = 8 Hz, 1H), 7.11 (t, *J* = 9 Hz, 2H), 5.29 (s, 2H), 3.90-3.88 (m, 2H), 3.59-3.57 (m, 2H), 3.38 (s, 3H), 1.69 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 162.9 ($J_{C,F}$ = 246 Hz), 154.5, 146.3, 141.3, 135.3 ($J_{C,F}$ = 3 Hz), 127.9 ($J_{C,F}$ = 9 Hz), 125.5, 115.4 ($J_{C,F}$ = 22 Hz), 112.2, 94.7, 80.2, 71.6, 68.0, 59.0, 28.8; HRMS (ESI) calculated for $C_{19}H_{24}FNO_4Na$ $(M+Na)^+$ 372.1582, found 372.1581.

**3-Bromo-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine (148).**

N-Bromosuccinimde (4.08 g, 22.90 mmol) in acetonitrile (100mL) was added over 30 minutes was added to a solution of 2-(*t*-butoxy)-6-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridine, **147**, (4.0 g, 11.45 mmol) in AcCN (100 mL) under nitrogen.. The reaction mixture was then stirred for 3 hours at room temperature. After the reaction was complete as determined by xxxx, it was diluted with ethyl acetate, which was then washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a white solid (3.92 g, 80%); mp 67-69 $^o$C $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.70-7.66 (m, 2H), 7.61 (s, 1H), 7.10 (t, *J* = 9Hz, 2H), 5.28 (s, 2H), 3.90-3.88 (m, 2H), 3.61-3.58 (m, 2H), 3.41 (s, 3H), 1.60 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 162.5 ($J_{C,F}$ = 245 Hz), 153.3, 145.8,

141.4, 135.5, 131.3 ($J_{C,F}$ = 8 Hz), 129.6, 114.6 ($J_{C,F}$ = 22 Hz), 108.4, 94.8, 81.0, 71.5, 68.2, 59.1, 28.7; HRMS (ESI) calculated for $C_{19}H_{24}BrFNO_4$ $(M+H)^+$ 428.0867, found 428.0867.

**4-(6-(*t*-Butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)benzoic acid (149).**

3-Bromo-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine, **148**, (200 mg, 0.47 mmol), 4-(carboxyphenyl) boronic acid (118 mg, 0.71 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and $Na_2CO_3$ (149 mg, 1.41 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 6 hours. After the reaction was completed as dteremined by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a white solid (109 mg, 49%); m.p. 142-144 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.03 (d, $J$ = 8 Hz, 2H), 7.44 (s, 1H), 7.31-7.29 (m, 4H), 6.93 (t, $J$ = 9 Hz, 2H), 5.36 (s, 2H), 3.96-3.94 (m, 2H), 3.63-3.61 (m, 2H), 3.40 (s, 3H), 1.71 (s, 9H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 171.4, 162.2 ($J_{C,F}$ = 246 Hz), 154.1, 145.8, 145.5, 140.9, 135.7, 131.6 ($J_{C,F}$ = 8 Hz), 130.3, 129.9, 127.61, 127.57 127.4, 114.8 ($J_{C,F}$ = 21 Hz), 94.8, 80.8, 71.6, 68.0, 59.0, 28.9; HRMS (ESI) calculated for $C_{26}H_{29}FNO_6$ $(M+H)^+$ 470.1973, found 470.1974.

**Methyl 4-(6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)benzoate (150).**

3-Bromo-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine, **148**, (200 mg, 0.47 mmol), 4-(methoxycarbonylphenyl) boronic acid (128 mg, 0.71 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and $Na_2CO_3$ (149 mg, 1.41 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 6 hours. After the reaction was completed as determined by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a colorless oil (116 mg, 51%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.96 (d, $J$ = 8 Hz, 2H), 7.42 (s, 1H), 7.29-7.24 (m, 4H), 6.91 (t, $J$ = 9 Hz, 2H), 5.34 (s, 2H), 3.94-3.75 (m, 5H), 3.61-3.59 (m, 2H), 3.39 (s, 3H), 1.70 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 166.9, 162.2 ($J_{C,F}$ = 246 Hz), 154.0, 145.5, 144.8, 140.9, 137.3 ($J_{C,F}$ = 3 Hz), 131.6 ($J_{C,F}$ = 8 Hz), 129.7, 129.6, 128.5, 127.7, 127.5, 114.7 ($J_{C,F}$ = 21 Hz), 94.8, 80.7, 71.6, 68.0, 59.0, 52.1, 28.0; HRMS (ESI) calculated for $C_{27}H_{31}FNO_6$ $(M+H)^+$ 484.2130, found 484.2130.

**2-(*t*-Butoxy)-6-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)-5-(4-(1-methyl-1*H*-tetrazol-5-yl)phenyl)pyridine (151).**

3-Bromo-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine, **148**, (197 mg, 0.46 mmol), 1-methyl-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl-1*H*-tetrazole (146 mg, 0.51 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and $Na_2CO_3$ (146 mg, 1.38 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 3 hours. After the reaction was completed as dteremined by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the desired product as a white solid (100 mg, 43%); mp 108-110 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.50 (d, $J$ = 8 Hz, 2H), 7.20 (d, $J$ = 8 Hz, 2H), 7.14-7.11 (m, 2H), 7.10 (s, 1H), 6.75 (t, $J$ = 9 Hz, 2H), 5.17 (s, 2H), 4.02 (s, 3H), 3.77-3.75 (m, 2H), 3.44-3.41 (m, 2H), 3.21 (s, 3H), 1.52 (s, 9H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 162.2 ($J_{C,F}$ = 246 Hz), 154.2, 154.1, 145.5, 143.4, 141.1, 135.7 ($J_{C,F}$ = 3 Hz), 131.6 ($J_{C,F}$ = 8 Hz), 130.6, 128.6, 127.4, 126.9, 122.0, 114.8 ($J_{C,F}$ = 21 Hz), 94.8, 80.9, 71.6, 68.0, 59.0, 35.1, 28.9; HRMS (ESI) calculated for $C_{27}H_{31}FN_5O_4$ $(M+H)^+$ 508.2355, found 508.2355.

**2-(*t*-Butoxy)-6-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)-5-(4-(2-methyl-2*H*-tetrazol-5-yl)phenyl)pyridine (152).**

3-Bromo-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine, **148**, (193 mg, 0.45 mmol), 2-methyl-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl-2*H*-tetrazole (195 mg, 0.68 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and $Na_2CO_3$ (143 mg, 1.35 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Then, reaction mixture was refluxed for 3 hours. After the reaction was completed as determined by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate. The ethyl acetate solution was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (199 mg, 87%); mp 97-99 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.05 (d, $J$ = 8 Hz, 2H), 7.44 (s, 1H), 7.35-7.29 (m, 2H), 6.91 (t, $J$ = 9 Hz, 2H), 5.35 (s, 2H), 4.41 (s, 3H), 3.95-3.93 (m, 2H), 3.62-3.59 (m, 2H), 3.39 (s, 3H), 1.70 (s, 9H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 165.0, 162.1 ($J_{C,F}$ = 246 Hz), 153.9, 145.4, 142.1, 140.9, 135.9 ($J_{C,F}$ = 3 Hz), 131.6 ($J_{C,F}$ = 8 Hz), 130.3, 127.82, 127.79, 126.8, 122.0, 114.7 ($J_{C,F}$ = 21 Hz), 94.8, 80.9, 71.6, 68.0, 59.0, 35.1, 28.9; HRMS (ESI) calculated for $C_{27}H_{31}FN_5O_4$ $(M+H)^+$ 508.2355, found 508.2355.

**4-(6-(*t*-Butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)benzenesulfonamide (153).**

3-Bromo-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine, **148**, (200 mg, 0.47mmol), 4-boronbenzene sulfonamide (143 mg, 0.71mmol), $Pd(PPh_3)_4$ (58

mg, 0.05 mmol) and $Na_2CO_3$ (149 mg, 1.41mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for 3 hours. After the reaction was completed as determined by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a colorless oil (225 mg, 95%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.81 (d, $J$ = 8 Hz, 2H), 7.37 (s, 1H), 7.29 (d, $J$ = 9 Hz, 2H), 7.27-7.23 (m, 2H), 6.91 (t, $J$ = 9 Hz, 2H), 5.22 (s, 2H), 3.92-3.90 (m, 2H), 3.59-3.57 (m, 2H), 3.35 (s, 3H), 1.68 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 162.2 ($J_{C,F}$ = 246 Hz), 154.1, 145.5, 144.8, 141.0, 140.3, 135.5 ($J_{C,F}$ = 4 Hz), 131.6 ($J_{C,F}$ = 8 Hz), 130.3, 127.4, 126.7, 126.5, 114.9 ($J_{C,F}$ = 21 Hz), 94.8, 81.0, 71.5, 68.0, 58.9, 28.8; HRMS (ESI) calculated for $C_{25}H_{30}FN_2O_6S$ $(M+H)^+$ 505.1803, found 505.1803.

**4-(2-(4-Fluorophenyl)-5-hydroxy-6-oxo-1,6-dihydropyridin-3-yl)benzoic acid (154).**

TFA (1 mL, x.xx mmol) was added to a solution of 4-(6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)benzoic acid, **149**, (75 mg, 0.16 mmol) in anhydrous dichloromethane (2 mL) under nitrogen. The reaction mixture was then stirred for 3 hours at room temperature. The solvent was removed under reduced pressure, and the product was crystallized as a white solid in EtOH:$Et_2O$ (1:2) (39 mg, 75%); dec. 301-303 $^o$C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 12.82 (brs, 1H), 12.00 (brs,

1H), 9.37 (brs, 1H), 7.76 (d, $J$ = 8 Hz, 2H), 7.22-7.18 (m, 2H), 7.15-7.10 (m, 4H), 6.85 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 167.0, 161.9 ($J_{C,F}$ =245 Hz), 158.0, 146.4, 142.9, 133.0, 132.2 ($J_{C,F}$ = 9 Hz), 130.1 ($J_{C,F}$ = 3 Hz), 129.6, 129.1, 128.6, 118.1, 117.0, 115.0 ($J_{C,F}$ = 22 Hz); HRMS (ESI) calculated for $C_{18}H_{13}FNO_4$ $(M+H)^+$ 326.0823, found 326.0812.

**Methyl 4-(2-(4-fluorophenyl)-5-hydroxy-6-oxo-1,6-dihydropyridin-3-yl)benzoate (155).**

TFA (1 mL) was added to a solution of methyl 4-(6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)benzoate, **150**, (75 mg, 0.16 mmol) in anhydrous dichloromethane (2 mL) under nitrogen.. It was then stirred for 3 hours at room temperature. The solvent was removed under reduced pressure, and the product was then crystallized as a white solid from EtOH:$Et_2O$ (1:2) (54 mg, 100%)**;** mp 160-162 $^o$C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 12.03 (brs, 1H), 9.42 (brs, 1H), 7.78 (d, $J$= 8 Hz, 2H), 7.22-7.18 (m, 2H), 7.16 (d, $J$ = 8 Hz, 2H), 7.12 (t, $J$ = 9 Hz, 2H), 6.86 (s, 1H), 3.82 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 165.9, 161.9 ($J_{C,F}$ = 245 Hz), 158.0, 146.4, 143.3, 133.1, 132.2 ($J_{C,F}$ = 8 Hz), 130.1, 129.8, 129.0, 127.5, 118.0, 116.9, 115.1 ($J_{C,F}$ = 21 Hz), 52.0; HRMS (ESI) calculated for $C_{19}H_{15}FNO_4$ $(M+H)^+$ 340.0980, found 340.0965.

**6-(4-Fluorophenyl)-3-hydroxy-5-(4-(1-methyl-1*H*-tetrazol-5-yl)phenyl)pyridin-2(1*H*)-one (156).**

TFA (1 mL) was added to a solution of 2-(*t*-butoxy)-6-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)-5-(4-(1-methyl-1*H*-tetrazol-5-yl)phenyl)pyridine, **151**, (100 mg, 0.20 mmol) in anhydrous dichloromethane (2 mL) under nitrogen.. It was stirred for 2 hours at room temperature. The solvent was removed under reduced pressure, and the product crystallized as a white solid in water:methanol (2:1) (66 mg, 90%); mp 137-139 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$+MeOD) δ 7.62 (d, $J$ = 7 Hz, 2H), 7.26 (d, $J$ = 8 Hz, 2H), 7.20-7.17 (m, 2H), 7.05 (s, 1H), 6.99 (t, $J$ = 8 Hz, 2H), 4.16 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$+MeOD) δ 162.9 ($J_{C,F}$ = 250 Hz), 158.6, 154.0, 145.9, 141.1, 132.9, 131.4 ($J_{C,F}$ = 8 Hz), 130.4, 129.6, 128.7, 122.2, 118.9, 118.8, 116.0 ($J_{C,F}$ = 22 Hz), 35.1; HRMS (ESI) calculated for $C_{19}H_{15}FN_5O_2$ $(M+H)^+$ 364.1204, found 364.1195.

**6-(4-Fluorophenyl)-3-hydroxy-5-(4-(2-methyl-2*H*-tetrazol-5-yl)phenyl)pyridin-2(1*H*)-one (157).**

TFA (1 mL) was added to a solution of 2-(*t*-butoxy)-6-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)-5-(4-(2-methyl-2*H*-tetrazol-5-yl)phenyl)pyridine, **152**, (109 mg, 0.21mmol) in anhydrous dichloromethane (2 mL) under nitrogen. It was then stirred for 3 hours at room temperature. The solvent was removed under reduced pressure, and the product was crystallized as a white solid in water:methanol (2:1) (64 mg, 84%); mp 244-245 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$+MeOD) δ 7.94 (d, $J$ = 8 Hz, 2H), 7.17-7.13 (m, 4H), 7.04 (s, 1H), 6.94 (t, $J$ = 9 Hz, 2H), 4.35 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$+MeOD) δ 164.8, 162.8 ($J_{C,F}$ = 248 Hz), 158.6, 145.7, 139.8, 132.6, 131.4 ($J_{C,F}$ =

8 Hz), 130.1, 129.8, 126.8, 126.0, 119.6, 119.4, 115.8 ($J_{C,F}$ = 21 Hz), 39.4; HRMS (ESI) calculated for $C_{19}H_{15}FN_5O_2$ $(M+H)^+$ 364.1204, found 364.1197.

**4-(2-(4-Fluorophenyl)-5-hydroxy-6-oxo-1,6-dihydropyridin-3-yl)benzenesulfonamide (158).**

TFA (1 mL) was added to a solution of 4-(6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)benzenesulfonamide, **153**, (100 mg, 0.20 mmol) in anhydrous dichloromethane (2 mL) under nitrogen. It was then stirred for 3 hours at room temperature. The solvent was removed under reduced pressure, and the product crystallized as a white solid in water:methanol (2:1) (62 mg, 87%); mp 176-178 ºC; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 12.02 (brs, 1H), 9.42 (brs, 1H), 7.53 (d, *J* = 8 Hz, 2H), 7.21-7.17 (m, 2H), 7.14 (d, *J* = 8 Hz, 2H), 7.10 (t, *J* = 9 Hz, 2H), 6.82 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 161.9 ($J_{C,F}$ = 245 Hz), 157.9, 146.3, 142.3, 139.3, 133.1, 132.2 ($J_{C,F}$ = 8 Hz), 129.8, 126.2, 125.5, 118.0, 116.4, 115.1 ($J_{C,F}$ = 21 Hz); HRMS (ESI) calculated for $C_{17}H_{14}FN_2O_4S$ $(M+H)^+$ 361.0653, found 361.0645.

**N-((4-(6-(*t*-Butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl)sulfonyl)acetamide (159).**

Acetic anhydride (0.1 mL, 1.06 mmol) followed by DMAP (11 mg, 0.09 mmol) were added to a solution of 4-(6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)benzenesulfonamide, **153**, (150 mg, 0.30 mmol) in

pyridine (1 mL) under nitrogen. It was stirred for 18 hours at room temperature. The reaction mixture was diluted with ethyl acetate, which was washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a white solid (116 mg, 71%); mp 162-164 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.81 (brs, 1H), 7.95 (d, *J* = 8 Hz, 2H), 7.39 (s, 1H), 7.35 (d, *J* = 8 Hz, 2H), 7.27-7.24 (m, 2H), 6.92 (t, *J* = 9 Hz, 2H), 5.34 (s, 2H), 3.94-3.92 (m, 2H), 3.62-3.60 (m, 2H), 3.38 (s, 3H), 2.10 (s, 3H), 1.69 (s, 9H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 168.0, 162.3 ($J_{C,F}$ = 246 Hz), 154.3, 146.3, 145.6, 141.0, 136.6, 135.4 ($J_{C,F}$ = 4 Hz), 131.6 ($J_{C,F}$ = 8 Hz), 128.3, 127.3, 126.4, 122.3, 114.9 ($J_{C,F}$ = 22 Hz), 94.8, 81.0, 71.6, 68.0, 59.0, 28.8, 23.5; HRMS (ESI) calculated for $C_{27}H_{32}FN_2O_7S$ $(M+H)^+$ 547.1909, found 547.1909.

**N-((4-(2-(4-Fluorophenyl)-5-hydroxy-6-oxo-1,6-dihydropyridin-3-yl)phenyl)sulfonyl)acetamide (160).**

TFA (1 mL) was added to a solution of N-((4-(6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl)sulfonyl)acetamide, **159**, (50 mg, 0.09 mmol) in anhydrous dichloromethane (2 mL) under nitrogen. The reaction mixture was then stirred for 3 hours at room temperature. The solvent was removed under reduced pressure, and the product was crystallized as a white solid in EtOH:$Et_2O$ (1:2) (33 mg, 92%); mp 291-293$^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 12.04 (brs, 2H), 9.45 (brs, 1H), 7.73 (d, *J* = 8 Hz, 2H), 7.26 (d, *J* = 8 Hz, 2H), 7.22-7.19 (m, 2H), 7.12 (t, *J* = 8 Hz, 2H),

6.87 (s, 1H), 1.92 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 168.7, 162.0 ($J_{C,F}$ = 244 Hz), 158.0, 146.5, 143.7, 137.1, 133.4, 132.2 ($J_{C,F}$ = 8 Hz), 123.0, 129.6, 127.3, 117.9, 116.4, 115.1 ($J_{C,F}$ = 21 Hz), 23.2; HRMS (ESI) calculated for $C_{19}H_{16}FN_2O_5S$ $(M+H)^+$ 403.0758, found 403.0743.

**4-(6-(*t*-Butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenol (161).**

3-Bromo-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine, **148**, (200 mg, 0.47 mmol), 4-hydroxyphenylboronic acid (100 mg, 0.71 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and $Na_2CO_3$ (150 mg, 1.42 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for 8 hours. After the reaction was completed as determined by TLC, it was allowed to cool to room temperature. The reaction mixture was diluted with ethyl acetate, which was then washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (200 mg, 96%); mp 102-104 $^oC$;$^1$H NMR (400 MHz) (MeOD) δ 7.38 (s, 1H), 7.33-7.29 (m, 2H), 6.96 (d, *J* = 9 Hz, 2H), 6.92 (t, *J* = 9 Hz, 2H), 6.71 (d, *J* = 9 Hz, 2H), 5.29 (s, 2H), 3.88-3.86 (m, 2H), 3.58-3.55 (m, 2H), 3.32 (s, 3H), 1.64 (s, 9H); $^{13}$C NMR (100 MHz) (MeOD) δ 163.4 ($J_{C,F}$ = 244 Hz), 157.7, 154.5, 146.3, 142.4, 138.0, 132.8 ($J_{C,F}$ = 8 Hz), 132.4, 131.9, 130.5, 129.1, 116.3,

115.3 ($J_{C,F}$ = 21 Hz), 95.8, 81.4, 72.8, 69.1, 59.1, 29.3; HRMS (ESI) calculated for $C_{25}H_{29}FNO_5$ $(M+H)^+$ 442.2024, found 442.2025.

**4-(6-(*t*-Butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl trifluoromethanesulfonate (162).**

N-Phenyl-bis(trifluoromethanesulfonamide) (100 mg, 0.28 mmol) was added to solution of 4-(6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenol, **161**, (100 mg, 0.23 mmol) in anhydrous dichloromethane (10 mL) under nitrogen. The reaction mixture was cooled to 0 $^oC$, and then $Et_3N$ (0.06 mL, 0.41 mmol) was added. The reaction mixture was allowed warm to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a colorless oil (121 mg, 92%); $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.40 (s, 1H), 7.28-7.19 (m, 6H), 6.92 (t, $J$ = 9 Hz, 2H), 5.34 (s, 2H), 3.95-3.93 (m, 2H), 3.62-3.60 (m, 2H), 3.38 (s, 3H), 1.70 (s, 9H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 162.2 ($J_{C,F}$ = 246 Hz), 154.1, 148.4, 145.4, 141.0, 140.6, 135.6 ($J_{C,F}$ = 3 Hz), 131.6 ($J_{C,F}$ = 8 Hz), 131.5, 127.5, 126.5, 121.3, 114.8 ($J_{C,F}$ = 22 Hz), 94.8, 80.8, 71.6, 68.0, 59.0, 28.8; HRMS (ESI) calculated for $C_{26}H_{28}F_4NO_7S$ $(M+H)^+$ 574.1518, found 574.1517.

**2-(*t*-Butoxy)-6-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)-5-(4-((trimethylsilyl)ethynyl)phenyl)pyridine (163).**

4-(6-(*t*-Butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl trifluoromethanesulfonate, **162**, (223 mg, 0.39 mmol), (trimethylsilyl) acetylene (0.17 ml, 1.17 mmol), $Pd(PPh_3)_2Cl_2$ (56 mg, 0.08 mmol), CuI (15 mg, 0.08mmol) and $Et_3N$ (0.16 ml, 1.17mmol) were dissolved in DMF (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then stirred for 6 hours at 100 $^oC$. After the reaction was completed as determined by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a colorless oil (84 mg, 41%); $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.385 (d, $J$ = 8 Hz, 2H), 7.383 (s, 1H), 7.30-7.27 (m, 2H), 7.11 (d, $J$ = 8 Hz, 2H), 6.91 (t, $J$ = 9 Hz, 2H), 5.33 (s, 2H), 3.94-3.92 (m, 2H), 3.61-3.59 (m, 2H), 3.39 (s, 3H), 1.69 (s, 9H), 0.28 (s, 9H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 162.2 ($J_{C,F}$ = 246 Hz), 153.9, 145.4, 140.9, 140.3, 136.0, 132.0, 131.6 ($J_{C,F}$ = 8 Hz), 129.6, 127.9, 127.8, 121.6, 114.7 ($J_{C,F}$ = 22 Hz), 105.0, 94.9, 80.7, 71.6, 59.0, 28.9, 0.0; HRMS (ESI) calculated for $C_{30}H_{37}FNO_4Si$ $(M+H)^+$ 522.2470, found 522.2470.

**2-(*t*-Butoxy)-5-(4-ethynylphenyl)-6-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridine (164).**

$K_2CO_3$ (47 mg, 0.34 mmol) was added to a solution of 2-(*t*-butoxy)-6-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)-5-(4-((trimethylsilyl)ethynyl)phenyl)pyridine, **163**, (90 mg, 0.17 mmol) in methanol (5 mL) under nitrogen. The reaction mixture was then stirred for 5 hours at room temperature. After the reaction was completed as determined by TLC, it was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the desired product as a yellow oil (76 mg, 100%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.31 (d, *J* = 8 Hz, 2H), 7.29 (s, 1H), 7.21-7.18 (m, 2H), 7.04 (d, *J* = 8 Hz, 2H), 6.82 (t, *J* = 9 Hz, 2H), 5.23 (s, 2H), 3.84-3.82 (m, 2H), 3.51-3.49 (m, 2H), 3.29 (s, 3H), 3.02 (s, 1H), 1.59 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 162.1 ($J_{C,F}$ = 246 Hz), 153.8, 145.3, 140.9, 140.6, 135.9, 132.1, 131.6 ($J_{C,F}$ = 8 Hz), 129.7, 127.7, 120.5, 114.7 ($J_{C,F}$ = 21 Hz), 94.9, 83.5, 80.6, 77.6, 71.6, 68.0, 59.0, 28.9; HRMS (ESI) calculated for $C_{27}H_{29}FNO_4$ $(M+H)^+$ 450.2075, found 450.2075.

**3-(4-(1*H*-1,2,3-Triazol-5-yl)phenyl)-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine (165).**

$TMSN_3$ (0.15 mL, 1.08 mmol) followed by CuI (6 mg, 0.03 mmol) were added to a solution of 2-(*t*-butoxy)-5-(4-ethynylphenyl)-6-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyri-dine, **164**, (120 mg, 0.27 mmol) in a mixture of DMF (0.9 mL) and methanol (0.1 mL) under nitrogen. The reaction mixture was then stirred overnight at 100°C. The reaction mixture was diluted with ethyl acetate, which was then

washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to provide the desired product as a white solid (39 mg, 30%); mp 154-156 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 12.34 (brs, 1H), 7.73 (s, 1H), 7.51 (d, *J* = 8 Hz, 2H), 7.14-7.11 (m, 2H), 7.07 (s, 1H), 7.02 (d, *J* = 8 Hz, 2H), 6.70 (t, *J* = 9 Hz, 2H), 5.16 (s, 2H), 3.75-3.73 (m, 2H), 3.43-3.40 (m, 2H), 3.19 (s, 3H), 1.49 (s, 9H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 162.1 ($J_{C,F}$ = 245 Hz), 162.7, 153.7, 146.8, 145.3, 140.9, 140.3, 136.1, 136.0, 131.6 ($J_{C,F}$ = 8 Hz), 130.2, 128.4, 128.0, 127.6, 126.0, 114.7 ($J_{C,F}$ = 22 Hz), 94.8, 80.6, 71.6, 68.0, 59.0, 28.9; HRMS (ESI) calculated for $C_{27}H_{30}FN_4O_4$ $(M+H)^+$ 493.2245, found 493.2246.

**5-(4-(1*H*-1,2,3-Triazol-5-yl)phenyl)-6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one (166).**

TFA (1 mL) was added to a solution of 3-(4-(1*H*-1,2,3-triazol-5-yl)phenyl)-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine, **165**, (50 mg, 0.10 mmol) in anhydrous dichloromethane (2 mL) under nitrogen.. The reaction mixture was then stirred for 3 hours at room temperature. The solvent was removed under reduced pressure, and the product was crystallized as a white solid in EtOH:$Et_2O$ (1:2) (27 mg, 77%); dec.142-144 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$+MeOD) δ 7.84 (s, 1H), 7.62 (d, *J* = 8 Hz, 2H), 7.17-7.14 (m, 2H), 7.08 (d, *J* = 8 Hz, 2H), 7.04 (s, 1H), 6.94 (t, *J* = 8 Hz, 2H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 161.8 ($J_{C,F}$ = 245 Hz), 158.0, 146.3, 138.0, 132.6,

132.2 ($J_{C,F}$ = 8 Hz), 132.0, 130.5, 130.0, 129.9, 125.4, 125.3, 118.3, 117.4, 115.0 ($J_{C,F}$ = 21 Hz); HRMS (ESI) calculated for $C_{19}H_{14}FN_4O_2$ $(M+H)^+$ 349.1084, found 349.1095.

**5-Bromo-2-fluoro-3-((2-methoxyethoxy)methoxy)pyridine (167).**

NaH, 60% dispersion in mineral oil (208 mg, 5.20 mmol) was added at 0 $^oC$ to a solution of 5-bromo-2-fluoropyridin-3-ol (500 mg, 2.60 mmol) in anhydrous tetrahydrofuran (30 mL). The reaction mixture was stirred for 30 min at 0 $^oC$. MEM-chloride (0.6 mL, 5.20 mmol) was then added, and the mixture was stirred for 3 hours at room temperature. After the reaction was completed as determined by TLC, it was diluted with ethyl acetate. The organic layer was washed with water, brine, dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to provide the product as a colorless oil (619 mg, 85%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.76 (t, $J$ = 2 Hz. 1H), 7.67 (dd, $J$ = 9 Hz, $J$ = 2 Hz, 1H), 5.25 (s, 2H), 3.80-3.77 (m, 2H), 3.50-3.47 (m, 2H), 3.28 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 153.1 ($J_{C,F}$ = 238 Hz), 140.7 ($J_{C,F}$ = 27 Hz), 139.2 ($J_{C,F}$ = 14 Hz), 129.0 ($J_{C,F}$ = 5 Hz), 115.9 ($J_{C,F}$ = 4 Hz).

**5-Bromo-2-(*t*-butoxy)-3-((2-methoxyethoxy)methoxy)pyridine (168).**

Potassium *t*-butoxide (496 mg, 4.42 mmol) in anhydrous DMF (5 mL) was added dropwise to a solution of 5-bromo-2-fluoro-3-((2-methoxyethoxy)methoxy)pyridine, **167**, (619 mg, 2.21 mmol) in anhydrous tetrahydrofuran (25 mL).. The reaction mixture was

stirred for 30 min at room temperature. After the reaction was completed as determined by TLC, it was diluted with ethyl acetate. The organic layer was washed with water, brine, dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a colorless oil (517 mg, 78%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.84 (d, *J* = 2 Hz, 1H), 7.48 (d, *J* = 2 Hz, 1H), 5.25 (s, 2H), 3.88-3.86 (m, 2H), 3.59-3.57 (m, 2H), 3.40 (s, 3H), 1.59 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 153.9, 142.7, 139.1, 127.0, 110.2, 94.4, 80.5, 71.4, 68.0, 58.7, 28.5.

**2-(*t*-Butoxy)-5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridine (169).**

5-Bromo-2-(*t*-butoxy)-3-((2-methoxyethoxy)methoxy)pyridine, **168**, (517 mg, 1.55 mmol), 4-fluorophenylboronic acid (326 mg, 2.33 mmol), $Pd(PPh_3)_4$ (185 mg, 0.16 mmol) and $Na_2CO_3$ (493 mg, 4.65 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 8 hours. After the reaction was completed as determined by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a colorless oil (385 mg, 71%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.98 (d, *J* = 2 Hz, 1H), 7.53 (d, *J* = 2 Hz, 1H), 7.49-7.46 (m, 2H), 7.11 (t, *J* = 9 Hz, 2H), 5.31 (s, 2H), 3.91-3.89 (m, 2H), 3.59-3.57 (m, 2H), 3.37 (s, 3H), 1.63 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ

162.4 ($J_{C,F}$ = 245 Hz), 154.6, 142.3, 137.1, 134.1 ($J_{C,F}$ = 4 Hz), 129.3, 128.3 ($J_{C,F}$ = 8 Hz), 123.7, 115.7 ($J_{C,F}$ = 21 Hz), 94.7, 80.6, 71.6, 68.0, 59.0, 28.8.

**5-(4-Fluorophenyl)-3-(methoxymethoxy)-1-(methoxymethyl)pyridin-2(1*H*)-one (170).**

5-Bromo-3-(methoxymethoxy)-1-(methoxymethyl)pyridin-2(1*H*)-one, **106b**, (150 mg, 0.54 mmol), 4-fluorophenyl boronic acid (113 mg, 0.81 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and $Na_2CO_3$ (172 mg, 1.62 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for 3 hours. After the reaction was completed as determined bt TLC, it was allowed to cool to room temperature. It was diluted with EtOA, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a yellow oil (116 mg, 73%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.41-7.38 (m, 2H), 7.28-7.26 (m, 2H), 7.10 (t, $J$ = 9 Hz, 2H), 5.42 (s, 2H), 5.29 (s, 2H), 3.52 (s, 3H), 3.43 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 163.0 ($J_{C,F}$ = 245 Hz),157.9, 147.3, 132.9 ($J_{C,F}$ = 3 Hz), 127.7 ($J_{C,F}$ = 8 Hz), 125.4, 119.0, 118.7, 115.9 ($J_{C,F}$ = 22 Hz), 95.2, 78.6, 57.3, 56.5; HRMS (ESI) calculated for $C_{15}H_{17}FNO_4$ $(M+H)^+$ 294.1136, found 294.1136.

**6-Chloro-5-(4-fluorophenyl)-3-(methoxymethoxy)-1-(methoxymethyl)pyridin-2(1*H*)-one (171).**

Palau's chlor (181 mg, 0.86 mmol) was added to a stirred solution of 5-(4-fluorophenyl)-3-(methoxymethoxy)-1-(methoxymethyl)pyridin-2(1*H*)-one, **170**, (212 mg, 0.72 mmol) in anhydrous dichloromethane (10 mL) under nitrogen.. The reaction mixture was then stirred overnight, forming a suspensionThe suspension was filtered. The filtrate was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the desired product as a yellow oil (100 mg, 42%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.34-7.30 (m, 2H), 7.10 (t, $J$ = 9 Hz, 2H), 7.01 (s, 1H), 5.74 (s, 2H), 5.22 (s, 2H), 3.50 (s, 3H), 3.48 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 162.3 ($J_{C,F}$ = 247 Hz), 158.8, 145.7, 133.1 ($J_{C,F}$ = 4 Hz), 131.2 ($J_{C,F}$ = 8 Hz), 126.7, 121.7, 117.7, 115.5 ($J_{C,F}$ = 21 Hz), 95.2, 76.6, 57.9, 56.6; HRMS (ESI) calculated for $C_{15}H_{16}ClFNO_4$ $(M+H)^+$ 328.0746, found 328.0739.

**4-(3-(4-Fluorophenyl)-5-(methoxymethoxy)-1-(methoxymethyl)-6-oxo-1,6-dihydropyridin-2-yl)benzoic acid (172).**

6-Chloro-5-(4-fluorophenyl)-3-(methoxymethoxy)-1-(methoxymethyl)pyridin-2(1*H*)-one, **171**, (100 mg, 0.31 mmol), 4-carboxyphenyl boronic acid (76 mg, 0.46 mmol), $Pd(PPh_3)_4$ (36 mg, 0.03 mmol) and $Na_2CO_3$ (97 mg, 0.92 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. Thereaction mixture was then refluxed for 3 hours. After the reaction was completed as determined by TLC, it was allowed to cool to room temperature. It was then diluted with ethyl acetate, which was washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under

reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as white solid (62 mg, 49%); mp 188-190 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.93 (d, *J* = 8 Hz, 2H), 7.26 (d, *J* = 8 Hz, 2H), 7.03 (s, 1H), 6.88-6.84 (m, 2H), 6,75 (t, *J* = 9 Hz, 2H), 5.23 (s, 2H), 5.12 (s, 2H), 3.47 (s, 3H), 3.34 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 168.2, 161.6 ($J_{C,F}$ = 246 Hz), 158.8, 146.2, 138.2, 137.6, 134.0 ($J_{C,F}$ = 3 Hz), 131.3, 131.2, 130.6, 129.5, 121.9, 119.1, 115.1 ($J_{C,F}$ = 22 Hz), 95.1, 75.7, 57.3, 56.5; HRMS (ESI) calculated for $C_{22}H_{20}FNO_6Na$ $(M+Na)^+$ 436.1167, found 436.1151.

**4-(3-(4-Fluorophenyl)-5-hydroxy-6-oxo-1,6-dihydropyridin-2-yl)benzoic acid (173).**

4-(3-(4-Fluorophenyl)-5-(methoxymethoxy)-1-(methoxymethyl)-6-oxo-1,6-dihydropyridin-2-yl)benzoic acid, **172**, (62 mg, 0.15 mmol) was dissolved in a mixture of 2N HCl (5 mL) and dioxane (5 mL). It was refluxed for 6 hours, and it was allowed to cool to room temperature. The white suspension was filtered, and provided the product as a white solid (49 mg, 100%); dec. 324-325 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 13.01 (brs, 1H), 12.04 (brs, 1H), 9.45 (brs, 1H) 7.79 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 7.06-7.04 (m, 4H), 6.81 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 166.8, 161.0 ($J_{C,F}$ = 242 Hz), 157.9, 146.5, 138.2, 134.5 ($J_{C,F}$ = 3 Hz), 132.6, 131.4 ($J_{C,F}$ = 8 Hz), 130.1, 128.6, 118.5, 117.6, 115.1 ($J_{C,F}$ = 21 Hz); HRMS (ESI) calculated for $C_{18}H_{13}FNO_4$ $(M+H)^+$ 326.0823, found 326.0814.

**5,6-Bis(4-fluorophenyl)pyridine-2,3-diyl diacetate (174).**

5,6-Bis(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one, **11**, (100 mg, 0.33 mmol) was dissolved in acetic anhydride (1 mL), and it was heated up to 100 $^{o}$C. The reaction mixture was stirred for overnight at 100 $^{o}$C. The cooled reaction mixturet was diluted with ethyl acetate, which was then washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$, and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a white solid (70 mg, 55%); mp. 131-133$^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.67 (s, 1H), 7.32-7.29 (m, 2H), 7.18-7.14 (m, 2H), 7.01 (t, $J$ = 8 Hz, 2H). 6.95 (t, $J$ = 9 Hz, 2H), 2.40 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 168.0, 167.8, 163.8 ($J_{C,F}$ = 249 Hz), 162.4 ($J_{C,F}$ = 247 Hz), 151.8, 148.3, 136.8, 135.2, 134.7, 134.3 ($J_{C,F}$ = 3 Hz), 134.0 ($J_{C,F}$ = 3 Hz), 131.8 ($J_{C,F}$ = 8 Hz), 131.2 ($J_{C,F}$ = 8 Hz), 115.7 ($J_{C,F}$ = 22 Hz), 115.1 ($J_{C,F}$ = 22 Hz), 20.8, 20.7.

**5-(4-Cyanophenyl)-6-(4-fluorophenyl)-1,2-dihydropyridine-2,3-diyl diacetate (175).**

4-(2-(4-Fluorophenyl)-5-hydroxy-6-oxo-1,6-dihydropyridin-3-yl)benzonitrile, **12**, (30 mg, 0.10 mmol) was dissolved in acetic anhydride (1 mL), and it was heated up to 100 $^{o}$C. The reaction mixture was stirred for overnight at 100 $^{o}$C. The reaction mixture was allowed to cool to room temperature, and was diluted with ethyl acetate. The ethyl acetate solution was washed with water, followed by brine. The organic layer was then dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as

colorless oil (29 mg, 76 %); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.70 (s, 1H), 7.63 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 7.30-7.26 (m, 2H), 6.97 (t, J = Hz, 2H) 2.41 (s, 3H), 2.38 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 167.9, 167.8, 151.9, 148.9, 142.8, 137.0, 135.1, 133.6, 132.4, 131.8 ($J_{C,F}$ = 8 Hz), 130.3, 118.3, 115.4 ($J_{C,F}$ = 22 Hz), 111.9, 20.79, 20.75.

**5-(4-(1-Acetyl-1*H*-tetrazol-5-yl)phenyl)-6-(4-fluorophenyl)pyridine-2,3-diyl diacetate (176).**

5-(4-(1*H*-tetrazol-5-yl)phenyl)-6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one, **13**, (30 mg, 0.09 mmol) was dissolved in acetic anhydride, and it was heated up to 100 $^{o}$C. The reaction mixture was stirred for overnight at the temperature. The reaction mixture was allowed to cool to room temperature, and was diluted with ethyl acetate, which was washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a colorless oil (39 mg, 95 %); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.89 (d, *J* = 8 Hz, 2H), 7.65 (s, 1H), 7.25-7.20 (m, 4H), 6.85 (t, *J* = 9 Hz, 2H), 2.54 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 167.94, 167.85, 164.4, 163.8, 162.8 ($J_{C,F}$ = 248 Hz), 151.9, 148.6, 141.3, 136.9, 135.1, 134.5, 134.0 ($J_{C,F}$ = 3 Hz), 131.8 ($J_{C,F}$ = 8 Hz), 130.2, 126.9, 123.4 115.2 ($J_{C,F}$ = 22 Hz), 20.8, 20.7, 11.1.

**6-(4-Cyanophenyl)-5-(4-fluorophenyl)-1,2-dihydropyridine-2,3-diyl diacetate (177).**

4-(3-(4-Fluorophenyl)-5-hydroxy-6-oxo-1,6-dihydropyridin-2-yl)benzonitrile, **14**, (20 mg, 0.07 mmol) was dissolved in acetic anhydride and was heated to 100 $^{o}$C. The reaction mixture was stirred for overnight at 100 $^{o}$C. The reaction mixture was allowed to cool to room temperature, and was diluted with ethyl acetate, which was then washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a colorless oil (10 mg, 39 %); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.70 (s, 1H), 7.54 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 8 Hz, 2H), 7.14-7.11 (m 2H), 7.12 (t, *J* = 8 Hz, 2H), 2.39 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 167.9, 167.7, 162.3 ($J_{C,F}$ = 247 Hz), 150.4, 148.6, 142.6, 137.6, 135.4, 135.2, 133.3, 131.9, 131.2 ($J_{C,F}$ = 9 Hz), 130.6, 118.5, 116.0 ($J_{C,F}$ = 21 Hz), 112.0, 20.8, 20.7.

**6-(4-(1-Acetyl-1*H*-tetrazol-5-yl)phenyl)-5-(4-fluorophenyl)pyridine-2,3-diyl diacetate (178).**

6-(4-(1*H*-Tetrazol-5-yl)phenyl)-5-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one, **15**, (20 mg, 0.06 mmol) was dissolved in acetic anhydride and was heated to 100 $^{o}$C. The reaction mixture was stirred for overnight at the temperature. The reaction mixture was allowed to cool to room temperature, and was diluted with ethyl acetate, which was then washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a colorless oil (10

mg, 37 %); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.84 (d, *J* = 8 Hz, 2H), 7.63 (s, 1H), 7.37 (d, *J* = 8 Hz, 2H), 7.10-7.07 (m, 2H), 6.92 (t, *J* = 9 Hz, 2H), 2.53 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 168.0, 167.8, 164.5, 163.7, 162.5 ($J_{C,F}$ = 247 Hz), 151.4, 148.5, 141.3, 137.2, 135.3, 135.1, 133.7 ($J_{C,F}$ = 4 Hz), 131.3 ($J_{C,F}$ = 9 Hz), 130.6, 126.4, 123.6 115.8 ($J_{C,F}$ = 22 Hz), 20.8, 20.7, 11.1.

**4-(6-(*t*-Butoxy)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenol (179).**

5-Bromo-2-(*t*-butoxy)-3-((2-methoxyethoxy)methoxy)pyridine, **168**, (300 mg, 0.90 mmol), 4-hydroxyphenylboronic acid (207 mg, 1.35 mmol), $Pd(PPh_3)_4$ (104 mg, 0.09 mmol) and $Na_2CO_3$ (286 mg, 2.70 mmol) were dissolved in a mixture of dioxane (30 mL) and water (10 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for overnight. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a colorless oil (312 mg, 100%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.98 (d, *J* = 2 Hz, 1H), 7.53 (d, *J* = 2 Hz, 1H), 7.35 (d, *J* = 9 Hz, 2H), 7.02 (brs, 1H), 6.88 (d, *J* = 9 Hz, 2H), 5.29 (s, 2H), 3.90-3.88 (m, 2H), 3.59-3.57 (m, 2H), 3.37 (s, 3H), 1.60 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 156.0, 153.8, 142.7, 136.8, 130.7, 129.8, 128.0, 123.4, 115.9, 94.6, 80.8, 71.6, 68.0, 58.9, 28.8.

**4-(6-(*t*-Butoxy)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl dimethylcarbamate (180).**

To a solution of 4-(6-(*t*-butoxy)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenol, **179**, (60 mg, 0.17 mmol) in DMF (5 mL), NaH, 60% dispersion in mineral oil (10 mg, 0.23 mmol) was added at 0 $^{o}$C. The reaction mixture was stirred for 15 minutes at 0 $^{o}$C. N,N-dimethyl carbamyl chloride (0.02 mL, 0.23 mmol) was then added at 0 $^{o}$C. The reaction mixture was stirred for 30 minutes at 0 $^{o}$C. After the reaction was completed as determined by TLC, it was diluted with ethyl acetate, which was washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give crude product as a colorless oil; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.53 (d, *J* = 2 Hz, 1H), 7.49 (d, *J* = 9 Hz, 2H), 7.17-7.15 (m, 3H), 5.29 (s, 2H), 3.90-3.87 (m, 2H), 3.58-3.55 (m, 2H), 3.36 (s, 3H), 3.11 (s, 3H), 3.01 (s, 3H), 1.62 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 154.8, 154.5, 142.2, 137.1, 134.9, 129.6, 127.5, 123.8, 122.1, 94.7, 80.5, 71.6, 67.9, 58.9, 38.5, 36.7, 28.7.

**4-(5-Hydroxy-6-oxo-1,6-dihydropyridin-3-yl)phenyl dimethylcarbamate (181).**

The crude 4-(6-(*t*-butoxy)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl dimethylcarbamate, **180**, was dissolved in a mixture of trifluoroacetic acid (1 mL) and anhydrous dichloromethane (1 mL). The reaction mixture was stirred for 5 hours at room temperature. The solvent was removed under reduced pressure, and the resulting residue

was suspended in dichloromethane. The suspension was filtered to give the product as a white solid (10 mg, 32% yields over two steps); dec. 276-278 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.9 (brs, 1H), 9.20 (brs, 1H), 7.53 (d, *J* = 9 Hz, 2H), 7.19 (d, *J* = 9 Hz, 1H), 7.13-7.09 (m, 3H), 3.05 (s, 3H), 2.92 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 157.6, 154.0, 150.2, 147.2, 133.6, 126.1, 122.2, 121.1, 117.9, 114.7, 36.3; HRMS (ESI) calculated for $C_{14}H_{13}N_2O_4$ $(M-H)^-$ 273.0881, found 273.0884.

**(4-(6-(*t*-Butoxy)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl)methanol (182).**

5-Bromo-2-(*t*-butoxy)-3-((2-methoxyethoxy)methoxy)pyridine, **168**, (300 mg, 0.90 mmol), 4-(hydroxymethyl)phenylboronic acid (205 mg, 1.35 mmol), $Pd(PPh_3)_4$ (104 mg, 0.09 mmol) and $Na_2CO_3$ (286 mg, 2.70 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for overnight. The reaction was then allowed to cool to room temperature. It was diluted with ethyl acetate and washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a colorless oil (352 mg, 100%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.06 (d, *J* = 2 Hz, 1H), 7.60 (d, *J* = 2 Hz, 1H), 7.53 (d, *J* = 8 Hz, 2H), 7.44 (d, *J* = 8 Hz, 2H), 5.33 (s, 2H), 4.75 (s, 2H), 3.94-3.91 (m, 2H), 3.61-3.59 (m, 2H), 3.40 (s, 3H), 1.66 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 154.7, 142.3, 139.9, 137.2, 129.9, 127.5, 126.9, 123.7, 115.4, 94.7, 80.6, 71.6, 67.9, 65.0, 59.0, 28.8.

**2-(*t*-Butoxy)-5-(4-(chloromethyl)phenyl)-3-((2-methoxyethoxy)methoxy)pyridine (183).**

Pyridine (0.09 mL, 1.10 mmol) followed by thionyl chloride (0.06 mL, 0.83 mmol) were added at 0 ºC to a solution of (4-(6-(*t*-butoxy)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl)methanol, **182**, (200 mg, 0.55 mmol) in anhydrous dichloromethane (10 mL). The reaction mixture was stirred for an hour at 0 ºC After the reaction was completed as determined by TLC, it was diluted with ethyl acetate. The organic layer was washed with sat. $NH_4Cl$, brine and dried over $Na_2SO_4$. It was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a colorless oil (16 mg, 8%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.96 (d, *J* = 2 Hz, 1H), 7.50 (d, *J* = 2 Hz, 1H), 7.45 (d, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H), 5.24 (s, 2H), 4.56 (s, 2H), 3.84-3.82 (m, 2H), 3.52-3.50 (m, 2H), 3.31 (s, 3H), 1.57 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 154.8, 142.3, 138.2, 137.3, 136.4, 129.5, 129.2, 127.1, 123.7, 94.7, 80.7, 71.6, 68.0, 59.0, 46.0, 28.8.

**5-(4-(Bromomethyl)phenyl)-2-(*t*-butoxy)-3-((2-methoxyethoxy)methoxy)pyridine (184).**

Pyridine (0.05 mL, 0.56 mmol) followed by thionyl bromide (0.05 mL, 0.56 mmol) were added at 0 ºC to a solution of (4-(6-(*t*-butoxy)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl)methanol, **182**, (100 mg, 0.28 mmol) in anhydrous dichloromethane (10 mL).

The reaction mixture was stirred for an hour at 0 $^{o}$C. After the reaction was completed as determined by TLC, it was diluted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$, brine and dried over $Na_2SO_4$. It was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give the product as a colorless oil (14 mg, 12%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.03 (d, *J* = 2 Hz, 1H), 7.56 (d, *J* = 2 Hz, 1H), 7.51 (d, *J* = 8 Hz, 2H), 7.45 (d, *J* = 8 Hz, 2H), 5.31 (s, 2H), 4.54 (s, 2H), 3.91-3.89 (m, 2H), 3.59-3.56 (m, 2H), 3.37 (s, 3H), 1.64 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 154.9, 142.3, 138.2, 137.3, 136.7, 129.6, 129.4, 127.1, 123.7, 94.8, 80.7, 71.6, 68.0, 59.0, 33.3, 28.8.

**5-(4-(Chloromethyl)phenyl)-3-hydroxypyridin-2(1*H*)-one (185).**

2-(*t*-Butoxy)-5-(4-(chloromethyl)phenyl)-3-((2-methoxyethoxy)methoxy)pyridine, **183**, (15 mg, 0.04 mmol) was dissolved in a mixture of trifluoroacetic acid (1 mL) and anhydrous dichloromethane (1 mL). The reaction mixture was stirred for 3 hours at room temperature. The solvent was removed under reduced pressure, and the resulting residue was suspended in dichloromethane. The suspension was filtered, and it was washed with diethyl ether. This afforded the product as a white solid (5 mg, 56%); dec. 282-284 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.93 (brs, 1H), 9.23 (brs, 1H), 7.55 (d, *J* = 8 Hz, 2H), 7.45 (d, *J* = 8 Hz, 2H), 7.24 (d, *J* = 2 Hz, 1H), 7.12 (d, *J* = 2 Hz, 1H), 4.76 (s, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 157.7, 147.3, 136.7, 135.9, 129.4, 125.5, 121.4, 117.9, 114.6, 46.0; HRMS (ESI) calculated for $C_{12}H_9ClNO_2$ $(M-H)^-$ 234.0327, found 234.0323.

**5-(4-(Bromomethyl)phenyl)-3-hydroxypyridin-2(1*H*)-one (186).**

2-(*t*-Butoxy)-5-(4-(bromomethyl)phenyl)-3-((2-methoxyethoxy)methoxy)pyridine, **184**, (150 mg, 0.35 mmol) was dissolved in a mixture of trifluoroacetic acid (4 mL) and anhydrous dichloromethane (4 mL). The reaction mixture was stirred for overnight at room temperature. The solvent was removed under reduced pressured, and the resulting residue was suspended in diethyl ether. The suspension was filtered, and it was washed with diethyl ether. This afforded the product as a white solid (98 mg, 100%); dec. 264-266 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.95 (brs, 1H), 7.53 (d, *J* = 8 Hz, 2H), 7.46 (d, *J* = 7 Hz, 2H), 7.26 (s, 1H), 7.13 (s, 1H), 4.73 (s, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 157.7, 147.2, 136.7, 136.3, 129.8, 125.5, 121.5, 118.0, 114.6, 37.4; HRMS (ESI) calculated for $C_{12}H_9BrNO_2$ $(M-H)^-$ 277.9822, found 277.9826.

**4-(6-(*t*-Butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)aniline (187).**

3-Bromo-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine, **148**, (250 mg, 0.58 mmol), 4-aminophenylboronic acid pinacol ester (191 mg, 0.87 mmol), $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and $Na_2CO_3$ (184 mg, 1.74 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl

acetate, which was then washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a white solid (256 mg, 100%); mp 96-98 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.34-7.31 (m, 3H), 6.93-6.86 (m, 4H), 6.58 (d, $J$ = 8 Hz, 2H), 5.30 (s, 2H), 3.91-3.89 (m, 2H), 3.58-3.56 (m, 2H), 3.36 (s, 3H), 1.65 (s, 9H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 161.9 ($J_{C,F}$ = 244 Hz), 153.1, 145.3, 144.9, 140.8, 136.5 ($J_{C,F}$ = 4 Hz), 131.5 ($J_{C,F}$ = 8 Hz), 130.6, 130.0, 128.8, 128.0, 115.0, 114.4 ($J_{C,F}$ = 21 Hz), 94.8, 80.3, 71.6, 67.9, 59.0, 28.9.

**1-(4-(6-(*t*-Butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl)-1*H*-pyrrole-2,5-dione (188).**

4-(6-(*t*-Butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)aniline, **187**, (183 mg, 0.42 mmol) in dichloromethane (5 mL) was added to a solution of maleic anhydride (42 mg, 0.42 mmol) in diethyl ether (5 mL). The reaction mixture was stirred for an hour at room temperature. The solvent was removed under reduced pressure, and the resulting solid was suspended in diethyl ether. The suspension was filtered. The collected solid was added to a suspension of NaOAc (17 mg, 0.21 mmol) in acetic anhydride (5 mL). The reaction mixture was heated up to 100 $^oC$ and was stirred for an hour. After the reaction was completed as determined by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate and then washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl

acetate/hexane) to give the product as a white solid (120 mg, 55%); mp 134-136 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.30 (s, 1H), 7.25-7.22 (m, 2H), 7.19-7.18 (m, 4H), 6.84 (t, *J* =9 Hz, 2H), 6.78 (s, 2H), 5.24 (s, 2H), 3.84-3.82 (m, 2H), 3.52-3.50 (m, 2H), 3.30 (s, 3H), 1.60 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 169.4, 163.4, 153.8, 145.3, 140.9, 139.6, 135.9, 134.3, 131.6 ($J_{C,F}$ = 8 Hz), 130.3, 130.0, 127.9, 127.5, 125.7, 114.7 ($J_{C,F}$ = 22 Hz), 94.9, 80.6, 71.6, 68.0, 59.0, 28.9.

**1-(4-(6-(*t*-Butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl)-1*H*-pyrrole-2,5-dione (189).**

TFA (2 mL) was added to a solution of 1-(4-(6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl)-1*H*-pyrrole-2,5-dione, **188**, (120 mg, 0.23 mmol) in anhydrous dichloromethane (4 mL) under nitrogen. It was then stirred for 3 hours at room temperature. The solvent was removed under reduced pressure, and the product was crystallized as a yellow solid in methanolmethanol:water (1:2); dec. 285-287 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$+MeOD) δ 7.15-7.04 (m, 6H), 6.93 (s, 1H), 6.90 (t, *J*=9 Hz, 2H), 6.78 (s, 2H); $^{13}$C NMR (100 MHz) ($CDCl_3$+MeOD) δ 173.5, 162.6, 149.7, 141.2, 138.2, 136.5, 135.4 ($J_{C,F}$ =8 Hz), 134.1, 134.0, 133.7, 129.6, 123.8, 123.3, 119.6 ($J_{C,F}$ = 22 Hz); HRMS (ESI) calculated for $C_{21}H_{12}FN_2O_4$ $(M-H)^-$ 375.0787, found 375.0787.

**(4-(6-(*t*-Butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl)methanol (190).**

3-Bromo-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine, **148**, (300 mg, 0.70 mmol), 4-(hydroxymethyl)phenylboronic acid (160 mg, 1.05 mmol), $Pd(PPh_3)_4$ (81 mg, 0.07 mmol) and $Na_2CO_3$ (223 mg, 2.10 mmol) were dissolved in a mixture of dioxane (15 mL) and water (5 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for overnight. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate and washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (319 mg, 100%); mp 80-82 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.29 (s, 1H), 7.22-7.18 (m, 4H), 7.07 (d, $J$ = 7 Hz, 2H), 6.80 (t, $J$ = 8 Hz, 2H), 5.23 (s, 2H), 4.58 (s, 2H), 3.84-3.82 (m, 2H), 3.52-3.50 (m, 2H), 3.29 (s, 3H), 1.59 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 162.0 ($J_{C,F}$ = 245 Hz), 153.5, 145.2, 140.8, 139.6, 136.1 ($J_{C,F}$ = 3 Hz), 131.6 ($J_{C,F}$ = 8 Hz), 129.8, 128.8, 128.4, 127.9, 126.9, 114.5 ($J_{C,F}$ = 21 Hz), 94.8, 80.6, 71.5, 67.9, 58.9, 28.8.

**3-(4-(Bromomethyl)phenyl)-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine (191).**

Pyridine (0.04 mL, 0.44 mmol) followed by thionyl bromide (0.04 mL, 0.44 mmol) were added at 0 $^oC$ to a solution of (4-(6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)phenyl)methanol, **190**, (100 mg, 0.22 mmol) in

anhydrous dichloromethane (20 mL). The reaction mixture was stirred for an hour at 0 $^{o}$C. After the reaction was completed as indicated by TLC, it was diluted with ethyl acetate. The organic layer was then washed with sat. $NaHCO_3$, brine and dried over $Na_2SO_4$. It was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a colorless oil (32 mg, 28%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.29 (s, 1H), 7.23-7.18 (m, 4H), 7.05 (d, *J* = 8 Hz, 2H), 6.82 (t, *J* = 9 Hz, 2H), 5.24 (s, 2H), 4.42 (s, 2H), 3.85-3.82 (m, 2H), 3.52-3.50 (m, 2H), 3.30 (s, 3H), 1.60 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 163.3, 153.7, 145.3, 140.9, 140.2, 136.3, 131.6 ($J_{C,F}$ = 8 Hz), 130.1, 129.1, 127.8, 126.6, 114.6 ($J_{C,F}$ = 22 Hz), 94.9, 80.6, 71.6, 68.0, 59.0, 33.3, 28.9.

**5-(4-(Bromomethyl)phenyl)-6-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one (192).**

3-(4-(Bromomethyl)phenyl-6-(*t*-butoxy)-2-(4-fluorophenyl)-5-((2-methoxyethoxy)methoxy)pyridine, **191**, (30 mg, 0.06 mmol) was dissolved in a mixture of trifluoroacetic acid (1 mL) and anhydrous dichloromethane (1 mL). The reaction mixture was stirred for 3 hours at room temperature. The solvent was removed under reduced pressured, and the resulting residue was suspended in dichloromethane. The suspension was filtered, and it was washed with diethyl ether. This afforded the product as a white solid (12 mg, 55%); dec. 213-215 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.95 (brs, 1H), 9.35 (brs, 1H), 7.29 (d, *J* = 8 Hz, 2H), 7.22-7.18 (m, 2H), 7.13-1.09 (m, 2H), 7.01 (d, J = 7 Hz, 2H), 6.82 (s, 1H), 4.66 (brs, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 146.4, 136.0, 132.3, 132.2, 132.1, 131.5, 130.4, 129.7, 129.1, 121.5, 118.4, 115.3 ($J_{C,F}$ =

22 Hz), 34.2; HRMS (ESI) calculated for $C_{18}H_{12}BrFNO_2$ $(M-H)^-$ 372.0041, found 372.0042.

**_t_-Butyl 2-(6-(_t_-butoxy)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)acetate (193).**

5-Bromo-2-(*t*-butoxy)-3-((2-methoxyethoxy)methoxy)pyridine, **168**, (250 mg, 0.75 mmol), 0.5 M (2-*t*-butyoxy-2-oxoethyl)zinc (II) chloride in diethyl ether (2.5 mL, 1.25 mmol), QPhos (57 mg, 0.08 mmol) and $Pd(dba)_2$ (46 mg, 0.08 mmol) were dissolved in anhydrous tetrahydrofuran (10 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then stirred for overnight at 60 $^oC$. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate and washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a colorless oil (130 mg, 47%); $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.65 (d, *J* = 2 Hz, 1H), 7.28 (d, *J* = 2 Hz, 1H), 5.24 (s, 2H), 3.87-3.84 (m, 2H), 3.56-3.54 (m, 2H), 3.40 (s, 2H), 3.37 (s, 3H), 1.58 (s, 9H), 1.43 (s, 9H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 170.5, 154.2, 142.1, 139.1, 125.7, 123.2, 94.6, 81.0, 80.2, 71.6, 67.9, 59.0, 38.9, 28.8, 28.0.

**2-(5-Hydroxy-6-oxo-1,6-dihydropyridin-3-yl)acetic acid (194).**

*t*-Butyl 2-(6-(*t*-butoxy)-5-((2-methoxyethoxy)methoxy)pyridin-3-yl)acetate, **193**, (50 mg, 0.14 mmol) was dissolved in a mixture of trifluoroacetic acid (1 mL) and anhydrous

dichloromethane (1 mL). The reaction mixture was stirred for 3 hours at room temperature. The solvent was removed under reduced pressure, and the resulting residue was suspended in dichloromethane. The suspension was filtered to give the product as a pink solid (10 mg, 42%); mp 252-254 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 12.27 (brs, 1H), 11.57 (brs, 1H), 8.98 (brs, 1H), 6.75 (d, *J* = 2 Hz, 1H), 6.63 (d, *J* = 2 Hz, 1H), 3.28 (s, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 172.7, 157.6, 146.5, 122.7, 117.9, 112.4, 36.4; HRMS (ESI) calculated for $C_7H_6NO_4$ $(M-H)^-$ 168.0302, found 168.0303.

**_t_-Butyl 2-(6-(_t_-butoxy)-5-((2-methoxyethoxy)methoxy)pyridin-2-yl)acetate (195).**

6-Iodo-2-(*t*-butoxy)-3-((2-methoxyethoxy)methoxy)pyridine, **111**, (300 mg, 0.79 mmol), 0.5 M (2-*t*-butyoxy-2-oxoethyl)zinc (II) chloride in diethyl ether (2.5 mL, 1.25 mmol), QPhos (57 mg, 0.08 mmol) and $Pd(dba)_2$ (46 mg, 0.08 mmol) were dissolved in anhydrous tetrahydrofuran (10 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then stirred for overnight at 60 $^{o}$C. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate and washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-15% ethyl acetate/hexane) to give the product as a colorless oil (80 mg, 27%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.26 (d, *J* = 8 Hz, 1H), 6.68 (d, *J* = 8 Hz, 1H), 5.22 (s, 2H), 3.86-3.84 (m, 2H), 3.56-3.54 (m, 2H), 3.53 (s, 2H), 3.36 (s, 3H), 1.59 (s, 9H), 1.43 (s, 9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ170.4, 154.4, 144.7, 140.8, 125.4, 115.8, 94.8, 80.6, 80.4, 71.6, 67.9, 59.0, 44.4, 28.7, 28.1.

**2-(5-Hydroxy-6-oxo-1,6-dihydropyridin-2-yl)acetic acid (196).**

*t*-Butyl 2-(6-(*t*-butoxy)-5-((2-methoxyethoxy)methoxy)pyridin-2-yl)acetate, **195**, (60 mg, 0.16 mmol) was dissolved in a mixture of trifluoroacetic acid (1 mL) and anhydrous dichloromethane (1 mL). The reaction mixture was stirred for 5 hours at room temperature. The solvent was removed under reduced pressure, and the resulting residue was suspended in dichloromethane. The suspension was filtered and washed with diethyl ether. This afforded the product as a gray solid (27 mg, 100%); mp 237-239 $^{o}$C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 12.36 (brs, 1H), 11.63 (brs, 1H), 8.77 (brs, 1H), 6.64-6.61 (m, 1H), 5.93-5.91 (m, 1H), 3.41 (s, 2H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 171.0, 158.5, 145.6, 130.7, 115.5, 105.5, 37.2; HRMS (ESI) calculated for $C_7H_6NO_4$ $(M-H)^-$ 168.0302, found 168.0303.

**5-Bromo-3-((2-methoxyethoxy)methoxy)pyridin-2(1*H*)-one (197).**

Potassium trimethylsilanolate (1.67 g, 13.04 mmol) was added to a solution of 5-bromo-2-fluoro-3-((2-methoxyethyoxy)methoxy)pyridine, **167**, (1.83 g, 6.52 mmol) in THF (70 mL). The reaction mixture was stirred for overnight at 50 $^{o}$C. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with sat. $NH_4Cl$, brine and dried over $Na_2SO_4$. It was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a white solid (1.15 g, 63%); mp 101-103 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$)

δ 11.90 (brs, 1H), 7.30 (d, *J* = 2 Hz, 1H), 7.12 (d, *J* = 2 Hz, 1H), 5.24 (s, 2H), 3.73-3.71 (m, 2H), 3.48-3.46 (m, 2H), 3.24 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 156.5, 146.5, 128.2, 123.3, 96.1, 93.3, 70.9, 67.7, 58.0.

**5-(4-Fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridin-2(1*H*)-one (198).**

5-Bromo-3-((2-methoxyethoxy)methoxy)pyridin-2(1*H*)-one, **197**, (1.15 g, 4.14 mmol), 4-fluorophenylboronic acid (869 mg, 6.21 mmol), $Pd(PPh_3)_2Cl_2$ (288 mg, 0.41 mmol) and $Na_2CO_3$ (1.32 g, 12.42 mmol) were dissolved in a mixture of dioxane (45 mL) and water (15 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for 6 hours. After the reaction was completed as indicated by TLC, it was allowed to cool to room temperature. It was diluted with ethyl acetate and washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% 2-propanol/ethyl acetate) to give the product as a white solid (448 mg, 37%); mp 103-105 $^o$C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 11.94 (brs, 1H), 7.59 (dd, *J* = 9 Hz, *J* = 5 Hz, 2H), 7.38 (m, 2H), 7.24 (t, *J* = 9 Hz, 2H), 5.30 (s, 2H), 3.77-3.75 (m, 2H), 3.49-3.46 (m, 2H), 3.22 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 162.5, 157.1, 146.2, 132.3, 127.4 ($J_{C,F}$ = 8 Hz), 124.9, 120.8, 116.5, 115.6 ($J_{C,F}$ = 22 Hz), 93.3, 71.0, 67.5, 58.0.

**5-(4-Fluorophenyl)-3-((2-methoxyethoxy)methoxy)-1-methylpyridin-2(1*H*)-one (199).**

$K_2CO_3$ (70 mg, 0.51 mmol) followed by $CH_3I$ (0.03 mL, 0.51 mmol) were added to a solution of 5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridin-2(1*H*)-one, **198**, (100 mg, 0.34 mmol) in DMF (5 mL).. The reaction mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with water, brine and dried over $Na_2SO_4$. The reaction mixture was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a colorless oil (68 mg, 65%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.38-7.33 (m, 3H), 7.15 (d, *J* = 2 Hz, 1H), 7.08 (t, *J* = 9 Hz, 2H), 5.36 (s, 2H), 3.89-3.86 (m, 2H), 3.63 (s, 3H), 3.57-3.54 (m, 2H), 3.35 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 162.3 ($J_{C,F}$ = 245 Hz), 157.8, 147.1, 133.0 ($J_{C,F}$ = 3 Hz), 128.1, 127.7 ($J_{C,F}$ = 7 Hz), 119.3, 118.3, 115.9 ($J_{C,F}$ = 21 Hz), 94.1, 71.5, 68.0, 58.9, 37.9.

**5-(4-Fluorophenyl)-3-hydroxy-1-methylpyridin-2(1*H*)-one (200).**

5-(4-Fluorophenyl)-3-((2-methoxyethoxy)methoxy)-1-methylpyridin-2(1*H*)-one, **199**, (68 mg, 0.22 mmol) was dissolved in a mixture of trifluoroacetic acid (3 mL) and anhydrous dichloromethane (3 mL). The reaction mixture was stirred for 6 hours at room temperature. The solvent was removed under reduced pressure, and the resulting residue was suspended in dichloromethane. The suspension was filtered to give the product as a white solid (48 mg, 100%); mp 154-155 $^o$C; $^1$H NMR (400 MHz) (DMSO-$d_6$) δ 9.30 (brs, 1H), 7.69-7.66 (m, 3H), 7.33 (t, *J* = 9 Hz, 2H), 7.17 (d, *J* = 2 Hz, 1H), 3.65 (s, 3H); $^{13}$C

NMR (100 MHz) (DMSO-$d_6$) δ 161.3 ($J_{C,F}$ = 242 Hz), 157.3, 146.5, 133.1 ($J_{C,F}$ = 3 Hz), 127.3 ($J_{C,F}$ = 8 Hz), 126.4, 117.0, 115.6 ($J_{C,F}$ = 21 Hz), 113.8, 37.0; HRMS (ESI) calculated for $C_{12}H_9FNO_2$ $(M-H)^-$ 218.0623, found 218.0625.

**2-Chloro-3-((2-methoxyethoxy)methoxy)pyridine (201).**

Sodium hydride (1.23 g, 30.86 mmol) was added to a solution of 2-chloro-3-hydroxypyridine (2 g, 15.43 mmol) in anhydrous tetrahydrofuran (15 mL).. The reaction mixture was stirred for an hour at room temperature. Then, MEM-chloride (3.52 mL, 30.86 mmol) was added, and the mixture was stirred for 3 hours at room temperature. After the reaction was completed as indicated by TLC, it was diluted with ethyl acetate. The organic layer was washed with water, brine and dried over $Na_2SO_4$. It was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a colorless oil (3.36 g, 100%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.06-8.04 (m, 1H), 7.55-7.53 (m, 1H), 7.21-7.18 (m, 1H), 5.37 (s, 2H), 3.89-3.86 (m, 2H), 3.57-3.54 (m, 2H), 3.36 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 160.5, 149.5, 141.9, 123.6, 123.2, 94.0, 71.3, 68.2, 58,9.

**2-Chloro-3-((2-methoxyethoxy)methoxy)pyridine 1-oxide (202).**

Sodium bicarbonate (3.89 g, 46.29 mmol) and mCPBA (5.91 g, 46.29 mmol) were added to a solution of 2-chloro-3-((2-methoxyethoxy)methoxy)pyridine, **201**, (3.36 g, 15.43 mmol) in anhydrous dichloromethane (50 mL). The reaction mixture was stirred for

overnight. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$, brine and dried over $Na_2SO_4$. It was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a colorless oil (1.0 g, 28%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.05 (d, *J* = 6 Hz, 1H), 7.14 (d, *J* = 9 Hz, 1H), 7.06 (dd, *J* = 9 Hz, *J* = 7 Hz, 1H), 5.33 (s, 2H), 3.81-3.79 (m, 2H), 3.50-3.48 (m, 2H), 3.29 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 152.6, 134.5, 134.3, 122.1, 112.7, 94.5, 71.3, 68.6, 59.0.

**2-Methoxy-3-((2-methoxyethoxy)methoxy)pyridine 1-oxide (203).**

Sodium methoxide (416 mg, 7.70 mmol) was added to a solution of 2-chloro-3-((2-methoxyethoxy)methoxy)pyridine 1-oxide, **202**, (900 mg, 3.85 mmol) in a mixture of methanol (10 mL) and THF (10 mL). The reaction mixture was stirred for overnight at room temperature. The reaction mixture was filtered to remove sodium methoxide. The filtrate was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% 2-propanol/ethyl acetate) to give the product as a colorless oil (418 mg, 47%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.94-7.92 (m, 1H), 7.20-7.18 (m, 1H), 6.95-6.91 (m, 1H), 5.33 (s, 2H), 4.16 (s, 3H), 3.87-3.84 (m, 2H), 3.57-3.54 (m, 2H), 3.36 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 151.9, 147.8, 133.9, 119.1, 115.3, 94.6, 71.4, 68.4, 60.3, 60.0.

**1,3-Dihydroxypyridin-2(1*H*)-one (204).**

2-Methoxy-3-((2-methoxyethoxy)methoxy)pyridine 1-oxide, **203**, (418 mg, 1.82 mmol) was dissolved in acetic chloride (10 mL), andthe mixture stirred for overnight at 50 ºC. Acetic chloride was then removed under reduced pressure, and the resulting residue dissolved in methanol (10 mL). The reaction mixture was stirred for overnight at room temperature. Then, the methanol was removed under reduced pressure, and the resulting residue was suspended in dichloromethane. It was filtered to provide the product as a white solid (187 mg, 81%); dec. 173-175 ºC; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.63 (brs, 1H), 9.33 (brs, 1H), 7.34 (d, *J* = 7 Hz, 1H), 6.69 (d, *J* = 7 Hz, 1H),6.06 (t, *J* = 7 Hz, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 154.3, 147.6, 126.0, 113.9, 103.3; HRMS (ESI) calculated for $C_5H_4NO_3$ $(M-H)^-$ 126.0197, found 126.0200.

**3-(4-Fluorophenyl)-5-methoxypyridine (205).**

3-Bromo-5-methoxypyridine (2.5 g, 13.30 mmol), 4-fluorophenylboronic acid (2.79 g, 19.95 mmol), $Pd(PPh_3)_2Cl_2$ (934 mg, 1.33 mmol) and $Na_2CO_3$(4.23 g, 39.30 mmol) were dissolved in a mixture of dioxane (180 mL) and water (60 mL). The air was evacuated from the reaction flask and replaced with $N_2$. The reaction mixture was then refluxed for overnight. The reaction mixture was allowed to cool to room temperature. It was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a white solid (2.64 g, 98%); mp 56-58 ºC; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.49 (d, *J* = 2 Hz, 1H), 8.38 (d, *J* = 2 Hz, 1H), 7.57-7.53 (m, 2H), 7.39-7.38 (m, 1H), 7.19

(t, $J$ = 9 Hz, 2H), 3.95 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 162.9 ($J_{C,F}$ = 247 Hz), 155.7, 140.5, 136.3, 136.1, 133.8, 133.8 ($J_{C,F}$ = 4 Hz), 128.9 ($J_{C,F}$ = 9 Hz), 118.9, 115.9 ($J_{C,F}$ = 22 Hz), 55.5.

**3-(4-Fluorophenyl)-5-methoxypyridine 1-oxide (206).**

Solid mCPBA (3.20 g, 14.29 mmol) was added at 0 $^{o}$Cto a mixture of 3-(4-fluorophenyl)-5-methoxypyridine, **205**, (2.64 g, 12.99 mmol) in anhydrous dichloromethane (130 mL). The reaction mixture was stirred for an hour at at 0 $^{o}$C. After the reaction was completed as determined by TLC, it was diluted with chloroform, which was washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a white solid (2.82 g, 99%); mp 85-87 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) 8.27 (s, 1H), 8.07 (s, 1H), 7.86-7.82 (m, 2H), 7.36-7.31 (m, 3H), 3.90 (s, 3H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 162.8 ($J_{C,F}$ = 245 Hz), 157.7, 137.7, 131.3 ($J_{C,F}$ = 3 Hz), 130.0, 129.4 ($J_{C,F}$ = 8 Hz), 125.7, 115.9 ($J_{C,F}$ = 21 Hz), 110.5, 56.5.

**2-Chloro-5-(4-fluorophenyl)-3-methoxypyridine (207).**

$POCl_3$ (6.01 mL, 64.30 mmol) was added to a mixture of 3-(4-fluorophenyl)-5-methoxypyridine 1-oxide, **206**, (2.82 g, 12.86 mmol) in anhydrous dichloromethane (130 mL). The reaction mixture was stirred for overnight at 100 $^{o}$C. The reaction mixture was

allowed to cool to room temperature, and was diluted with dichloromethane, which was then washed with sat. $NaHCO_3$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give the product as a white solid (1.12 g, 37%); mp 75-77 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.15 (d, $J$ = 2 Hz, 1H), 7.54-7.50 (m, 2H), 7.30 (d, $J$ = 2 Hz, 1H), 7.17 (t, $J$ = 9 Hz, 2H), 3.98 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 163.1 ($J_{C,F}$ = 247 Hz), 151.6, 139.7, 138.5, 136.2, 133.0 ($J_{C,F}$ = 3 Hz), 129.0 ($J_{C,F}$ = 8 Hz), 117.6, 116.2 ($J_{C,F}$ = 22 Hz), 56.2.

**2-Chloro-5-(4-fluorophenyl)pyridin-3-ol (208).**

A solution of 1M $BBr_3$ in dichloromethane (14 mL, 14.13 mmol) was added to a mixture of 2-chloro-5-(4-fluorophenyl)-3-methoxypyridine, **207**, (1.12 g, 4.71 mmol) in anhydrous dichloromethane (50 mL). The reaction mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, which was then washed with 2N HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the desired product as a white solid (726 mg, 69%); mp 245-247 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 10.72 (brs, 1H), 8.00 (d, $J$ = 2 Hz, 1H), 7.56-7.53 (m, 2H), 7.35 (d, $J$ = 2 Hz, 1H), 7.17 (t, $J$ = 9 Hz, 2H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 162.3 ($J_{C,F}$ = 244 Hz), 149.6, 137.3, 137.2, 135.4, 132.5 ($J_{C,F}$ = 3 Hz), 129.0 ($J_{C,F}$ = 8 Hz), 121.7, 116.0 ($J_{C,F}$ = 21 Hz).

**2-Chloro-5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridine (209).**

NaH, 60% dispersion in mineral oil (260 mg, 6.50 mmol) was added at 0 $^{o}$C to a mixture of 2-chloro-5-(4-fluorophenyl)pyridin-3-ol, **208**, (726 mg, 3.25 mmol) in tetrahydrofuran (32 mL). The reaction mixture was stirred for 30 minutes at room temperature. Then, MEM-chloride (0.74 mL, 6.50 mmol) was added to the mixture. The reaction mixture was then stirred for 3 hours at room temperature. After the reaction was completed as determined by TLC, it was diluted with ethyl acetate, which was washed with water, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give the product as a colorless oil (1.01 g, 100%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.24 (d, $J$ = 2 Hz, 1H), 7.72 (d, $J$ = 2 Hz, 1H), 7.56-7.52 (m, 2H), 7.18 (t, $J$ = 9 Hz, 2H), 5.44 (s, 2H), 3.94-3.92 (m, 2H), 3.61-3.58 (m, 2H), 3.38 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 163.1 ($J_{C,F}$ = 247 Hz), 149.4, 140.4, 140.0, 136.1, 132.6 ($J_{C,F}$ = 3 Hz), 129.0 ($J_{C,F}$ = 8 Hz), 122.3, 116.1 ($J_{C,F}$ = 21 Hz), 94.2, 71.4, 68.3, 59.0.

**2-Chloro-5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridine 1-oxide (210).**

Sodium bicarbonate (210 mg, 2.50 mmol) followed by mCPBA (560 mg, 2.50 mmol) was added to a mixture of 2-chloro-5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridine, **209**, (390 mg, 1.25 mmol) in dichloromethane (5 mL). The reaction mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, which was washed with water, followed by brine.

The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a colorless oil (210 mg, 51%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.36 (s, 1H), 7.52-7.48 (m, 2H), 7.40 (s, 1H), 7.17 (t, *J* = 9 Hz, 2H), 5.45 (s, 2H), 3.91-3.89 (m, 2H), 3.58-3.56 (m, 2H), 3.36 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 163.6 ($J_{C,F}$ = 249 Hz), 152.4, 135.7, 133.2, 132.5, 130.9, 128.9 ($J_{C,F}$ = 8 Hz), 116.5 ($J_{C,F}$ = 21 Hz), 112.5, 94.6, 71.3, 68.6, 59.0.

**5-(4-Fluorophenyl)-2-methoxy-3-((2-methoxyethoxy)methoxy)pyridine 1-oxide (211).**

2-Chloro-5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridine 1-oxide, **210**, (434 mg, 1.32 mmol) and sodium methoxide (357 mg, 6.60 mmol) were dissolved in a mixture of methanol (12 mL) and DMF (3 mL). The reaction mixture was stirred for overnight at room temperature. Methanol was removed under reduced pressure. The residue was diluted with ethyl acetate, which was then washed with sat. $NH_4Cl$, followed by brine. The organic layer was dried over $Na_2SO_4$ and was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane) to give the product as a brown oil (185 mg, 43%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.36 (s, 1H), 7.52-7.48 (m, 2H), 7.40 (s, 1H), 7.17 (t, *J* = 9 Hz, 2H), 8.07 (d, *J* = 2 Hz, 1H), 7.41-7.38 (m, 2H), 7.27 (d, *J* = 2 Hz, 1H), 7.09 (t, *J* = 9 Hz, 2H), 5.32 (s, 2H), 4.13 (s, 3H), 3.84-3.82 (m, 2H), 3.52-3.50 (m, 2H), 3.30 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ

162.0, 150.9, 147.4, 132.5, 132.1, 131.6, 128.6 ($J_{C,F}$ = 9 Hz), 116.3 ($J_{C,F}$ = 22 Hz), 114.0, 94.8, 71.4, 68.4, 59.0.

**5-(4-Fluorophenyl)-1,3-dihydroxypyridin-2(1*H*)-one (212).**

5-(4-Fluorophenyl)-2-methoxy-3-((2-methoxyethoxy)methoxy)pyridine 1-oxide, **211**, (185 mg, 0.57 mmol) was dissolved in acetic chloride (10 mL), and it was heated for overnight at 50 $^{o}$C. Acetic chloride was then removed under reduced pressure. The resulting residue was dissolved in methanol, and it was stirred for overnight at room temperature. Methanol was removed under reduced pressure. Then, it was suspended in dichloromethane, and it was filtered to give the product as a white solid (100 mg, 79%); dec. 237-239 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.47 (brs, 1H), 9.58 (brs, 1H), 7.73 (s, 1H), 7.59-7.56 (m, 2H), 7.19 (t, $J$ = 8 Hz, 2H), 7.05 (s, 1H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 161.4 ($J_{C,F}$ = 243 Hz), 153.5, 147.2, 132.5, 123.4, 127.6 ($J_{C,F}$ = 8 Hz), 123.4, 115.6 ($J_{C,F}$ = 21 Hz), 113.0; HRMS (ESI) calculated for $C_{11}H_7FNO_3$ $(M-H)^-$ 220.0415, found 220.0413.

**1-Amino-5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridin-2(1*H*)-one (213).**

$K_2CO_3$ (106 mg, 0.77 mmol) followed by O-(2,4-dinitrophenyl)hydroxylamine (153 mg, 0.77 mmol) was added to a solution of 5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridin-2(1*H*)-one, **198**, (150 mg, 0.51 mmol) in DMF (5 mL). The reaction mixture was stirred for overnight at room temperature. The reaction mixture

was diluted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$, brine and dried over $Na_2SO_4$. It was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the desired product as a yellow oil (70 mg, 45%); $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.50 (d, $J$ = 2 Hz, 1H), 7.38-7.35 (m, 3H), 7.10-7.06 (m, 2H), 5.36 (s, 2H), 5.29 (brs, 2H), 3.88-3.86 (m, 2H), 3.56-3.54 (m, 2H), 3.34 (s, 3H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 162.4 ($J_{C,F}$ = 246 Hz), 156.8, 146.6, 132.6, 128.1, 127.7 ($J_{C,F}$ = 8 Hz), 119.4, 117.5, 116.0 ($J_{C,F}$ = 22 Hz), 94.2, 71.4, 68.0, 58.9.

**1-(N,N-Bis-(*t*-butoxycarbonyl)amino)-5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridin-2(1*H*)-one (214a) and 6-(4-fluorophenyl)-8-((2-methoxyethoxy)methoxy)-2-oxo-[1,3,4]oxadiazolo[3,2-a]pyridin-4-ium-3-ide (214b).**

1-Amino-5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridin-2(1*H*)-one, **213**, (52 mg, 0.17 mmol) was dissolved in Boc anhydride (1 mL). Triethyl amine (0.05 mL, 0.34 mmol) was added, and the mixture was stirred for 2 hours at 50 ºC. After the reaction was completed as determined by TLC, it was diluted with ethyl acetate. The organic layer was washed with water, brine and dried over $Na_2SO_4$. It was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give 1-(N,N-bis-(*t*-butoxycarbonyl)amino)-5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridin-2(1*H*)-one as a white solid (19 mg, 22%). mp 133-135 ºC; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.40-7.36 (m, 3H), 7.11-7.07 (m, 3H), 5.36 (s, 2H), 3.89-3.87 (m, 2H), 3.57-3.55 (m, 2H), 3.37 (s, 3H), 1.50 (s, 18 H); $^{13}$C NMR (100

MHz) ($CDCl_3$) δ 162.4 ($J_{C,F}$ = 231Hz), 155.3, 149.2, 147.9, 132.3, 128.6, 127.8 ($J_{C,F}$ = 8 Hz), 119.6, 117.9, 115.9 ($J_{C,F}$ = 22 Hz), 94.4, 85.2, 71.5, 68.1, 58.9, 27.9. along with 6-(4-fluorophenyl)-8-((2-methoxyethoxy)methoxy)-2-oxo-[1,3,4]oxadiazolo[3,2-a]pyridin-4-ium-3-ide as a white solid (33 mg, 58%). m.p. 116-118 $^oC$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.20 (d, *J* = 2 Hz, 1H), 7.74 (d, *J* = 2 Hz, 1H), 7.54-7.51 (m, 2H), 7.25-7.21 (m, 2H), 5.52 (s, 2H), 3.96-3.94 (m, 2H), 3.61-3.59 (m, 2H), 3.37 (s, 3H); $^{13}C$ NMR (100 MHz) ($CDCl_3$) δ 163.6 ($J_{C,F}$ = 249 Hz), 158.9, 142.6, 138.7, 132.0, 130.7 ($J_{C,F}$ = 4 Hz), 129.0 ($J_{C,F}$ = 9 Hz), 120.3, 120.0, 116.7 ($J_{C,}$F = 22 Hz), 95.3, 71.3, 68.9, 59.0.

**1-Amino-5-(4-fluorophenyl)-3-hydroxypyridin-2(1*H*)-one (215).**

4N HCl (0.09 mL, 0.37 mmol) was added at 0 $^oC$ to a solution of 1-(N,N-bis-(*t*-butoxycarbonyl)amino)-5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)-pyridin-2(1*H*)-one, **214a**, (19 mg, 0.04 mmol) in methanol (1 mL). The reaction mixture was stirred for 2 hours at 0 $^oC$, then it was stirred for 4 hours at room temperature. The solvent was removed under reduced pressure, and the resulting residue was suspended in dichloromethane. The suspension was filtered to give the product as a gray solid (3 mg, 38%); mp 191-193 $^oC$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) δ 7.60-7.56 (m, 3H), 7.23 (t, *J* = 9 Hz, 2H), 7.08 (d, *J* = 2 Hz, 1H); $^{13}C$ NMR (100 MHz) (DMSO-$d_6$) δ 161.3 ($J_{C,F}$ = 242 Hz), 155.0, 146.2, 132.8 ($J_{C,F}$ = 3 Hz), 127.4 ($J_{C,F}$ = 9 Hz), 124.5, 116.1, 115.6 ($J_{C,F}$ = 21 Hz), 113.5; HRMS (ESI) calculated for $C_{11}H_8FN_2O_2$ $(M-H)^-$ 219.0575, found 219.0577.

**6-(4-Fluorophenyl)-8-hydroxy-2-oxo-[1,3,4]oxadiazolo[3,2-a]pyridin-4-ium-3-ide (216).**

4N HCl (0.25 mL, 1.00 mmol) was added at 0 $^{o}$C to a solution of 6-(4-fluorophenyl)-8-((2-methoxyethoxy)methoxy)-2-oxo-[1,3,4]oxadiazolo[3,2-a]pyridin-4-ium-3-ide, **214b**, (33 mg, 0.10 mmol) in methanol (1 mL). The reaction mixture was stirred for 3 hours at 0 $^{o}$C, providing a white suspension. The suspension was filtered to give the product as a white solid (23 mg, 96%); mp 284-286 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 11.76 (brs, 1H), 8.63 (d, *J* = 2Hz, 1H), 7.79-7.75 (m, 2H), 7.55 (d, *J* = 2 Hz, 1H), 7.36 (t, *J* = 9 Hz, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 162.5 ($J_{C,F}$ = 245 Hz), 158.4, 141.3, 138.8, 131.1, 130.6, 129.2 ($J_{C,F}$ = 8 Hz), 119.0, 118.2, 116.0 ($J_{C,F}$ = 21 Hz); HRMS (ESI) calculated for $C_{12}H_6FN_2O_3$ $(M-H)^-$ 245.0368, found 245.0371.

***t*-Butyl 2-(5-(4-Fluorophenyl)-3-((2-methoxyethoxy)methoxy)-2-oxopyridin-1(2*H*)-yl)acetate (217).**

$K_2CO_3$ (70 mg, 0.51 mmol) followed by *t*-butyl bromoacetate (0.08 mL. 0.51 mmol) were added to a solution of 5-(4-fluorophenyl)-3-((2-methoxyethoxy)methoxy)pyridin-2(1*H*)-one, **198**, (100 mg, 0.34 mmol) in DMF (5 mL).. The reaction mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with water, brine and dried over $Na_2SO_4$. It was then concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a colorless oil (122

mg, 88%); $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.37-7.33 (m, 3H), 7.08-7.04 (m, 3H), 5.34 (s, 2H), 4.61 (s, 2H), 3.87-3.84 (m, 2H), 3.55-3.50 (m, 2H), 3.34 (s, 1H), 1.47 (9H); $^{13}$C NMR (100 MHz) ($CDCl_3$) δ 166.6, 162.5, 157.4, 147.2, 132.9 ($J_{C,F}$ = 3 Hz), 127.8 ($J_{C,F}$ = 7 Hz), 119.5, 118.4, 115.8 ($J_{C,F}$ = 22 Hz), 94.1, 82.9, 71.5, 68.0, 58.9, 51.4, 28.0.

**2-(5-(4-Fluorophenyl)-3-hydroxy-2-oxopyridin-1(2*H*)-yl)acetic acid (218).**

*t*-Butyl 2-(5-(4-Fluorophenyl)-3-((2-methoxyethoxy)methoxy)-2-oxopyridin-1(2*H*)-yl)acetate, **217**, (122 mg, 0.30 mmol) was dissolved in a mixture of trifluoroacetic acid (3 mL) and anhydrous dichloromethane (3 mL). The reaction mixture was stirred for overnight at room temperature. The solvent was removed under reduced pressure, and the resulting residue was suspended in dichloromethane. The suspension was filtered to give the product as a gray solid (60 mg, 76%); dec. 254-256 $^{o}$C; $^{1}$H NMR (400 MHz) (DMSO-$d_6$) δ 13.04 (brs, 1H), 9.37 (brs, 1H), 7.59 (d, *J* = 2 Hz, 1H), 7.57-7.53 (m, 2H), 7.24 (t, *J* = 9 Hz, 2H), 7.11 (d, *J* = 2 Hz, 1H), 4.70 (s, 2H); $^{13}$C NMR (100 MHz) (DMSO-$d_6$) δ 169.2, 157.1, 146.6, 127.3 ($J_{C,F}$ = 8 Hz), 126.4, 116.9, 115.7 ($J_{C,F}$ = 22 Hz), 114.3, 50.4; HRMS (ESI) calculated for $C_{13}H_9FNO_4$ $(M-H)^-$ 262.0521, found 262.0522.

# APPENDIX

List of Compounds Evaluated for Endonuclease Inhibition

and Their Corresponding HY Codes

| Final Compound Number | Corresponding HY Code |
|---|---|
| **16** | **HY-1-109** |
| **17** | **HY-1-119** |
| **22** | **HY-1-161** |
| **23** | **HY-1-160** |
| **24** | **HY-1-138** |
| **25** | **HY-1-144** |
| **30** | **HY-1-162** |
| **31** | **HY-1-164** |
| **32** | **HY-1-140** |
| **33** | **HY-1-134** |
| **34** | **HY-1-175** |
| **35** | **HY-1-191** |
| **36** | **HY-1-163** |
| **37** | **HY-2-34** |
| **38** | **HY-2-5** |
| **39** | **HY-2-8** |
| **40** | **HY-2-39** |
| **44** | **HY-2-47** |
| **48** | **HY-2-69** |
| **52** | **HY-2-55** |
| **63** | **HY-3-148** |

| | |
|---|---|
| **64** | **HY-3-130** |
| **65** | **HY-3-139** |
| **66** | **HY-3-149** |
| **67** | **HY-3-154** |
| **73** | **HY-2-99** |
| **74** | **HY-2-82** |
| **75** | **HY-2-142** |
| **76** | **HY-2-148** |
| **83** | **HY-2-135** |
| **87** | **HY-2-114** |
| **90** | **HY-2-166** |
| **91** | **HY-2-168** |
| **99** | **HY-4-24** |
| **100** | **HY-4-30** |
| **101** | **HY-4-25** |
| **102** | **HY-4-131** |
| **103** | **HY-4-37** |
| **104** | **HY-4-133** |
| **105** | **HY-4-162** |
| **123** | **HY-4-87** |
| **124** | **HY-4-104** |
| **125** | **HY-4-93** |
| **126** | **HY-4-89** |
| **127** | **HY-4-105** |
| **128** | **HY-4-94** |
| **141** | **HY-3-106** |
| **142** | **HY-4-46** |
| **143** | **HY-4-10** |
| **144** | **HY-3-112** |

| | |
|---|---|
| **145** | **HY-4-47** |
| **146** | **HY-4-11** |
| **154** | **HY-5-114** |
| **155** | **HY-5-103** |
| **156** | **HY-6-22** |
| **157** | **HY-6-9** |
| **158** | **HY-6-50** |
| **160** | **HY-6-68** |
| **166** | **HY-6-81** |
| **173** | **HY-5-171** |
| **174** | **HY-5-1** |
| **175** | **HY-5-8** |
| **176** | **HY-5-9** |
| **177** | **HY-5-4** |
| **178** | **HY-5-5** |
| **181** | **HY-7-57** |
| **185** | **HY-7-51** |
| **186** | **HY-8-44** |
| **189** | **HY-5-192** |
| **192** | **HY-7-68** |
| **194** | **HY-7-17** |
| **196** | **HY-7-18** |
| **200** | **HY-7-142** |
| **204** | **HY-7-129** |
| **212** | **HY-8-17** |
| **215** | **HY-8-130** |
| **216** | **HY-8-131** |
| **218** | **HY-7-141** |

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