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Short Communication

Novel synthetic approach to fluoro- and amido-disubstituted 3-hydroxypyridin-4-ones

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ABSTRACT

Starting from fluoropyridines as a building block, with chelating functional groups being introduced, several fluoro- and amido-disubstituted 3-hydroxypyridin-4-ones have been synthesized with the intention of improving the pharmaceutical profile of 3-hydroxypyridin-4-ones.

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1. Introduction

3-Hydroxypyridin-4-ones (HPOs) are currently one of the main candidates for the development of orally active iron chelators [1]. They are also one of the two general classes of molecules having been reported to possess potential for the treatment of neurodegenerative diseases [2]. Dimethyl-3-hydroxypyridin-4-one (deferiprone) has been used clinically as an orally active iron chelator for treating transfusion-induced iron overload for over a period of 20 years [3]. It has been reported to be effective and safe in the reversal of oxidative stress in the neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and Friedreich's ataxia (FA) [4–6]. The efficacy of deferiprone is limited by extensive metabolism in the liver and therefore a relatively high dose is required to maintain iron overloaded patients in negative iron balance [7]. In addition, deferiprone is not particularly efficient at crossing the blood–brain barrier [8].

An introduction of fluorine into an organic molecule can significantly improve the chemical and biological properties, such as its metabolic stability, bioavailability, selective reactivity and receptor binding interactions [9]. In fact, the role of fluorine in drug design has been frequently reviewed [10–12]. It is clear that fluorine plays an increasingly important role in the design of pharmaceuticals.

Many synthetic methods to introduce a fluorine atom directly into the pyridine-4-one ring have been attempted but all have failed [13]. Schlosser's group has reported that fluoropyridines can be readily and site selectively metalated by using different lithium reagents. Subsequent reaction with a suitable electrophile achieves the target product [14,15]. This approach subverts our conventional approach and has directed us to redesign synthetic pathways of fluorinated 3-hydroxypyridin-4-ones. It is possible to obtain the target products by starting with a fluorine-containing precursor and then introducing chelating functional groups. As an introduction of an electron-withdrawing group on the pyridinone ring can decrease pK_a value of the 3-pyridinone oxygen atom and correspondingly result enhanced metal stability constant [16,17], we would like to report fluorinated HPOs in this present paper which contain another functional group, the amido group, in order to enhance the pFe^{3+} value and possibly also the metabolic stability of the ligands [16,18].

2. Results and discussion

The novel synthetic route to 2-fluoro-5-amido substituted 3-hydroxypyridin-4-one is summarized in Scheme 1. It starts from the commercially available 2-fluoropyridine (**1**). Due to the strong inductive effect of fluorine atom at C2, the starting material

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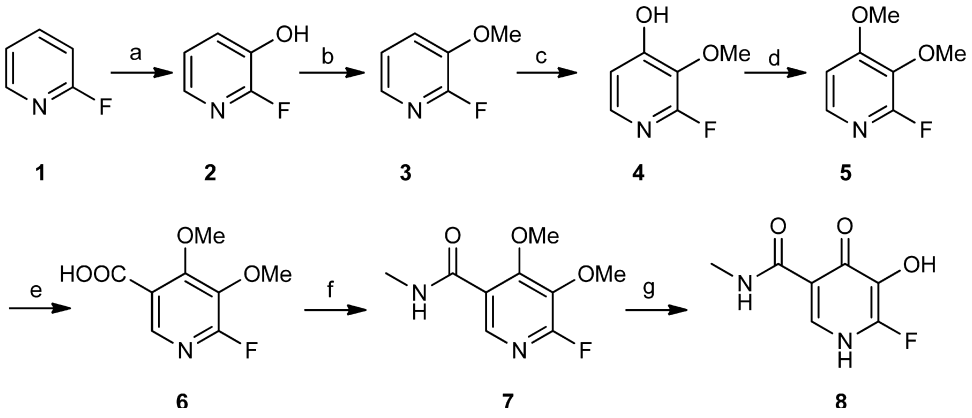
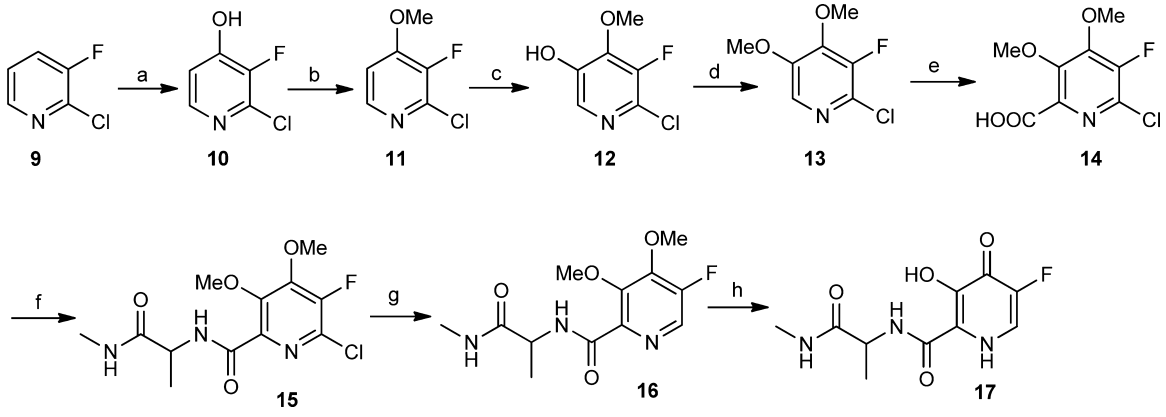


Scheme 1. Synthesis of 2-fluoro-5-amido substituted 3-hydroxypyridin-4-one. (a) (1) LDA, THF, −75 °C, 2 h, (2) $B(OMe)_3$, −75 °C, 2 h, (3) CH_3CO_3H, 0 °C, 1 h, 92%; (b) K_2CO_3/MeI/acetone, reflux overnight, 95%; (c) (1) LTMP, THF, −75 °C, 20 h; (2) $B(OMe)_3$, −75 °C, 2 h, (3) CH_3CO_3H, 0 °C, 1 h, 87%; (d) K_2CO_3/MeI/acetone, reflux overnight, 40%; (e) (1) LTMP, THF, −75 °C, 20 h; (2) dry ice, thaw to r.t., 87%; (f) DCC/NHS/$MeNH_2$, r.t., overnight, 67%; (g) BBr_3, 0 °C to r.t., overnight, 70%.

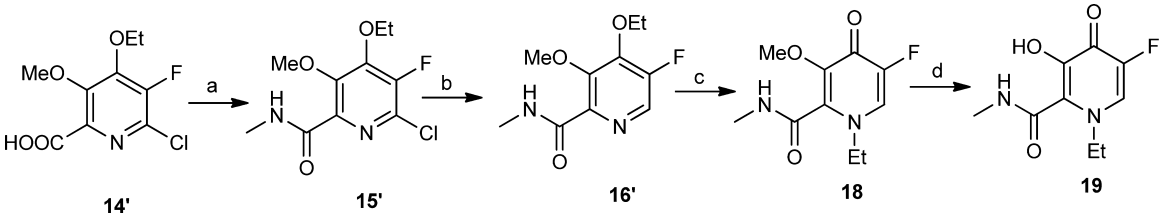
undergoes lithiation at the *ortho*-position (C3) by lithium diisopripylamide (LDA). The lithiated fluoropyridine was trapped with trimethylborate, followed by *in situ* reaction with peracetic acid to afford 2-fluoro-3-hydroxypyridine (**2**). The hydroxy group of compound **2** needs to be protected before lithiation and a simple methyl group was introduced by reacting compound **2** with methyl iodide in the presence of potassium carbonate. When we attempted to lithiate compound **3** using LDA, no product was isolated. This may be due to the relatively weaker inductive effect of methoxy group at *ortho*-position (C3) as compared to that of the fluorine atom. Therefore, a stronger metalation reagent lithium 2,2,6,6-tetramethylpiperidide (LTMP) was investigated. The resulting lithiated intermediate was again trapped with trimethylborate and oxidized by peracetic acid to afford 2-fluoro-4-hydroxy-3-methoxypyridine (**4**). Compound **4** can react with MeI/K_2CO_3 to afford two isomers due to its two resonance forms. To minimize the formation of the N-methyl isomer, polar solvents such as methanol were avoided as they favor polar products. When compound **5** was lithiated with LTMP, the lithiation only occurs at C5, due to neighboring group assistance. The resulting lithiating intermediate was trapped with dry ice to afford 5-carboxy-3,4-dimethoxy-2-fluoropyridine (**6**). The carboxyl group of compound **6** was activated with dicyclohexylcarbodiimide (DCC)/N-hydroxy succinimide (NHS), followed by coupling with methylamine to afford compound **7**. The methyl protecting group was then readily removed using BBr_3 to form the corresponding target iron chelator **8**.

The synthesis of 2-amido-5-fluoro substituted 3-hydroxypyridin-4-one is outlined in Scheme 2. Although 3-fluoropyridine is commercial available, the lithiation of 3-fluoropyridine derivatives readily occurs at C2 due to the neighboring fluorine effect. To avoid this, 2-chloro-3-fluoropyridine (**9**) was selected as a building block, where C2 is blocked by chlorine. A similar procedure as that outlined in Scheme 1 led to the formation of 2-chloro-3-fluoro-4-hydroxypyridine (**10**). Subsequent to the conversion of the hydroxyl function to the methoxy group, another hydroxyl group was introduced at C5, adjacent to the 4-methoxy group. To obtain compound **14**, the 5-hydroxy group of compound **12** required protection. The resulting compound **13** was lithiated at C6 and trapped with dry ice. The carboxy group of compound **14** is readily converted to amido group by activation with DCC/NHS followed by amine coupling. To remove the 6-chloro group of compound **15**, hydrogenation in the presence of Pd/C was adopted to afford **16** in quantitative yield. This procedure does not influence the methoxy groups which were readily removed by BBr_3 to obtain the target product **17**.

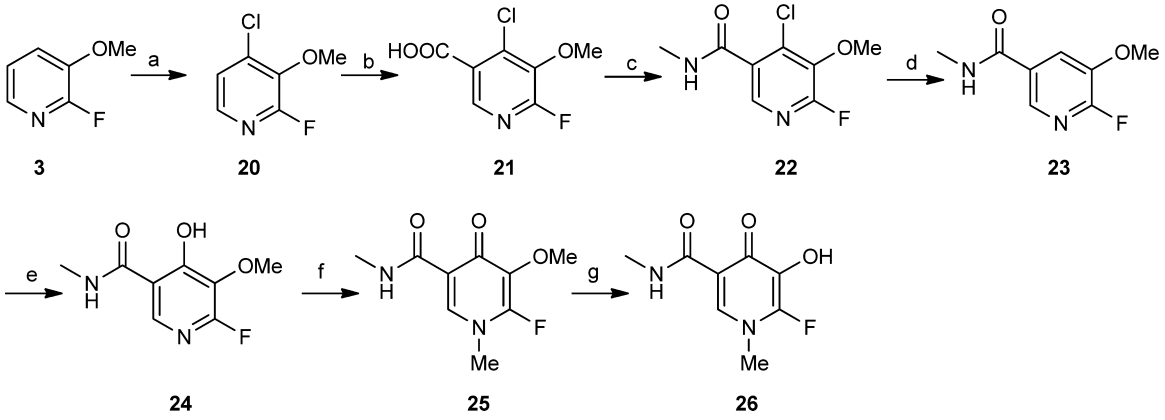
In comparison with the 1-nonsubstituted HPOs, an introduction of alkyl group at N1 can dramatically influence its physiochemical properties such as pK_as and iron affinity constants [18]. To introduce an additional alkyl group at N1 of the 2-amido-5-fluoro substituted HPOs, compound **16′** was reacted with ethyl iodide in acetone overnight to afford 1-ethyl substituted compound **18** (Scheme 3). The phenomenon may be explained by a mechanism which involves the production of an intermediate 1-alkyl



Scheme 2. Synthesis of 2-amido-5-fluoro substituted 3-hydroxypyridin-4-one. (a) (1) LDA, THF, −75 °C, 2 h, (2) $B(OMe)_3$, −75 °C, 2 h, (3) CH_3CO_3H, 0 °C, 1 h, 80%; (b) K_2CO_3/MeI/acetone, reflux overnight, 52%; (c) (1) LTMP, THF, −75 °C, 20 h; (2) $B(OMe)_3$, −75 °C, 2 h, (3) CH_3CO_3H, 0 °C, 1 h, 96%; (d) K_2CO_3/MeI/acetone, reflux overnight, 97%; (e) (1) LTMP, THF, −75 °C, 20 h; (2) dry ice, thaw to r.t., 89%; (f) DCC/NHS/$MeNHCOCH(Me)NH_2$, r.t., overnight, 58%; (g) Pd/H_2/Et_3N, 85%; (h) BBr_3, 0 °C to r.t., overnight, 63%.



Scheme 3. Synthesis of 1-alkyl-2-amido-5-fluoro substituted HPO. (a) DCC/NHS/$MeNH_2$, r.t., overnight, 61%; (b) Pd/H_2/Et_3N, 87%; (c) EtI/acetone, r.t., overnight, 85%; (d) BCl_3 or BBr_3 in dichloromethane, 0 °C to r.t., overnight, 68%.



Scheme 4. Synthesis of 1-alkyl-2-fluoro-5-amido 3-hydroxypyridin-4-one. (a) (1) LTMP, THF, −75 °C, 16 h; (2) CCl_2FCClF_2, −75 °C, 2 h, 85%; (b) (1) LTMP, THF, −75 °C, 16 h; (2) dry ice, thaw to r.t., 82%; (c) DCC/NHS/$MeNH_2$, r.t., overnight, 61%; (d) Pd/H_2/Et_3N, 90%; (e) (1) LTMP, THF, −75 °C, 20 h; (2) $B(OMe)_3$, −75 °C, 2 h, (3) CH_3CO_3H, 0 °C, 1 h, 64%; (f) K_2CO_3/MeI/MeOH, reflux overnight, 35%; (g) BBr_3, 0 °C to r.t.; overnight, 73%.

pyridinium iodide salt. This salt will not be stable and simultaneously converts into the more stable 1-alkyl pyridin-4-one analog and release ethyl iodide. Indeed, when 4-methoxy substituted **16** reacts with ethyl iodide, a mixture of 1-ethyl and 1-methyl HPO analogs are produced. Therefore, in order to afford a clean quantitative product 1-ethyl HPO, ethyl group must be used to protect the 4-hydroxy group. Compounds **18** were deprotected to afford the 1-alkyl-2-amido-5-fluoro HPO **19** (Scheme 3).

In contrast to the conversion from 3-fluoropyridine derivatives **16**–**18**, the 2-fluoropyridine analog **25** could not be obtained by treatment of compound **7** with methyl iodide. This may be due to the presence of fluorine at C2, which by virtue of its strong electronegativity, decreases the nucleophilicity of nitrogen. Therefore a new synthetic strategy for 1-alkyl-2-fluoro-5-amido substituted HPO **26** has been designed (Scheme 4). C4 of 2-fluoro-3-methoxypyridine **3** is first blocked with chlorine. Carboxylation of the resulting compound **20** at C5 was achieved with LTMP/dry ice. This step was followed with a coupling reaction with methylamine in the presence of DCC/NHS, yielding **22**, which was hydrogenated to remove the chloro group at C4. Another hydroxyl group was introduced at C4 by sequential lithiation, electrophilic substitution and oxidation. Compound **24** has two resonance forms and when it reacts with MeI/K_2CO_3, the methyl group can be attacked by either N1 or the oxygen at C4. In order to obtain the desired N-substituted product **25** in maximum yield, a polar solvent MeOH was adopted. Similar to the reactions mentioned above, the methyl protecting group can be removed by BBr_3 to afford the 1-alkyl-2-fluoro-5-amido substituted 3-hydroxypyridin-4-one.

3. Conclusion

In conclusion, several fluoro- and amido-disubstituted 3-hydroxypyridin-4-ones with either hydrogen or an alkyl group at N1 of the pyridine ring have been synthesized. The synthetic pathway for 3(5)-fluoro HPOs is slightly different from that of the 2-fluoro analogs, mainly due to the influence of the electronegativity of the fluorine. Physicochemical characterizations and metabolic studies of these ligands are currently in progress.

4. Experimental

General information: Fluorinated pyridines were purchased from Fluorochem. Reagents were from Sigma–Aldrich and reagent grade quality and were used without further purification. Column chromatography purifications were performed on Merck silica gel 60 (0.04–0.063 mm). ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 400 (400 MHz) NMR spectrometer. Chemical shifts (δ) are reported in ppm downfield from the internal standard tetramethylsilane (TMS) for ^1H and ^{13}C NMR. ESI mass spectra were obtained by infusing samples into an LCQ Deca XP ion trap mass instrument. HRMS were monitored on MicroMass Q-TOF instrument.

2-Fluoropyridin-3-ol (2): A solution of 2-fluoropyridine (10 mmol) in anhydrous THF (20 ml) under N_2 was cooled to −78 °C in a dry ice/acetone bath. To this solution was added a solution of lithium diisopropylamide (LDA; 11 mmol) in hexane slowly. The mixture was stirred for 0.5 h at −78 °C. To the mixture was added trimethoxyborane (2.4 ml) and stirred for 2 h, followed by an addition of peracetic acid (3.6 ml; 32% in dilute acetic acid). The mixture was allowed to warm to 0 °C under stirring for 1 h. After the mixture was cooled to −20 °C, sodium dithionite (4 g in 10 ml water) was added slowly. The mixture was extracted with ethyl acetate and the extract was dried and concentrated. The residue was purified by chromatography, eluting with 1:5 EtOAc:hexane to give a white solid [19] (92%). ^1H NMR ($CDCl_3$): δ 9.46 (brs, 1H, OH), 7.45–7.47 (m, 1H, C_6–H), 7.13–7.18 (m, 1H, C_4–H), 6.85–6.88 (m, 1H, C_5–H). ESI-MS: 114 $(M+1)^+$.

2-Fluoro-3-methoxypyridine (3): 2-Fluoropyridin-3-ol (10 mmol), methyl iodide (20 mmol) and potassium carbonate (20 mmol) in

acetone (100 ml) was refluxed overnight. The inorganic salt was filtered and the solvent was evaporated. The residue was purified on column (eluent: EtOAc:hexane = 1:5) to afford a colorless liquid [19] (95%). ^{1}H NMR ($CDCl_3$): δ 7.74–7.75 (m, 1H, C_6–H), 7.26–7.31 (m, 1H, C_4–H), 7.11–7.15 (m, 1H, C_5–H), 3.91 (s, 3H, OMe). ^{19}F NMR ($CDCl_3$): δ −90.15 (s). ESI-MS: 128 $(M+1)^+$.

2-Fluoro-3-methoxypyridin-4-ol (4): At −78 °C, 2,2,6,6-tetramethylpiperidine (12 mmol) was added to a solution of n-butyllithium (11 mmol; 2 M in hexane) in THF (20 ml) under N_2, after 15 min, followed by 2-fluoro-3-methoxypyridine (10 mmol). After stirring for 0.5 h, to this solution was added trimethoxyborane (2.4 ml) and stirred for 2 h, followed by an addition of peracetic acid (3.6 ml; 32% in dilute acetic acid). The mixture was allowed to warm to 0 °C under stirring for 1 h. After the mixture was cooled to −20 °C, sodium dithionite (4 g in 10 ml water) was added slowly. The mixture was extracted with DCM and the extract was dried and concentrated. The residue was purified by chromatography, eluting with 1:9 MeOH:DCM to give a white solid [19] (87%). ^{1}H NMR (d_6-DMSO): δ 7.63 (d, J = 5.4 Hz, 1H, C_6–H), 6.80 (d, J = 5.6 Hz, 1H, C_5–H). 3.86 (s, 3H, OMe). ^{19}F NMR (d_6-DMSO): δ −83.03 (s). ESI-MS: 144 $(M+1)^+$.

2-Fluoro-3,4-dimethoxypyridine (5): To a solution of 2-fluoro-3-methoxypyridin-4-ol (5 mmol) in acetone (20 ml) was added potassium carbonate (10 mmol) and methyl iodide (10 mmol). The mixture was refluxed overnight. Inorganic salt was filtered and the solvent was evaporated. The residue was purified on column chromatography, eluting with EtOAc to afford oil [19] (40%). ^{1}H NMR ($CDCl_3$): δ 7.82 (dd, J = 0.7, 5.6 Hz, 1H, C_6–H), 6.76 (d, J = 5.6 Hz, 1H, C_5–H), 3.95 (s, 3H, 4-OMe), 3.93 (d, J = 1.3 Hz, 3H, 3-OMe). ESI-MS: 158 $(M+1)^+$.

4,5-Dimethoxy-6-fluoropyridin-3-carboxylic acid (6): At −78 °C, 2,2,6,6-tetramethylpiperidine (12 mmol) was added to a solution of n-butyllithium (11 mmol; 2 M in hexane) in THF (20 ml), after 15 min, followed by 2-fluoro-3,4-dimethoxypyridine (10 mmol). After 20 h, to this solution was added excess dry ice and stirred for 1 h. The mixture was neutralized by HCl and extracted with DCM and the extract was dried and concentrated. The residue was purified by chromatography, eluting with 1:4 MeOH:DCM to give a white solid (87%). ^{1}H NMR ($CDCl_3$): δ 8.57 (d, J = 0.48 Hz, 1H, C_2–H), 4.20 (br s, 1H, COOH), 3.99 (s, 3H, 4-OMe), 3.97 (d, J = 1.73 Hz, 3H, 5-OMe). ^{19}F NMR ($CDCl_3$): δ −74.59 (s, 1F). ESI-MS: 202 $(M+1)^+$. HRMS: Calcd for $C_8H_9NO_4F$ $(M+1)^+$, 202.0516; Found, 202.0503.

4,5-Dimethoxy-6-fluoro-N-methylpyridine-3-carboxamide (7): To a solution of 4,5-dimethoxy-6-fluoropyridin-3-carboxylic acid (5 mmol) in dry dichloromethane (50 ml), dicyclohexylcarbodiimide (DCC) (1.1 g, 5.5 mmol, 1.1 equiv.) and N-hydroxysuccinimide (NHS) (0.69 g, 6 mmol, 1.2 equiv.) were added. The mixture was allowed to stir for 20 min before methylamine (1 M in THF, 5 mmol, 1 equiv.) was added, and the reaction was left to stir at room temperature overnight. The DCU was filtered, and the organic layer was washed with 0.1 M NaOH (3×) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by column chromatography (eluent: ethyl acetate) to afford white solid (67%). ^{1}H NMR ($CDCl_3$): δ 8.64 (d, J = 0.7 Hz, 1H, C_2–H), 7.62 (br s, 1H, NH), 3.96 (s, 3H, 4-OMe), 3.94 (d, J = 1.7 Hz, 3H, 5-OMe), 3.00 (d, J = 4.9 Hz, 3H, NH*Me*). ^{19}F NMR ($CDCl_3$): δ −77.75 (s, 1F). ESI-MS: 215 $(M+1)^+$. HRMS: Calcd for $C_9H_{12}N_2O_3F$ $(M+1)^+$, 205.08325; Found, 205.0834.

6-Fluoro-1,4-dihydro-5-hydroxy-N-methyl-4-oxopyridine-3-carboxamide (8): 4-Ethoxy-6-fluoro-5-methoxy-*N*-pyridine-3-carboxamide (2 mmol) was dissolved into CH_2Cl_2 (20 ml) and flushed with nitrogen. Boron tribromide (1 M in CH_2Cl_2, 8 ml) was slowly added and the reaction mixture was stirred at room temperature for 20 h. The excess BBr_3 was eliminated at the end of the reaction by the addition of methanol (10 ml) and left to stir for another half an hour. After removal of the solvents under reduced pressure, the residues were purified by recrystallization to afford a white solid (70%). ^{1}H NMR (d_6-DMSO) δ 9.04 (br s, 1H, OH), 8.18 (s, 1H, C_2–H), 5.94 (br s, 1H, NH), 2.83 (d, J = 4.6 Hz, 3H, NH*Me*). ^{19}F NMR (d_6-DMSO): −84.19 (s). ^{13}C NMR (d_6-DMSO): δ 25.83 (s, CH_3), 112.03 (s), 127.62 (d, J = 29 Hz), 135.79 (d, J = 18 Hz), 154.82 (d, J = 230 Hz), 158.41 (d, J = 10 Hz), 168.13 (s). HRMS: Calcd for $C_7H_8N_2O_3F$ $(M+1)^+$, 187.0519; Found, 187.0517.

2-Chloro-3-fluoro-4-hydroxypyridine (10): A solution of 2-chloro-3-fluoropyridine (2 mmol) in anhydrous THF (10 ml) was cooled to −78 °C. To this solution was added a solution of lithium diisopropylamide (LDA; 2.2 mmol) in hexane slowly at same temperature. After 2 h at −78 °C, to the mixture was added trimethoxyborane (0.48 ml) and stirred for 2 h, followed by an addition of peracetic acid (0.72 ml; 32% in dilute acetic acid). The mixture was allowed to warm to 0 °C under stirring for 1 h. After the mixture was cooled to −20 °C, sodium dithionite (0.8 g in 2 ml water) was added dropwise. The mixture was extracted with ethyl acetate and the extract was dried and concentrated. The residue was purified by chromatography, eluting with 1:19 MeOH:DCM to give the expected product as a white solid [19] (80%). ^{1}H NMR (d_6-DMSO): δ 11.86 (brs, 1H, OH), 7.89 (d, J = 5.3 Hz, 1H, C_6–H), 6.95 (t, J = 5.8 Hz, 1H, C_5–H). ^{19}F NMR (d_6-DMSO): δ −141.29 (s). ESI-MS: 148 $(M+1)^+$.

2-Chloro-3-fluoro-4-methoxypyridine (11): 2-Chloro-3-fluoro-4-hydroxypyridine (10 mmol), methyl iodide (20 mmol) and potassium carbonate (20 mmol) in acetone (100 ml) was refluxed overnight. The inorganic salt was filtered and the solvent was evaporated. The residue was purified on column (eluent: ethyl acetate:hexane = 1:5) to afford a colorless liquid [19] (52%). ^{1}H NMR ($CDCl_3$): δ 8.08 (dd, J = 1.0, 5.8 Hz, 1H, C_6–H), 6.88 (t, J = 5.7 Hz, 1H, C_5–H), 3.97 (s, 3H, OMe). ^{19}F NMR ($CDCl_3$): δ −143.49 (s). ESI-MS: 162 $(M+1)^+$.

2-Chloro-3-fluoro-5-hydroxy-4-methoxypyridine (12): At −78 °C, 2,2,6,6-tetramethylpiperidine (12 mmol) was added to a solution of n-butyllithium (11 mmol; 2 M in hexane) in THF (20 ml), after 15 min, followed by **11** (10 mmol). After 20 h, to this solution was added trimethoxyborane (2.4 ml) and stirred for 2 h, followed by an addition of peracetic acid (3.6 ml; 32% in dilute acetic acid). The mixture was allowed to warm to 0 °C under stirring for 1 h. After the mixture was cooled to −20 °C, sodium dithionite (4 g in 10 ml water) was added slowly. The mixture was extracted with ethyl acetate and the extract was dried and concentrated. The residue was purified by chromatography, eluting with 1:1 EtOAc:hexane to give a white solid [19] (96%). ^{1}H NMR ($CDCl_3$): δ 7.88 (d, J = 0.8 Hz, 1H, C_6–H), 5.88 (brs, 1H, OH), 4.22 (d, J = 4.0 Hz, 3H, OMe). ^{19}F NMR ($CDCl_3$): δ −139.00 (s). ESI-MS: 178 $(M+1)^+$.

2-Chloro-4,5-dimethoxy-3-fluoropyridine (13): **12** (10 mmol), methyl iodide (20 mmol) and potassium carbonate (20 mmol) in acetone (100 ml) was refluxed overnight. The inorganic salt was filtered and the solvent was evaporated. The residue was purified on column (eluent: EtOAc:hexane = 1:3) to afford a white solid [19] (97%). ^{1}H NMR ($CDCl_3$): δ 7.80 (d, J = 0.9 Hz, 1H, C_6–H), 4.14 (s, 3H, 4-OMe), 3.95 (s, 3H, 5-OMe). ^{19}F NMR ($CDCl_3$): δ −138.34 (s). ESI-MS: 192 $(M+1)^+$.

6-Chloro-5-fluoro-3,4-dimethoxy-pyridine-2-carboxylic acid (14): At −78 °C, 2,2,6,6-tetramethylpiperidine (12 mmol) was added to a solution of n-butyllithium (11 mmol; 2 M in hexane) in THF (20 ml), after 15 min, followed by 2-chloro-4,5-dimethoxy-3-fluoropyridine (10 mmol). After 16 h, to this solution was added excess dry ice and the mixture was left to thaw to room temperature. The mixture was neutralized by HCl and concentrated. The residue was purified by chromatography, eluting with ethyl acetate to give a white solid (89%). ^{1}H NMR ($CDCl_3$): δ 4.24 (d, J = 3.6 Hz, 3H, 4-OMe), 4.02 (s, 3H, 5-OMe). ^{19}F NMR ($CDCl_3$): δ −128.84 (s). ESI-MS: 236

$(M+1)^+$. HRMS: Calcd for $C_8H_8NO_4ClF$ $(M+1)^+$, 236.0126; Found, 236.0122.

6-Chloro-5-fluoro-3,4-dimethoxy-pyridine-2-carboxylic acid (1-methylcarbamoyl-ethyl)-amide (15): To a solution of 6-chloro-5-fluoro-3,4-dimethoxy-pyridine-2-carboxylic acid (5 mmol) in dry dichloromethane (50 ml), DCC (1.1 g, 5.5 mmol, 1.1 equiv.) and NHS (0.69 g, 6 mmol, 1.2 equiv.) were added. The mixture was allowed to stir for 20 min before (L)-2-amino-*N*-methylpropanamide (0.5 g, 5 mmol, 1 equiv.) was added, and the reaction was left to stir at room temperature overnight. Then, the DCU was filtered, and the organic layer was washed with 0.1 M NaOH (3×) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by column chromatography (MeOH:DCM = 1:19) to afford a white solid (58%). ^{1}H NMR ($CDCl_3$): δ 7.89 (d, J = 7.7 Hz, 1H, CH*NH*), 6.31 (br s, 1H, *NH*Me), 4.61 (m, 1H, CH), 4.20 (d, J = 3.4 Hz, 3H, 4-OMe), 3.97 (s, 3H, 3-OMe), 2.83 (d, J = 4.9 Hz, 3H, NH*Me*), 1.50 (d, J = 7.0 Hz, 3H, CH*Me*). ^{19}F NMR ($CDCl_3$): δ −131.26 (s). ESI-MS: 320 $(M+1)^+$. HRMS: Calcd for $C_{12}H_{16}N_3O_4ClF$ $(M+1)^+$, 320.0813; Found, 320.0830.

6-Chloro-4-ethoxy-5-fluoro-3-methoxy-N-methylpicolinamide (15′). ^{1}H NMR ($CDCl_3$): δ 7.36 (br s, 1H, NH), 4.42 (dq, J = 2.2, 7.2 Hz, 1H, CH_2), 3.98 (s, 3H, 3-OMe), 2.97 (d, J = 5.2 Hz, 3H, NH*Me*), 1.43 (d, J = 7.2 Hz, 3H, Me). ^{19}F NMR ($CDCl_3$): δ −130.39 (s). ESI-MS: 263 $(M+1)^+$. HRMS: Calcd for $C_{10}H_{13}N_2O_3ClF$ $(M+1)^+$, 263.0599; Found, 263.0587.

5-Fluoro-3,4-dimethoxy-pyridine-2-carboxylic acid (1-methylcarbamoyl-ethyl)-amide (16): To a solution of **15** (1.5 mmol) in ethyl acetate (20 ml), catalytic 10% Pd/C (0.2 g) and triethylamine (2 mmol) were added. The mixture was hydrogenated at room temperature and 3 atms for 24 h. Then the catalyst was filtered off through celite, and the clear solution, taken to dryness, afforded the title compound. Column chromatography eluting with 1:3 EtOAc:hexane yields a white crystal (85%). ^{1}H NMR ($CDCl_3$): δ 8.20 (d, J = 2.0 Hz, 1H, C_6–H), 8.09 (d, J = 7.6 Hz, 1H, CH*NH*), 6.43 (br s, 1H, *NH*Me), 4.61–4.68 (m, 1H, CH), 4.17 (d, J = 3.2 Hz, 3H, 4-OMe), 3.98 (s, 3H, 3-OMe), 2.82 (d, J = 4.9 Hz, 3H, NH*Me*), 1.49 (d, J = 7.0 Hz, 3H, CH*Me*). ^{19}F NMR ($CDCl_3$): δ −140.71 (s). ESI-MS: 286 $(M+1)^+$. HRMS: Calcd for $C_{12}H_{17}N_3O_4F$ $(M+1)^+$, 286.1203; Found, 286.1225.

4-Ethoxy-5-fluoro-3-methoxy-N-methylpicolinamide (16′): ^{1}H NMR ($CDCl_3$): δ 8.15 (d, J = 2.0 Hz, 1H, C_6–H), 7.52 (br s, 1H, NH), 4.40 (dq, J = 2.2, 7.2 Hz, 2H, CH_2), 3.99 (s, 3H, 3-OMe), 2.98 (d, J = 5 Hz, 3H, NH*Me*), 1.41 (d, J = 7.2 Hz, 3H, Me). ^{19}F NMR ($CDCl_3$): δ −139.9 (s). ESI-MS: 229 $(M+1)^+$. HRMS: Calcd for $C_{10}H_{14}N_2O_3F$ $(M+1)^+$, 229.0988; Found, 229.0981.

5-Fluoro-3-hydroxy-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (1-methylcarbamoyl-ethyl)-amide (17): Compound **16** (5 mmol) was dissolved into CH_2Cl_2 (20 ml) and flushed with nitrogen. Boron tribromide (1 M in CH_2Cl_2, 20 ml) was slowly added and the reaction mixture was stirred at room temperature for 3 d. The excess BBr_3 was eliminated at the end of the reaction by the addition of methanol (10 ml) and left to stir for another half an hour. After removal of the solvents under reduced pressure, the residues were purified by recrystallization to afford a white solid (63%). ^{1}H NMR (d_6-DMSO): δ 8.90 (d, J = 7.5H, 1H, CH*NH*), 8.12 (q, J = 4.5 Hz, 1H, *NH*Me), 8.02 (d, J = 3.2 Hz, 1H, C_6–H), 4.44–4.51 (m, 1H, CH), 2.62 (d, J = 4.6 Hz, 3H, NH*Me*), 1.35 (d, J = 7.0 Hz, 3H, CH*Me*). ^{19}F NMR (d_6-DMSO): δ −146.89 (s). ^{13}C NMR (d_6-DMSO): δ 18.81 (s), 25.55 (s), 48.29 (s), 124.91 (s), 126.56 (d, J = 27 Hz), 149.07 (s), 149.36 (s), 150.49 (d, J = 209 Hz), 164.18 (s), 171.46 (s). ESI-MS: 258.0 $(M+1)^+$. HRMS: Calcd for $C_{10}H_{12}N_3O_4FNa$ $(M+Na)^+$, 280.0710; Found, 280.0693.

1-Ethoxy-5-fluoro-3-methoxy-N-methyl-4-oxo-1,4-dihydropyridine-2-carboxamide (18): A solution of 4-ethoxy-5-fluoro-3-methoxy-N-methylpicolinamide (5 mmol) in acetone (30 ml) was added ethyl iodide (20 mmol) and the mixture was heated at 60 °C for 20 h. The solvent was then evaporated and the residue was purified by column chromatography eluting with 1:9 MeOH:DCM to afford a white solid (85%). ^{1}H NMR ($CDCl_3$): δ 8.05 (br s, 1H, NH), 7.34 (d, J = 6.4 Hz, 1H, C_6–H), 3.96 (q, J = 7.0 Hz, 2H, CH_2), 3.81 (s, 3H, 3-OMe), 3.02 (d, J = 4.5 Hz, 3H, NH*Me*), 1.46 (t, J = 7.0 Hz, 3H, Me). ^{19}F NMR ($CDCl_3$): δ −150.22 (s). ESI-MS: 229 $(M+1)^+$. HRMS: Calcd for $C_{10}H_{14}N_2O_3F$ $(M+1)^+$, 229.0988; Found, 229.0997.

1-Ethyl-5-fluoro-3-hydroxy-N-methyl-4-oxo-1,4-dihydropyridine-2-carboxamide (19): A similar procedure of making compound **8** started from compound **18** with BBr_3 gave white solid (68%). ^{1}H NMR (d_6-DMSO): δ 8.84 (brs, 1H, OH), 8.36 (d, J = 7.0 Hz, 1H, C_6–H), 6.15 (brs, 1H, NH), 4.01 (q, J = 7.1 Hz, 2H, CH_2), 2.78 (d, J = 4.6 Hz, 3H, NH*Me*), 1.33 (t, J = 7.1 Hz, 3H, Me). ^{19}F NMR (d_6-DMSO): δ −152.53 (d, J = 7.4 Hz). ^{13}C NMR (d_6-DMSO): δ 16.34 (s), 25.83 (s), 50.30 (s), 125.60 (d, J = 35 Hz), 130.41 (s), 145.94 (d, J = 12 Hz), 149.53 (d, J = 236 Hz), 158.00 (d, J = 12 Hz), 160.29 (s). HRMS: Calcd for $C_9H_{12}N_2O_3F$ $(M+1)^+$, 215.0832; Found, 215.0843.

4-Chloro-2-fluoro-3-methoxypyridine (20): At −78 °C, 2,2,6,6-tetramethylpiperidine (12 mmol) was added to a solution of n-butyllithium (11 mmol; 2 M in hexane) in THF (20 ml) under N_2, after 15 min, followed by 2-fluoro-3-methoxypyridine (10 mmol). After stirring for 16 h, to this solution was added 1,1,2-trichloro-1,2,2-trifluoroethane (20 mmol) and stirred for 2 h. The mixture was then extracted with ethyl acetate and the extract was dried and concentrated. The residue was purified by chromatography to give an oil (85%). ^{1}H NMR ($CDCl_3$): δ 7.83 (dd, J = 2.0, 5.2 Hz, 1H, C_6–H), 7.12 (dd, J = 2.8, 5.2 Hz, 1H, C_5–H). 3.95 (d, J = 2.8 Hz, 3H, OMe). ^{19}F NMR ($CDCl_3$): δ −81.98 (s). ESI-MS: 162 $(M+1)^+$. HRMS: Calcd for C_6H_6NOClF $(M+1)^+$, 162.0122; Found, 162.0106.

4-Chloro-6-fluoro-5-methoxynicotinic acid (21): A similar procedure of making compound **6** started from 4-chloro-2-fluoro-3-methoxypyridine to afford white solid (82%). ^{1}H NMR ($CDCl_3$): δ 8.07 (d, J = 2.0 Hz, 1H, C_2-H), 4.08 (d, J = 4 Hz, 3H, OMe). ^{19}F NMR ($CDCl_3$): δ −81.07 (s). ESI-MS: 206 $(M+1)^+$. HRMS: Calcd for $C_7H_6NO_3ClF$ $(M+1)^+$, 206.0020; Found, 206.0039.

4-Chloro-6-fluoro-5-methoxy-N-methylnicotinamide (22): A similar procedure of making compound **7** started from 4-chloro-6-fluoro-5-methoxynicotinic acid to afford white solid (61%). ^{1}H NMR ($CDCl_3$): δ 8.04 (d, J = 2.0 Hz, 1H, C_2–H), 7.52 (br s, 1H, NH), 3.97 (d, J = 3.6 Hz, 3H, OMe), 2.98 (d, J = 5.2 Hz, 3H, NH*Me*). ^{19}F NMR ($CDCl_3$): δ −82.44 (s). ESI-MS: 219 $(M+1)^+$. HRMS: Calcd for $C_8H_9N_2O_2ClF$ $(M+1)^+$, 219.0337; Found, 219.0340.

6-Fluoro-5-methoxy-N-methylnicotinamide (23): A similar procedure of making compound **16** started from 4-chloro-6-fluoro-5-methoxy-N-methylnicotinamide to afford white solid (90%). ^{1}H NMR ($CDCl_3$): δ 8.05 (d, J = 8 Hz, 1H, C_2–H), 7.50 (br s, 1H, NH), 7.37 (dd, J = 8, 9.6 Hz, 1H, C_4–H), 3.95 (s, 3H, OMe), 2.98 (d, J = 5.2 Hz, 3H, NH*Me*). ESI-MS: 185 $(M+1)^+$. HRMS: Calcd for $C_8H_{10}N_2O_2F$ $(M+1)^+$, 185.0726; Found, 185.0707.

6-Fluoro-4-hydroxy-5-methoxy-N-methylnicotinamide (24): A similar procedure of making compound **12** started from 4-chloro-5-methoxy-N-methylnicotinamide to afford white solid (64%). ^{1}H NMR ($CDCl_3$): δ 13.1 (brs, 1H, OH), 8.05 (s, 1H, C_2–H), 6.60 (brs, 1H, NH), 3.96 (s, 3H, OMe), 3.04 (d, J = 4.8 Hz, 3H, NH*Me*). ^{19}F NMR ($CDCl_3$): δ −77.53 (s). ESI-MS: 201 $(M+1)^+$. HRMS: Calcd for $C_8H_{10}N_2O_3F$ $(M+1)^+$, 201.0675; Found, 201.0686.

6-Fluoro-5-methoxy-N,1-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (25): To a solution of 6-fluoro-4-hydroxy-5-methoxy-N-methylnicotinamide (5 mmol) in methanol (20 ml) was added potassium carbonate (10 mmol) and methyl iodide (10 mmol). The mixture was refluxed overnight. Inorganic salt was filtered and the solvent was evaporated. The residue was purified on column chromatography, eluting with 1:9 MeOH:DCM to afford white solid (35%). ^{1}H NMR ($CDCl_3$): δ 8.26 (d, J = 0.7, 7.2 Hz, 1H, C_2–H), 3.96 (s, 3H, OMe), 3.76 (d, J = 3.2 Hz, 3H, NMe), 2.95 (d, J = 5.2 Hz, 3H, NH*Me*). ^{19}F NMR ($CDCl_3$): δ −113.15 (s). ESI-MS: 215

$(M+1)^+$. HRMS: Calcd for $C_9H_{12}N_2O_3F$ $(M+1)^+$, 215.0832; Found, 215.0820.

6-Fluoro-5-hydroxy-N,1-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (26). A similar procedure of making compound **19** started from compound **25** with BBr_3 gave white solid (73%). ^1H NMR (d_6-DMSO): δ 9.86 (brs, 1H, OH), 8.27 (d, J = 7.1 Hz, 1H, C_2–H), 3.79 (d, J = 3.6 Hz, 3H, NMe), 3.32 (brs, 1H, NH), 2.84 (d, J = 4.8 Hz, 3H, NH*Me*). ^{19}F NMR (d_6-DMSO): δ −120.11 (s). ^{13}C NMR: 25.33 (s), 38.07 (d, J = 5 Hz), 114.49 (s), 132.42 (d, J = 4 Hz), 136.53 (s), 147.00 (d, J = 260 Hz), 163.94 (s), 171.64 (d, J = 10 Hz). HRMS: Calcd for $C_8H_{10}N_2O_3F$ $(M+1)^+$, 201.0675; Found, 201.0669.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2015.02.005.

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