Tetrahedron Letters 51 (2010) 5230–5233

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Design and synthesis of fluorine-substituted 3-hydroxypyridin-4-ones

Yong Min Ma, Robert C. Hider *

Pharmaceutical Science Division, King's College London, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH, UK

ARTICLE INFO

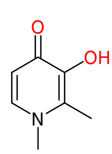
Article history:
Received 20 April 2010
Revised 12 July 2010
Accepted 23 July 2010
Available online 30 July 2010

ABSTRACT

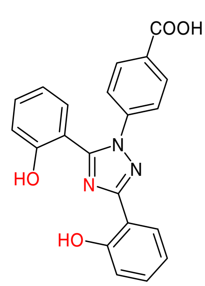
The presence of fluorine in an organic molecule can dramatically alter its chemical and biological properties due to its unique characteristics. Several 2- and 5-fluorine-substituted 3-hydroxypyridin-4-ones have been synthesised with the intention of improving the pharmaceutical profile of deferiprone.

Deferiprone (1,2-dimethyl-3-hydroxypyridin-4-one, **1**), one of the three clinical iron-chelating agents, is used to treat patients suffering from iron overload diseases, such as thalassaemia and sickle cell anaemia.[1] The efficacy of deferiprone is limited by extensive metabolism in the liver. Urinary recovery studies with deferiprone in man have demonstrated that more than 85% of the administered dose recovered in the urine is the nonchelating glucuronide conjugate.[2] The other two iron chelators in clinical use are deferasirox (**2**) which suffers from renal toxicity[3] and deferoxamine (**3**) which is not orally active.[4] Consequently, an orally active iron chelator with improved metabolism and toxicity profiles is urgently needed.

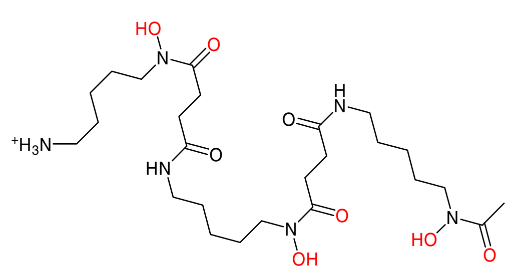
The occurrence of fluorine at a particular position in an organic molecule can significantly alter the chemical and biological properties of that molecule, including its metabolic stability and bioavailability.[5] This influence results from the unique characteristics of fluorine: (1) it is the smallest atom apart from hydrogen; (2) it is the most electronegative atom; (3) it forms strong bonds with carbon. The bond-strengthening effect of fluorine in fluorinated molecules increases the thermal and oxidative stability and therefore slows down metabolic transformations; (4) introducing fluorine into a molecule can modify its lipophilicity; (5) fluorine is an H-bond acceptor. Prior to 1970, fluorinated compounds were scarce amongst pharmaceuticals.[6] However, the situation has since changed dramatically, for example, 9 of a total 31 new drugs approved in 2002,[6] and the two best-selling drugs in 2006[7] contained fluorine. It is clear that fluorine plays an increasingly important role in pharmaceutical design.



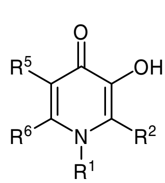
1



2



3



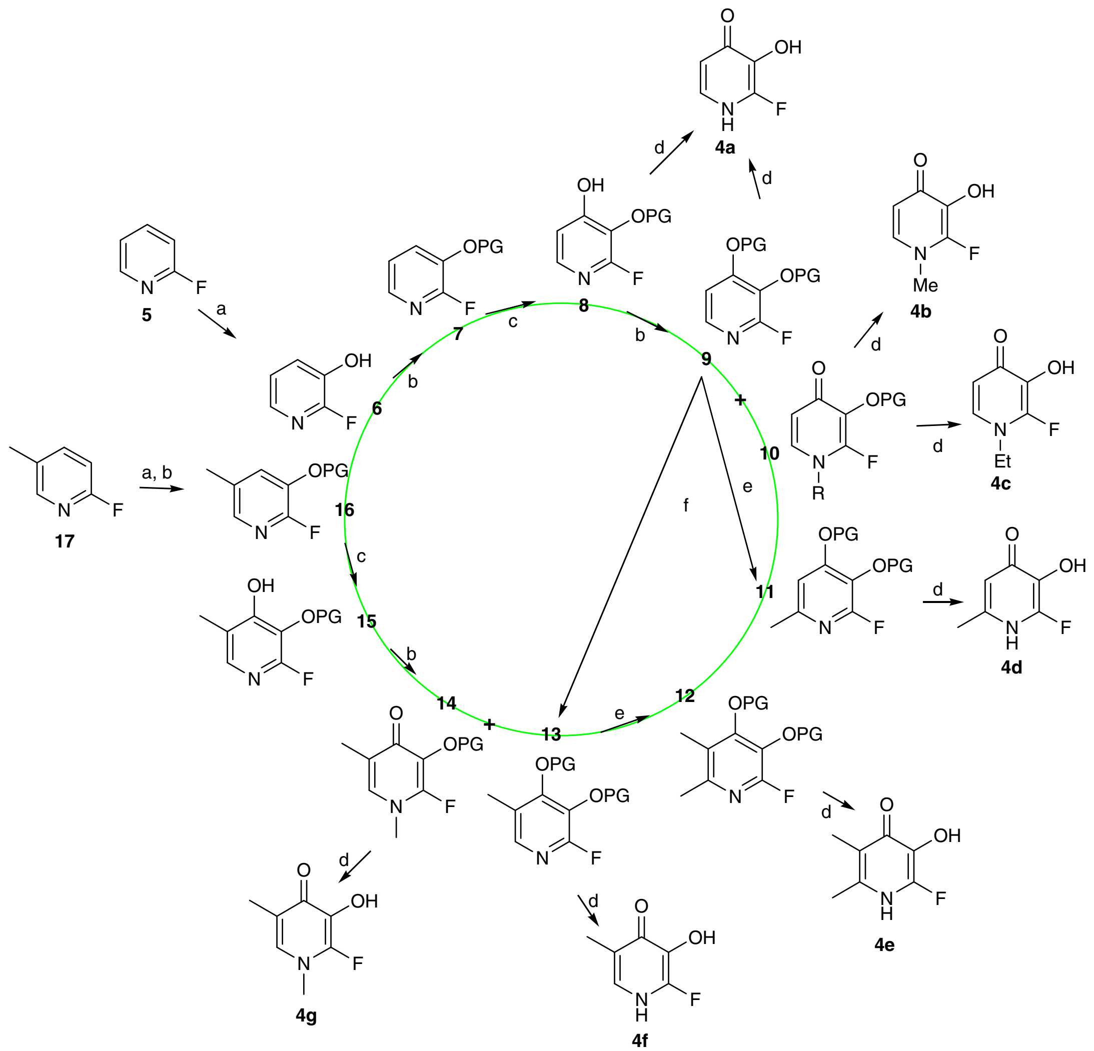
4

4a-g
R^1=H, Me or Et
R^2=F
R^5, R^6 =H or Me

4h-m
R^1=H, Me or Et
R^5=F
R^2, R^6 =H or Me

* Corresponding author. Fax: +44 207 848 4800.
E-mail address: robert.hider@kcl.ac.uk (R.C. Hider).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.07.134



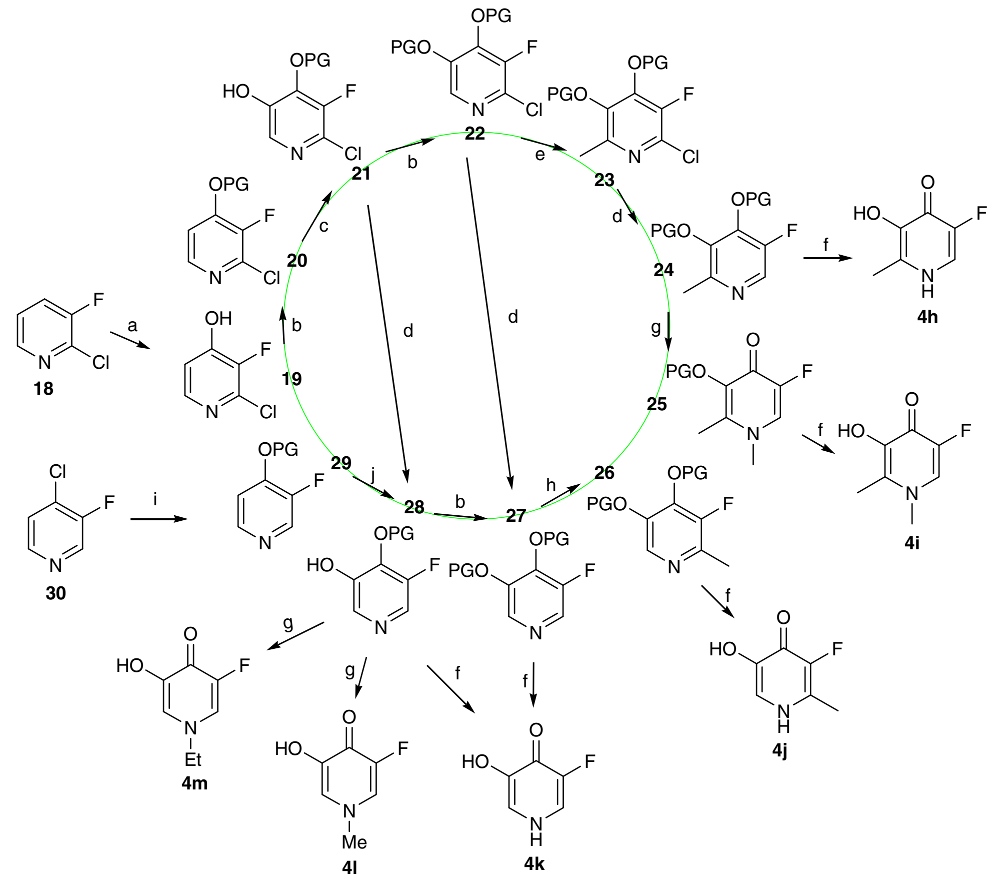
Scheme 1. Synthesis of 2-fluoro-substituted 3-hydroxypyridin-4-one derivatives. Reagents and conditions: (a) (1) LDA, THF, −75 °C, 0.5 h; (2) $B(OMe)_3$, −75 °C, 2 h; (3) CH_3CO_3H, 0 °C, 1 h; (b) K_2CO_3, MeI or EtI, acetone, reflux, overnight; (c) (1) LTMP, THF, −75 °C, 1 h; (2) $B(OMe)_3$, −75 °C, 2 h; (3) CH_3CO_3H, 0 °C, 1 h; (d) BBr_3, CH_2Cl_2, 0 °C, overnight; (e) (1) USB, THF, −75 °C, 20 h; (2) MeI; (f) (1) LTMP, THF, −75 °C, 20 h; (2) MeI. PG = protecting group.

Stimulated by these developments we considered it to be of interest to introduce fluorine atoms directly on to carbon atoms of the deferiprone heterocyclic ring, especially at adjacent sites (i.e., at C2 and C5) to the chelating moiety. There are two approaches to this target: one is to introduce a fluorine atom into the preformed 3-hydroxypyridin-4-one matrix, and a second is to start with a fluorine-containing precursor, with the chelating functional groups being introduced at a later stage.

There are three vacant positions on the deferiprone heterocyclic ring, where fluorine can be introduced. Firstly, several NF-fluorinating agents[8] such as Selectfluor,[9] Accufluor[10] or *N*-fluorobenzenesulfonimide[11] were investigated as electrophilic reagents, with maltol and kojic acid derivatives (pyranones and pyridinones) as the reactants. However, all attempts at the intended substitution failed. It would appear to be a considerable challenge to attach fluorine to aromatic rings using this method. Therefore, we turned our attention to the use of fluorine-containing building blocks as starting materials and two chelating hydroxy groups were introduced sequentially. We report here the synthesis of several 2- and 5-fluoro-3-hydroxypyridin-4-ones (**4**), starting from readily accessible 2- or 3(5)-fluoropyridine analogues.

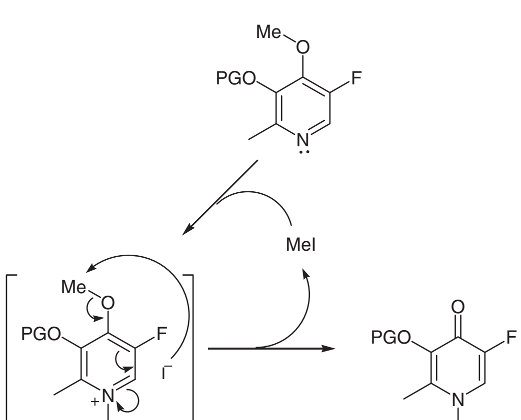
2-Fluoro-3-hydroxypyridin-4-ones (**4a–g**; Scheme 1). 2-Fluoropyridine (**5**) undergoes lithiation at the *ortho* position (C3) when treated with lithium diisopropylamide (LDA), due to the strong inductive effect of the fluorine atom at C2.[12,13] The resulting 3-lithio derivative was trapped by trimethylborate as an electrophile, followed by in situ reaction with peracetic acid to afford 2-fluoro-3-hydroxypyridine (**6**). After protection of the 3-hydroxy group, the C4 atom was deprotonated using lithium 2,2,6,6-tetramethylpiperidide (LTMP, pK_a 37.3) as a metalation reagent.[14] This choice was made because we experienced no reaction after 20 h using LDA (pK_a 35.7). Surprisingly, when the 4-hydroxy derivative **8** was reacted with methyl iodide in acetone in the presence of Ag_2CO_3 or K_2CO_3, two alkylated products **9** and **10** were obtained in a ratio of 4:5. This phenomenon is different to that previously reported[15] where only the 4-alkoxy derivative was obtained, when both positions 2 and 6 of the pyridine ring are occupied by an iodine atom. The formation of both **9** and **10** in this study is attributed to the ambident nature of the anion of **8**, in the presence of K_2CO_3. By increasing the size of the protecting group (PG), the ratio of 9:10 was enhanced dramatically. For instance, when **8** was reacted with ethyl iodide, a 65% yield of the corresponding 4-ethoxypyridine derivative was obtained, with a 28% yield for the 1-ethylpyridin-4-one isomer.

Compound **9** can be selectively lithiated at either C5 or C6, depending on the choice of the metalation reagents. Unimetal



Scheme 2. Synthesis of 5-fluoro-substituted 3-hydroxypyridin-4-one derivatives. Reagents and conditions: (a) (1) LDA, THF, −75 °C, 2 h; (2) $B(OMe)_3$, −75 °C, 2 h; (3) CH_3CO_3H, 0 °C, 1 h; (b) K_2CO_3, MeI or EtI, acetone reflux, overnight; (c) (1) LTMP, THF, −75 °C, 20 h; (2) $B(OMe)_3$, −75 °C, 2 h; (3) CH_3CO_3H, 0 °C, 1 h; (d) $Pd(OH)_2/H_2/Et_3N$; (e) (1) LTMP, THF, −75 °C, 24 h; (2) MeI; (f) BBr_3, CH_2Cl_2, 0 °C overnight; (g) MeI or EtI, acetone, reflux, overnight; (h) (1) LDA, THF, −75 °C, 20 h; (2) MeI; (i) NaOMe, reflux, overnight; (j) same as (a) except 20 h with LDA. PG = protecting group.

superbase[12,16] [USB: 1:1 ratio of butyllithium and lithium 2-(dimethylamino)ethoxide] favours the deprotonation of the pyridine derivative at C6 while LTMP has a preference for C5. After being trapped by methyl iodide, clean 6- or 5-methyl-substituted pyridine derivatives were obtained, respectively. Contrary to the pyridine derivative **9**, the 1-alkylpyridine-4-one analogues **10** cannot be lithiated at either of the vacant positions. The intermediate **13** can also be synthesised from 2-fluoro-5-methylpyridine (**17**) via



Scheme 3. Possible mechanism for the conversion of 4-methoxypyridine into 1-methylpyridin-4-one.

16 and **15** in less steps compared with the route starting from **5**. However, analogue **11** cannot be obtained from this route, as the 6-methyl group of 2-fluoro-6-methylpyridine is prone to lithiation. Compound **13** was again lithiated at the sole vacant position of the pyridine ring with USB, followed by quenching with methyl iodide to afford compound **12**. Again, an attempt to convert **11** into **12** failed because the methyl group at C6 was firstly deprotonated. When compound **15** was refluxed with methyl iodide in the presence of K_2CO_3, an almost equimolecular mixture of **13** and **14** was obtained. A conventional method to introduce a methyl group on the N1 of pyridine using methyl iodide or dimethyl sulfate to form 1-methylpyridinium failed with 2-fluoropyridine derivatives, most likely due to the strong electron-withdrawing nature of F from N1 through C2, resulting in the inability of the N atom to donate electrons to the methyl group. The protecting groups of **8**–**14** were removed using BBr_3 to yield **4a–g**, respectively.

5-Fluoro-3-hydroxypyridin-4-ones (**4h–m**; Scheme 2). Although 3-fluoropyridine is readily accessible and its lithiation by LDA occurs at C4 rather than at C2,[17] further lithiation by various bases will likely lead to attack at C2, as the C–H at this position is more acidic than those at the 5- and 6-positions due to the presence of the adjacent fluorine. Therefore, we selected commercially available 2-chloro-3-fluoropyridine (**18**) as a building block, where C2 is protected by chlorine. The hydroxy group was introduced at C4 by sequential lithiation, electrophilic substitution and oxidation.[18] Subsequent to the protection of the 4-hydroxy group, another hydroxy group was introduced at C5 using the stronger base LTMP as the metalation reagent. To obtain compound **24**, the 5-hydroxy group of **21** required protection, which was followed by lithiation at C6 with LTMP for 20 h and methylation and hydrogenation. In contrast to the 2-fluoropyridine derivatives, when the 3-fluoropyridine analogue **24** was treated with methyl iodide overnight, TLC showed that the starting material was consumed and a single product was detected. NMR and MS demonstrated that the expected product, the 1-methylpyridinium derivative, was not formed, but instead the 1-methylpyridin-4-one derivative **25** was obtained. To the best of our knowledge, this type of reaction has not been previously reported to occur under such mild conditions. A possible mechanism for this rearrangement is outlined in Scheme 3. Although fluorine at C2 inactivates the lone pair of electrons on N1 and prevents reaction with methyl iodide, fluorine at C3 apparently has less of an effect on the reactivity of N1. However, the resulting intermediate 1-methylpyridinium iodide salt is unstable due to the inductive effect of the fluorine at C3, which simultaneously converts into the more stable 1-methylpyridin-4-one analogue and releases methyl iodide. In fact, when an excess of ethyl iodide was used instead of methyl iodide, a mixture of 1-ethyl- and 1-methyl-pyridin-4-ones was produced. Thus in order to obtain a clean quantitative 1-alkylpyridin-4-one, the same alkyl group must be used to protect the 4-hydroxy group as is demonstrated with the preparation of **4m**. Intermediate **27** can be produced from **21** by either protection of the 5-hydroxy group followed by reduction to remove the 2-chlorine or a reverse procedure via **28**. When **27** was lithiated with LDA, C2 had priority over C6 to be deprotonated, and upon methylation gave **26**. Intermediate **28** (where PG = methyl) can also be obtained from 4-chloro-3-fluoropyridine (**30**) via alkoxylation at C4 followed by the introduction of a hydroxy group at C5. However, when the 4-OH group was ethyl-protected (**29**, PG = ethyl), a clean 2-hydroxy analogue was produced under the same conditions. In similar fashion to **24**, compound **28**, when reacted with methyl or ethyl iodide, resulted in the formation of **4l** and **4m**, respectively, in quantitative yields. The 5- and 4-alkyl protecting groups of **24–28** were removed by reacting with BBr_3 to produce **4h–k**, respectively.[19]

In conclusion, several 2- or 5-fluoro-containing 3-hydroxypyridin-4-ones have been synthesised where one or more methyl or ethyl groups were also introduced to modulate the lipophilicity for improved membrane permeability. Overall, the choice of a specific lithiating reagent is the key factor for the site specific proton–lithium exchange. Generally, metalation occurs at the *ortho* position of an electronegative element except for reactions with USB, which prefers to attack the 6-position. When two different types of electronegative atom are present at adjacent vacant positions, metalation predominates at the more electronegative site (see the conversion from **27** into **26**). Contrary to 2-fluoro 4-alkoxypyridines, the 3-fluoro analogues behave in a different way, where not only the alkyl group is attached to N1, but also the 4-hydroxy alkyl-protecting group is removed simultaneously when reacted with an alkyl iodide. Metabolic studies are currently in progress and we believe that several of the fluoro analogues described in this work will have advantages over deferiprone.

Acknowledgement

The financial support from British Technology Group (BTG) is gratefully acknowledged.

References and notes

1. Porter, J. B. *Semin. Hematol.* **2001**, *38*, 63–68.
2. Singh, S.; Epemolu, R. O.; Dobbin, P. S.; Tilbrook, G. S.; Ellis, B. L.; Damani, L. A.; Hider, R. C. *Drug Metab. Dispos.* **1992**, *20*, 256–261.
3. Rafat, C.; Fakhouri, F.; Ribeil, J. A.; Delarue, R.; Le, Q. M. *Am. J. Kidney Dis.* **2009**, *54*, 931–934.
4. Cappellini, M. D.; Pattoneri, P. *Annu. Rev. Med.* **2009**, *60*, 25–38.
5. Dolbier, W. R. *J. Fluorine Chem.* **2005**, *126*, 157–163.
6. Bohm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637–643.
7. Yamazaki, I.; Taguchi, T.; Ojima, L. In *Fluorine in Medicinal Chemistry and Chemical Biology, Unique Properties of Fluorine and their Relevance to Medicinal Chemistry and Chemical Biology*; Ojima, L., Ed.; John Wiley & Sons: Chichester, 2009; pp 3–46.
8. Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737–1755.
9. Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192–212.
10. Syvret, R. G.; Butt, K. M.; Nguyen, T. P.; Bulleck, V. L.; Rieth, R. D. *J. Org. Chem.* **2002**, *67*, 4487–4493.
11. Rostami, A. *Synlett* **2007**, 2924–2925.
12. Bobbio, C.; Schlosser, M. *J. Org. Chem.* **2005**, *70*, 3039–3045.
13. Estel, L.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 2740–2744.
14. Mongin, F.; Trecourt, F.; Mongin, O.; Quéguiner, G. *Tetrahedron* **2002**, *58*, 309–314.
15. Mongin, F.; Trecourt, F.; Gervais, B.; Mongin, O.; Quéguiner, G. *J. Org. Chem.* **2002**, *67*, 3272–3276.
16. Gros, P.; Fort, Y.; Caubere, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3071–3080.
17. Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161–1172.
18. *General procedure for introduction of a hydroxy group on the pyridine ring:* A solution of fluorine-substituted pyridine derivative (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 a lithium base as indicated in Schemes 1 and 2 (11 mmol), slowly. The mixture was stirred at −78 °C for the amount of time indicated. To the mixture was added trimethoxyborane (2.4 ml) and the reaction mixture was stirred for 2 h, followed by addition of peracetic acid (3.6 ml; 32% in dilute AcOH). The mixture was allowed to warm to 0 °C with stirring for 1 h. Next, the mixture was cooled to −20 °C, and sodium dithionite (4 g in 10 ml of H_2O) was added slowly. The mixture was extracted with EtOAc (80 ml) or CH_2Cl_2 (80 ml) and the extract dried and concentrated. The residue was purified by chromatography to give the desired products.
19. Selected NMR and MS data: *2-Fluoro-3-hydroxy-6-methyl-1H-pyridin-4-one* (**4d**): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.61 (s, 1H, C5-H), 5.99 (br s), 2.21 (s, 3H, Me). ^{19}F NMR (376 MHz, DMSO-d_6) δ: −90.71 (s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.23 (s, Me), 109.50 (d, J = 3 Hz, C5–H), 125.04 (d, J = 29 Hz, C3), 144.52 (d, J = 13 Hz, C6), 152.92 (d, J = 227 Hz, C2), 156.26 (d, J = 8 Hz, C4). HRMS: Calcd for $C_6H_7NO_2F$ (M+1)$^+$, 144.0461. Found, 144.0463. *2-Fluoro-3-hydroxy-5-methyl-1H-pyridin-4-one* (**4f**): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.59 (br s), 7.36 (s, 1H, C6-H), 2.07 (s, 3H, Me). ^{19}F NMR (376 MHz, DMSO-d_6) δ: −91.60 (s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.53 (s, Me), 119.84 (d, J = 3 Hz, C5), 126.56 (d, J = 29 Hz, C3), 135.54 (d, J = 16 Hz, C6–H), 152.69 (d, J = 224 Hz, C2), 154.12 (d, J = 8 Hz, C4). HRMS: Calcd for $C_6H_7NO_2F$ (M+1)$^+$, 144.0461. Found, 144.0478. *5-Fluoro-3-hydroxy-2-methyl-1H-pyridin-4-one* (**4h**): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.55 (d, J = 5.0 Hz, 1H, C6–H), 4.54 (br s), 2.54 (s, 3H, Me). ^{19}F NMR (376 MHz, DMSO-d_6) δ: −148.82 (s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.04 (s, Me), 121.88 (d, J = 32 Hz, C6–H), 137.31 (s, C2), 144.11 (d, J = 7 Hz, C3), 148.73 (d, J = 238 Hz, C5), 150.48 (d, J = 12 Hz, C4). HRMS: Calcd for $C_6H_7NO_2F$ (M+1)$^+$, 144.0461. Found, 144.0468. *3-Fluoro-5-hydroxy-2-methyl-1H-pyridin-4-one* (**4j**): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.04 (d, J = 0.5 Hz, 1H, C6–H), 4.30 (br s), 2.64 (d, J = 2.8 Hz, 3H, Me). ^{19}F NMR (376 MHz, DMSO-d_6) δ: −146.32 (s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.67 (s, Me), 123.02 (s, C6–H), 134.77 (d, J = 27 Hz, C2), 145.25 (d, J = 7 Hz, C5), 147.32 (d, J = 238 Hz, C3), 150.60 (d, J = 11 Hz, C4). HRMS: Calcd for $C_6H_7NO_2F$ (M+1)$^+$, 144.0461. Found, 144.0468.