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Synthesis and In Vitro Biological Evaluation of Fluoro-Substituted-4-phenyl-1,2,3,6-tetrahydropyridines as Monoamine Oxidase B Substrates

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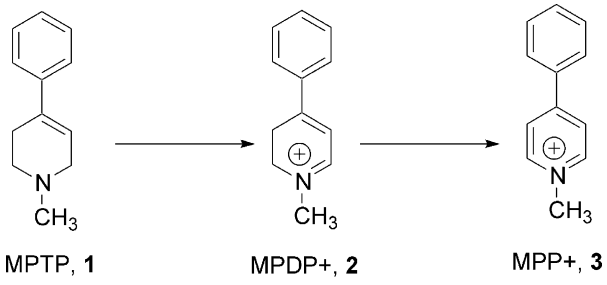
Abstract—The substrate properties of three β-fluoro-4-phenyl-1,2,3,6-tetrahydropyridines related to the proneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine have been examined in an effort to evaluate the contribution of electronic parameters to the MAO-B catalyzed allylic-α-carbon oxidation of the tetrahydropyridinyl system. The design, synthesis, and biological evaluation of these analogues are presented and correlations to amine ionization potentials versus substrate activity are discussed.

Introduction

The proneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, **1**) has been studied extensively as an experimental model of neurodegeneration due to its selective destruction of dopaminergic nigrostriatal neurons coupled with the production of behavioral and pathological symptoms resembling Parkinsonism.[1,2] This cyclic tertiary amine is an excellent substrate for monoamine oxidase (MAO) B that catalyzes an initial bioactivation event leading to the corresponding dihydropyridinium intermediate $MPDP^+$ (**2**) (Scheme 1). Autoxidation of **2** to the pyridinium species MPP^+ (**3**) is accompanied with the generation of superoxide radicals.[3] MPP^+ is actively transported into striatal nerve terminals and localized in the mitochondrial matrix where it inhibits complex I of the electron transport system resulting in depletion of ATP.[4] MPP^+ has also been shown to induce apoptosis via cytochrome c release and caspase activation, properties that may contribute further to its neurotoxicity.[5,6]

Extensive structure–activity relationship (SAR) studies on MPTP analogues have revealed several critical requirements for maintaining reasonable MAO substrate properties.[7] These include the presence of unsaturation at C4–C5 and a small *N*-alkyl substituent (methyl optimal).



Scheme 1. MAO catalyzed oxidation of MPTP (**1**).

Substitution or functional group elaboration of the phenyl group at the C-4 carbon with a variety of aromatic and heteroaromatic groups can enhance substrate properties and/or isozyme selectivity[8] while substitution of one or more tetrahydropyridinyl hydrogen(s) with an alkyl group(s) greatly diminishes substrate properties.[9,10] These SAR characteristics are reasonable when one considers the accessible active site volume of MAO-B. The X-ray structure of human MAO-B, which has been determined recently to 3 Å resolution, reveals an

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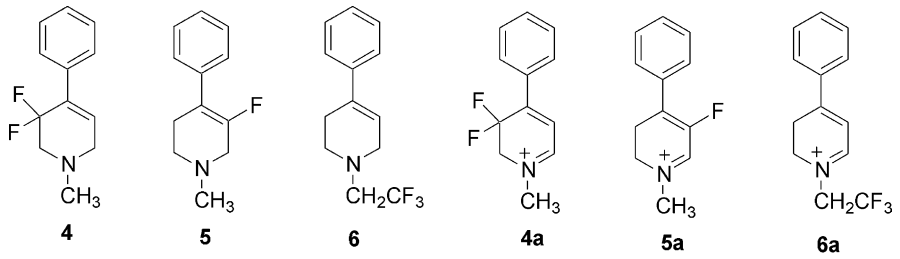


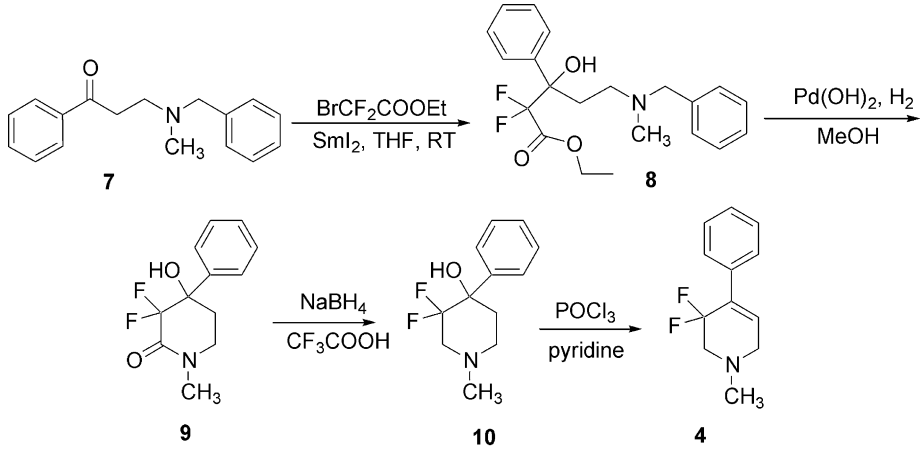
Figure 1. Fluorinated derivatives and their corresponding oxidation products.

active pocket consisting of an amine recognition site made up of an aromatic cage formed by two tyrosinyl groups.[11] The volume of the active site cavity (420 Å^3) is interconnected to an entrance cavity of 290 Å^3, which may interfere with substrate binding, particularly with tetrahydropyridinyl ring-substituted derivatives of MPTP. This has been supported further by an earlier study invoking semi-empirical quantum mechanical calculations and conformational analysis.[12] In order to investigate further the electronic requirements that 1,2,3,6-tetrahydropyridines in general exhibit for MAO-B catalysis, we chose to design the alkyl-fluorinated MPTP-analogues **4**, **5**, and **6** (Fig. 1). Substitution of fluorine for an active hydrogen can dramatically alter the physiochemical properties (log P, pK_a) of bioactive substances and may influence reactivity, metabolic stability, and biodistribution characterisitics.[13] The similarities in van der Walls radii between fluorine (1.47 Å) relative to hydrogen (1.20 Å) or oxygen (1.57 Å) have been used as a framework to justify fluorine as a bioisosteric substitution for hydrogen. In the present studies, the MAO-B substrate properties of the targeted compounds were evaluated by monitoring for the formation of the corresponding dihydropyridinium species (**4a**, **5a**, and **6a**).

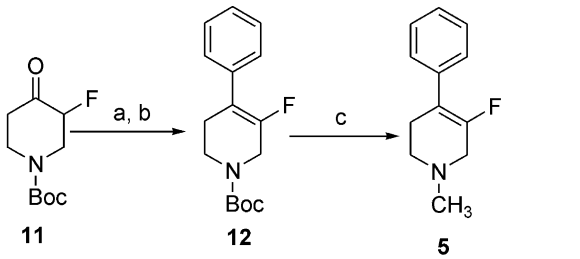
Results and Discussion

Chemistry

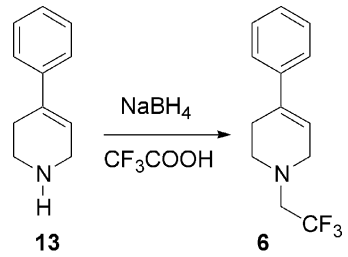
With respect to 3,3-difluoro-MPTP (**4**), we chose to utilize a conventional Reformatsky reaction to install the geminal-difluoro group. The reaction of ethyl bromodifluoroacetate with an appropriately functionalized β-aminoketone has been reported to provide β-hydroxy-δ-amino esters when non-fluorinated bromoacetates are utilized in the zinc-mediated Reformatsky reaction.[14] However, reaction of ethyl bromodifluoroacetate with activated zinc dust (in THF or DMF) and subsequent reaction with 3-(*N*-methyl-*N*-benzylamino) propiophenone (**7**) failed to produce measurable amounts of condensation product. This is in direct contrast to Reformatsky reactions involving fluorinated zinc reagents with ketones and aldehydes.[15,16] The failure to produce the requisite condensation product may be attributed to a collateral quaternization reaction of the amine with the bromoacetate, which has been postulated in similar reaction types.[14] In order to overcome this lack of reactivity, we turned our attention to a recently reported modification of this reaction using samarium diiodide (SmI_2) as an alternative to zinc.[17,18] Addition of a premixed solution of ethyl bromodifluoroacetate and **7** to SmI_2 at room temperature led to an immediate reaction and afforded the requisite β-hydroxy-γ-amino ester **8** in 75% yield. The scope and utility of this samarium-mediated transformation currently is being examined with a wide array of β-aminoketones as substrates. Removal of the *N*-benzyl protecting group of **8** was accomplished by hydrogenation using Pearlman's catalyst [$Pd(OH)_2$] in MeOH.[19] The removal of the *N*-benzyl protecting group occurred concomitant with cyclization to provide the lactam **9** directly. The amino ester intermediate was not detected during the course of the reaction. Undoubtedly, the reactivity of the carbonyl ester was increased towards the nucleophilic secondary amine due to the presence of the geminal-difluoro group. Lactam **9** was then sub-



Scheme 2. Preparation of 3,3-difluoro-MPTP (**4**).



Scheme 3. Preparation of 5-fluoro-MPTP (**5**).



Scheme 4. Preparation of *N*-trifluoroethyl-MPTP (**6**).

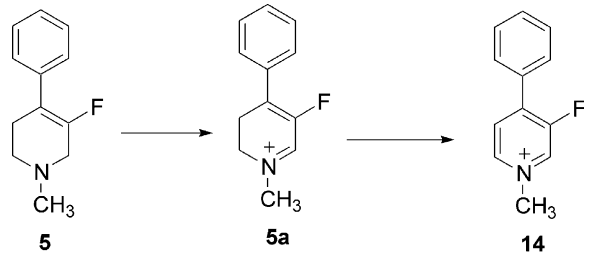
jected to carbonyl reduction using sodium trifluoroacetoxy-borohydride (prepared in situ from sodium borohydride and trifluoroacetic acid) to afford amine **10**.[20] The final product **4** was obtained by reaction of **10** with either $POCl_3$[21] or $SOCl_2$[22] in pyridine, albeit in approximately 18% yield (Scheme 2).

The synthesis of the 5-fluoro-1,2,3,6-tetrahydropyridinyl analogue **5** was accomplished by initially reacting the fluoropiperidone **11** (prepared by electrophilic fluorination of *N*-Boc-4-piperidone with Selectfluor®[23]) with phenylmagnesium bromide, followed by reaction with $POCl_3$ to yield the vinylfluoride **12**. DIBAL reduction[24] of the *N-tert*-butoxycarbonyl group of **12** to the requisite *N*-methyl group afforded the target compound 5-fluoro-1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**5**) (Scheme 3).

Preparation of the *N*-trifluoroethyl derivative **6** was accomplished by reaction of the secondary amine **13** with trifluoracetic acid and sodium borohydride (Scheme 4).[25] This reaction was sensitive to the quality of trifluoracetic acid used. All compounds were characterized using a combination of spectroscopic techniques, including ^1H NMR, ^{13}C NMR, high resolution mass spectrometry and/or elemental analysis.

Enzyme studies

The ability of these fluorinated analogues to serve as potential monoamine oxidase-B substrates was evaluated by monitoring for the formation of the respective dihydropyridinium species (**4a**, **5a**, and **6a**) from the corresponding tetrahydropyridinyl substrates (**4**, **5**, and **6**) (Figure 1). Spectrophotometric monitoring of 5 mM solutions of analogues **4**, **5**, and **6** by repeated UV scans (200–600 nm) in the presence of 0.1 μM baboon liver mitochondrial MAO-B served as a facile metabolic screen to determine whether any of the analogues served as substrates. Compounds **4** and **6** failed to lead to any measurable formation of **4a** and **6a**, respectively, while incubation of analogue **5** resulted in the time-dependent formation of a expected chromophore at $\lambda_{max} = 350$ nm corresponding to **5a**. An additional chromophore appeared over longer time periods with $\lambda_{max} = 302$ nm (corresponding to the fully oxidized pyridinium species **14**, Scheme 5).



Scheme 5. Oxidation of **5** to fully oxidized pyridinium **14**.

Quantitative kinetic analysis established the V_{max} (6 min^{-1}) and K_m (0.086 mM) for analogue **5** ($V_{max}/K_m = 70$). These fluorinated analogues were also screened for activity with human placental mitochondrial MAO-A, but all lacked substrate properties with this form of the enzyme. These compounds also failed to inhibit the oxidation of MPTP to MPDP+ when incubated with MAO-B, suggesting that they do not compete effectively for the active site of the enzyme (Table 1).

The lack of substrate properties for compounds **4** and **6**, relative to the modest substrate properties of **5** and N-ethyl MPTP[26] and the excellent substrate properties of MPTP,[27] may be partially explained by evaluating several important physiochemical parameters. An evaluation of the LogP (partition coefficient) and LogD (distribution coefficient) at pH = 7.4 do not reveal any distinct correlation between lipophilicity and activity, but an examination of both the pK_a (ACD Labs) and ionization potential (IP) reveal several correlates. As anticipated, the sequential replacement of β-alkyl hydrogens with fluorine leads to a proportional decrease in basicity relative to the parent compound MPTP (**1**). The ACD pK_a predictions are in close agreement with potentiometric titration results reported for structurally similar β-fluoroamines.[28,29] However, this decrease in basicity cannot solely be responsible for the lack of substrate properties against MAO-B. The active site of MAO-B, containing an aromatic caged environment, responsible for recognition of the amino group, lacks

Table 1. Properties calculated for fluorinated derivatives

Compound	V_{max}/K_m[a]	Log P	Log D (7.4)	pKa	Ionization potential (eV) AMPAC
MPTP (**1**)	748[b]	2.74	1.45	8.66	8.827
N-ethyl MPTP	68[c]	3.27	1.91	8.74	8.780
4	–	1.93	1.93	4.60	9.277
5	70	3.31	3.24	6.63	8.818
6	–	4.12	4.12	3.45	9.118

[a]nmol metabolite/min-nmol enzyme mM.
[b]Ref. 26.
[c]Ref. 27.

anionic residues. This property is in agreement with the known preference of MAO to bind deprotonated substrate.[30] An examination of the gas phase ionization potentials (IP) calculated for each of the derivatives (AMPAC), relative to MPTP and the related *N*-ethyl-MPTP, reveal a significant increase in IP with the introduction of fluorine. Empirical studies on β-fluoroamines by ion cyclotron resonance (ICR) and photoelectron spectroscopy (PES) techniques have been used to measure gas phase ionization potentials; substantial increases in ionization potentials with the introduction of fluorine relative to hydrogen were calculated, and were interpreted in terms of various contributions from polarization, inductive, and hyperconjugative interactions.[31] Quantitative interpretations of gas phase ionization potentials using computational approaches for a variety of fluoroamines have generated similar trends.[32]

Although the details concerning the mechanism of substrate processing by MAO have not been established fully, a single electron transfer (SET) pathway has been proposed and supported by a number of mechanistic studies.[33] The SET pathway proceeds by an electron-transfer step from the amine substrate resulting in the initial formation of an aminyl radical cation. The lack of substrate properties for compounds **4** and **6** relative to **1** and **5** may be explained partially by their high ionization potentials and the corresponding energy barrier for electron transfer from the amine lone pair to the flavin acceptor. Compounds **4** and **6** may not compete effectively for the active site of the enzyme, based on their failure to inhibit the oxidation of **1** to **2**. Additional studies are being conducted to expand our understanding of the molecular basis of substrate processing by MAO.

Experimental

CAUTION! MPTP is a known nigrostriatal neurotoxin, and therefore, compounds of this class should be handled using disposable gloves in a properly ventilated hood following good laboratory practices. Detailed procedures for the safe handling of MPTP have been reported.[34]

General procedures

All non-aqueous reactions were conducted using glassware that had been flame-dried under an inert atmosphere of argon immediately prior to use. All common reagents and solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA) and used without purification. Selectfluor® was obtained gratis from Air-Products, Inc. 3-(*N*-Benzyl-*N*-methylamino)propriophenone hydrochloride (**7**) was prepared according to the method of Sakuraba and Achiwa,[35] and was converted to the free base prior to use. 3-Fluoro-4-oxopiperidine-1-carboxylic acid *tert*-butyl ester (**11**) was prepared according to the method of ref 23. Tetrahydrofuran, dioxane, and diethyl ether was distilled from sodium/benzophenone ketyl under an inert atmosphere of argon. Hydrochloride and oxalate salts were converted to their corresponding free bases using saturated sodium carbonate, followed by extraction into ethyl acetate, and subjected to high vacuum prior to use. UV absorption spectra were recorded on a Beckman DU-7400 spectrophotometer. Proton and carbon NMR spectra were recorded on either a Bruker-400 or Bruker-500 spectrometer. Chemical shifts (δ) are reported relative to tetramethylsilane as an internal standard. Spin multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling values (*J*) are given in Hertz (Hz). Melting points were performed on a Mettler Toledo FP62. Pka values were calculated using the ACD/LogD suite software (ACD/Labs), and ionization potentials were calculated using Tripos SYBYL AMPAC. High resolution mass spectral data were acquired using a Bruker FT-ICR MS. Elemental Analyses were performed by Galbraith Laboratories Inc. (Knoxville, TN, USA). Low-resolution mass spectral data were acquired using a Waters-Micromass ZQ LC–MS platform in ES+ mode.

Enzyme procedures

MAO-B was isolated from baboon liver mitochondria according to the purification method of Salach and Weyler with minor modifications as described previously.[36] The purified enzyme concentration was calculated to be 0.1 μM. All enzyme assays were performed at 37 °C on a Beckman DU-7400 spectrophotometer. Stock solutions (5 mM) of the new compounds were prepared in 100 mM sodium phosphate buffer, pH 7.4. In preliminary experiments, the potential MAO-B substrate properties of each test compound were examined by recording repeated scans (250–500 nm) in the presence of 0.1 μM MAO-B. For kinetic analysis, initial rates of oxidation of the compounds were determined at four substrate concentrations, which bracketed the K_m value. A mixture of each test compound and MAO-B was added to a sample cuvette, and the initial rates of oxidation were estimated by monitoring the increase in absorbance of the corresponding dihydropyridinium meatabolite every 5 min for 45 min. The V_{max} and K_m values were calculated from Lineweaver–Burke plots. Duplicate analyses gave V_{maxt}/K_m values that differed by 10% or less.

5-(Benzyl-methyl-amino)-2,2-difluoro-3-hydroxy-3-phenyl-pentanoic acid ethyl ester (8). To a solution of SmI_2 (0.1 M in THF, 17.4 mmol, 174 mL) was added a premixed solution of ethyl bromodifluoroacetate (8.7 mmol, 1.76 g, 1.1 mL) and 3-(benzyl-methyl-amino)-1-phenyl-propan-1-one (**7**) (7.9 mmol, 2.0 g) in 10 mL THF at room temperature. The solution turned from a deep-blue to yellow color immediately and was stirred for an additional 15 min. The solution was quenched carefully with 1 N HCl (20 mL), and the resulting solution was diluted with diethyl ether and washed successively with 5% aq $NaHCO_3$ (75 mL×2), water (75 mL×2), and brine (75 mL×2). Evaporation resulted in an orange oil that was reconstituted in diethyl ether, and a solution of ethereal oxalic acid was added, pro-

ducing the crude oxalate salt of **8**, crystallized from acetonitrile–ether (2.75 g, 75% yield). Mp 174–175 °C; ^{1}H NMR (400 MHz, $CDCl_3$, free base) δ 7.57 (d, J = 7.4 Hz, 2H), 7.15–7.30 (m, 8H), 4.21 (dq, J = 7.1 Hz, J = 1.2 Hz, 2H), 3.52 (d, J = 12.7 Hz, 1H), 3.23 (d, J = 12.7 Hz, 1H), 2.75 (m, 2,), 2.53 (m, 2H), 2.13 (s, 3H), 1.17 (dt, J = 7.1 Hz, J = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.98 (t, J = 28.0 Hz), 140.20, 137.24, 129.73, 128.9, 128.41, 128.14, 127.97, 127.23, 115.33 (t, J = 255 Hz), 80.12 (t, J = 24.5 Hz), 62.90, 62.77, 54.34, 41.44, 29.25, 14.20; Exact mass calcd for $C_{21}H_{26}F_2NO_3$ (MH^+) 378.1881, found: 378.1895. Anal. calcd for $C_{23}H_{27}F_2NO_7$ (**8**-$(COOH)_2$): C, 59.10; H, 5.82; N, 3.00, found: C, 59.06; H, 5.91; N, 2.94.

3,3-Difluoro-4-hydroxy-1-methyl-4-phenyl-piperidin-2-one (9). The free base of **8** (1.6 mmol, 0.60 g) was dissolved in methanol (15 mL) and a catalytic amount of $Pd(OH)_2$ (50 mg, 10% Pd content) was added. The solution was vacuum purged several times, and allowed to react under a blanket of hydrogen gas (1 atm) for 24 h at room temperature. The solution was filtered to remove catalyst, and the solvent evaporated to yield an amorphous solid that was recrystallized from EtOAc–hexane yielding lactam **9** (0.360 g, 95%): mp 163–165 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (d, J = 7.54 Hz, 2H), 7.36 (m, 3H), 3.71 (m, 1H), 3.36 (dd, J = 12 Hz, J = 5.6 Hz, 1H), 3.00 (s, 3H), 2.87 (m, 1H), 2.11 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) 163.32 (dd, J = 31.3 Hz, J = 27.9), 139.38, 128.39, 128.08, 127.08 (d, J = 1 Hz), 111.70 (dd, J = 254.2, J = 243.3), 73.40 (dd, J = 24.9, J = 20.4), 45.41, 33.92, 30.85 (d, J = 4.5). Exact mass calcd for $C_{12}H_{14}F_2NO_2^+$ (MH^+) 242.0993, found 242.0983. Anal. calcd for $C_{12}H_{13}F_2NO_2$: C, 59.75; H, 5.43; N, 5.81, found: C, 59.38; H, 5.37; N, 5.66.

3,3-Difluoro-4-hydroxy-1-methyl-4-phenyl-piperidine (10). Lactam **9** (1.25 mmol, 0.3 g) and sodium borohydride (12.5 mol, 0.475 g) were dissolved in 5 mL dioxane, and trifluoroacetic acid (12.5 mol, 1.43 g, 0.93 mL) was added very slowly at 0 °C. The reaction was refluxed for 24 h. The resulting solution was cooled to 0 °C, quenched with water (10 mL), and basified to pH 8 with 1 N aq NaOH. The resulting solution was extracted several times with EtOAc, and evaporated to dryness. The crude product was reconstituted in diethyl ether, and an ethereal solution of HCl was added to produce compound **10** as the hydrochloride salt. Recrystallization from acetonitrile yielded **10**-HCl (0.21 g, 65%): mp 269–270 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (d, J = 7.4, 2H), 7.38 (m, 3H), 3.90 (m, 2H), 3.60 (M, 2H), 3.06 (s, 3H), 2.83 (m, 1H), 2.15 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 138.24, 128.64, 128.16, 127.28, 118.0 (dd, J = 254.8, J = 243.6) 71.03 (t, J = 20.5), 53.62 (t, J = 26.2), 49.94, 43.07, 32.57; Exact mass calcd for $C_{12}H_{16}F_2NO$ (MH +) 228.1200, found: 228.1224. Anal. calcd for $C_{12}H_{16}ClF_2NO$: C, 54.65; H, 6.12; N 5.31 Found: C, 54.55; H, 6.41; N 5.40.

3,3-Difluoro-1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (4). Compound **10** (100 mg, 0.438 mmol) was dissolved in 0.40 mL of pyridine and $POCl_3$ (4.3 mmol) was added dropwise at 0 °C. The reaction was stirred for 2 h and evaporated to dryness under high vacuum. The residue was treated with 1 N NaOH (10 mL) and extracted with EtOAc several times. The organic portion was dried over magnesium sulfate and solvent removed under vacuum. The crude product was dissolved in anhydrous ether, an ethereal solution of HCl was added, and **4**-HCl was recrystallized from methanol–ether (20 mg, 18%): mp 203–205 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.56–7.43 (m 5H), 6.53 (t, 1H, J = 3.2), 4.16 (s, 2H), 4.08 (t, 2H, J = 10.8), 3.15 (s 3H); ^{13}C NMR (MeOD) δ 134.22 (t, J = 23.9). 132.92, 129.24, 128.74, 127.71, 127.01, 115.63, 55.8 (t, J = 34.3), 52.32, 42.67; Exact mass calcd for $C_{12}H_{14}F_2N$ (MH^+) 210.1094, found: 210.0960. Anal. calcd for $C_{12}H_{14}ClF_2N$: C, 58.66; H, 5.74; N, 5.70 found: C, 58.86; H, 5.54; N, 5.60.

3-Fluoro-4-phenyl-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (12). To a round bottomed flask containing magnesium powder (0.22 g, 9.1 mmol) and anhydrous THF (50 mL) at 0 °C was added bromobenzene (0.960 mL, 9.1 mmol). After the magnesium had been consumed (1 h), fluoroketone **11** (1.8 g, 8.3 mmol) dissolved in THF (10 mL) was added, and the mixture was warmed to room temperature allowed to stir for an additional 4 h. The reaction was quenched with water (10 mL) and diluted with diethyl ether. The organic layer was washed successively with water and brine, dried over sodium sulfate, evaporated to dryness, and chromatographed over silica gel (1:1 EtOAc–hexanes) yielding 1.1 g of a white amorphous solid (46%). ^{1}H NMR ($CDCl_3$) δ 7.48–7.31 m (aromatic), 4.95 (ddd, 1H J = 2.1, 2.1, 20 Hz), 4.35 (bs, 1H), 3.94 (bs, 1H), 3.25 (m, 2H), 2.53 (s, 1H), 1.88 (m, 2H), 1.49 (s, 9H). This product contained an impurity that co-eluted with the product, and was carried through the next step without further purification. The Grignard product (0.750 g, 2.5 mmol) was dissolved in anhydrous pyridine (2.0 mL) and $POCl_3$ (300 μL) was added dropwise over 20 min at 0 °C. The resulting orange solution was stirred for 24 h and quenched with water. The solution was diluted with EtOAc, washed with saturated sodium carbonate, water, and brine, respectively. The organic layer was dried over sodium sulfate, concentrated under vacuum, and chromatographed (silica gel, 30:70 EtOAc–hexanes) resulting in a yellow oil (75 mg, 10%). ^{1}H NMR ($CDCl_3$) δ 7.45–7.24 (m, 5H), 4.12 (bs, 2H), 3.60 (bs, 2H), 2.51 (m, 2H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.88, 136.06, 128.96, 128.70, 127.85, 127.67, 126.63, 112.94, 80.73, 60.78, 28.82. Exact mass calcd for $C_{16}H_{21}FNO_2$ (MH +) 278.1556, found: 278.1562.

5-Fluoro-1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (5). N-Boc derivative **12** (60 mg, 0.22 mmol) was dissolved in THF (5 mL) and diisobutylaluminum hydride (1 M in THF, 770 μL, 0.78 mmol) was added dropwise at −78 °C. This solution was allowed to warm to room temperature and stirred for 72 h. The solution was quenched with water, diluted with EtOAc, washed successively with water and brine, dried over sodium sulfate, and evaporated to dryness. The resulting crude product was dissolved in anhydrous ether and an anhydrous ethereal solution of HCl was added. Recrystallization from methanol–ether yielded **5**-HCl (22 mg,

45%): mp 224–225 °C; ^{1}H NMR (CD_3OD) δ 7.49–7.34 (m, 5H), 4.11 (s, 2H), 3.58 (bs, 2H), 3.10 (s, 3H), 2.91 (bs, 2H); ^{13}C NMR (CD_3OD) δ 146.76 (d, $J=202$), 134.96, 129.59, 129.33, 128.70 (d, $J=93.3$), 114.37 (d, $J=4.9$), 52.01, 51.27 (d, $J=33.5$), 43.03, 25.52 (d $J=2.8$). Anal. calcd for $C_{12}H_{15}ClFN$. C, 63.30; H, 6.64; N 6.15, found: C, 63.30; H, 6.81; N, 6.22.

4-Phenyl-1-trifluorethyl-1,2,3,6-tetrahydropyridine (6). Trifluoroacetic acid (3 mL) was added dropwise slowly to a mixture of 4-phenyl-1,2,3,6-tetrahydropyridine (**13**) (0.1 g, 0.63 mmol) and sodium borohydride (0.17 g, 4.41 mmol) at 0 °C. It is imperative to use fresh, anhydrous trifluoroacetic acid in this reaction. The heterogeneous mixture was stirred for 3 h while warming to ambient temperature. An additional 0.1 g of sodium borohydride was added and the mixture heated for 3 h. After cooling, the reaction was quenched carefully with water (15 mL), and basified to pH 9 with 1 N aqueous NaOH. The resulting solution was extracted sequentially with diethyl ether, washed with brine, dried over magnesium sulfate, and evaporated to yield an oily residue. This was reconstituted in diethyl ether, and the corresponding hydrochloride salt was prepared by the addition of ethereal–HCl. The crude yellow solid was recrystallized from methanol–acetonitrile–diethylether to yield **6**-HCl (82 mg, 48% yield); mp 213 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, 2H, $J=7.2$), 7.38 (m, 3H), 6.18 (bs, 1H), 4.40 (q, 2H), 4.14 (bs, 2H), 3.74 (bs, 2H), 2.98 (bs, 2H). Exact mass calcd for $C_{13}H_{14}F_3N$ (MH+) 242.1157, found: 278.1169. Anal. calcd for $C_{13}H_{15}ClF_3N{\cdot}0.5H_2O$: C, 54.41; H, 5.41; N, 4.88 found: C, 54.46; H, 5.10; N, 4.88.

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