

# Direct Access to New *Gem*-Difluorinated Pyrido[1,2-*a*]Pyrimidine-2-one Systems

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## ABSTRACT

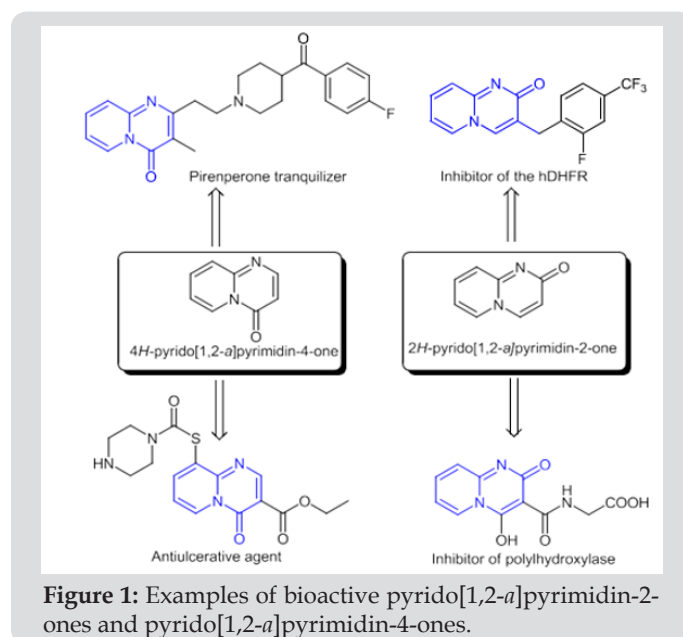
Efficient method for the synthesis of *gem*-difluorinated pyrido[1,2-*a*]pyrimidine-2-ones using addition/heterocyclization followed by Heck and Suzuki cross coupling reactions is reported. A variety of substituted products are obtained in good to excellent yields starting from 2-aminopyridines and *gem*-difluorinated alkynes.

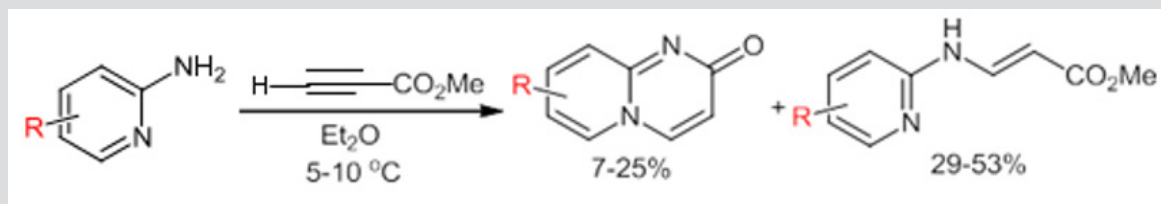
**Keywords:** *Gem*-Difluorinated Pyrido[1,2-*a*]Pyrimidine-2-Ones; 2-Aminopyridines; *Gem*-Difluorinated Alkynes; Heck Reaction; Suzuki Reaction

## Introduction

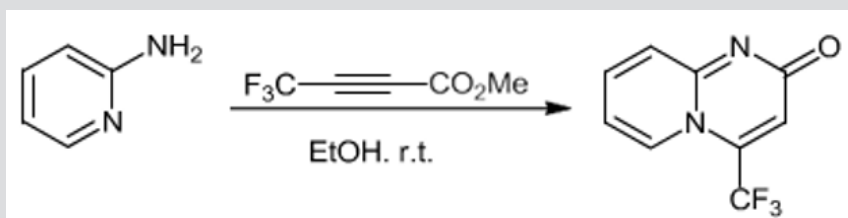
The pyrido[1,2-*a*]pyrimidine core is of great pharmaceutical importance due to its potent and significant biological activities as an anti-inflammatory,[1] antiallergic,[2] analgesic,[3] and anticancer agent (3-5 antifolate),[4] and its anti-aggressive activities.[5] In fact, there are two types of position isomers within the same family; pyrido[1,2-*a*]pyrimidin-2-ones and pyrido[1,2-*a*]pyrimidin-4-ones (Figure 1). They are associated in the synthesis of broad range of biologically active heterocycles such as antiulcerative agents,[6] tranquilizers and antipsychotic drugs (Pirenperone),[7] inhibitors of polyhydroxylase, or inhibitors of dihydrofolate reductase in humans (hDHFR)[8] (Figure 1). The first synthesis of pyrido[1,2-*a*]pyrimidin-2-ones was described in 1961 by Lappin et al. by cyclocondensation between various 2-aminopyridines and  $\alpha,\beta$ -acetylenic esters such as methyl propiolate. However, the use of these conditions leads to the formation of two different compounds[9] (Scheme 1). While several synthetic routes have been developed to obtain these pyrido[1,2-*a*]pyrimidin-2-ones, few synthetic methodologies have been published in the literature for the regioselective synthesis of pyrido[1,2-*a*]pyrimidin-2-ones. The Harriman group investigated the reactivity of the fluorinated alkyne ethyl 4,4,4-trifluorobut-2-ynoate with the 2-aminopyridine that led

to the formation of 4-(trifluoromethyl)-2*H*-pyrido[1,2-*a*]pyrimidin-2-one as the sole product with an excellent yield[10] (Scheme 2).





**Scheme 1:** The first synthesis of pyrido[1,2-*a*]pyrimidin-2-ones.



**Scheme 2:** The first synthesis of pyrido[1,2-*a*]pyrimidin-2-ones.

In view of the importance of the 2*H*-pyrido[1,2-*a*]pyrimidin-2-one scaffold, our laboratory team studied the extension of this heterocyclic family. We discovered a new series of synthesized molecules exhibiting *in vitro* activity against the host cell invasion by *E. tenella* parasites. This investigation revealed a “chief” compound with a “pyrido[1,2-*a*]pyrimidin-2-one”, with an IC<sub>50</sub> value of 15 μM.[11] Furthermore, it is well established that the incorporation of a fluorine atom into organic compounds can alter or modify their physicochemical properties and enhance their metabolic stability. The unique properties of fluorine have an exceptional impact on the electronic, lipophilic, and steric parameters, and acidity or basicity of organofluorinated molecules.[12] Much attention has been drawn in recent years to the difluoromethylene group (CF<sub>2</sub>) due to its special physical and chemical properties.[13]

## Methods

### General Methods

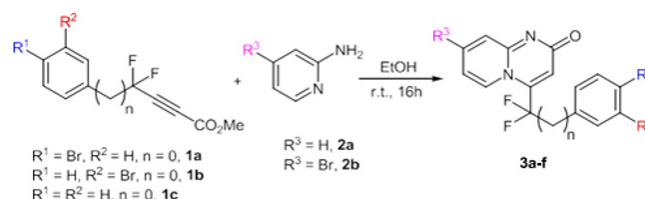
Most reagents were obtained from commercial sources and used as received. Thin-Layer Chromatography (TLC) was performed on Merck 60F254 plates. Column Chromatography was carried out with Merck silica gel 60 (0.040-0.063 mm, 230-400 mesh). All <sup>1</sup>H NMR, <sup>13</sup>C NMR and <sup>19</sup>F NMR spectra were recorded on a 300 MHz Bruker Avance FT- NMR spectrometer (300 MHz, 75 or 282 MHz, respectively). All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The coupling constants *J* are reported in Hertz (Hz). Electrospray ionization High-Resolution Mass Spectrometry Experiments (HRMS) were performed on a hybrid Tandem Quadrupole/Time-Of Flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, U.K.) operated in positive mode.

## Results and Discussion

Due to the valuable role of 2*H*-pyrido[1,2-*a*]pyrimidin-2-one derivatives as well as the important pharmacological role of the CF<sub>2</sub> moiety, we planned to look for an access to new *gem*-difluorinated-

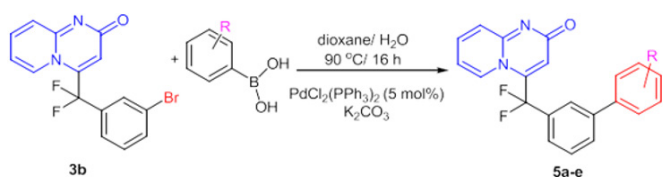
2*H*-pyrido[1,2-*a*]pyrimidin-2-one derivatives. Our investigation started by exploring the cycloaddition reaction between two different 2-aminopyridines and *gem*-difluorinated alkynes. The corresponding *gem*-difluorinated alkynes were prepared in the laboratory following a known synthetic strategy.[14] The cycloaddition reaction was done in ethanol at room temperature. Following the same mechanism as that described by Harriman's group.[10] The cycloaddition reactions between three different *gem*-difluorinated alkynes **1a-c** and 2-aminopyridines **2a-b** were successfully conducted, leading to the formation of pyrido[1,2-*a*]pyrimidin-2-ones **3a-f** with good to excellent yields (70-93%) (Table 1). Moreover, the reactions proceeded very cleanly, and the desired products were obtained as a solid in pure form after filtration. As product **3b** bears a reactive carbon-bromide bond connected to the phenyl group, it seemed important to test the reactivity of this bond in order to achieve further transformations. Therefore, a palladium catalyzed Heck coupling reaction was carried out on pyrido[1,2-*a*]pyrimidin-2-one **3b** with methyl acrylate.

**Table 1:** Cycloaddition reaction between *gem*-difluorinated alkynes and 2-aminopyridines.



Entry	R <sup>1</sup>	R <sup>2</sup>	n	R <sup>3</sup>	Product	Yield* (%)
1	Br	H	0	H	3a	70
2	H	Br	0	H	3b	84
3	H	H	2	H	3c	79
4	Br	H	0	Br	3d	77
5	H	Br	0	Br	3e	93
6	H	H	2	Br	3f	85

\*=Isolated yield

**Table 2:** Suzuki coupling reaction of 4-[(3-bromophenyl)difluoromethyl]-2H-pyrido[1,2-a]pyrimidin-2-one **3b**.

Entry	Boronic Acid	Product	Yield* (%)
1			90
2			80
3			87
4			94
5			70

\* = Isolated yield

The best conditions for performing this coupling reaction were found to be a catalytic amount of palladium (II) acetate [Pd(OAc)<sub>2</sub>, 5 mol%], triphenyl phosphine [PPh<sub>3</sub>, 10 mol%] and triethylamine as base and heating in a sealed tube at 120°C. The reaction gave the desired product **4** (*E/Z* = 94/6) that was easily purified by recrystallization and was isolated with a 60% of overall yield. A typical Suzuki-Miyaura cross coupling reaction[15] was then tested on pyrido[1,2-*a*]pyrimidin-2-one **3b** using a variety of phenyl boronic acids in order to achieve further transformation. The reactions were performed in a mixture of dioxane/water (3/1) with Palladium (II)bis(triphenylphosphine) dichloride [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] (5 mol%) as catalyst and Potassium carbonate (K<sub>2</sub>CO<sub>3</sub>) as base. The desired products **5a-e** were isolated in a yield ranging between 70-

94%. The results are summarized in Table 2. Despite of their ability to facilitate the oxidative addition step in Suzuki-Miyaura cross coupling reaction, the presence of EWG such as a CF<sub>3</sub> group (entry 5, Table 2) in phenyl boronic acids has the disadvantage to induce a partial protodeboronation in presence of aqueous base which globally decreases the yield of the cross-coupling reaction.[16-18]

## Experimental Part

### Methyl 4,4-difluoro-6-phenylhex-2-ynoate (**1c**):

Colorless oil; C<sub>13</sub>H<sub>12</sub>F<sub>2</sub>O<sub>2</sub>; yield = 70%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ (ppm) = 7.34-7.19 (m, 5H), 3.84 (s, 3H), 2.81-2.83 (m, 2H), 2.46-2.29 (m, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ (ppm) = 152.3 (t, CO, J<sub>CF</sub> = 2.4 Hz), 139.2, 128.8 (CH), 128.7 (2CH), 128.4 (2CH), 113.7 (t, CF<sub>2</sub>, J<sub>CF</sub> = 234.7 Hz), 77.2 (t, J<sub>CF</sub> = 40.7 Hz), 76.8 (t, J<sub>CF</sub> = 6.7 Hz), 53.4 (CH<sub>3</sub>), 40.5 (t, CH<sub>2</sub>, J<sub>CF</sub> = 25.1 Hz), 28.7 (t, CH<sub>2</sub>, J<sub>CF</sub> = 4.0 Hz). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ (ppm) = - 86.53. HRMS(ESI): m/z [M+H]<sup>+</sup> +calcd for C<sub>13</sub>H<sub>13</sub>F<sub>2</sub>O<sub>2</sub>: 239.08781; found: 239.08736.

### General procedure for cycloaddition reaction between fluorinated alkynes **1a** and 2-aminopyridine derivatives:

2-Aminopyridine (12 mg, 0.13 mmol) in 2 ml of ethanol was introduced in a small round bottom flask. The *gem*-difluorinated alkyne **1a** (41 mg, 0.14 mole, 1.1 equiv.) was added drop by drop. Once the reaction was completed, the solvent was evaporated under vacuum. The product was rinsed with ether and then dried under vacuum yielding the pure product **3a** without any additional treatment.

### 4-[(4-Bromophenyl)difluoromethyl]-2H-pyrido[1,2-*a*]pyrimidin-2-one (**3a**):

Yellow soli; C<sub>15</sub>H<sub>9</sub>BrF<sub>2</sub>N<sub>2</sub>O; Yield = 70%; m.p = 219-221°C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ (ppm) = 7.90 (d, 1H, J = 7.2 Hz), 7.79 (d, 2H, J = 8.5 Hz), 7.73-7.67 (m, 3H), 7.28 (dd, 1H, J = 9.9/1.2 Hz), 6.90 (dt, 1H, J = 1.2/7.2 Hz), 6.66 (s, 1H). <sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>): δ (ppm) = 166.1 (CO), 152.7, 140.2 (t, J<sub>CF</sub> = 29.7 Hz), 137.2 (CH), 132.6 (2CH), 131.1 (t, J<sub>CF</sub> = 25.8 Hz), 130.2 (t, CH, J<sub>CF</sub> = 5.2 Hz), 128.3 (t, 2CH, J<sub>CF</sub> = 5.1 Hz), 126.0 (t, J<sub>CF</sub> = 2.1 Hz), 124.7 (CH), 117.2 (t, CF<sub>2</sub>, J<sub>CF</sub> = 241.9 Hz), 116.9 (t, CH, J<sub>CF</sub> = 6.0 Hz), 113.8 (CH). <sup>19</sup>F NMR (282 MHz, DMSO-d<sub>6</sub>): δ (ppm) = - 89.76. HRMS(ESI): m/z [M+H]<sup>+</sup> +calcd for C<sub>15</sub>H<sub>10</sub>BrF<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 350.99291; found: 350.99237.

### 4-[(3-Bromophenyl)difluoromethyl]-2H-pyrido[1,2-*a*]pyrimidin-2-one (**3b**):

Yellow solid; C<sub>15</sub>H<sub>9</sub>BrF<sub>2</sub>N<sub>2</sub>O; Yield = 84%; m.p = 219-221°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ (ppm) = 8.05 (d, 1H, J = 7.3 Hz), 7.74 (m, 2H), 7.55-7.39 (m, 4H), 6.78 (dt, 1H, J = 1.3/7.3 Hz), 6.57 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ (ppm) = 167.1 (CO), 153.2, 141.1 (t, J<sub>CF</sub> = 28.5 Hz), 136.5 (CH), 136.4 (CH), 134.2 (t, J<sub>CF</sub> = 25.7 Hz), 131.1 (CH), 130.1 (t, CH, J<sub>CF</sub> = 6.5 Hz), 129.1 (t, CH, J<sub>CF</sub> = 5.9 Hz), 126.1 (CH), 124.7 (t, CH, J<sub>CF</sub> = 5.4 Hz), 123.7 (CH), 118.8 (t, CH, J<sub>CF</sub> = 4.7 Hz), 117.6 (t, CF<sub>2</sub>, J<sub>CF</sub> = 244.4 Hz), 133.6. <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ (ppm) = - 89.76. HRMS(ESI): m/z [M+H]<sup>+</sup> +calcd for C<sub>15</sub>H<sub>10</sub>BrF<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 350.99391; found: 350.99507.

### 4-(1,1-Difluoro-3-phenylpropyl)-2H-pyrido[1,2-*a*]pyrimidin-2-one (**3c**):

Yellow solid; C<sub>17</sub>H<sub>14</sub>F<sub>2</sub>N<sub>2</sub>O; Yield = 79%; m.p = 120-122°C. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ (ppm) = 8.47 (t, 1H, J = 7.1 Hz), 7.95 (t, 1H, J = 7.8 Hz), 7.41 (d, 2H, J = 9 Hz), 7.26-7.17 (m, 5H), 6.94 (s, 1H), 2.88-2.75 (m, 4H). <sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>): δ (ppm) = 163.4 (CO), 151.6, 141.2 (t, J<sub>CF</sub> = 28.4 Hz),

139.3 (CH), 139.1 (CH), 131.7 (t,  $J_{CF} = 6.6$  Hz), 128.4 (2CH), 128.3 (2CH), 126.3 (CH), 122.3 (CH), 119.6 (t,  $CF_2$ ,  $J_{CF} = 245.4$  Hz), 116.8 (t, CH,  $J_{CF} = 7.0$  Hz), 115.4 (CH), 36.10 (t,  $CH_2$ ,  $J_{CF} = 23.2$  Hz), 27.2 (t,  $CH_2$ ,  $J_{CF} = 4.6$  Hz).  $^{19}F$  NMR (282 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = -95.70. HRMS (ESI):  $m/z$  [M+H]<sup>+</sup> +calcd for  $C_{17}H_{15}F_2N_2O_2$ : 301.11470; found: 301.11340.

**8-Bromo-4-[(4-bromophenyl) difluoromethyl]-2H-pyrido[1,2-a]pyrimidin-2-one (3d):** Yellow solid;  $C_{15}H_8Br_2F_2N_2O$ ; Yield = 77%; m.p. = 200-202°C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 7.87-7.82 (m, 4H), 7.70 (d, 2H,  $J = 8.6$  Hz), 7.25 (dd,  $J = 1.0/9.3$  Hz, 1H), 6.62 (s, 1H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 165.9 (CO), 151.4, 139.7 (t,  $J_{CF} = 29.7$  Hz), 139.5 (CH), 132.7 (2CH), 130.8 (t,  $J_{CF} = 25.8$  Hz), 128.9 (t, CH,  $J_{CF} = 5.7$  Hz), 128.2 (t, 2CH,  $J_{CF} = 5.2$  Hz), 126.4, 126.2 (t, CH,  $J_{CF} = 2.3$  Hz), 117.2 (t,  $CF_2$ ,  $J_{CF} = 241.7$  Hz), 111.9 (t, CH,  $J_{CF} = 5.8$  Hz), 106.6 (CH).  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = -90.02. HRMS(ESI):  $m/z$  [M+H]<sup>+</sup> +calcd for  $C_{15}H_8Br_2F_2N_2O$ : 428.90442; found: 428.90269.

**7-Bromo-4-[(3-bromophenyl) difluoromethyl]-2H-pyrido[1,2-a]pyrimidin-2-one (3e):** Yellow solid;  $C_{15}H_8Br_2F_2N_2O$ ; Yield = 93%; m.p. = 200-202°C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 8.27 (s, 1H), 7.75 (d,  $J = 7.6$  Hz, 1H), 7.73 (t,  $J = 7.6$  Hz, 1H), 7.59 (dd,  $J = 1.6/9.6$  Hz, 1H), 7.51-7.41 (m, 2H), 7.29 (m, 1H), 6.46 (s, 1H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 166.7 (CO), 151.7, 140.8 (t,  $J_{CF} = 29.4$  Hz), 139.7, 135.6, 133.9 (t,  $J_{CF} = 25.7$  Hz), 131.2, 126.7 (t,  $J_{CF} = 7.5$  Hz), 129.3 (t,  $J_{CF} = 6.0$  Hz), 126.9, 124.8 (t,  $J_{CF} = 5.8$  Hz), 123.8, 119.0 (t,  $J_{CF} = 5.0$  Hz), 117.9 (t,  $CF_2$ ,  $J_{CF} = 244.5$  Hz), 107.6.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = -92.83. HRMS(ESI):  $m/z$  [M+H]<sup>+</sup> +calcd for  $C_{15}H_8Br_2F_2N_2O$ : 428.90442; found: 428.90632.

**8-Bromo-4-(1,1-difluoro-3-phenylpropyl)-2H-pyrido[1,2-a]pyrimidin-2-one (3f):** Yellow solid;  $C_{17}H_{13}BrF_2N_2O$ ; Yield = 85%; m.p. = 146-148°C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 8.26 (d, 1H,  $J = 1.7$  Hz), 7.59 (dd, 1H,  $J = 1.8/9.6$  Hz), 7.33-7.16 (m, 6H), 6.85 (s, 1H), 2.97 (m, 2H), 2.69 (m, 2H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 166.7 (CO), 151.6, 140.5 (t,  $J_{CF} = 28.5$  Hz), 139.4 (CH), 138.4, 129.4 (t, CH,  $J_{CF} = 8.7$  Hz), 128.2 (2CH), 128.2 (2CH), 126.8 (CH), 126.9 (CH), 119.4 (t,  $CF_2$ ,  $J_{CF} = 243.5$  Hz), 116.6 (t,  $J_{CF} = 6.1$  Hz), 107.6 (CH), 37.3 (t,  $CH_2$ ,  $J_{CF} = 24.0$  Hz), 28.0 (t,  $CH_2$ ,  $J_{CF} = 4.6$  Hz).  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = -95.84. HRMS(ESI):  $m/z$  [M+H]<sup>+</sup> +calcd for  $C_{17}H_{14}BrF_2N_2O$ : 379.02340; found: 379.02340.

**Procedure of Heck Reaction for Preparation of Compound 4:** Compound **3b** (30 mg, 0.08 mmol), triphenyl phosphine  $PPh_3$  (2.2 mg, 10 mol%), and Palladium (II) acetate [ $Pd(OAc)_2$ ] (1 mg, 5 mol%) were introduced in a sealed tube with an excess of methyl acrylate. Then trimethylamine [ $Et_3N$ ] (0.04 ml) was added slowly. The reaction mixture was set at 120°C under Argon. After the reaction was completed, extraction using ethyl acetate and water was done. The reaction mixture was dried over Magnesium sulfate and the solvent was evaporated under vacuum. The pure product was isolate using silica gel column chromatography in 60% yield (18.2 mg, yellow solid). m.p = 175-177°C.

**Methyl-3-[3-(difluoro(2-oxo-2H-pyrido[1,2-a]pyrimidin-4-yl)methyl)phenyl]acrylate (4-E):**  $C_{19}H_{14}F_2N_2O_3$ ;  $^1H$ NMR (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 8.10 (d,  $J = 7.0$

Hz, 1H), 7.73 (d,  $J = 6.8$  Hz, 1H), 7.71 (s, 1H), 7.68 (d, 1H,  $J_{alkene} = 16.0$  Hz), 7.56-7.55 (m, 3H), 7.40 (d,  $J = 9.1$  Hz, 1H), 6.72 (dt,  $J = 1.4/7.1$  Hz, 1H), 6.52 (s, 1H), 6.43 (d,  $J = 16.0$  Hz, 1H), 3.75 (s, 3H).  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = -92.47. HRMS(ESI):  $m/z$  [M+H]<sup>+</sup> +calcd for  $C_{19}H_{15}F_2N_2O_3$ : 357.10453; found: 357.10416.

**General Procedure of Suzuki Cross Coupling Reaction on Compound 3b:** Compound **3b** (30 mg, 0.085 mmole), phenyl-boronic acid (42 mg, 0.34 mmole, 4 equiv.), Palladium(II) bis(triphenylphosphine) dichloride  $PdCl_2(PPh_3)_2$  (0.5 mol%), Potassium carbonate [ $K_2CO_3$ ] (23.5 mg, 0.17 mmole, 2 equiv.), and a mixture of dioxane/ $H_2O$  (3/0.6 ml) were introduced in a sealed tube. The reaction mixture was heated to 90°C. When the reaction was finished, Sodium chloride [ $NaCl$ ] was added. Extraction was done with ethyl acetate and water. The organic phase was dried over Magnesium sulfate, filtered followed by the evaporation of the solvent. The desired product **5a** was isolated in 90% yield (26.5 mg, white solid) using silica gel column chromatography, eluent EA/ PE = 9/1.

**4-[(1,1'-Biphenyl)-3-yl] difluoromethyl-2H-pyrido[1,2-a]pyrimidin-2-one (5a):** White solid;  $C_{21}H_{14}F_2N_2O$ ; m.p. = 199-201°C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 8.18 (d, 1H,  $J = 7.0$  Hz), 7.82 (d, 1H,  $J = 7.0$  Hz), 7.77 (s, 1H), 7.63-7.40 (m, 8H), 7.27 (t, 1H,  $J = 7.0$  Hz), 6.80 (t, 1H,  $J = 7.0$  Hz), 6.72 (s, 1H).  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = -92.02.  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 167.1 (CO), 153.1, 142.8, 141.5 (t,  $J_{CF} = 30.4$  Hz), 139.3, 136.1 (CH), 130.8 (t, CH,  $J_{CF} = 9.8$  Hz), 130.8 (CH), 130.3 (t, CH,  $J_{CF} = 6.9$  Hz), 129.9 (CH), 129.1 (2CH), 128.3 (CH), 127.2 (2CH), 129.9, 124.6 (t, CH,  $J_{CF} = 5.8$  Hz), 124.5 (t, CH,  $J_{CF} = 5.2$  Hz), 118.7 (t, CH,  $J_{CF} = 5.3$  Hz), 118.4 (t,  $CF_2$ ,  $J_{CF} = 244.3$  Hz), 113.2 (CH). HRMS(ESI):  $m/z$  [M+H]<sup>+</sup> +calcd for  $C_{21}H_{15}F_2N_2O$ : 349.1042; found: 349.11409.

**4-[(4'-Acetyl-[1,1'-biphenyl]-3-yl) difluoromethyl]-2H-pyrido[1,2-a]pyrimidin-2-one (5b):** Yellow solid;  $C_{23}H_{16}F_2N_2O_2$ ; Yield = 80%; m.p. = 215-217°C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 8.20 (d,  $J = 7.1$  Hz, 1H), 8.06 (t,  $J = 8.3$  Hz, 2H), 7.84 (d,  $J = 7.5$  Hz, 1H), 7.80 (bs, 1H), 7.67 (d,  $J = 8.4$  Hz, 2H), 7.62-7.55 (m, 3H), 7.41 (d,  $J = 9.0$  Hz, 1H), 6.79 (dt,  $J = 6.9/1.0$  Hz, 1H), 6.62 (s, 1H), 2.65 (s, 3H).  $^{13}C$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 197.8 (COCH<sub>3</sub>), 166.3 (CO), 152.8, 143.1, 140.4 (t,  $J_{CF} = 25.8$  Hz), 140.3, 137.3, 136.3 (CH), 132.9 (t,  $J_{CF} = 25.3$  Hz), 130.9 (CH), 130.5 (CH), 130.4 (t, CH,  $J_{CF} = 5.7$  Hz), 129.0 (2CH), 127.5 (2CH), 125.9 (t, CH,  $J_{CF} = 5.2$  Hz), 124.7 (CH), 124.3 (t, CH,  $J_{CF} = 5.2$  Hz), 177.5 (t,  $CF_2$ ,  $J_{CF} = 241.3$  Hz), 117.0 (t, CH,  $J_{CF} = 5.7$  Hz), 113.9 (CH), 26.9 (CH<sub>3</sub>).  $^{19}F$  NMR (282 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = -92.26. HRMS(ESI):  $m/z$  [M+H]<sup>+</sup> +calcd for  $C_{23}H_{17}F_2N_2O_2$ : 391.12526; found: 391.12649.

**4-[(2'-Acetyl-[1,1'-biphenyl]-3-yl) difluoromethyl]-2H-pyrido[1,2-a]pyrimidin-2-one (5c):** Yellow solid;  $C_{23}H_{16}F_2N_2O_2$  Yield = 87%; m.p. = 215-217°C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 8.06 (d,  $J = 7.2$  Hz, 1H), 7.64 (dd,  $J = 1.2/7.5$  Hz, 1H), 7.58-7.48 (m, 7H), 7.41-7.34 (m, 2H), 6.79 (dt,  $J = 1.5/6.9$  Hz, 1H), 6.74 (s, 1H), 2.20 (s, 3H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  (ppm) = 202.6 (COCH<sub>3</sub>), 167.2 (CO), 153.1, 142.5, 141.5 (t,  $J_{CF} = 29.8$  Hz), 139.7, 139.0, 136.3 (CH), 132.4 (t,  $J_{CF} = 25.3$  Hz), 132.2 (CH), 131.3 (CH), 130.8 (CH), 130.2 (t, CH,  $J_{CF} = 6.0$  Hz), 129.8 (CH), 128.5 (CH), 128.4 (CH), 126.3 (t, CH,  $J_{CF} = 5.6$  Hz), 125.9 (CH), 124.9 (t, CH,  $J_{CF} = 5.4$  Hz), 118.1 (t, CH,  $J_{CF} = 5.5$  Hz), 117.9 (t,  $CF_2$ ,  $J_{CF} = 243.6$  Hz), 113.4

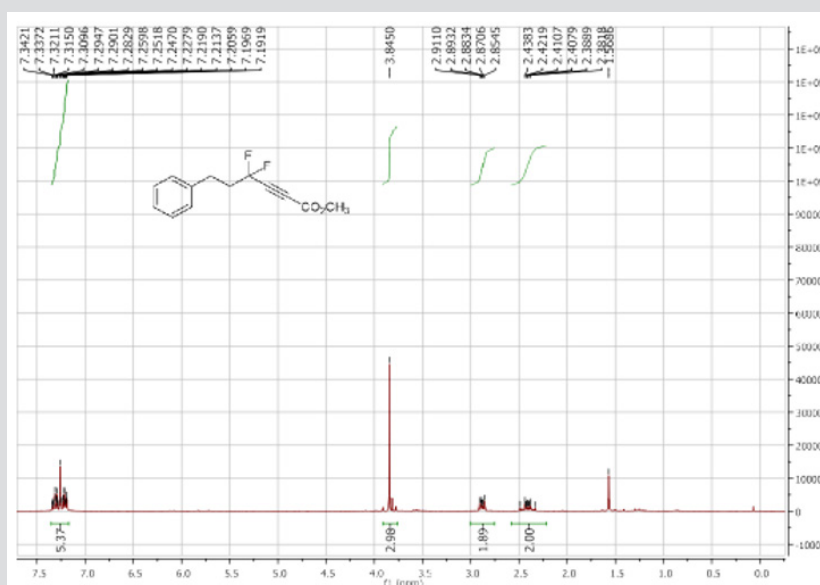
(CH), 30.2 (CH<sub>3</sub>). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ (ppm) = -92.33. HRMS (ESI): m/z [M+H]<sup>+</sup> + calcd for C<sub>23</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 378.12426; found: 378.12653.

**4-(Difluoro(2'-methoxy-[1,1'-biphenyl]-3-yl)methyl)-2H-pyrido[1,2-a]pyrimidin-2-one:** Yellow solid; C<sub>22</sub>H<sub>16</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub>; Yield = 94%; m.p. = 201-203°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ (ppm) = 8.05 (d, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.62 (s, 1H), 7.49-7.40 (m, 3H), 7.32-7.18 (m, 3H), 6.96-6.87 (m, 2H), 6.67 (s, 1H), 6.66 (m, 1H), 3.67 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ (ppm) = 171.2 (CO), 167.4, 156.3, 153.1, 141.7 (t, *J*<sub>CF</sub> = 29.7 Hz), 139.9, 136.2 (CH), 133.1 (CH), 131.7 (t, *J*<sub>CF</sub> = 25.1 Hz), 130.6 (CH), 130.4 (t, CH, *J*<sub>CF</sub> = 6.4 Hz), 129.7 (CH), 129.2 (CH), 128.6 (CH), 127.2 (t, CH, *J*<sub>CF</sub> = 5.6 Hz), 125.8 (CH), 124.1 (t, CH, *J*<sub>CF</sub> = 5.5 Hz), 121.1 (CH), 118.5 (t, CH, *J*<sub>CF</sub> = 5.5 Hz), 118.4 (t, CF<sub>2</sub>, *J*<sub>CF</sub> = 243.2 Hz), 111.3 (CH), 55.5 (CH<sub>3</sub>). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ (ppm) = -91.85. HRMS (ESI):

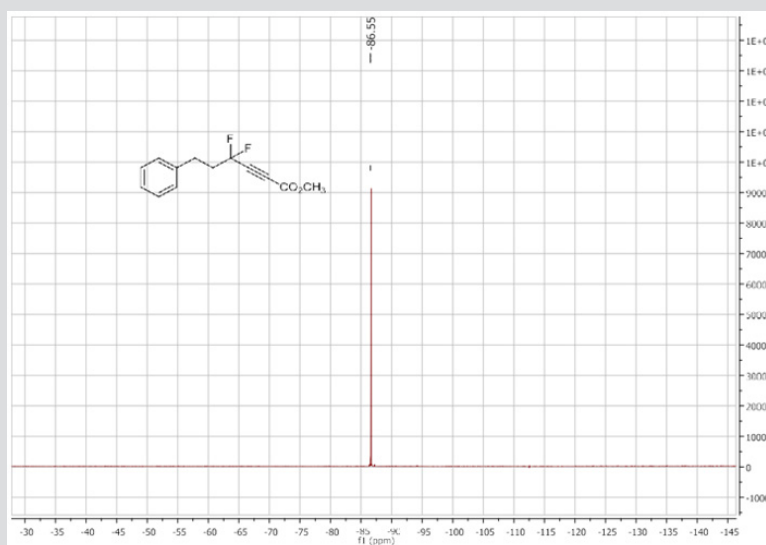
m/z [M+H]<sup>+</sup> + calcd for C<sub>22</sub>H<sub>17</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 391.12526; found: 391.12649.

**4-(Difluoro(4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methyl)-2H-pyrido[1,2-a]pyrimidin-2-one (5e):** Yellow solid; C<sub>22</sub>H<sub>13</sub>F<sub>5</sub>N<sub>2</sub>O; Yield = 70%; m.p. = 214-216°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ (ppm) = 8.20 (d, *J* = 7.3 Hz, 1H), 7.83-7.54 (m, 9H), 7.42 (d, *J* = 9.0 Hz, 1H), 6.80 (t, *J* = 7.2 Hz, 1H), 6.61 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ (ppm) = 167.3 (CO), 153.3, 143.0, 141.5 (t, *J*<sub>CF</sub> = 29.1 Hz), 141.4, 136.3 (CH), 133.2 (t, *J*<sub>CF</sub> = 25.2 Hz), 131.0 (CH), 130.6 (q, *J*<sub>CF</sub> = 25.0 Hz), 130.4 (t, CH, *J*<sub>CF</sub> = 6.9 Hz), 130.3 (CH), 127.7 (2CH), 126.2 (CH), 126.1 (2CH), 125.7 (t, CH, *J*<sub>CF</sub> = 5.5 Hz), 124.8 (t, CH, *J*<sub>CF</sub> = 5.4 Hz), 124.2 (q, CF<sub>3</sub>, *J*<sub>CF</sub> = 270.6 Hz), 119.1 (t, CH, *J*<sub>CF</sub> = 5.0 Hz), 118.6 (t, CF<sub>2</sub>, *J*<sub>CF</sub> = 243.2 Hz), 113.4 (CH). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ (ppm) = -62.58 (CF<sub>3</sub>), -92.28 (CF<sub>2</sub>). HRMS (ESI): m/z [M+H]<sup>+</sup> + calcd for C<sub>22</sub>H<sub>14</sub>F<sub>5</sub>N<sub>3</sub>O: 417.10208; found: 417.10357.

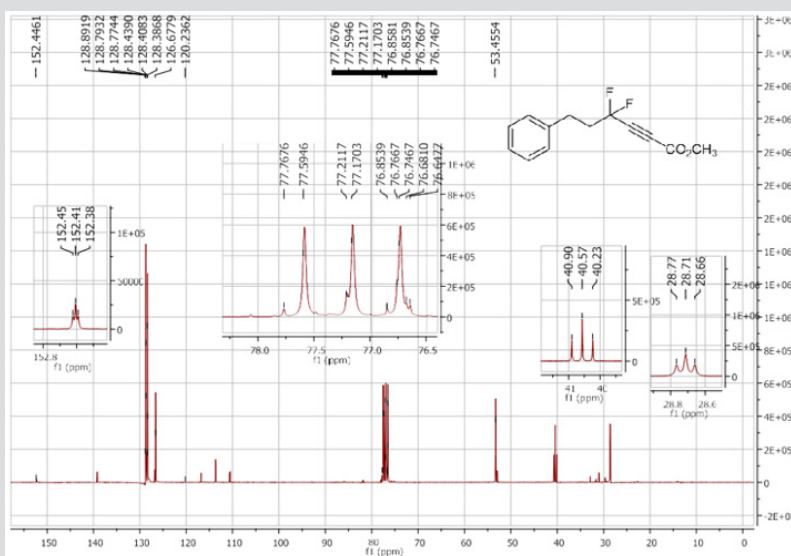
**NMR Data:** (Graphs 1-38)



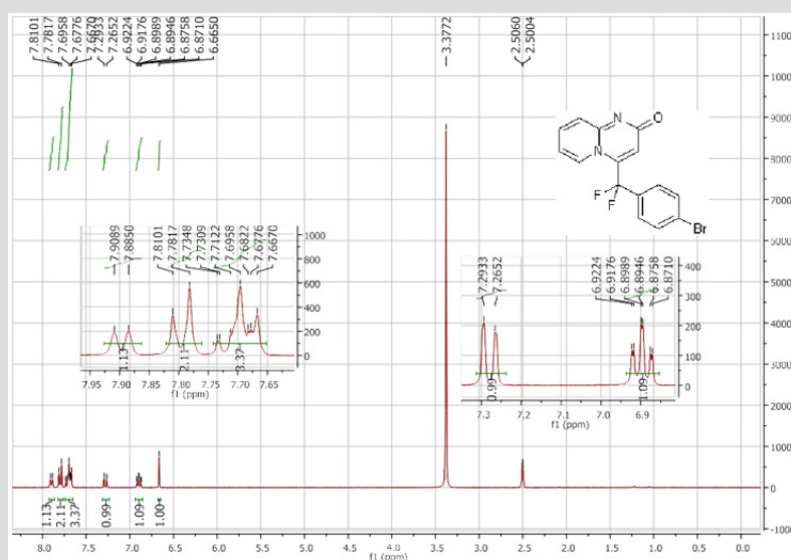
Graph 1: <sup>1</sup>H NMR (1c).



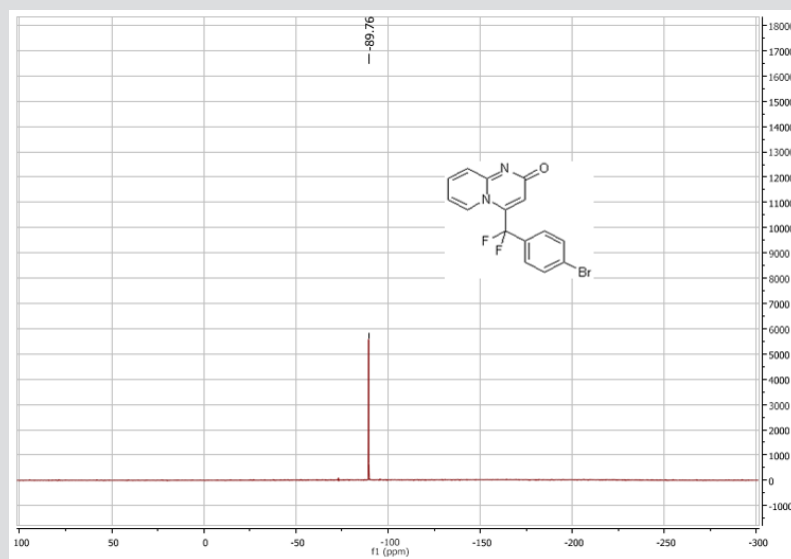
Graph 2: <sup>19</sup>F NMR (1c).



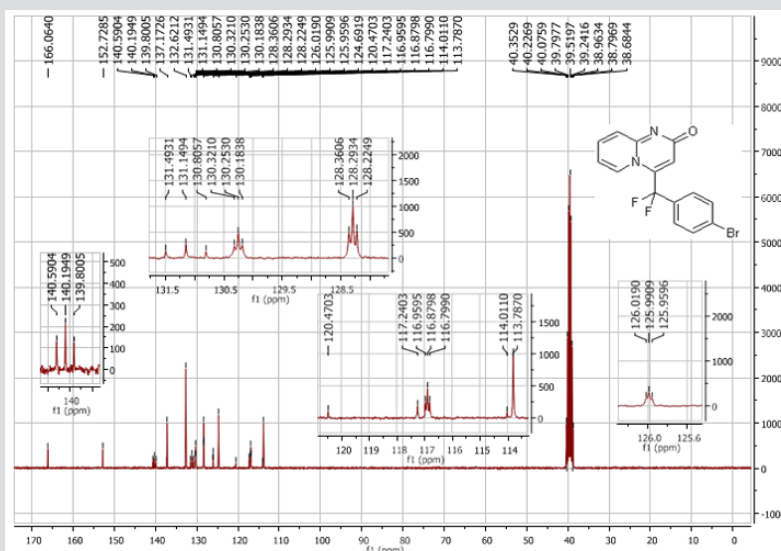
Graph 3: <sup>13</sup>C NMR (1c).



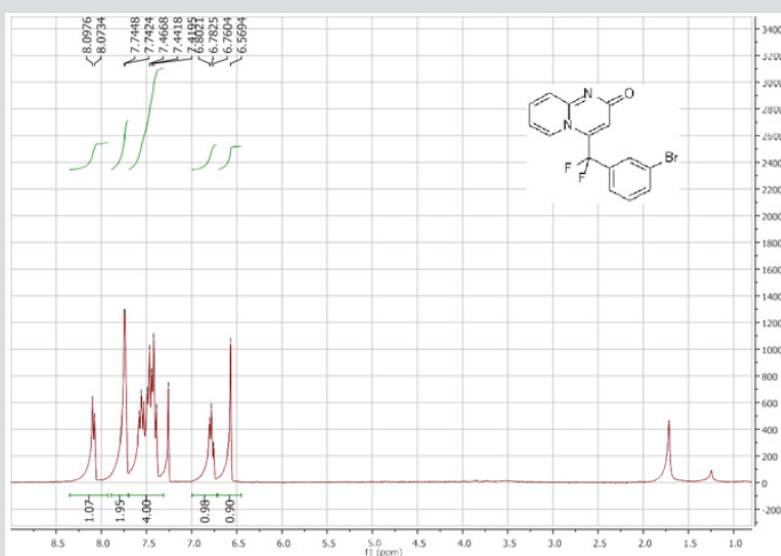
Graph 4: <sup>1</sup>H NMR (3a).



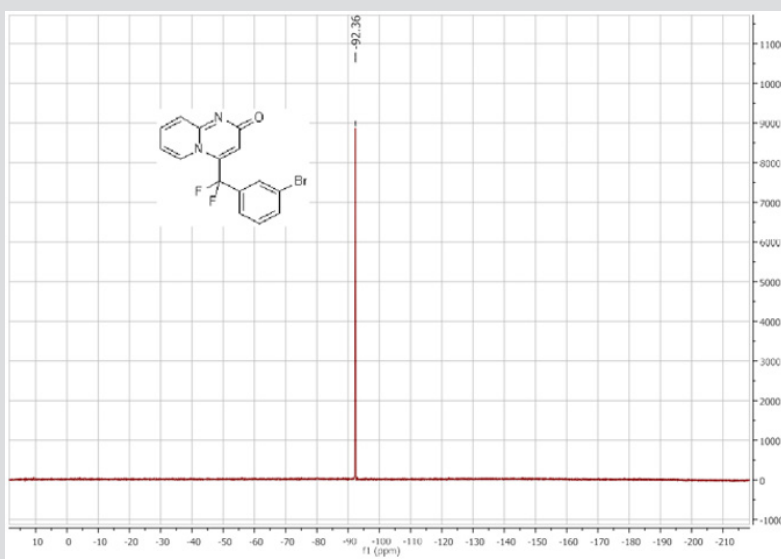
Graph 5: <sup>19</sup>F NMR (3a).



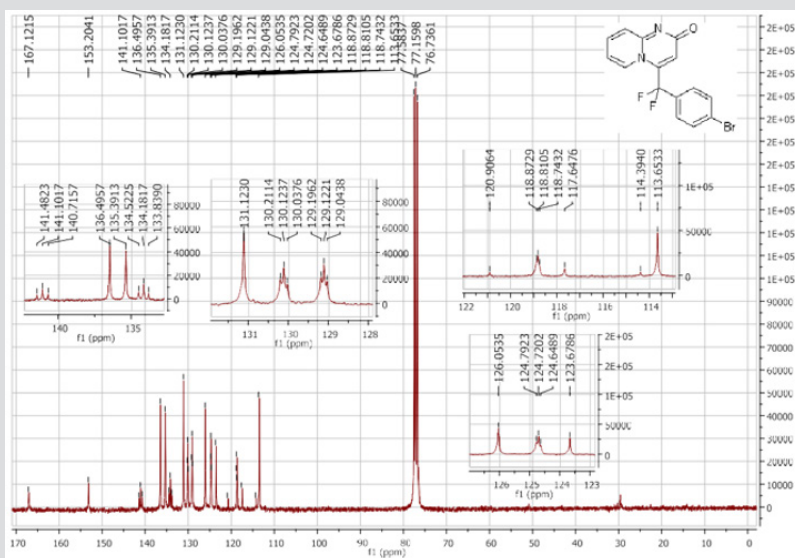
Graph 6: <sup>13</sup>C NMR (3a).



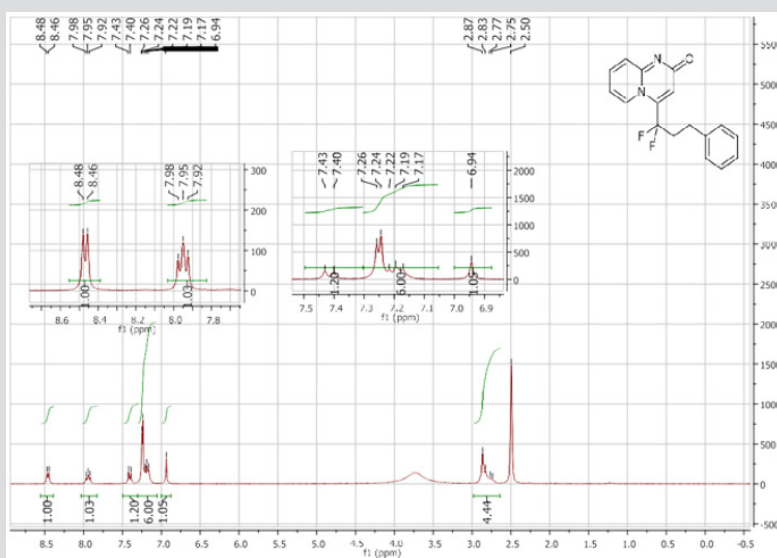
Graph 7: <sup>1</sup>H NMR (3b).



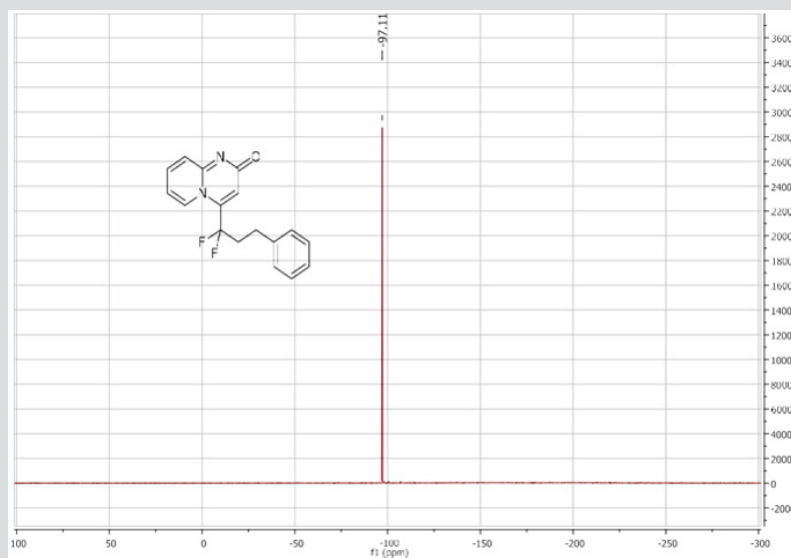
Graph 8: <sup>19</sup>F NMR (3b).



Graph 9: <sup>13</sup>C NMR (3b).

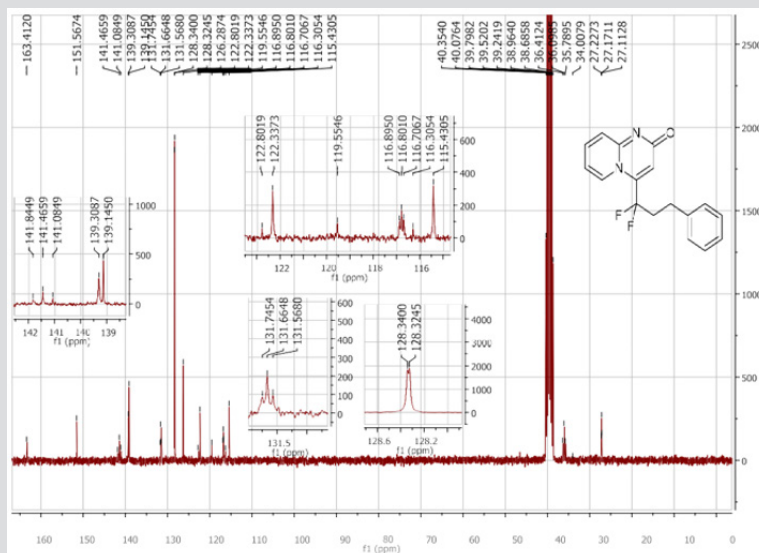


Graph 10: <sup>1</sup>H NMR (3c).

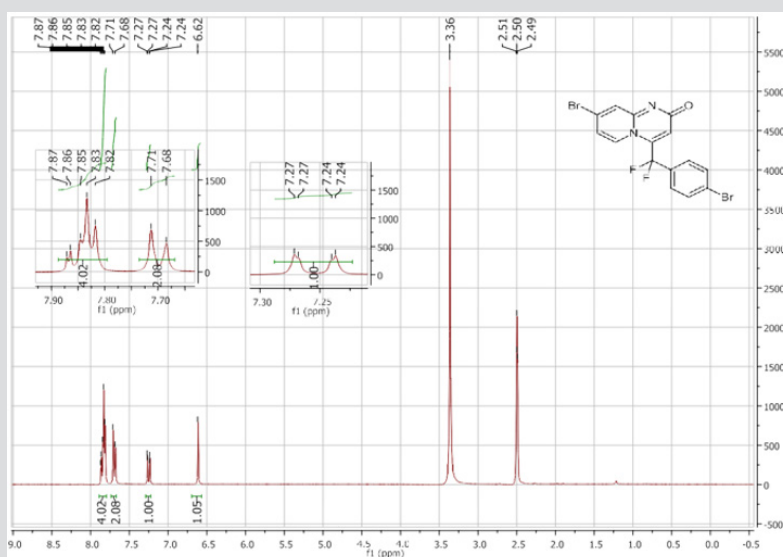


Graph 11: <sup>19</sup>F NMR (3c).

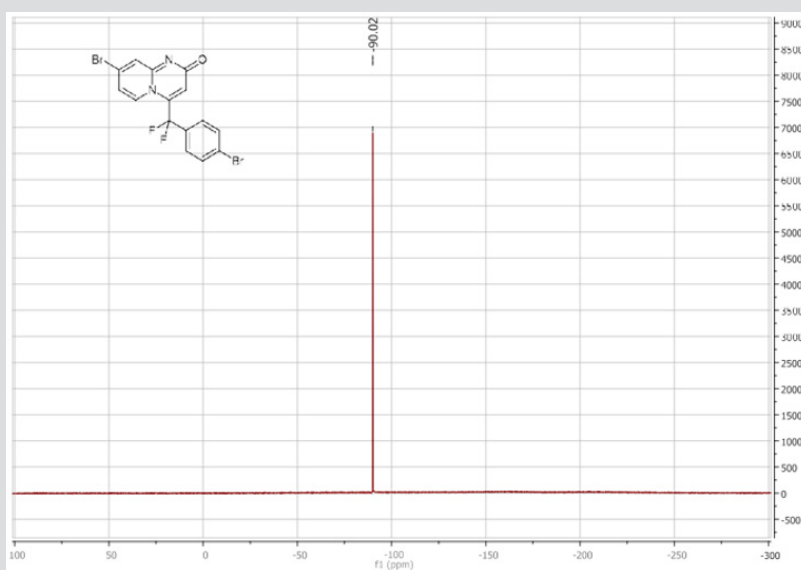




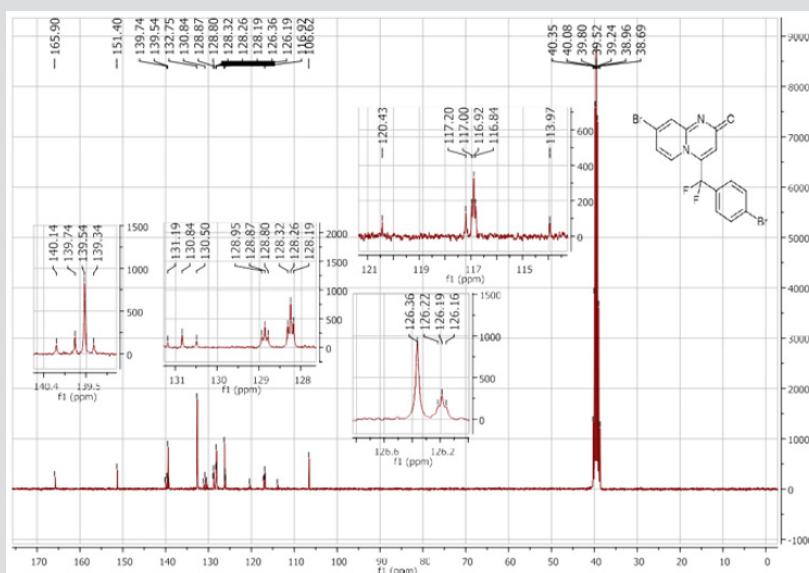
Graph 12: <sup>13</sup>C NMR (3c).



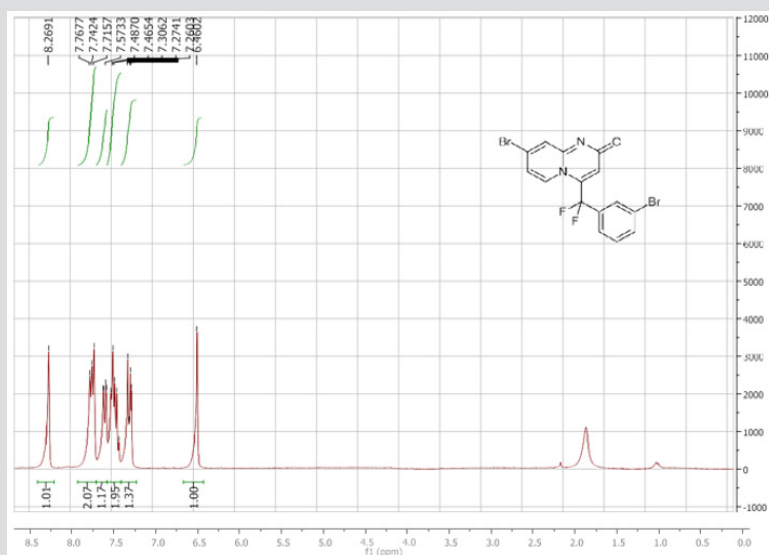
Graph 13: <sup>1</sup>H NMR (3d).



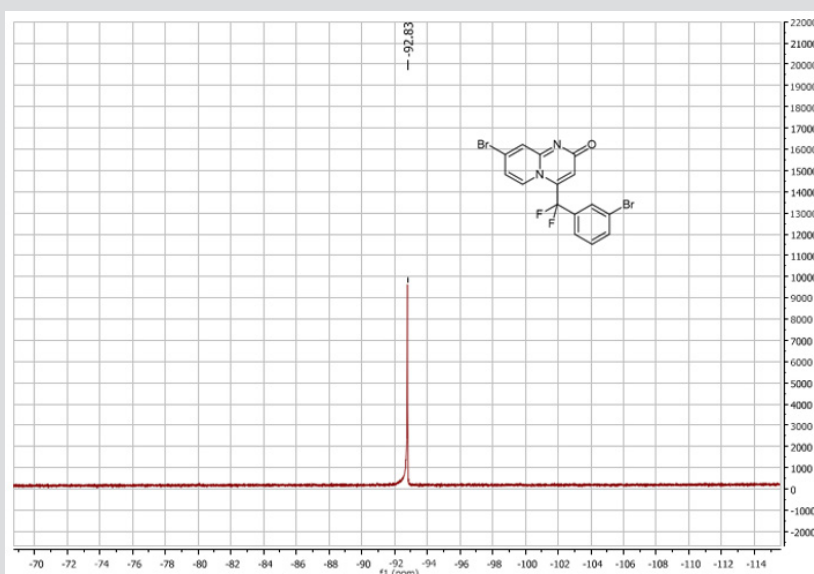
Graph 14: <sup>19</sup>F NMR (3d).



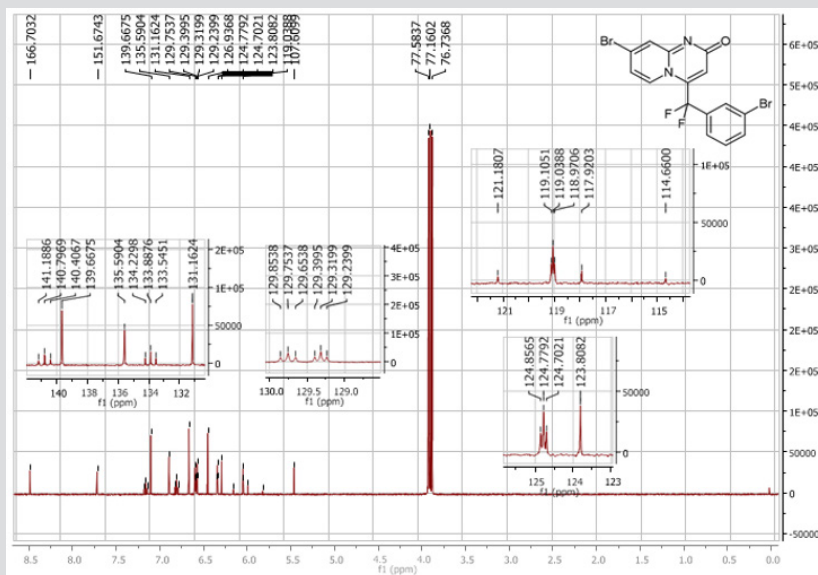
Graph 15:  $^{13}\text{C}$  NMR (3d).



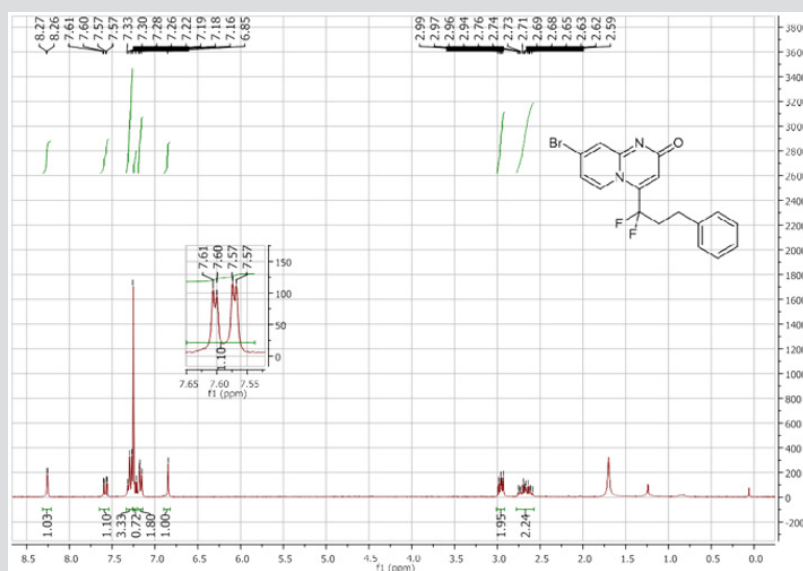
Graph 16:  $^1\text{H}$  NMR (3e).



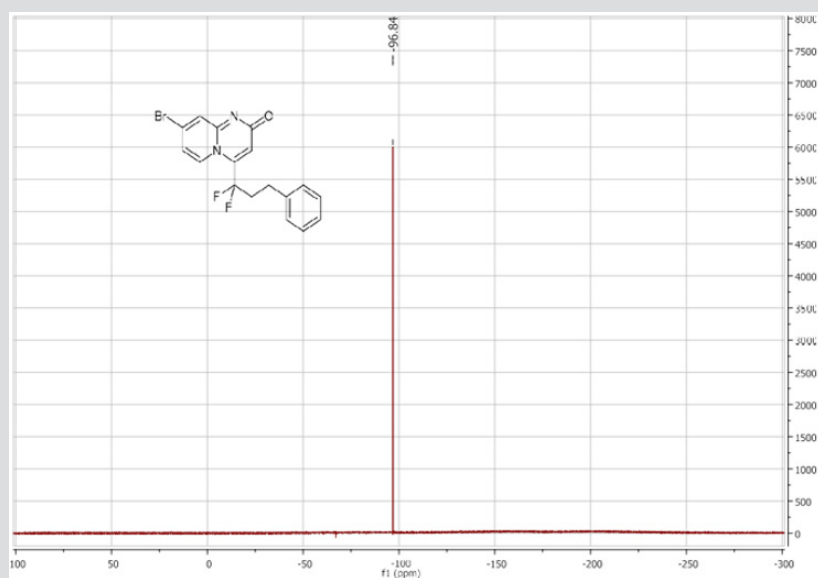
Graph 17:  $^{19}\text{F}$  NMR (3e).



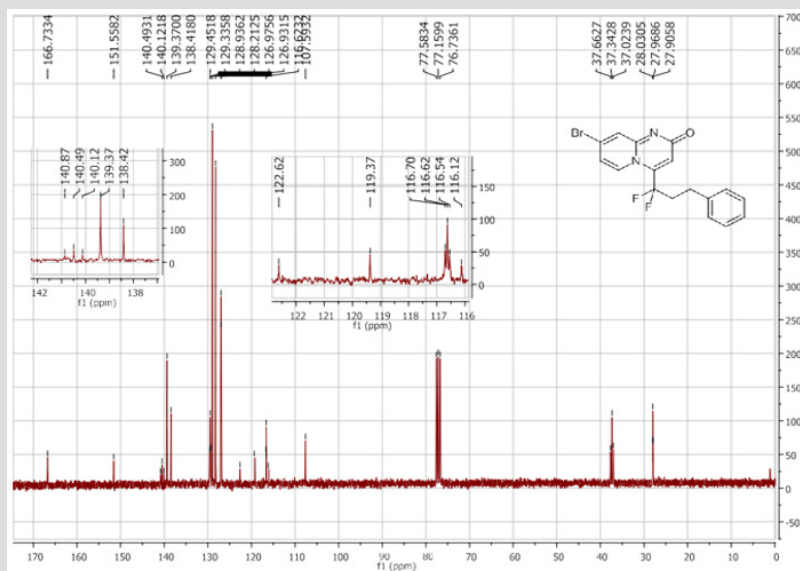
Graph 18: <sup>13</sup>C NMR (3e).



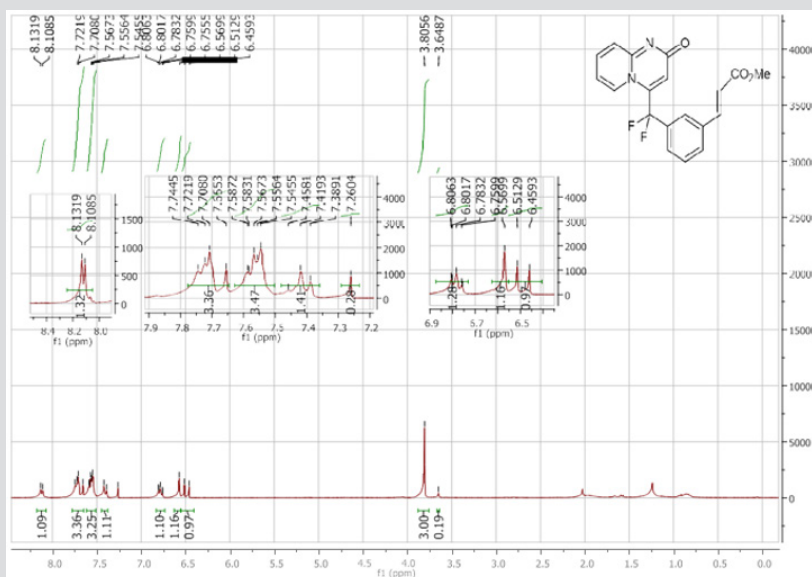
Graph 19: <sup>1</sup>H NMR (3f).



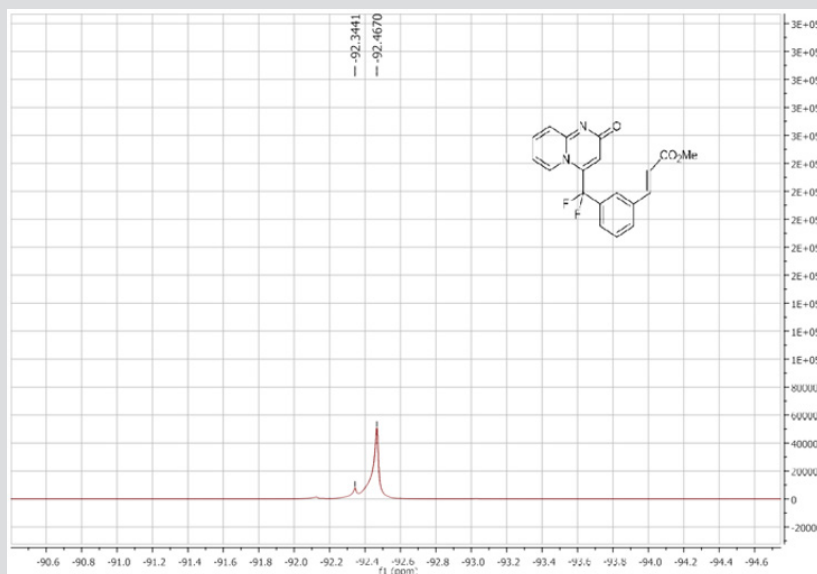
Graph 20: <sup>19</sup>F NMR (3f).



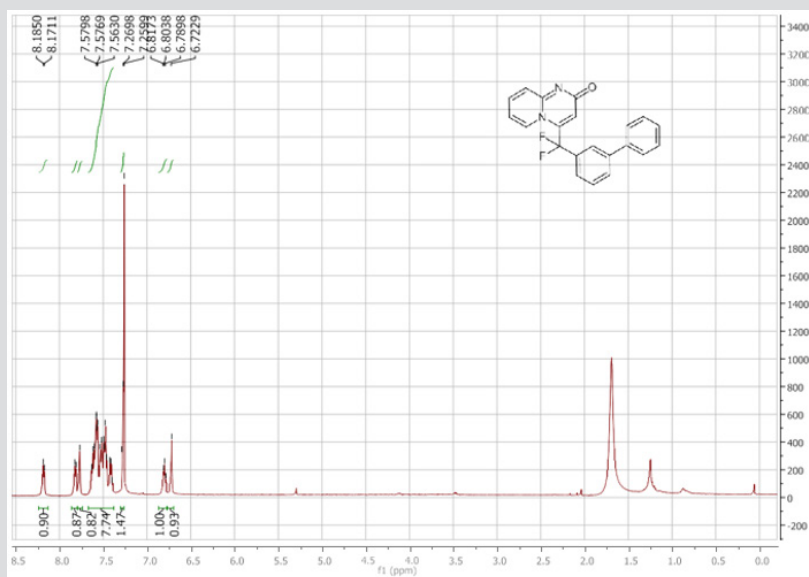
Graph 21: <sup>13</sup>C NMR (3f).



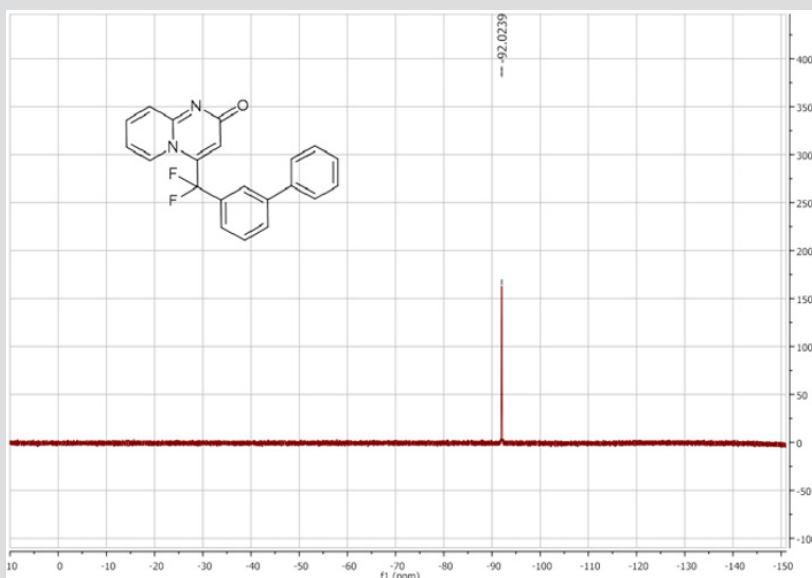
Graph 22: <sup>1</sup>H NMR (4a).



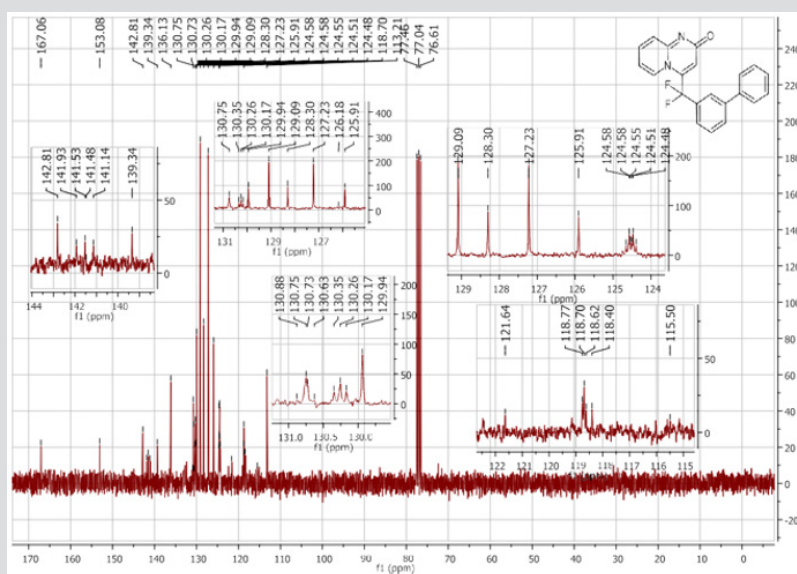
Graph 23: <sup>19</sup>F NMR (4a).



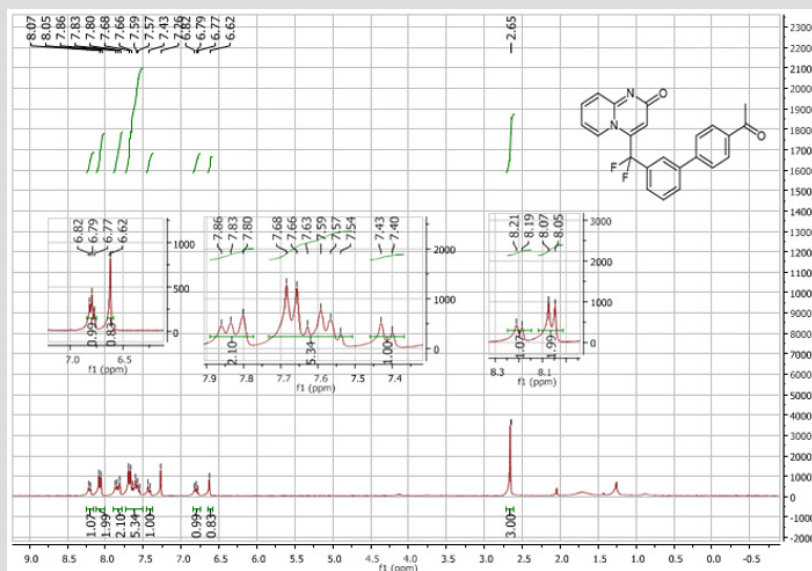
Graph 24: <sup>1</sup>H NMR (5a).



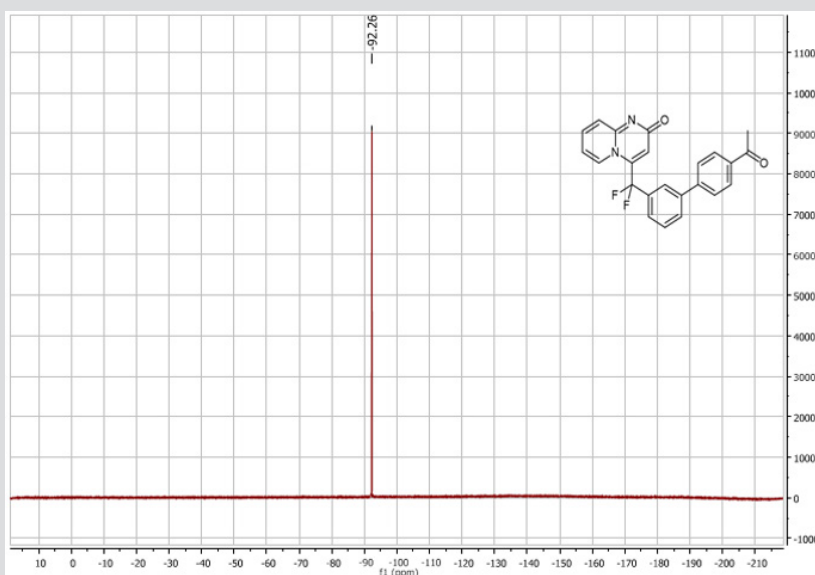
Graph 25: <sup>19</sup>F NMR (5a).



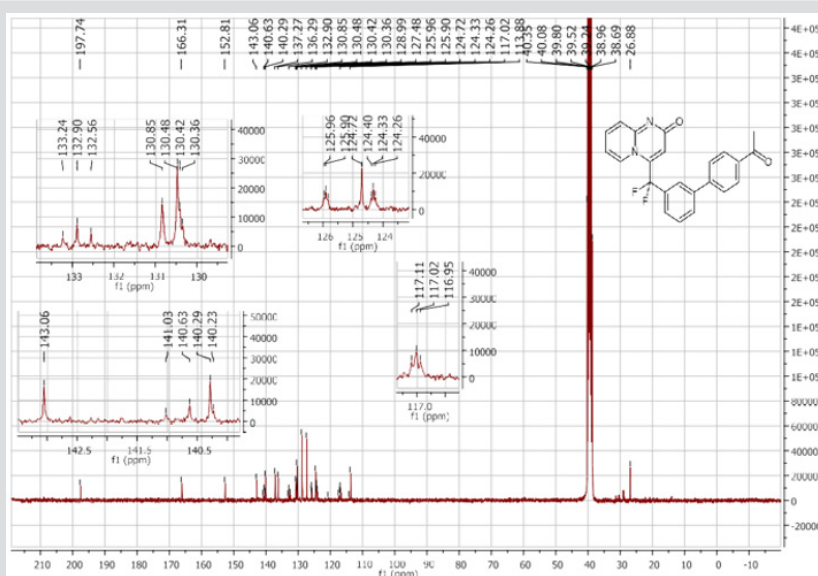
Graph 26: <sup>13</sup>C NMR (5a).



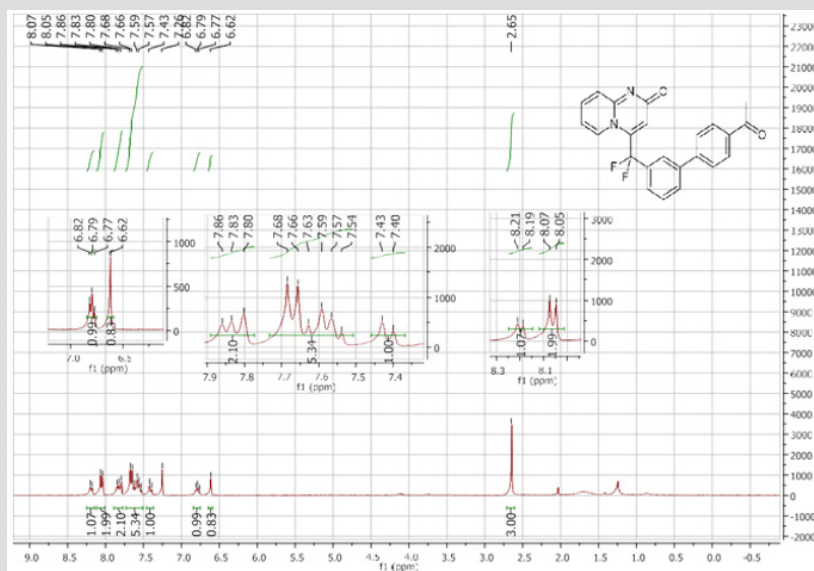
Graph 27: <sup>1</sup>H NMR (5b).



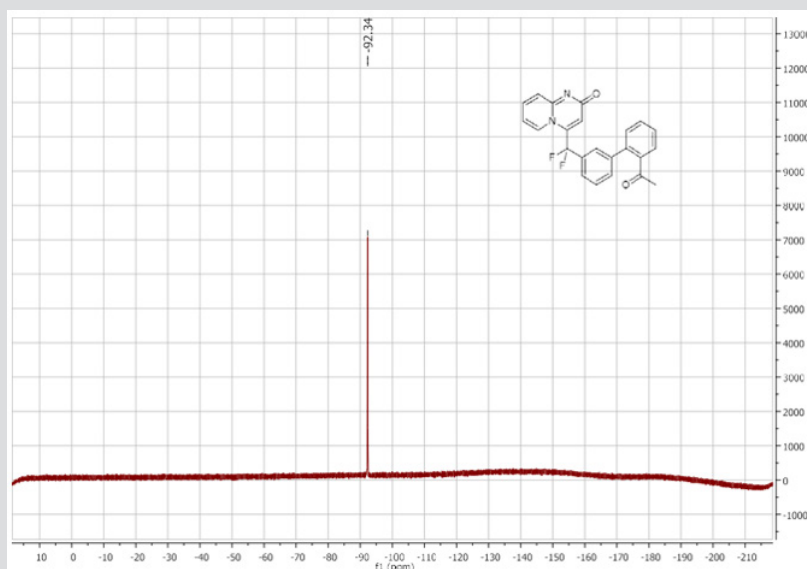
Graph 28: <sup>19</sup>F NMR (5b).



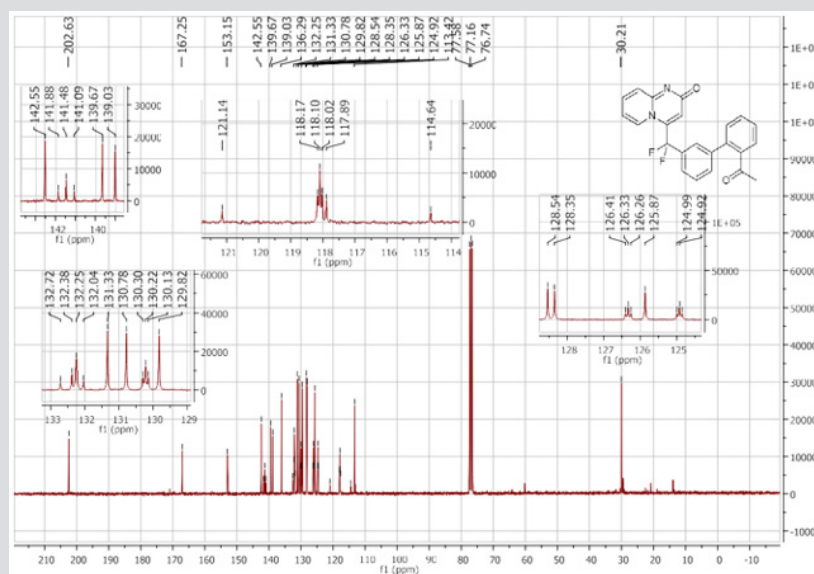
Graph 29: <sup>13</sup>C NMR (5b).



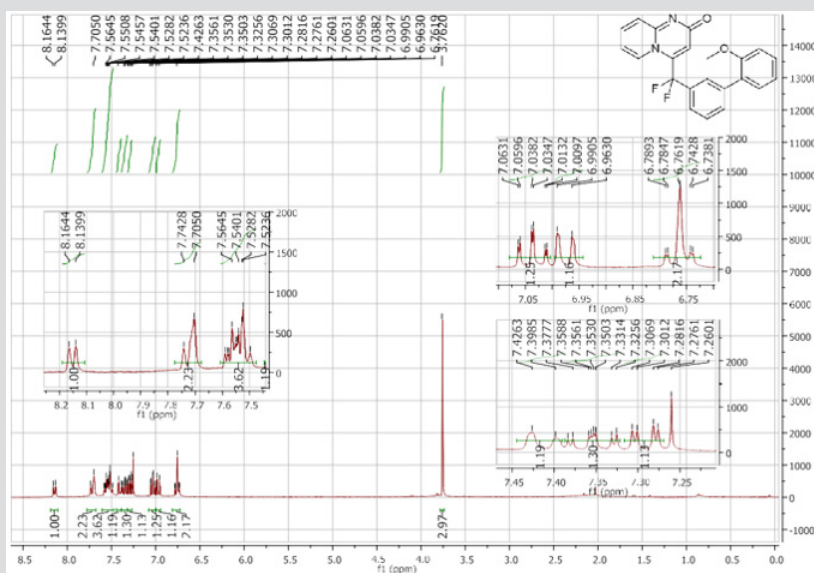
Graph 30: <sup>1</sup>H NMR (5c).



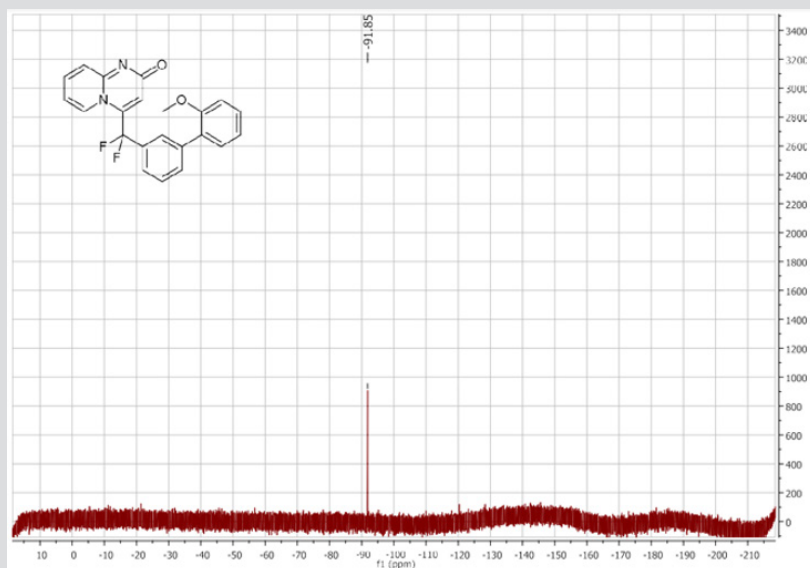
Graph 31: <sup>19</sup>F NMR (5c).



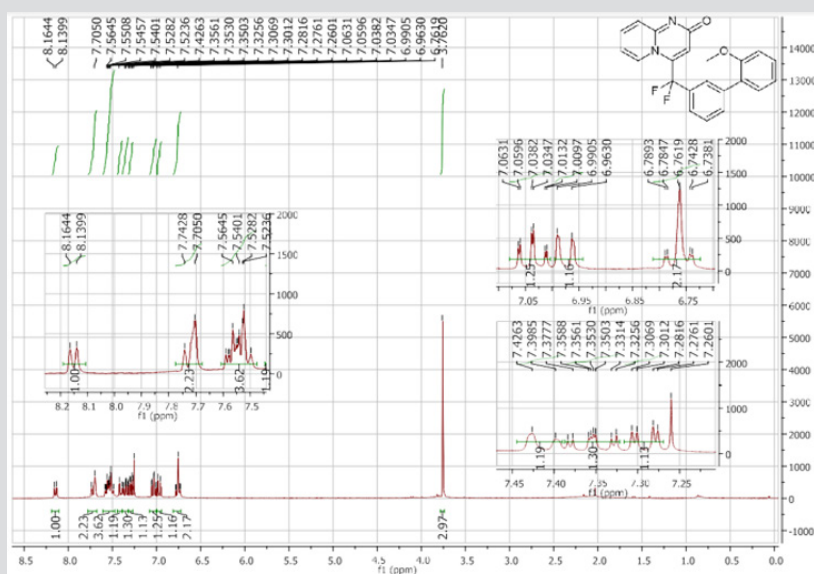
Graph 32: <sup>13</sup>C NMR (5c).



Graph 33: <sup>1</sup>H NMR (5d).

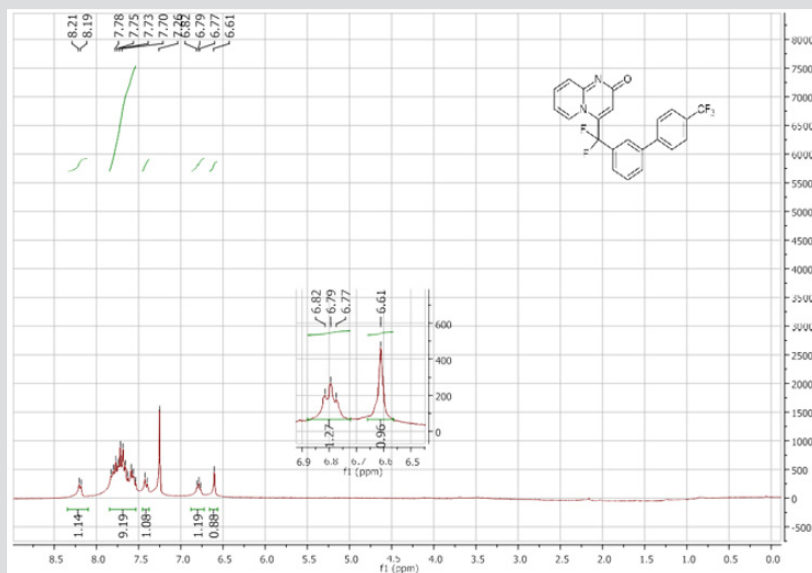


Graph 34: <sup>19</sup>F NMR (5d).

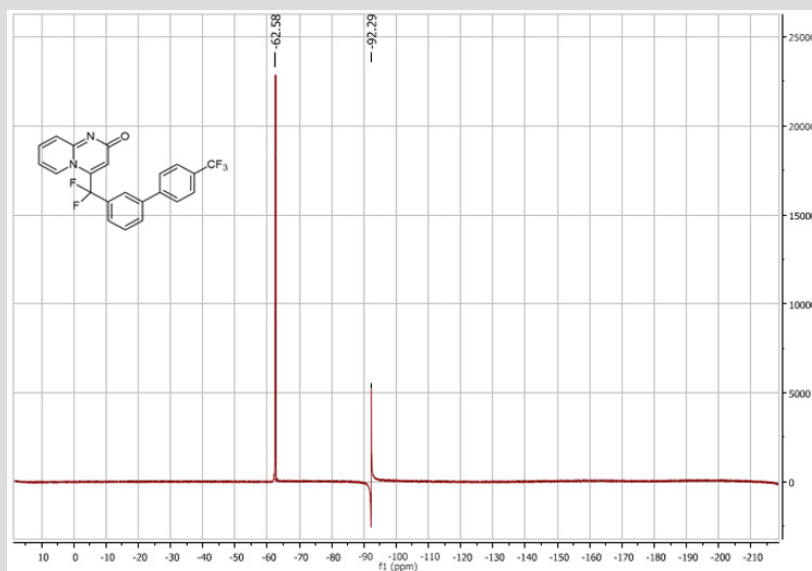


Graph 35: <sup>13</sup>C NMR (5d).

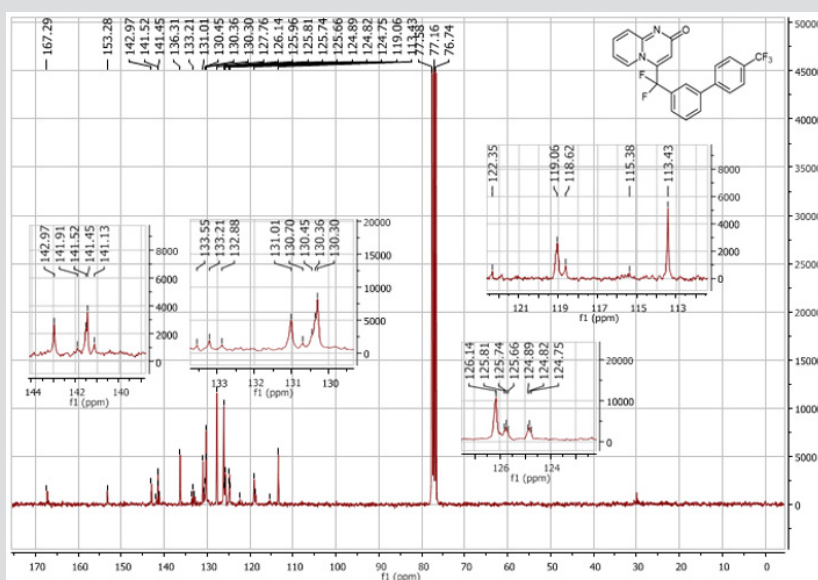




Graph 36: <sup>1</sup>H NMR (5e).



Graph 37: <sup>19</sup>F NMR (5e).



Graph 38: <sup>13</sup>C NMR (5e).

## Summary

In summary, we have provided a straightforward access to a new *gem*-difluorinated pyrido[1,2-*a*]pyrimidine-2-ones using a practical and general method. We first established a concise one-pot strategy for the synthesis of *gem*-difluorinated pyrido[1,2-*a*]pyrimidin-2-ones by condensation of 2-aminopyridines with *gem*-difluorinated methyl propiolates. These compounds were then used as building blocks to synthesize a new 4-[(3-substitutedphenyl)difluoromethyl]-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones via cross-coupling reactions. This valuable strategy is being applied to the production of a wide range of compounds that are currently under biological evaluation.

## Acknowledgment

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