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The amination of difluoro(diethoxyphosphoryl)acetyl chloride: Facile synthetic route to novel amides containing difluoromethylenephosphonate moiety

Romana Pajkert [a], Magdalena Milewska [a], Gerd-Volker Röschenthaler [b], Henryk Koroniak [a,*]

[a] Adam Mickiewicz University, Faculty of Chemistry, Grunwaldzka 6, 60-780 Poznan, Poland
[b] Institute for Inorganic and Physical Chemistry, The University of Bremen, Leobener Str, D-28334, Germany

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ABSTRACT

A convenient route for the synthesis of novel amides containing at least one β-keto-α,α-difluoromethylenephosphonate group has been elaborated. The procedure requires simple stirring of an amine and difluoro(diethoxyphosphoryl)acetyl chloride in THF in the presence of a catalytic amount of DMAP. A wide range of amines has been accepted, including aliphatic and aromatic diamines, diaminobenzidine or amine derivatives, such as Ciprofloxacin.

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1. Introduction

The phosphate moiety is one of the most popular functionality that can be found in living systems and which plays an essential role in metabolic pathways, regulation processes or in the creation of the genetic information [1]. However, in spite of its significance, this functional group easily undergoes hydrolysis in the presence of enzymes (phosphatases). On the other hand, the ubiquity of the phosphate group in various biochemical processes has stimulated intensive researches on the synthesis of various phosphate analogues in which the labile P–O bond is replaced by phosphatase resistant P–C bond [2]. One of these strategies, proposed by Blackburn and McKenna in 1981, includes the substitution of the bridging oxygen in phosphate moiety by the difluoromethylene substituent [3]. This conception has been especially attractive due to the electronic and steric similarity of the CF_2 group to the oxygen atom [4]. Indeed, the importance of α,α-difluoromethylenephosphonates as hydrolytically stable phosphate mimics and enzyme inhibitors has been already well-established giving rise to the synthesis of several analogues of natural products with enhanced biological activity [5]. For example, compounds **1** and **2** are analogues of 1,3-*bis*phosphoglyceric acid with micromolar binding affinity for yeast phosphoglycerate kinase (PGK) while compound **3** was considered as an inhibitor of aspartate transcarbamylase (ATCase)(Fig. 1) [6].

Although, despite interesting properties that could exhibit difluorinated phosphonamides **1**, **2** and **3**, there is only a limited number of synthetic pathways for the preparation of such compounds [6]. These methods often requires the use of some expensive reagents (*e.g.* benzotriazol-1-yloxy(dimethylamino)-phosphonium hexafluorophosphate) or permits to obtain products with moderate yields (50–80%). Therefore, we would like to report an easy and high-yielding route to fluorinated phosphonamides by the reaction of difluoro(diethoxyphosphoryl)acetyl chloride with various amines and amine derivatives, in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP).

2. Results and discussion

The key substrate, difluoro(diethoxyphosporyl)acetyl chloride **5**, was prepared by the treatment of difluoro(diethoxyphosphoryl)acetic acid **4** with an excess of oxalyl chloride (3 equiv.) in dry benzene (Scheme 1).

This method, which is a modification of the procedure developed by Blackburn and Burton [7], afforded **4** in excellent yield. Moreover, **5** though hydrolytically unstable, has been easily isolated without decomposition. First trap-to-trap distillation of the remaining excess of oxalyl chloride, followed by the distillation of the product *in vacuo* (0.04 mmHg) gave 98% of pure **5** as a clear, yellowish liquid. We have also observed, that produced by this

* Corresponding author.
E-mail addresses: gvr@chemie.uni-bremen.de (G.-V. Röschenthaler), koroniak@amu.edu.pl (H. Koroniak).

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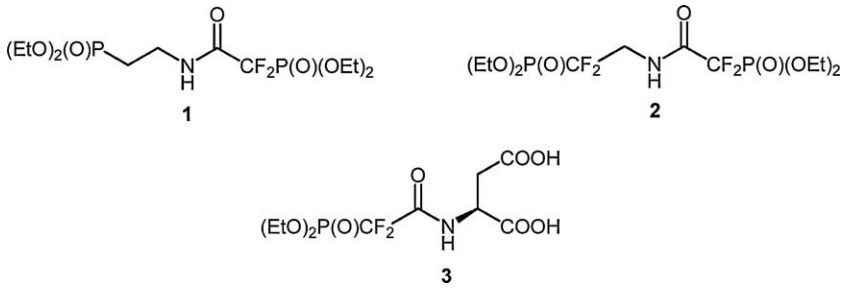
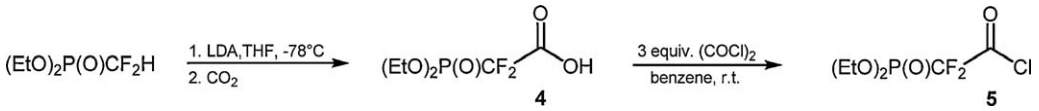
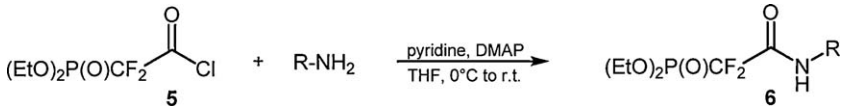


Fig. 1.



Scheme 1.



Scheme 2.

method **5**, can be stored under nitrogen in a freezer for months without any change [9].

The reactivity of difluoro(diethoxyphosphoryl)acetyl chloride **5** has been then investigated toward some simple primary amines. As shown in Scheme 2, the typical procedure was performed by adding **5** (1 equiv.) to the mixture of an appropriate amine (1 equiv.), pyridine (1 equiv.) and DMAP (5 mol%) in dry THF at 0 °C. The reaction was completed after 2 h of stirring at room temperature (the progress of the conversion was monitored by ^{19}F NMR). Subsequently, an acidic work-up and purification gave the expected products in good to excellent yield (Table 1). It should be noted, that the acylation proceeds also without the addition of DMAP but we found, that the yield of the desired products was significantly lower (up to 68%, entries **1** and **4**).

Based on the results with simple primary amines, we next explored a similar experiments to incorporate β-keto-α,α-difluorophosphonate moiety into di- and tetraamines or into amine derivatives showing interesting biological activity, such as L-aspartic acid, 2,2,4,4-tetramethylpiperidine and Ciprofloxacin®—a highly potent and orally active antibacterial agent [10]. We

Table 1
Fluorinated phosphonamides produced *via* Scheme 2.

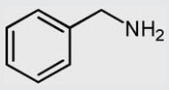
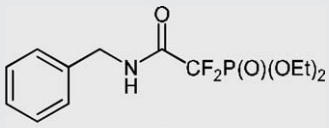
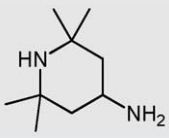
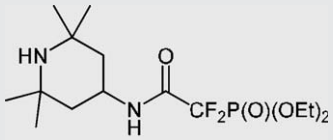
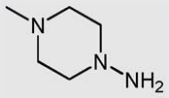
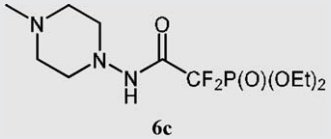
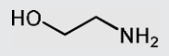
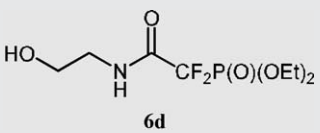
Entry	Amine	**5**	Product (**6**)	Yield (%)[a]
1		1 equiv.	 **6a**	66[b]
2		1 equiv.	 **6b**	96
3		1 equiv.	 **6c**	93
4		1 equiv.	 **6d**	68[b]

Table 1 (*Continued*)

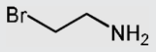
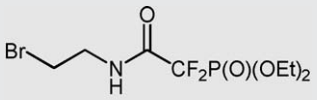
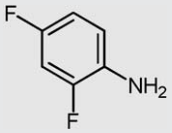
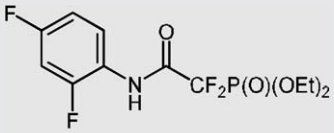
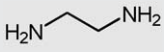
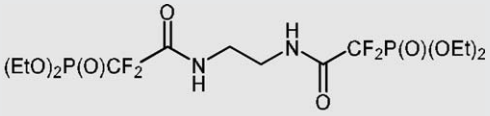
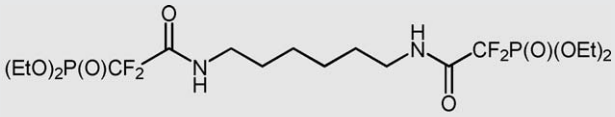
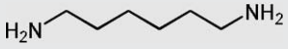
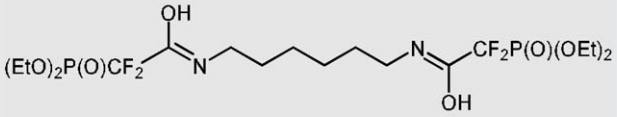
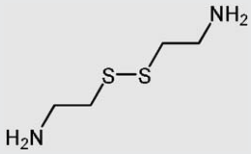
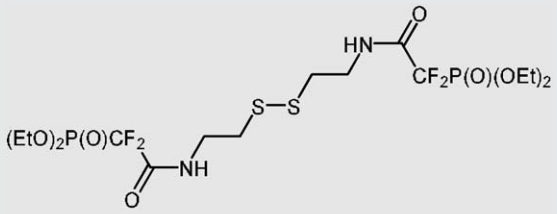
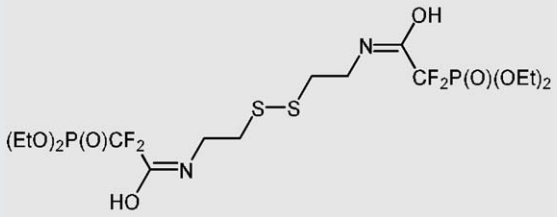
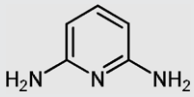
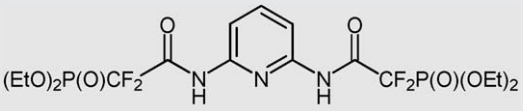
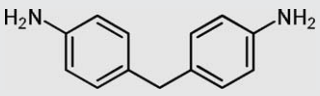
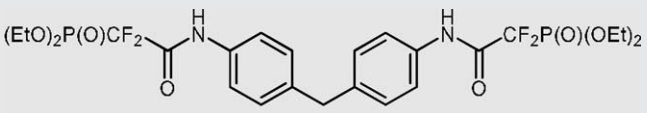
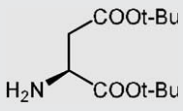
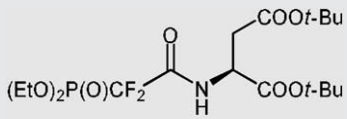
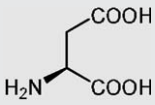
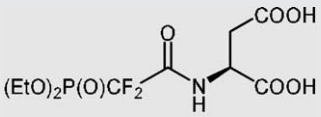
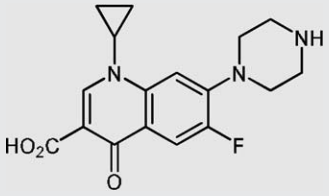
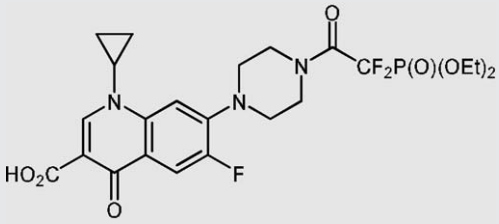
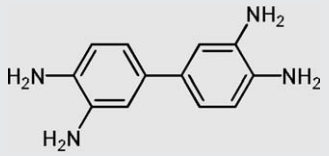
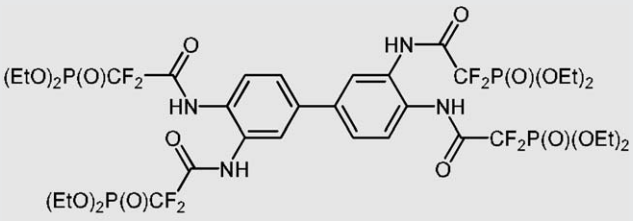
Entry	Amine	**5**	Product (**6**)	Yield (%)[a]
5		1 equiv.	 **6e**	92
6		1 equiv.	 **6f**	98
7		2 equiv.	 **6g**	97
			 **6h**	
8		2 equiv.		93
			 **7h**	
9		2 equiv.	 **6i**	93
			 **7i**	
10		2 equiv.	 **6j**	98
11		2 equiv.	 **6k**	92

Table 1 (*Continued*)

Entry	Amine	5	Product (**6**)	Yield (%)[a]
12		1 equiv.	 **6l**	96
13		1 equiv.	 **6m**	20
14		1 equiv.	 **6n**	30[c]
15		4 equiv.	 **6o**	90

[a] Isolated yields, based on the total amount of **5** used in the reaction.
[b] The reaction was conducted without addition of DMAP.
[c] The mixture of two conformers was obtained.

suppose, that the modification of these compounds by the introduction of β-keto-α,α-difluorophosphonate group, may represent a simple way in the designing of molecules with interesting biological activity.

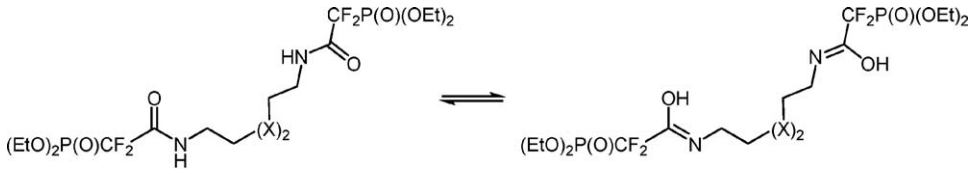
As expected, aliphatic and aromatic diamines and diaminobenzidine, when mixing with twofold excess of **5** and pyridine in the presence of DMAP, react also smoothly giving corresponding fluorinated tetraethyl diphosphonate and octaethyl tetraphosphonate in very good yields (Table 1).

We observed however, that for entries **13** and **14** the yield of the acylation decreased, which can be probably explained by the bad solubility of L-aspartic acid and Ciprofloxacin® in common organic solvents. Besides, compound **6n** has been obtained as a mixture of two structural conformers **A** and **B** (in a ratio of 70:30, as determined by ^{19}F NMR) as schematically presented at Fig. 2.

What is more, chemical shifts of difluoromethylene moieties, as well as phosphonate groups of each conformers (**A** and **B**, Fig. 2) vary, which is due to the different surrounding for each $CF_2P(O)(OEt)_2$ functionality (caused by dissimilar conformation on the piperazine ring of Ciprofloxacin®).

On the other hand, when chloride **5** was used in the acylation of 1,6-diaminohexane or cystamine (entry **8** and **9**, Table 1), acetylated products **6h**, **6i** were obtained as mixtures of amidic **6** and imidic forms **7** (ratio 50:50), which could be deduced from the tautomerism observed for this group of compounds (Scheme 3).

The presence of these two forms was detected by ^{1}H, ^{19}F and ^{31}P NMR spectra of crude products **6h** and **6i** in $CDCl_3$ at room temperature. The ratio of **6**–**7** increased with the addition of protic solvent, CD_3OD, to the solution of **6h** or **6i** in $CDCl_3$. Only the amide structure **6** was finally observed when ^{1}H, ^{19}F and ^{31}P NMR spectra were measured in CD_3OD. What is more, the purification of crude products **6h** and **6i** by column chromatography on silica gel changes the amidic/imidic equilibrium, giving pure amidic forms of **6h** and **6i** as sole products.



6h (X=CH_2)
6i (X=S)

7h (X=CH_2)
7i (X=S)

Scheme 3.

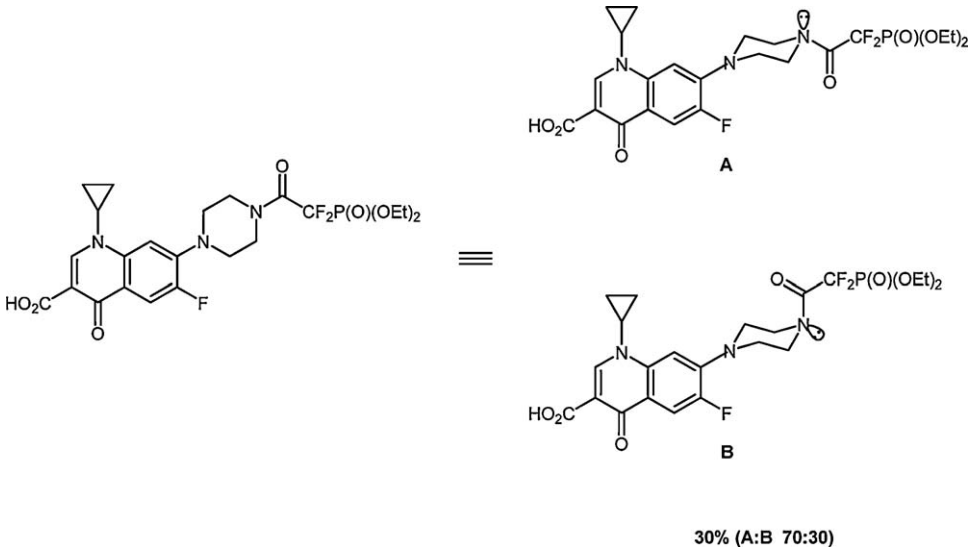


Fig. 2.

In conclusion, a simple and high-yielding procedure for the preparation and amination of difluoro(diethoxyphosphoryl)acetyl chloride with various amines under mild conditions has been accomplished. The reaction accepts a wide range of substrates, including aliphatic and aromatic amines, diamines and amine derivatives. Produced by this methodology functionalized phosphonamides are often of interest, due to their potential biological activity [6]. They can also serve as convenient precursors for the preparation of novel heterocycles containing difluoromethylenephosphonate moiety (*e.g.* oxazolines) [11] or as substrates in the synthesis of fluorinated β-amino acid derivatives [12].

3. Experimental

All reactions were carried out under an atmosphere of dry nitrogen. THF was freshly distilled from sodium benzophenone ketyl. Difluoro(diethoxyphosphoryl)acetic acid was prepared according to the procedure described by Blackburn [7], with following an aqueous acid–base work-up by Hamilton and Roberts [8]. All other reagents were distilled or recrystallized, if necessary. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM) and TLCs using Merck silica gel 60 F_{254}. Visualization was achieved by UV light or by spraying with $Ce(SO_4)_2$ solution in 5% H_2SO_4. ^1H (200.13 MHz), ^{13}C (50.32 MHz), ^{19}F (188.31 MHz) and ^{31}P NMR (80.99 MHz) have been achieved on a Bruker Avance DPX-200 spectrometer in $CDCl_3$ as a solvent. TMS was the internal standard in ^1H NMR, $CFCl_3$ was used as a reference for ^{19}F NMR and 85% H_3PO_4 in ^{31}P NMR. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. ^{31}P NMR spectra were broadband decoupled from hydrogen nuclei. Mass spectra were recorded on a Varian MAT CH7A instrument at 70 eV. Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected.

3.1. General procedure for the synthesis of difluoro(diethoxyphosphoryl)acetyl chloride (5)

The mixture of 1 equiv. (10.6 g, 45.7 mmole) of (diethoxyphosphoryl)difluoroacetic acid **4**, in dry benzene was put in the flask, equipped with magnetic stirrer, nitrogen in–out system, bubble-counter and septum. Then, 3 equiv. (17.4 g, 137 mmole) of oxalyl chloride were added dropwise at room temperature. Stirring at r.t. was continued overnight. Afterwards, all volatiles were condensed off *in vacuo*. Brown residue was distilled under reduced pressure to give 11.24 g of pure **5**, as a clear, yellowish oil. Yield: 98%; b.p. 55 °C/0.04 mmHg; ^{19}F NMR ($CDCl_3$): δ −112.3 (d, $^2J_{FP}$ 93.1 Hz); ^{31}P NMR ($CDCl_3$): δ 1.83 (t, $^2J_{PF}$ 93.6 Hz); ^1H NMR ($CDCl_3$): δ 1.40 (t, 6H, OCH_2CH_3), 4.35 (q, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 16.63 (d, $^3J_{CP}$ 5.65 Hz, OCH_2CH_3), 66.75 (d, $^2J_{CP}$ 6.70 Hz, OCH_2CH_3), 111.9 (td, $^1J_{CF}$ 278.3 Hz, $^1J_{CP}$ 204.2 Hz, CF_2), 166.3 (td, $^2J_{CF}$ 33.8 Hz, $^2J_{CP}$ 22.6 Hz, C=O).

3.2. Typical procedure for the synthesis of fluorinated phosphonamides (6)

To a stirred solution of an amine (1 equiv.) and pyridine (1 equiv. **6b–f** and **6l–n**; 2 equiv. **6g–k**; 4 equiv. **6o**) in dry THF (15 ml) at 0 °C, an appropriate amount of difluoro(diethoxyphosphoryl)acetyl chloride was added, followed by addition of DMAP (5 mol%). The resulting suspension was then stirred for 2 h at room temperature. An aqueous solution of HCl was added (pH ~ 5) and the mixture was stirred for additional 10 min. The reaction mixture was extracted three times with CH_2Cl_2, combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo*, to give crude product which was purified by flash column chromatography on silica gel (eluent: petroleum ether: ethyl acetate 1:1 or ethyl acetate). Compounds **6b**, **6j**, **6k** and **6n** were additionally recrystallized from chloroform–petroleum ether).

3.2.1. Diethyl 2-(benzylamino)-1,1-difluoro-2-oxoethylphosphonate (6a)

Yield: 66%; Yellow oil; ^{19}F NMR ($CDCl_3$): δ −118.4 (d, $^2J_{FP}$ 96.4 Hz); ^{31}P NMR ($CDCl_3$): δ 4.67 (t, $^2J_{PF}$ 96.4 Hz); ^1H NMR ($CDCl_3$): δ 1.38 (t, 6H, OCH_2CH_3), 4.31 (q, 4H, OCH_2CH_3), 4.54 (d, 2H, CH_2), 7.0 (br. s., NH), 7.31 (m, 5H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ 16.9 (d, $^3J_{CP}$ 5.65 Hz, OCH_2CH_3), 44.2 (s, CH_2), 66.3 (d, $^2J_{CP}$ 6.70 Hz, OCH_2CH_3), 112.7 (td, $^1J_{CF}$ 271.6 Hz, $^1J_{CP}$ 200.9 Hz, CF_2), 128.2 (s, C_{Ar}), 129.3 (s, C_{Ar}), 129.4 (s, C_{Ar}), 137.5 (s, C_{Ar}), 162.0 (td, $^2J_{CF}$ 24.3 Hz, $^2J_{CP}$ 16.9 Hz, C=O); MS (EI) m/z (%): 321 $[M]^{+\bullet}$ (25), 187 $[M-C_7H_7NHCO]^+$ (10), 106 $[M-C(O)CF_2P(O)(OEt)_2]^+$ (88), 91 $[C_7H_7]^+$(100).

3.2.2. Diethyl 1,1-difluoro-2-oxo-2-(2,2,6,6,-tetramethylpiperidin-4-ylamino) ethylphosphonate (6b)

Yield: 96%; yellowish crystals; m.p. 104–109 °C; ^{19}F NMR ($CDCl_3$): δ −118.2 (d, $^2J_{FP}$ 96.5 Hz); ^{31}P NMR ($CDCl_3$): δ 4.92 (td, $^2J_{PF}$ 96.2 Hz); ^1H NMR ($CDCl_3$): δ 1.02 (t, 2H, CH_2), 1.12 (s, 6H, CH_3), 1.23 (br. s., 1H, NH), 1.25 (s, 6H, CH_3), 1.39 (t, 6H, OCH_2CH_3), 1.91 (dd,

2H, CH_2), 4.29 (m, 1H, C*H*), 4.32 (q, 4H, OCH_2CH$_3$), 8.36 (br. d., 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 16.8 (d, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 28.9 (s, *C*H$_3$), 35.3 (s, *C*H), 44.1 (s, *C*H$_2$), 44.9 (s, *C*H$_2$), 51.5 (s, *C*-CH$_3$), 66.0 (d, $^2J_{CP}$ 6.70 Hz, O*C*H$_2$CH$_3$), 112.3 (td, *C*F$_2$, $^1J_{CF}$ 273.3 Hz, $^1J_{CP}$ 273.3 Hz), 160.9 (td, $^2J_{CF}$ 24.4 Hz, $^2J_{CP}$ 16.9 Hz, *C* = O); MS (EI) *m*/*z* (%): 370 [M]$^{+\bullet}$ (2), 355 [M−CH$_3$]$^+$ (33), 124 [M−C$_6$H$_{12}$NO$_4$PF$_2$]$^+$ (100); HRMS: Calculated for $C_{15}H_{29}N_2O_4PF_2$ ($M^{+\bullet}$) 370. 18330, found 370.18458.

3.2.3. Diethyl 1,1-difluoro-2-(4-methylpiperazin-1-ylamino)-2-oxoethylphosphonate(6c)

Yield: 98%; yellowish oil; ^{19}F NMR ($CDCl_3$): δ −118.6 (d, $^2J_{FP}$ 96.5 Hz); ^{31}P NMR ($CDCl_3$): δ 4.28 (t, $^2J_{PF}$ 96.2 Hz); ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 6H, OCH$_2$C*H*$_3$), 2.27 (s, 3H, C*H*$_3$), 2.57 (t, 4H, C*H*$_2$), 2.91 (t, 4H, C*H*$_2$), 4.30 (q, 4H, OC*H*$_2$CH$_3$), 7.65 (br. s., 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 16.8 (d, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 45.8 (s, *C*H$_3$), 49.5 (s, *C*H$_2$), 60.9 (s, *C*H$_2$), 66.0 (d, $^2J_{CP}$ 6.70 Hz, O*C*H$_2$CH$_3$), 112.3 (td, *C*F$_2$, $^1J_{CF}$ 273.3 Hz, $^1J_{CP}$ 273.3 Hz), 160.9 (td, $^2J_{CF}$ 24.4 Hz, $^2J_{CP}$ 16.9 Hz, *C* = O); MS (EI) *m*/*z* (%): 329 [M]$^{+\bullet}$ (5), 314 [M−CH$_3$]$^+$ (33), 142 [M−CF$_2$P(O)(OEt)$_2$]$^+$ (100).

3.2.4. Diethyl 1,1-difluoro-2-(hydroxyethylamino)-2-oxoethylphosphonate (6d)

Yield: 68%; colorless oil; ^{19}F NMR ($CDCl_3$): δ −118.9 (d, $^2J_{FP}$ 96.6 Hz); ^{31}P NMR ($CDCl_3$): δ 4.69 (t, $^2J_{PF}$ 96.5 Hz); ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 6H, OCH$_2$C*H*$_3$), 3.46 (t, 2H, C*H*$_2$), 3.50 (br. s., O*H*), 3.70 (t, 2H, C*H*$_2$), 4.31 (q, 4H, OC*H*$_2$CH$_3$), 7.52 (br. s., 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 16.7 (d, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 42.8 (s, *C*H$_2$), 60.9 (s, *C*H$_2$), 66.3 (d, $^2J_{CP}$ 6.70 Hz, O*C*H$_2$CH$_3$), 112.5 (td, *C*F$_2$, $^1J_{CF}$ 273.3 Hz, $^1J_{CP}$ 273.3 Hz), 162.3 (td, $^2J_{CF}$ 24.4 Hz, $^2J_{CP}$ 16.9 Hz, *C*═O); MS (EI) *m*/*z* (%): 257 [M−H$_2$O]$^{+\bullet}$ (2), 187 [257−C$_3$H$_4$NO]$^+$ (100).

3.2.5. Diethyl 2-(2-bromoethylamino)-1,1-difluoro-2-oxoethylphosphonate (6e)

Yield: 92%; colorless oil; ^{19}F NMR ($CDCl_3$): δ −118.5 (d, $^2J_{FP}$ 97.0 Hz); ^{31}P NMR ($CDCl_3$): δ 4.44 (t, $^2J_{PF}$ 98.8 Hz); ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 6H, OCH$_2$C*H*$_3$), 3.42 (t, 2H, C*H*$_2$), 3.68 (t, 2H, C*H*$_2$), 4.28 (q, 4H, OC*H*$_2$CH$_3$), 7.55 (br. s., 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 16.7 (d, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 30.8 (s, *C*H$_2$), 41.8 (s, *C*H$_2$), 66.2 (d, $^2J_{CP}$ 6.70 Hz, O*C*H$_2$CH$_3$), 112.2 (td, *C*F$_2$, $^1J_{CF}$ 272.3 Hz, $^1J_{CP}$ 201.1 Hz), 162.0 (td, $^2J_{CF}$ 24.4 Hz, $^2J_{CP}$ 16.9 Hz, *C*═O); MS (EI) *m*/*z* (%): 337 [M+H]$^{+\bullet}$ (6), 188 [338−C$_3$H$_5$NOBr]$^+$ (100).

3.2.6. Diethyl 2-(2,4-difluorophenylamino)-1,1-difluoro-2-oxoethylphosphonate (6f)

Yield: 98%; colorless oil; ^{19}F NMR ($CDCl_3$): δ −116.7 (m, 1F), −118.4 (d, 2F, $^2J_{FP}$ 95.6 Hz), −136.4 (m, 1F); ^{31}P NMR ($CDCl_3$); δ 4.58 (t, $^2J_{PF}$ 96.0); ^{1}H NMR ($CDCl_3$): δ 1.39 (dt, 6H, OCH$_2$C*H*$_3$), 4.36 (m, 4H, OC*H*$_2$CH$_3$), 6.81 (m, 1H, H_{Ar}), 7.06 (m, 1H, H_{Ar}), 8.07 (m, 1H, H_{Ar}), 8.65 (br. s., 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 16.9 (d, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 66.7 (d, $^2J_{CP}$ 6.70 Hz, O*C*H$_2$CH$_3$), 109.9 (dd, J_{CF} 30.9 Hz, J_{CF} 0.9 Hz, C_{Ar}), 112.7 (dd, J_{CF} 24.5 Hz, J_{CF} 10.3 Hz, C_{Ar}), 112.9 (td, *C*F$_2$, $^1J_{CF}$ 272.9 Hz, $^1J_{CP}$ 200.4 Hz), 116.4 (dd, J_{CF} 21.6 Hz, J_{CF} 9.5 Hz, C_{Ar}), 126.0 (t, J_{CF} 12.4 Hz, C_{Ar}), 149.5 (dd, J_{CF} 241.4 Hz, J_{CF} 3.1 Hz, C_{Ar}), 159.1 (dd, J_{CF} 242.4 Hz, J_{CF} 2.5 Hz, C_{Ar}), 159.8 (td, $^2J_{CF}$ 25.1 Hz, $^2J_{CP}$ 17.9 Hz, *C* = O); MS (EI) *m*/*z* (%): 343 [M]$^{+\bullet}$ (27), 188 [M−C$_7$H$_4$F$_2$NO]$^+$, 161 [188−CO]$^+$, 132 (100), 84 (83); HRMS: Calculated for $C_{12}H_{14}NO_4PF_4$ ($M^{+\bullet}$) 343.05966, found 343.06065.

3.2.7. Tetraethyl 2,2′-(ethane-1,2-diylbis(azanediyl)bis(1,1-difluoro-2-oxoethane-2,1-diyl)diphosphonate (6g)

Yield: 97%; white crystals; ^{19}F NMR ($CDCl_3$): δ −120.5 (d, $^2J_{FP}$ 95.9 Hz); ^{31}P NMR ($CDCl_3$): δ 5.19 (t, $^2J_{PF}$ 95.6 Hz); ^{1}H NMR ($CDCl_3$): δ 1.40 (dt, 12H, OCH$_2$C*H*$_3$), 3.51 (t, 4H, C*H*$_2$), 4.34 (q, 8H, OC*H*$_2$CH$_3$), 7.85 (br. s., 2H, N*H*); ^{13}C NMR ($CDCl_3$): δ 16.7 (d, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 39.0 (s, *C*H$_2$), 66.3 (d, $^2J_{CP}$ 6.70 Hz, O*C*H$_2$CH$_3$), 112.7 (td, *C*F$_2$, $^1J_{CF}$ 273.3 Hz, $^1J_{CP}$ 273.3 Hz), 162.9 (td, $^2J_{CF}$ 24.4 Hz, $^2J_{CP}$ 16.9 Hz, *C*═O); MS (EI) *m*/*z* (%): 488 [M]$^{+\bullet}$ (28), 301 [M−CF$_2$P(O)(OEt)$_2$]$^+$, 245 [301−CH$_2$NHCO]$^+$ (100).

3.2.8. Tetraethyl 2,2′-(hexane-1,6-diylbis(azanediyl)bis(1,1-difluoro-2-oxoethane-2,1-diyl)diphosphonate (6h)

Yield: 93%; yellowish oil; ^{19}F NMR ($CDCl_3$): δ −117.9 (d, 2F, $^2J_{FP}$ 98.1 Hz); ^{31}P NMR ($CDCl_3$): δ 4.21 (t, 1P, $^2J_{PF}$ 97.1 Hz); ^{1}H NMR ($CDCl_3$): δ 1.30 (m, 2H, CH_2), 1.34 (t, 12H, OCH$_2$C*H*$_3$), 1.52 (t, 4H, CH_2), 3.27 (dd, 4H, CH_2), 4.28 (q, 8H, OCH_2CH$_3$), 8.63 (br. s., 2H, N*H*); ^{13}C NMR ($CDCl_3$): δ 16.9 (t, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 26.4 (s, *C*H$_2$), 29.1 (s, *C*H$_2$), 40.1 (s, *C*H$_2$), 66.5 (t, $^2J_{CP}$ 6.70 Hz, O*C*H$_2$CH$_3$), 112.6 (td, *C*F$_2$, $^1J_{CF}$ 272.8 Hz, $^1J_{CP}$ 202.2 Hz), 176.8 (td, $^2J_{CF}$ 19.8 Hz, $^2J_{CP}$ 16.8 Hz, *C*═O); MS (EI) *m*/*z* (%): 544 [M]$^{+\bullet}$ (10), 357 [M−CF$_2$P(O)(OEt)$_2$]$^+$ (98), 188 (81), 132 (100).

Imidic form (**7h**): ^{19}F NMR ($CDCl_3$): δ −118.7 (d, 2F, $^2J_{FP}$ 97.4 Hz), ^{31}P NMR ($CDCl_3$): δ 4.62 (t, 1P, $^2J_{PF}$ 97.5 Hz), ^{1}H NMR ($CDCl_3$): δ 1.30 (m, 2H, CH_2), 1.34 (t, 12H, OCH$_2$C*H*$_3$), 1.52 (t, 4H, CH_2), 3.27 (dd, 4H, CH_2), 4.28 (q, 8H, OCH_2CH$_3$), 7.30 (br. t., 2H, O*H*); ^{13}C NMR ($CDCl_3$): δ 16.9 (t, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 26.4 (s, *C*H$_2$), 29.1 (s, *C*H$_2$), 40.1 (s, *C*H$_2$), 66.5 (t, $^2J_{CP}$ 6.70 Hz, O*C*H$_2$CH$_3$), 112.6 (td, *C*F$_2$, $^1J_{CF}$ 272.8 Hz, $^1J_{CP}$ 202.2 Hz), 178.4 (td, $^2J_{CF}$ 19.8 Hz, $^2J_{CP}$ 16.8 Hz, *C*═O).

3.2.9. Tetraethyl 2,2′-(2,2′-disulfanediylbis(ethane-2,1-diyl)bis(azanediyl)bis(1,1-difluoro-2-oxoethane-2,1-diyl)diphosphonate (6i)

Yield: 93%; colorless oil; ^{19}F NMR ($CDCl_3$): δ −117.9 (d, 2F, $^2J_{FP}$ 97.7 Hz); ^{31}P NMR ($CDCl_3$): δ 4.26 (t, 1P, $^2J_{PF}$ 97.5 Hz); ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 12H, OCH$_2$C*H*$_3$), 2.89 (t, 4H, C*H*$_2$), 3.65 (dd, 4H, C*H*$_2$), 4.33 (q, 8H, OC*H*$_2$CH$_3$), 7.49 (br. t., 2H, N*H*); ^{13}C NMR ($CDCl_3$): 16.8 (d, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 37.3 (s, *C*H$_2$), 39.0 (s, *C*H$_2$), 66.1 (d, $^2J_{CP}$ 6.70 Hz, OCH$_2$CH$_3$), 112.4 (td, *C*F$_2$, $^1J_{CF}$ 272.7 Hz, $^1J_{CP}$ 201.3 Hz), 162.1 (td, $^2J_{CF}$ 24.3 Hz, $^2J_{CP}$ 17.0 Hz, *C*═O); MS (EI) *m*/*z* (%): 580 [M]$^{+\bullet}$ (15), 290 [M−SC$_2$H$_4$NHCOCF$_2$P(O)(OEt)$_2$]$^+$ (93), 258 [290−S]$^+$ (100).

Imidic form (**7i**): ^{19}F NMR ($CDCl_3$): δ −118.5 (d, 2F, $^2J_{FP}$ 97.2 Hz),); ^{31}P NMR ($CDCl_3$): 4.39 (t, 1P, $^2J_{PF}$ 97.9 Hz); ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 12H, OCH$_2$C*H*$_3$), 2.89 (t, 4H, C*H*$_2$), 3.65 (dd, 4H, C*H*$_2$), 4.33 (q, 8H, OC*H*$_2$CH$_3$), 7.64 (br. t., 2H, O*H*); ^{13}C NMR ($CDCl_3$): 16.8 (d, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 37.3 (s, *C*H$_2$), 39.0 (s, *C*H$_2$), 66.1 (d, $^2J_{CP}$ 6.70 Hz, OCH$_2$CH$_3$), 112.4 (td, *C*F$_2$, $^1J_{CF}$ 272.7 Hz, $^1J_{CP}$ 201.3 Hz), 162.1 (td, $^2J_{CF}$ 24.3 Hz, $^2J_{CP}$ 17.0 Hz, *C*═O).

3.2.10. Tetraethyl 2,2′-(pyridine-2,6-diylbis(azanediyl)bis(1,1-difluoro-2-oxoethane-2,1-diyl)diphosphonate (6j)

Yield: 98%; colorless crystals; m.p. 109–110 °C; ^{19}F NMR ($CDCl_3$): δ −118.5 (d, $^2J_{FP}$ 95.2 Hz); ^{31}P NMR ($CDCl_3$): δ 4.32 (t, $^2J_{PF}$ 95.4 Hz); ^{1}H NMR ($CDCl_3$): δ 1.42 (dt, 12H, OCH$_2$C*H*$_3$), 4.38 (q, 8H, OC*H*$_2$CH$_3$), 7.78 (dd, 1H, H_{Ar}), 7.96 (d, 2H, H_{Ar}), 8.86 (br. s., 2H, N*H*); ^{13}C NMR ($CDCl_3$): δ 16.8 (d, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 66.4 (d, $^2J_{CP}$ 6.70 Hz, O*C*H$_2$CH$_3$), 112.1 (td, *C*F$_2$, $^1J_{CF}$ 273.8 Hz, $^1J_{CP}$ 200.6 Hz), 114.0 (s, C_{Ar}), 141.6 (s, C_{Ar}), 148.5 (s, C_{Ar}), 160.1 (td, $^2J_{CF}$ 25.0 Hz, $^2J_{CP}$ 17.7 Hz, *C*═O); MS (EI) *m*/*z* (%): 537 [M]$^{+\bullet}$ (5), 492 [M−OEt]$^+$ (51), 350 [M−CF$_2$P(O)(OEt)$_2$]$^+$ (100), 322 [350−CO]$^+$ (14); HRMS: Calculated for $C_{17}H_{24}N_3O_8P_2F_4$ ([M−H]$^+$) 536.09748, found 536.09797.

3.2.11. Tetraethyl 2,2′-(4,4′-methylenebis(4,1-phenylene)bis(azanediyl)bis(1,1-difluoro-2-oxoethane-2,1-diyl)diphosphonate (6k)

Yield: 90%; white crystals; m.p. 112–114 °C; ^{19}F NMR ($CDCl_3$): δ −118.0 (d, $^2J_{FP}$ 96.5 Hz); ^{31}P NMR ($CDCl_3$): δ 4.79 (t, $^2J_{PF}$ 96.5 Hz); ^{1}H NMR ($CDCl_3$): δ 1.41 (t, 12H, OCH$_2$C*H*$_3$), 3.94 (s, 2H, C*H*$_2$), 4.37 (q, 8H, OC*H*$_2$CH$_3$), 7.14 (d, 4H, H_{Ar}), 7.50 (d, 4H, H_{Ar}), 8.45 (br. s., 2H, N*H*); ^{13}C NMR ($CDCl_3$): δ 16.7 (d, $^3J_{CP}$ 5.65 Hz, OCH$_2$*C*H$_3$), 41.2 (s, *C*H$_2$), 66.4 (d, $^2J_{CP}$ 6.70 Hz, O*C*H$_2$CH$_3$), 112.8 (td, *C*F$_2$, $^1J_{CF}$ 273.3 Hz,

$^{1}J_{CP}$ 273.3 Hz), 121.0 (s, C_{Ar}), 129.0 (s, C_{Ar}), 129.9 (s, C_{Ar}), 138.8 (s, C_{Ar}), 159.4 (td, $^{2}J_{CF}$ 24.4 Hz, $^{2}J_{CP}$ 16.9 Hz, *C*=O); MS (EI) *m*/*z* (%): 626 $[M]^{+\bullet}$ (5), 439 $[M-CF_2P(O)(OEt)_2]^{+}$ (100).

*3.2.12. (S)-di-tert-butyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)succinate (**6l**)*

Yield: 96%; yellow oil; All NMR and MS analysis were consistent with the literature data [6d].

*3.2.13. (S)-2-(2-(diethoxyphosphoryl)-2,2-difluoro acetamido)succinic acid (**6m**)*

Yield: 20%; yellowish oil; All NMR and MS analysis were consistent with the literature data [6d].

*3.2.14. 1-cyclopropyl-7-(4-(2-(diethoxyphosphoryl)-2,2-difluoroacetyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**6n**)*

Yield: 30%; yellowish solid; m.p. 159–162 °C;

Conformer **A**: ^{19}F NMR ($CDCl_3$): δ −110.4 (d, 2F, CF_2 $^{2}J_{FP}$ 94.0 Hz), −122.2 (m, 1F, F_{Ar}); ^{31}P NMR ($CDCl_3$): δ 4.39 (t, 1P, $^{2}J_{PF}$ 94.2 Hz); ^{1}H NMR ($CDCl_3$): δ 1.36 (m, 4H, CH_2), 1.41 (m, 8H, OCH_2CH_3), 3.41 (m, 4H, CH_2), 3.58 (m, 1H, C*H*), 4.0 (dm, 4H, CH_2), 4.35 (m, 4H, OCH_2CH_3), 7.28 (s, 1H, H_{vinyl}), 7.38 (d, 1H, H_{Ar}), 8.02 (d, 1H, H_{Ar}), 8.76 (br. s., 1H, COO*H*); ^{13}C NMR ($CDCl_3$): δ 8.72 (s), 16.8 (dd, OCH_2CH_3), 35.9 (s), 43.5 (s), 46.1 (t), 49.8 (d), 50.3 (d), 66.3 (dd, OCH_2CH_3), 105.7 (s), 108.5 (s), 112.7 (d), 112.9 (td, CF_2, $^{1}J_{CF}$ 275.5 Hz, $^{1}J_{CP}$ 208.0 Hz), 139.4 (s), 120.7 (d), 145.6 (d), 160.4 (td, $^{2}J_{CF}$ 24.1 Hz, $^{2}J_{CP}$ 18.6 Hz, *C*=O), 148.0 (s), 151.5 (s), 156.5 (s), 167.6 (s), 177.4 (s); MS (EI) *m*/*z* (%): 545 $[M]^{+\bullet}$ (8), 329 $[M-COCF_2P(O)(OEt)_2]^{+}$ (100).

Conformer **B**: δ −117.9 (d, 2F, CF_2, $^{2}J_{FP}$ 96.4 Hz), −122.4 (m, 1F, F_{Ar}); ^{31}P NMR ($CDCl_3$): δ 4.44 (t, 1P, $^{2}J_{FP}$ 96.2 Hz); ^{1}H NMR ($CDCl_3$): δ 1.36 (m, 4H, CH_2), 1.41 (m, 8H, OCH_2CH_3), 3.41 (m, 4H, CH_2), 3.58 (m, 1H, C*H*), 4.0 (dm, 4H, CH_2), 4.35 (m, 4H, OCH_2CH_3), 7.28 (s, 1H, H_{vinyl}), 7.38 (d, 1H, H_{Ar}), 8.02 (d, 1H, H_{Ar}), 8.76 (br. s., 1H, COO*H*); ^{13}C NMR ($CDCl_3$): δ 8.72 (s), 16.8 (dd, OCH_2CH_3), 35.9 (s), 43.5 (s), 46.1 (t), 49.8 (d), 50.3 (d), 66.3 (dd, OCH_2CH_3), 105.7 (s), 108.5 (s), 112.7 (d), 112.9 (td, CF_2, $^{1}J_{CF}$ 275.5 Hz, $^{1}J_{CP}$ 208.0 Hz), 139.4 (s), 120.7 (d), 145.6 (d), 160.7 (td, $^{2}J_{CF}$ 26.7 Hz, $^{2}J_{CP}$ 17.8 Hz, *C*=O), 148.0 (s), 151.5 (s), 156.5 (s), 167.6 (s), 177.4 (s).

*3.2.15. Octaethyl 2,2′,2″,2‴-(biphenyl-3,3′,4,4′-tetrayltetrakis(azanediyl)tetrakis(1,1-difluoro-2-oxoethane-2,1-diyl)tetraphosphonate (**6o**)*

Yield: 92%; viscosous oil; ^{19}F NMR ($CDCl_3$): δ −118.4 (d, 8F, $^{2}J_{FP}$ 96.4 Hz); ^{31}P NMR ($CDCl_3$): δ 4.14 (t, 2P, $^{2}J_{PF}$ 96.2 Hz), 4.25 (t, 2P, $^{2}J_{FP}$ 96.2 Hz); ^{1}H NMR ($CDCl_3$): δ 1.41 (tdd, 24H, 4xOCH_2CH_3), 4.41 (dq, 16H, 4xOCH_2CH_3), 7.23 (dd, 2H, H_{Ar}), 7.49 (d, 2H, H_{Ar}), 7.55 (d, 2H, H_{Ar}), 9.53 (br. d., 4H, N*H*); ^{13}C NMR ($CDCl_3$): δ 16.8 (d, $^{3}J_{CP}$ 5.65 Hz, OCH_2CH_3), 66.4 (dd, $^{2}J_{CP}$ 6.70 Hz, OCH_2CH_3), 115.8 (td, CF_2, $^{1}J_{CF}$ 273.3 Hz, $^{1}J_{CP}$ 200.2 Hz), 124.3 (s, C_{Ar}), 126.2 (s, C_{Ar}), 128.5 (s, C_{Ar}), 128.7 (s, C_{Ar}), 128.9 (s, C_{Ar}), 138.4 (s, C_{Ar}), 161.4 (td, $^{2}J_{CF}$ 24.4 Hz, $^{2}J_{CP}$ 16.9 Hz, *C*=O); MS (ESI, CH_3CN) *m*/*z* 1070 $[M-H]^{-}$.

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