Electrophilic Fluorination of 5-(Cyanomethyl)imidazole-4-carboxylate Nucleosides: Facile Entry to 3-Fluoro-3-deazaguanosine Analogues

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Abstract: A facile and efficient methodology is described for the synthesis of 3-fluoro-3-deazaguanosines based on a novel electrophilic fluorination of 5-(cyanomethyl)imidazole-4-carboxylate nucleosides. This general methodology can be readily applied to the synthesis of sugar-modified 3-fluoro-3-deazaguanosine analogues.

Key words: nucleosides, 3-deazaguanosine, 3-deazapurine, fluorinated nucleosides, electrophilic fluorination

The synthesis of organofluorine compounds has attracted an enormous amount of interest in recent years because of these compounds' interesting biological properties.[2] The introduction of one or more fluorine atoms into biologically active compounds often affects their chemical properties and enhances, for example, their bioavailability and bioactivity.[3] Many fluorinated nucleoside analogues have been synthesized and studied as potential inhibitors of enzymes and as therapeutics agents.[4] Because of their interesting base pairing properties, enzyme recognition, and cellular uptake, the synthesis of novel fluorine-substituted nucleosides is not only of major interest to researchers interested in nucleoside chemistry[5] but also to those working on antisense oligonucleotides[6] and siRNA therapeutics.[7] It was reported[4b] quite recently that 2′-C-methyl-7-fluoro-7-deazaadenosine (**1a**), a nucleoside derivative in which a C–F bond appears at the 7-position of 2′-C-methyladenosine (**1b**) or 2′-C-methyl-7-deazaadenosine (**1c**), inhibits the replication of hepatitis C virus (HCV) with higher inhibitory potency ($EC_{50} = 0.07$ μM) than its parent compounds **1b** ($EC_{50} = 0.25$ μM) and **1c** ($EC_{50} = 0.26$ μM). 3-Deazaguanosine (3-deaza-G, **2a**)[8] display broad-spectrum antiviral and anticancer activities, and 3′-deoxyribonucleosides exhibit interesting antiviral, antifungal, antibacterial, antiparasitic, and anticancer properties.[9] Furthermore, studies on the identification of NS5B hepatitis C RNA-dependent RNA polymerase inhibitors have revealed that 3′-deoxyguanosine (**2b**) and 2′-*C*-methylguanosine (**2c**) display potent anti-HCV activity.[10] These findings warranted us to synthesize a series of 3-fluoro-3-deazaguanosine analogues, **3a–c**, that combine the 3-fluoro-3-deazaguanine heterocycle with the active compounds' ribosugar moieties (Figure 1).

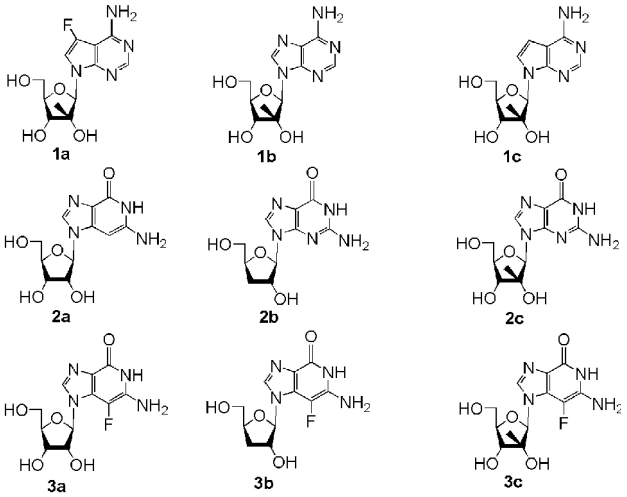

Figure 1 Rationale for the synthesis of target fluorinated nucleosides **3a–c**.

Although Matsuda and coworkers[11] first synthesized 3-F-3-deaza-G (**3a**) in 1999, its biological properties have not been well established.[12] Perhaps, this may be due to the complexity in the chemical synthesis. Moreover, the reported multistep synthesis begins with 5-aminoimidazole-4-carboxamideriboside (AICAR, **1d**), which is not a readily accessible starting material, especially for the syntheses of sugar-modified analogues of 3-F-3-deaza-G nucleoside (Scheme 1). Even the syntheses of sugar-modified AICAR derivatives, while possible, would be challenging using existing methods.[13] To simplify and generalize the synthesis of 3-F-3-deaza-G nucleosides with different sugar modifications, we envisioned the synthesis depicted in Scheme 1, which uses as a key reaction the electrophilic fluorination of 5-(cyanomethyl)imidazole-4-carboxylate nucleosides, which can be obtained in large quantities by using a reported procedure. In this paper, we report the most general, convenient, and facile methodology to date for the synthesis of 3-F-3-deaza-G nucleosides prepared through electrophilic fluorination.

Following reported procedures, we coupled the silylated 5-(cyanomethyl)imidazole-4-carboxylate[14] (**6**) with two different sugars, 1,2,3,5-tetra-*O*-benozyl-β-D-ribofuranose and 5-*O*-(4-methylbenzoyl)-3-deoxy-1,2-di-*O*-acetyl-β-D-ribofuranose, in the presence of tin(IV) chloride to give the desired nucleosides **4a** and **4b**, respectively.[15] In contrast, the coupling reaction between 2-*C*-methyl-1,2,3,5-tetra-*O*-benzoyl-β-D-ribofuranose[16] and **6**

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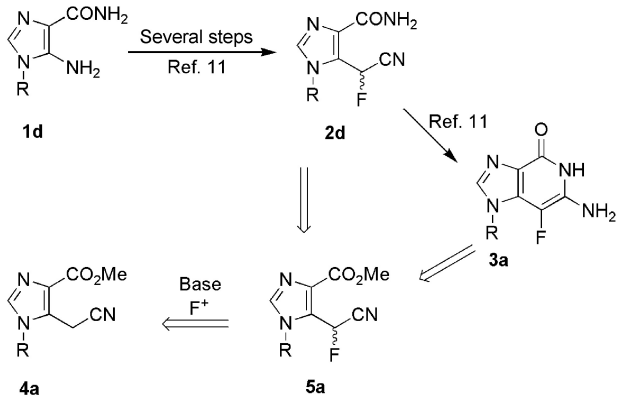
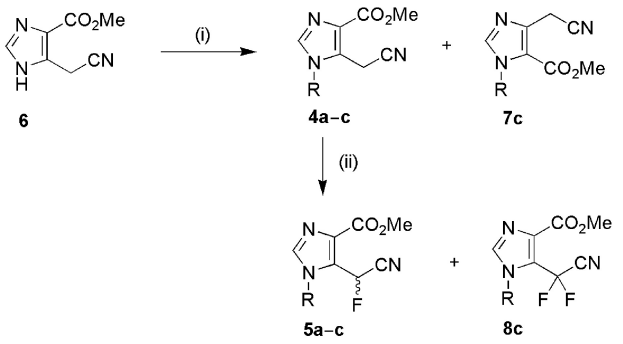


Scheme 1 R = β-D-ribofuranosyl.



a: R = 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl
b: R = 5-*O*-(4-methylbenzoyl)-2-*O*-acetyl-3-deoxy-β-D-ribofuranosyl
c: R = 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl

Scheme 2 *Reagents and conditions*: (i) for **4a** and **4b**: a) HMDS, cat. ammonium sulphate, reflux; b) 1,2,3,5-tetra-*O*-benzoyl-D-ribofuranose or 1,2-*O*-diacetyl-5-*O*-(4-methylbenzoyl)-3-deoxy-D-ribofuranose, MeCN, Sn(IV)Cl_4; for **4c**: 1,2,3,5-tetra-*O*-benzoyl-2-*C*-methyl-D-ribofuranose, MeCN, TMSOTf, DBU, 0 °C to r.t., 24 h; (ii) a) NaH (95%), MeCN, 0 °C; b) Selectfluor™, DMF, –45 °C.

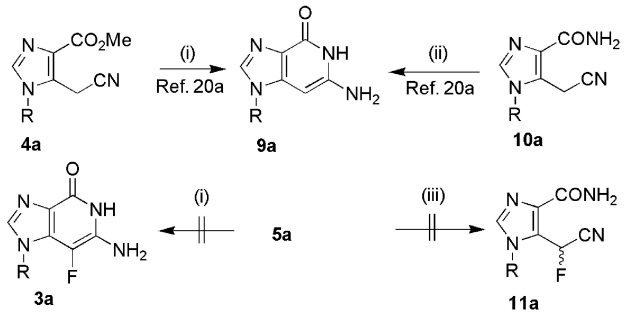
in the presence of tin(IV) chloride did not yield any glycosylated product. In addition, under Vorbrüggen glycosylation conditions,[17] this coupling reaction provided the undesired positional isomer **7c** as the major product in a 10:1 ratio with respect to the desired **4c**.

Interestingly, when **6** and 2-*C*-methyl-1,2,3,5-tetra-*O*-benzoyl-β-D-ribofuranose[16] were reacted with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of 1,8-diazabicyclo[4,5,0]undec-7-ene (DBU) at room temperature, the desired positional isomer **4c** was formed as the major product in a 3:1 ratio (82% combined yield). The two positional isomers **4c** and **7c** were readily separated by column chromatography on silica gel and we assigned their structures from analyses of ^{1}H NMR spectra (NOE experiments). It has been reported that the carbanion generated by sodium hydride at the methylene carbon atom adjacent to the cyano group can react with various alkyl halides.[18] Under such conditions, one can perform electrophilic fluorination of the generated carbanion using readily available fluorine electrophiles.

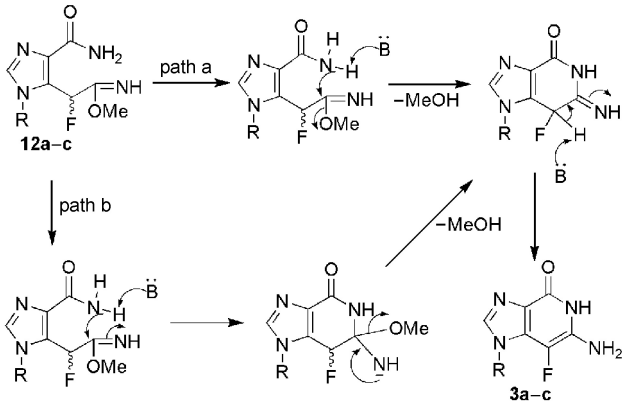
We reacted nucleoside **4a** with sodium hydride (95%, Aldrich) in anhydrous MeCN at 0 °C for one hour and then cooled the resulting mixture to –45 °C. A solution of 1-(chloromethyl)-4-fluoro-1,4-diazonia bicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) in DMF was injected slowly into the mixture, which was then stirred at –45 °C for 30 minutes. Quenching the reaction mixture with 5% aqueous AcOH, followed by the usual workup, gave the desired fluorinated product **5a** in 60% yield as a 1:1 mixture of diastereoisomers.[19] We were pleased by this result because the fluorinated product **5a**, after conversion to its carboxamide derivative **11a**, should provide facile entry to the preparation of the 3-fluorinated 3-deazapurine nucleosides 3-F-3-deaza-G, 3-F-3-deaza-A, and 3-F-3-deaza-2,6-diaminopurine.[11] For the preparation of **5a**, the use of other commercially available F^+ reagents did not provide any advantages over the use of Selectfluor. To generalize this electrophilic fluorination reaction, we also fluorinated the 3′-deoxy and 2′-*C*-methyl sugar-modified analogues **4b** and **4c** in a similar manner to give **5b** (1:1 dr, 65%) and **5c** (1:1 dr, 67%), respectively.[19] In the case of the 2′-*C*-methyl sugar analogue, we also isolated the difluorinated product **8c** (ca. 5%, Scheme 2).

In an effort to synthesize the desired 3-F-3-deaza-G **3a**, we made several attempts to cyclize the fluorinated product **5a** in one-pot reactions using reaction conditions that have been reported[20] for the synthesis of 3-deaza-G **9a** from **4a** (Scheme 3). Unfortunately, one-pot ring-closure reactions of **5a** using methanolic NH_3, liquid NH_3, and NH_4OH provided complex mixtures of highly fluorescent products. LC/Mass spectrometric analyses of the crude reaction mixtures indicated neither the carboxamide intermediate **11a** nor the desired product **3a.** Cyclization reactions of compound **5a** mediated by either HBr or hydrazine also failed to produce the corresponding ring-closed products.[21] We believe that electron-withdrawing fluorine substituent in **5a** causes trouble in the one-pot ring-closure reaction. It has, however, been demonstrated in the literature that the 5-(cyanomethyl)imidazole-4-carboxamide nucleoside analogues **2d** and **10a** undergo smooth ring-closure reactions to give the 3-deaza-G analogues **3a** and **9a**, respectively, under mild basic conditions (5% aq Na_2CO_3 in EtOH).[11,20a] To proceed with this type of ring-closure, we attempted to synthesize the carboxamide analogue **11a** from the methyl ester **5a**.

Unfortunately, when we reacted **5a** with liquid NH_3, complete decomposition of the starting material occurred, even at room temperature. Interestingly, however, upon reaction with methanolic NH_3 at room temperature for 48 hours, the fluorinated methyl ester **5a** produced exclusively (Scheme 4) the imidomethoxy imidazolecarboxamide analogue **12a** (1:3 diastereoisomeric mixture, 75% yield);[22] the formation of carboxamide **11a** was not detected.[23] When this reaction was stopped after 24 hours, the products isolated from the mixture were **12a** and the intermediate **13a**. Formation of **13a** clearly indicates that methanolic NH_3 reacts first with the cyano group before it



Scheme 3 *Reagents and conditions*: (i) aq NH_4OH, 80 °C or liquid NH_3, MeOH, aq NH_4OH or liquid NH_3, MeOH, 85 °C; (ii) 5% Na_2CO_3 in aq EtOH, reflux; (iii) liquid NH_3, r.t., 12 h. R = β-D-ribofuranosyl.

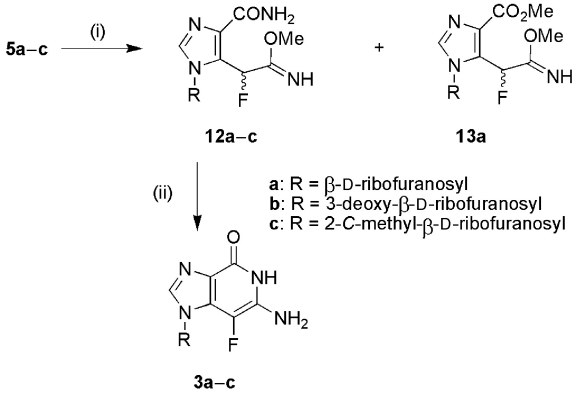


Scheme 5 Mechanism of ring-closure reaction.

reacts with the methyl ester unit. In a similar manner, we also reacted compounds **5b** and **5c** with saturated methanolic NH_3 to give **12b** (80%) and **12c** (78%), respectively.

Treatment of compound **12a** with 1 M triethylamine in 20% aqueous MeOH (60 °C, 8 h) led to a novel ring-closure reaction that gave 3-F-3-deaza-G **3a** in 60% yield.[24] We confirmed the structure of **3a** by comparing its ^1H NMR, ^{13}C NMR and UV spectra with those of a compound reported by Matsuda and coworkers.[11] To indicate the generality of this synthetic methodology, we also successfully cyclized the sugar-modified analogues **5b** and **5c** in a similar fashion to give the 3-F-3-deaza-G analogues **3b** (62%) and **3c** (68%), respectively.[25,26]

The mechanism of these cyclization reactions may occur through either of the two pathways illustrated in Scheme 5. Nucleophilic addition of the carboxamide anion (generated by the base) onto the methoxy imidate could take place either by an S_N2-type mechanism (path a) or through a tetrahedral intermediate (path b). After the nucleophilic attack, ring-closure products undergo base-assisted tautomerization to give the desired products **3a–c**.



Scheme 4 *Reagents and conditions*: (i) MeOH saturated with NH_3 at 0 °C, r.t., 24–48 h; (ii) 1 M Et_3N in 20% aq MeOH, 60 °C, 8 h.

In conclusion, we have successfully developed an efficient strategy for the synthesis of 3-F-3-deaza-G nucleosides by using electrophilic fluorination as the key reaction. We have also demonstrated that this methodology can be applied generally to the synthesis of a range of modified sugar analogues of 3-F-3-deaza-G. The fluorinated products **5a–c** are good intermediates that provide facile entry to the preparation of 3-F-3-deaza-purine nucleosides. Detailed synthetic applications of this strategy and a study of the biological properties of the fluorinated 3-deazapurine nucleosides will be published in due course.

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(19) Compound **5a** (diastereomers 1:1): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 3 H, OCH_3), 4.66–4.90 (m, 3 H, 4′, 5′,5″-H), 5.90–6.06 (m, 2 H, 2′,3′-H), 6.48 (d, *J* = 6.7 Hz, 1 H, 1′-H), 7.31–7.63 (m, 10 H, 9 Ar-H, Imi-2-H), 7.92–8.14 (m, 7 H, 6 × Ar-H, CHFCN). ^{19}F NMR (282 MHz, $CDCl_3$): δ (diastreomers) = –175.76 (d, J_{F-H} = 43.6 Hz), –172.72 (d, J_{F-H} = 43.6 Hz). HRMS: *m/z* calcd for $C_{33}H_{26}FN_3O_9$ [MNa^+]: 650.1551; found: 650.1550. ESI-MS: *m/z* = 650 [MNa^+].
Compound **5b** (diastereomers 1:1): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, $COCH_3$), 2.20–2.50 (m, 5 H, 3′,3″-H, Tol-CH_3), 3.94 (s, 3 H, OCH_3), 4.53–4.75 (m, 3 H, 4′, 5′,5″-H), 5.40–5.46 (m, 1 H, 2′-H), 6.13–6.16 (m, 1 H, 1′-H), 7.25 (m, 2 H, Ar-H), 7.41 (d, 1 H, *J* = 43.1 Hz, CHFCN), 7.86–7.98 (m, 3 H, 2 × Ar-H, Imi-2-H). ^{19}F NMR (282 MHz, $CDCl_3$): δ (diastreomers) = –176.41 (d, J_{F-H} = 43.6 Hz), –174.03 (d, J_{F-H} = 43.6 Hz). HRMS: *m/z* calcd for $C_{22}H_{22}FN_3O_7$ [MNa^+]: 482.1334; found: 482.1333. ESI-MS: *m/z* = 482 [MNa^+].
Compound **5c** (diastereomers 1:1): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58 (2 × s, 3 H, CH_3), 3.98 (2 × s, 3 H, OCH_3), 4.78–4.96 (m, 3 H, 4′, 5′,5″-H), 5.75 (2 × d, 1 H, 3′-H), 6.66 and 6.80 (2 × s, 1 H, 1′-H), 7.26–7.62 (m, 10 H, 9 × Ar-H, Imi-2-H), 7.80–8.19 and 8.20 (m, 7 H, 6 × Ar-H, CHFCN). ^{19}F NMR (282 MHz, $CDCl_3$): δ (diastereomers) = –179.31 (d, J_{F-H} = 41.6 Hz), –170.0 (d, J_{F-H} = 41.6 Hz). HRMS: *m/z* calcd for $C_{34}H_{28}FN_3O_9$ [MNa^+]: 664.1707; found: 664.1704. ESI-MS: *m/z* = 664 [MNa^+].

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(22) Compound **12a** (diastereomers 1:3): ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.45–3.70 (m, 5 H, 2′, 3′-H, OCH_3), 3.85–3.86 (m, 1 H, 4′-H), 4.04–4.16 (m, 2 H, 5′,5″-H), 5.08–5.22 (m, 2 H, 3′, 5″-OH), 5.40 and 5.49 (2 × d, *J* = 4.1, 4.7 Hz, 1 H, 2′-OH), 5.51 (d, *J* = 5.56 Hz, 1 H, 1′-H), 7.17 (d, J_{H-F} = 44.8 Hz, 0.3 H, CHF), 7.22 (d, J_{H-F} = 44.8 Hz, 0.7 H, CHF), 7.40 and 7.60 (2 × br s, 2 H, NH_2), 8.21 and 8.24 (2 × br s, 1 H, Imi-2H), 8.50 (br s, 1 H, NH). ^{19}F NMR (282 MHz, $CDCl_3$): δ (diastereomers) = –176.84 (d, J_{F-H} = 43.6 Hz), –173.84 (d, J_{F-H} = 43.6 Hz). HRMS: *m/z* calcd for $C_{12}H_{17}FN_4O_6$ [MNa^+] = 355.1030; found: 355.1034. ESI-MS: *m/z* = 355 [MNa^+].

(23) To our surprise, 5-imidomethoxy imidazole-4-carboxamide riboside analogues similar to **12a** have never been detected, or proposed to form, during the cyclization reactions of **4a** or **10a** in basic alcoholic solutions. See ref. 11 and ref. 20.

(24) A similar ring-closure was also effected successfully when using 5% Na_2CO_3 in EtOH, but, because of its high polarity, we had difficulties in isolating the product from the inorganic salt. Although the ring-closure reaction could also be realized using several organic amine bases (DBU, pyridine, *N*,*N*-diisopropylethylamine, etc.), we prefer to use less volatile Et_3N base.

(25) Although the conversions of the ring-closure reactions were >80%, the high polarities of products **3a–c** restricted their isolated yields to only 60–68%.

(26) Compound **3b**: UV (0.5 N NaOH): λ_{max} = 287 nm (ε 9400). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.80–1.88 (m, 1 H, 3′-H), 2.08–2.18 (m, 1 H, 3″-H), 3.51–3.55 (m, 1 H, 5′-H), 3.64–3.67 (m, 1 H, 5″-H), 4.28–4.42 (m, 2 H, 4′-H, 2′-OH), 5.01 (t, 1 H, *J* = 5.3 Hz, 5′-OH), 5.52 (br s, 2 H, NH_2), 5.61 (d, *J* = 4.4 Hz, 1 H, 2′-H), 5.78 (s, 1 H, 1′-H), 8.04 (s, 1 H,

2-H), 10.44 (br s, 1 H, NH). ^{19}F NMR (282 MHz, DMSO-d_6): δ = –186.70. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.6, 62.9, 76.4, 81.7, 93.1 (d, *J* = 5.5 Hz), 122.2 (d, *J* = 215.0 Hz), 123.2, 132.1 (d, *J* = 9.0 Hz), 135.9 (d, *J* = 22.0 Hz), 137.6, 155.0. HRMS: *m/z* calcd for $C_{11}H_{14}FN_4O_4$ [MH$^+$] = 285.0999; found: 285.0991; [MNa$^+$]: 307.0819; found: 307.0809. ESI-MS: *m/z* = 285 [MH$^+$].

Compound **3c**: UV (H_2O): λ_{max} = 272 nm (ε 8200), 310 nm (ε 7100). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.71 (s, 3 H, CH_3), 3.62–3.69 (m, 1 H, 5′-H), 3.82–3.93 (m, 3 H, 3′,4′,5″-H), 5.15 (s, 1 H, 2′-OH), 5.21–5.27 (m, 2 H, 3′,5′-OH), 5.54 (br s, 2 H, NH_2), 5.77 (s, 1 H, 1′-H), 8.24 (s, 1 H, 2-H), 10.46 (br s, 1 H, NH). ^{19}F NMR (282 MHz, DMSO-d_6): δ = –186.46. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.5, 59.7, 71.7, 79.5, 83.0, 93.3 (d, *J* = 7 Hz), 122.2 (d, *J* = 214 Hz), 122.9, 132.2 (d, *J* = 9 Hz), 135.9 (d, *J* = 22 Hz), 137.5, 155.0. HRMS: *m/z* calcd for $C_{12}H_{16}FN_4O_5$ [MH$^+$]: 315.1105; found: 315.1102; [MNa$^+$]: 337.0924; found: 337.0920. ESI-MS: *m/z* = 315 [MH$^+$].