# Supporting Information

**Manuscript Title**: Sustained Intracellular Raltegravir Depots Generated with Prodrugs Designed for Nanoparticle Delivery

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**Supporting Information Content**:

- 19 pages
- Synthetic procedures and characterization for RAL and analogs **1**–**7.**
- Table S1
- Figures S1 – S16

**Table S1**. Properties of ARV loaded PLGA-NP containing RAL and analogs **1** – **4** and **7**.

| Compound | RAL | **1** | **2** | **3** | **4** | **7** |
|---|---|---|---|---|---|---|
| ARV M.W. (g/mol) | 444.42 | 486.46 | 528.21 | 570.62 | 548.18 | 560.20 |
| NP diameter[a] (nm) | 317 ± 35 | 267 ± 6 | 263 ± 7 | 357 ± 1 | 257 ± 44 | 301 ± 12 |
| polydispersity index[a] | 0.17 ± 0.10 | 0.08 ± 0.01 | 0.11 ± 0.01 | 0.28 ± 0.05 | 0.12 ± 0.02 | 0.14 ± 0.01 |
| zeta-potential[a] (mV, pH 7) | –24.2 ± 1.6 | –24.5 ± 0.9 | –23.5 ± 2.2 | –22.4 ± 0.4 | –21.3 ± 1.8 | –19.1 ± 0.6 |
| drug loading[a,b] (wt %) | 0.30 ± 0.02 | 0.10 ± 0.01 | 1.2 ± 0.1 | 6.9 ± 0.1 | 7.7 ± 0.2 | 0.40 ± 0.04 |
| encapsulation efficiency[a,b](%) | 3.0 ± 0.2 | 1.0 ± 0.1 | 12. ± 1 | 69. ± 1 | 77. ± 2 | 4.0 ± 0.4 |

[a]Measured properties are reported as the mean ± SD from replicates including a minimum of two independent nanoparticle fabrications. [b]Drug loading and encapsulation efficiency were calculated as follows.

$$\text{drug loading} = \left(\frac{\text{mass of drug detected in ARV - NP}}{\text{mass of ARV - NP}}\right) \cdot 100$$

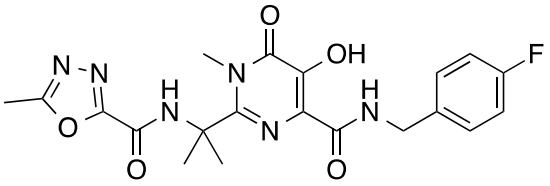
$$\text{encapsulation efficiency} = \left(\frac{\text{observed drug loading}}{\text{theoretical drug loading}}\right) \cdot 100$$

**Methods and Materials:**

Reaction solvents were commercially available anhydrous grade and used without further purification. Synthetic glassware was oven-dried before use and reactions were conducted under a $N_2(g)$ atmosphere with magnetic stirring. TLC was performed on EMD 60G silica gel ($SiO_2$) plates and visualized with 254 nm UV light. NMR spectra were recorded on a Bruker 400 MHz Avance III instrument with chemical shift values referenced to the residual solvent peak of DMSO-$d_6$. Mass spectra were recorded on a Bruker Esquire ion trap mass spectrometer and measured in positive ion mode following electrospray ionization. Reversed-phase HPLC analysis was carried out on an Agilent 1100 series instrument using a Phenomenex Luna 5.0 μm C-18 column (250 x 4.6 mm). The reported yields are for isolated compounds of >95% purity as assessed by $^1$H NMR and were not optimized.

**Experimental Procedures:**

Detailed reaction conditions, purification techniques and characterization data are provided for RAL and analogs **1**–**7** below.



**RAL**
Chemical Formula: $C_{20}H_{21}FN_6O_5$
Exact Mass: 444.16
Molecular Weight: 444.42

***N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-(1-methyl-1-{[(5-methyl-1, 3,4-oxadiazol-2-yl)carbonyl]amino]}ethyl)-6-oxo-4-pyrimidinecarboxamide (Raltegravir).** Raltegravir was isolated as a neutral compound from ISENTRESS® tablets (400 mg per tablet, Merck & Co.). Four crushed tablets were stirred in dichloromethane (200 mL) containing acetic acid (4 mL) for 24 h at room temperature. The resulting slurry was filtered through a bed of celite and the filtrate was extracted with 0.5 M NaOH (3 x 100 mL). The aqueous layer was washed with dichloromethane (2 x 75 mL) and adjusted to pH 2 by the dropwise addition of 5.0 M HCl at 0 °C. The resulting suspension was extracted with dichloromethane (3 x 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallization of the crude material from isopropanol (75 °C → 25 °C, overnight) provided raltegravir as a white solid (0.885 g, 55% recovery). $R_f$ = 0.33 (10:90 MeOH:$CH_2Cl_2$). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.23 (s, 1H), 9.88 (s, 1H), 9.10 (t, $J$ = 6.5 Hz, 1H), 7.39 (dd, $J$ = 8.6, 5.6 Hz, 2H), 7.17 (t, $J$ = 8.9 Hz, 2H), 4.51 (d, $J$ = 6.4 Hz, 2H), 3.48 (s, 3H), 2.56 (s, 3H), 1.74 (s, 6H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 168.4, 165.7, 161.3 (d, $J_{F,C}$ = 242.5 Hz), 158.6, 158.1, 152.6, 151.8, 145.7, 134.9 (d, $J_{F,C}$ = 3.0 Hz), 129.5 (d, $J_{F,C}$ = 8.2 Hz), 124.4, 115.2 (d, $J_{F,C}$ = 21.4 Hz), 57.6, 41.7, 33.0, 27.0, 10.7. $^{19}$F NMR (376 MHz, DMSO) $\delta$ -115.7. MS *m/z* 467.6 $(M + Na)^+$.

**Figure S1**. Electrospray mass spectrum of purified RAL acquired in positive-ion mode.

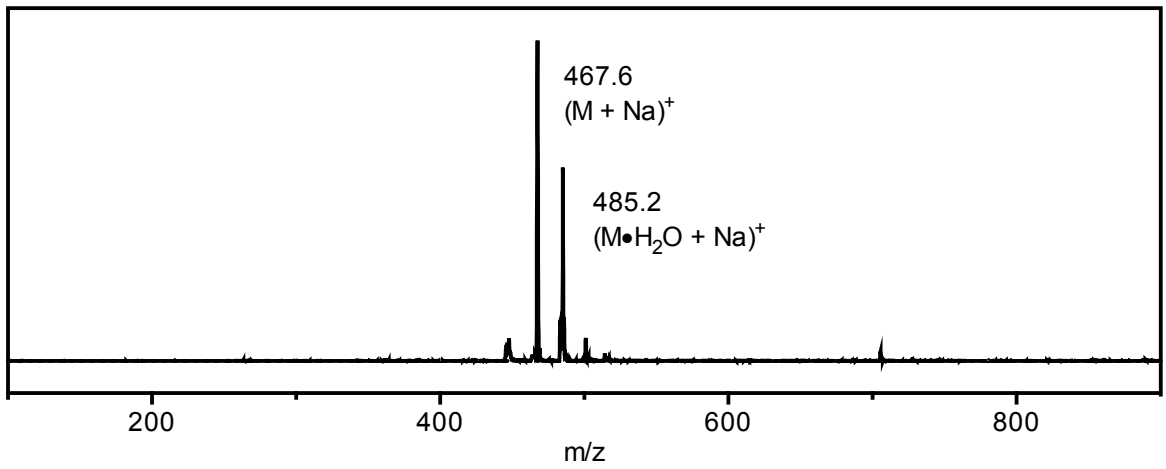
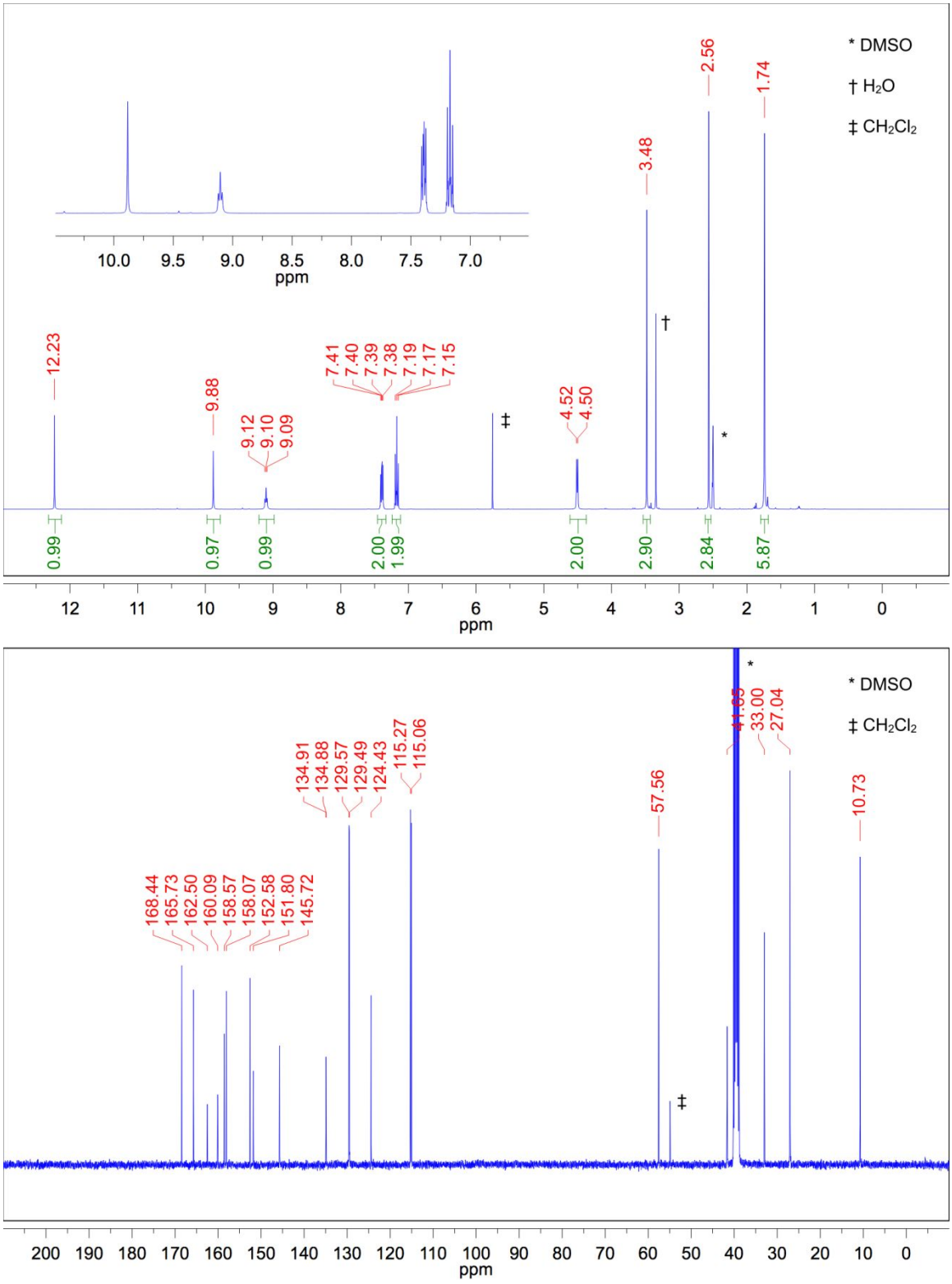
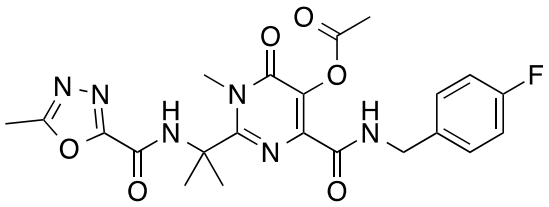


**Figure S2**. $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (101 MHz) of purified RAL in DMSO-$d_6$.





**1**
Chemical Formula: $C_{22}H_{23}FN_6O_6$
Exact Mass: 486.17
Molecular Weight: 486.46

**5-(Acetyloxy)-*N*-[(4-fluorophenyl)methyl]-1,6-dihydro-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]}ethyl)-6-oxo-4-pyrimidinecarboxamide (1).** Acetyl chloride (0.048 mL, 0.68 mmol, 1.5 equiv) was added dropwise to a solution of raltegravir (0.200 g, 0.45 mmol) and triethylamine (0.176 mL, 1.26 mmol, 2.8 equiv) in dichloromethane (3.0 mL) and stirred at room temperature. After 3 h the reaction was diluted with dichloromethane (20 mL), washed with saturated aq. $NaHCO_3$ (1 x 25 mL) and brine (1 x 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (3:2 acetone:hexanes) to provide compound **1** as a white solid (0.061 g, 27.9 % yield). $R_f$ = 0.19 (ethyl acetate). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.02 (s, 1H), 8.93 (t, $J$ = 6.4 Hz, 1H), 7.35 (dd, $J$ = 8.6, 5.7 Hz, 2H), 7.16 (t, $J$ = 8.9 Hz, 2H), 4.43 (d, $J$ = 6.3 Hz, 2H), 3.51 (s, 3H), 2.57 (s, 3H), 2.23 (s, 3H), 1.77 (s, 6H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 167.8, 165.8, 161.9, 161.2 (d, $J_{F,C}$ = 242.3 Hz), 159.2, 158.9, 157.9, 152.7, 140.4, 135.4 (d, $J_{F,C}$ = 3.0 Hz), 133.8, 129.2 (d, $J_{F,C}$ = 8.2 Hz), 115.1 (d, $J_{F,C}$ = 21.3 Hz), 57.9, 41.5, 33.2, 26.7, 20.4, 10.7. $^{19}$F NMR (376 MHz, DMSO) $\delta$ -116.0. MS *m/z* 509.5 $(M + Na)^+$.

**Figure S3**. Electrospray mass spectrum of **1** acquired in positive-ion mode.

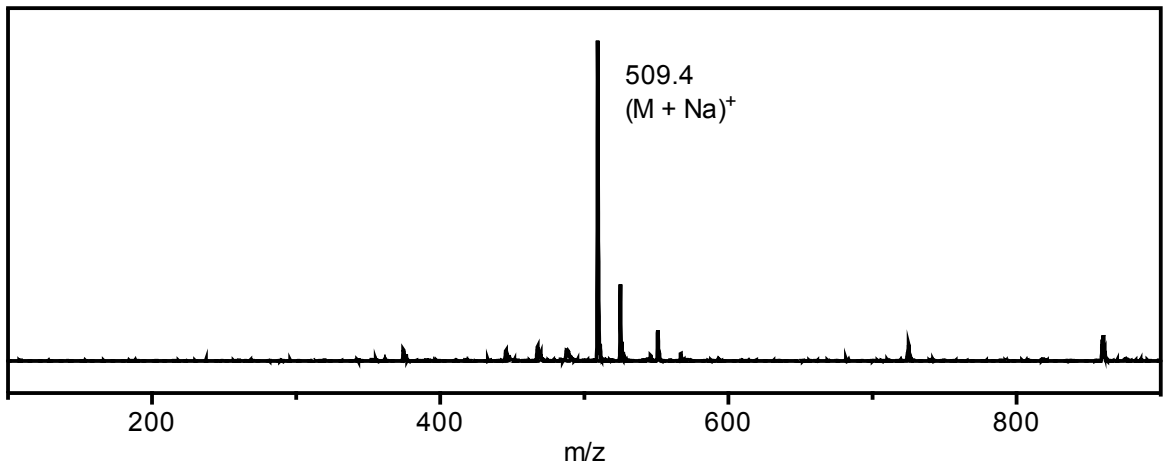
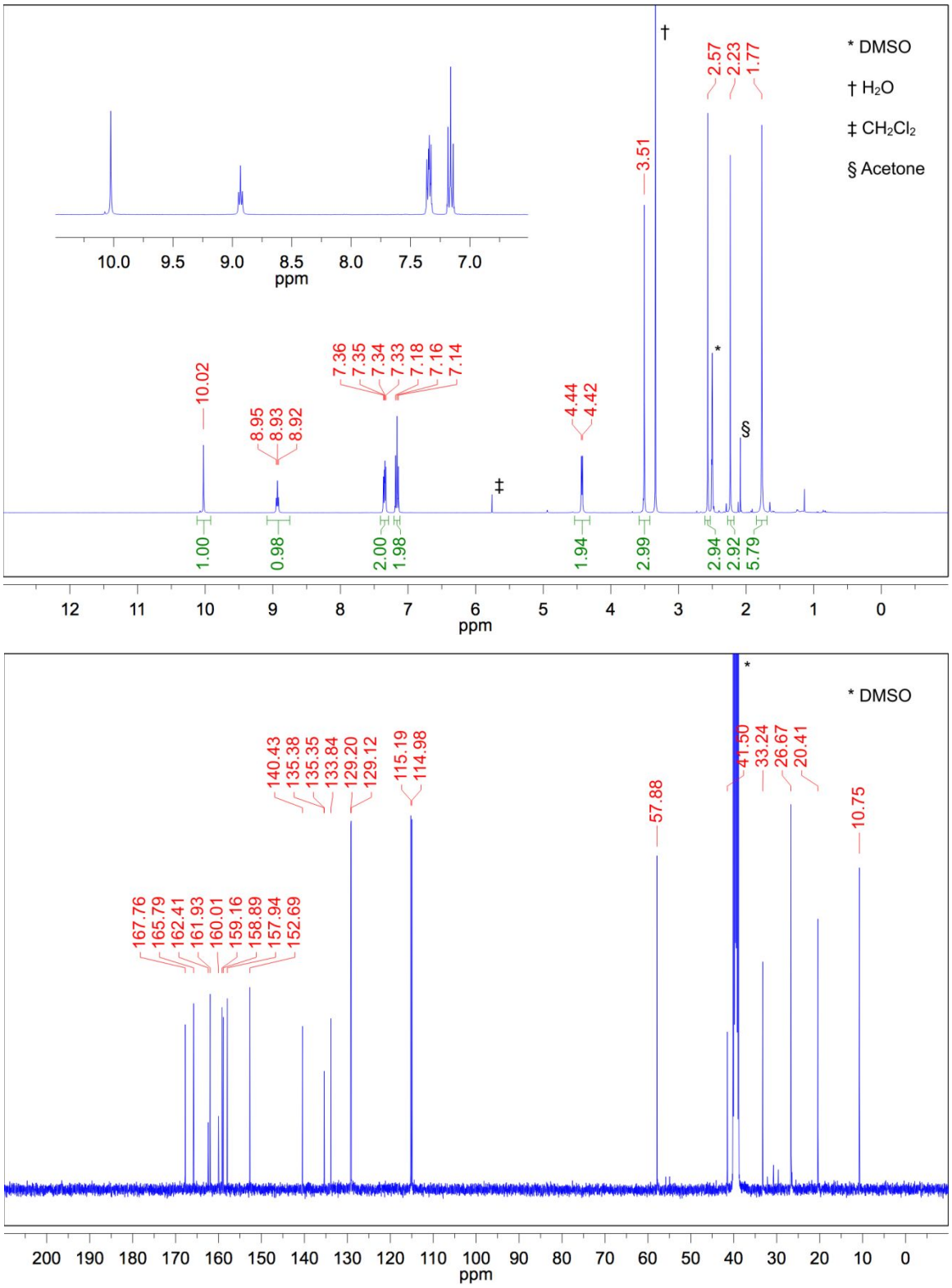
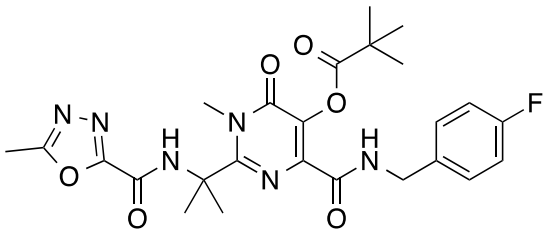


**Figure S4**. $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (101 MHz) of **1** in DMSO-$d_6$.





**2**
Chemical Formula: $C_{25}H_{29}FN_6O_6$
Exact Mass: 528.21
Molecular Weight: 528.54

***N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]}ethyl)-5-(2,2-dimethyl-propanoyloxy)-6-oxo-4-pyrimidinecarboxamide (2).** Pivaloyl chloride (0.083 mL, 0.68 mmol, 1.5 equiv) was added dropwise to a solution of raltegravir (0.200 g, 0.45 mmol) and triethylamine (0.176 mL, 1.26 mmol, 2.8 equiv) in dichloromethane (3.0 mL) and stirred at room temperature. After 3 h the reaction was diluted with dichloromethane (20 mL), washed with saturated aq. $NaHCO_3$ (1 x 25 mL) and brine (1 x 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (ethyl acetate) to provide compound **2** as a white solid (0.152 g, 63.6 % yield). $R_f$ = 0.33 (ethyl acetate). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.05 (s, 1H), 8.93 (t, $J$ = 6.4 Hz, 1H), 7.38 (dd, $J$ = 8.7, 5.5 Hz, 2H), 7.19 (t, $J$ = 8.9 Hz, 2H), 4.46 (d, $J$ = 6.3 Hz, 2H), 3.54 (s, 3H), 2.61 (s, 3H), 1.80 (s, 6H), 1.29 (s, 9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 174.6, 165.8, 162.0, 161.2 (d, $J_{F,C}$ = 242.3 Hz), 159.0, 158.7, 158.0, 152.7, 141.0, 135.4 (d, $J_{F,C}$ = 3.0 Hz), 133.9, 129.2 (d, $J_{F,C}$ = 8.1 Hz), 115.0 (d, $J_{F,C}$ = 21.2 Hz), 57.9, 41.5, 38.4, 33.1, 26.8, 26.7, 10.8. $^{19}$F NMR (376 MHz, DMSO) $\delta$ -116.1. MS *m/z* 551.4 $(M + Na)^+$.

**Figure S5**. Electrospray mass spectrum of **2** acquired in positive-ion mode.

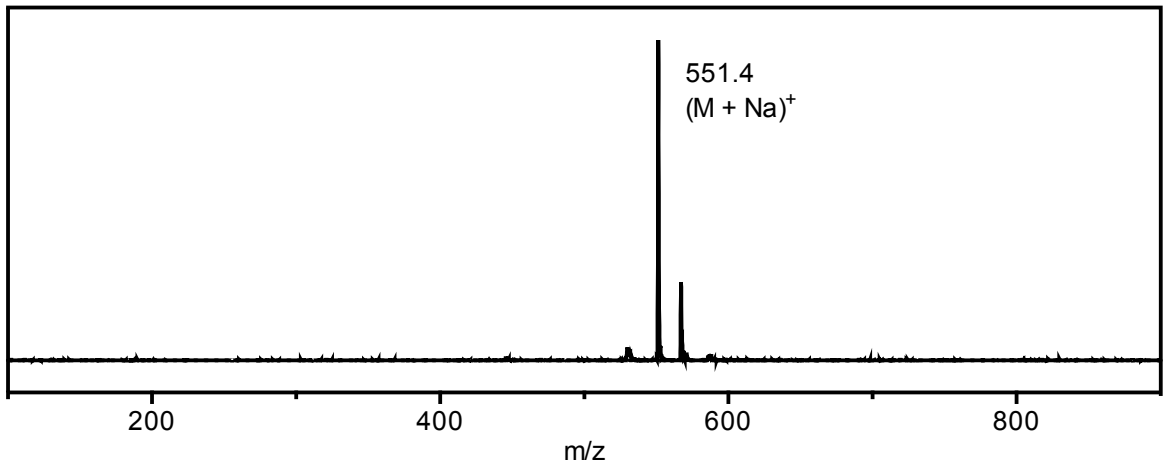
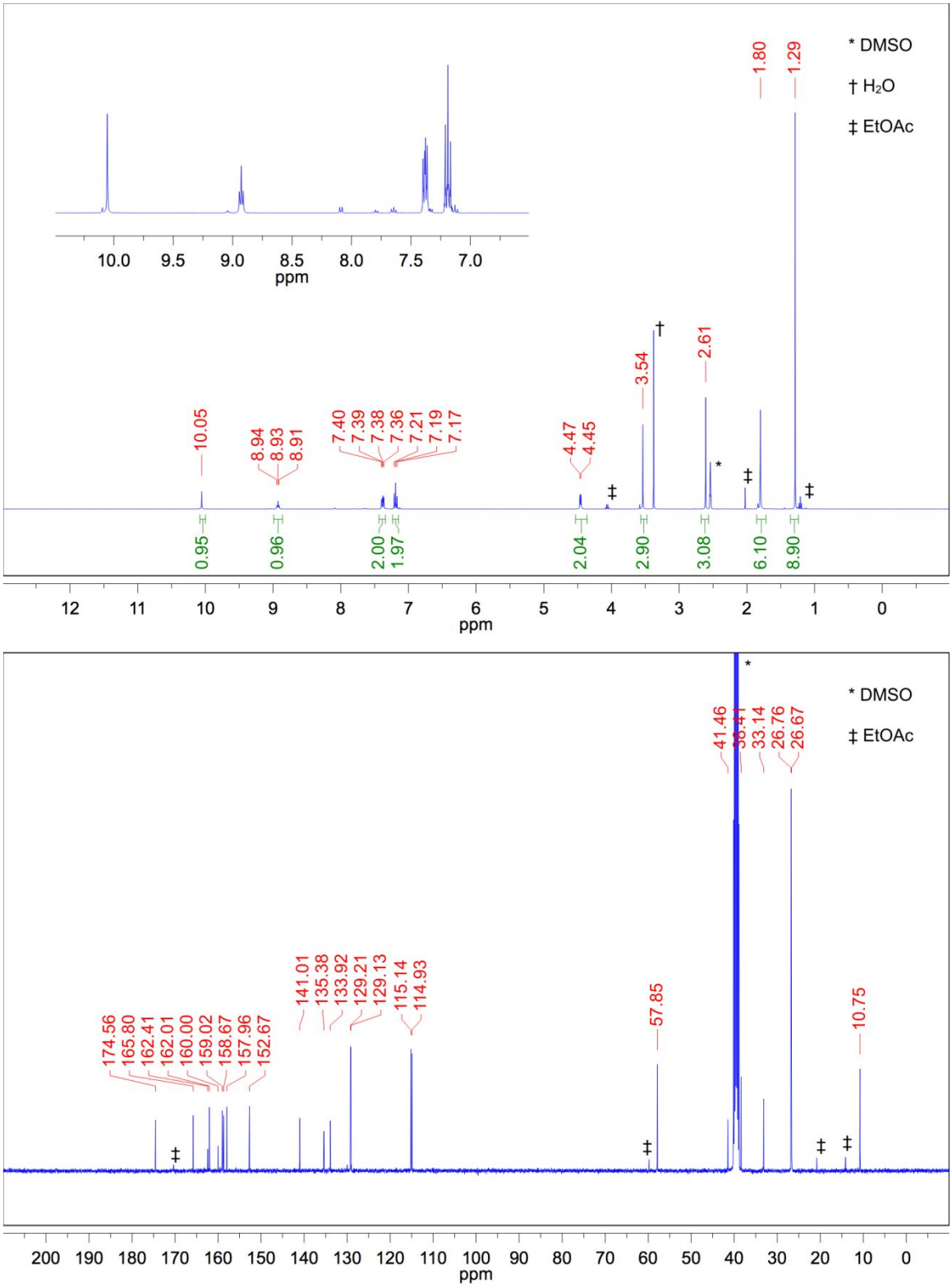
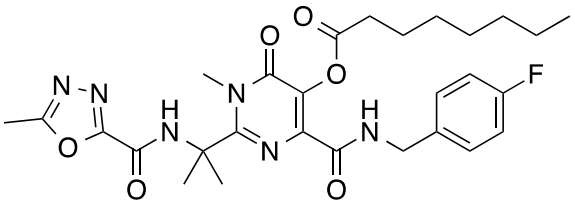


**Figure S6**. $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (101 MHz) of **2** in DMSO-$d_6$.





**3**
Chemical Formula: $C_{28}H_{35}FN_6O_6$
Exact Mass: 570.26
Molecular Weight: 570.62

***N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]}ethyl)-5-(octanoyloxy)-6-oxo-4-pyrimidinecarboxamide (3).** Octanoyl chloride (0.115 mL, 0.68 mmol, 1.5 equiv) was added dropwise to a solution of raltegravir (0.200 g, 0.45 mmol) and triethylamine (0.176 mL, 1.26 mmol, 2.8 equiv) in dichloromethane (3.0 mL) and stirred at room temperature. After 3 h the reaction was diluted with dichloromethane (20 mL), washed with saturated aq. $NaHCO_3$ (1 x 25 mL) and brine (1 x 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (ethyl acetate) to provide compound **3** as a white solid (0.123 g, 47.9 % yield). $R_f$ = 0.35 (ethyl acetate). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.02 (s, 1H), 8.92 (t, $J$ = 6.4 Hz, 1H), 7.34 (dd, $J$ = 8.6, 5.6 Hz, 2H), 7.15 (t, $J$ = 8.9 Hz, 2H), 4.42 (d, $J$ = 6.3 Hz, 2H), 3.50 (s, 3H), 2.57 (s, 3H), 2.51 (t, $J$ = 7.5 Hz, 2H), 1.76 (s, 6H), 1.62 – 1.54 (m, 2H), 1.37 – 1.21 (m, 8H), 0.85 (t, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 170.3, 165.8, 162.0, 161.2 (d, $J_{F,C}$ = 242.1 Hz), 159.1, 158.8, 157.9, 152.7, 140.7, 135.4 (d, $J_{F,C}$ = 2.9 Hz), 133.8, 129.1 (d, $J_{F,C}$ = 8.1 Hz), 115.0 (d, $J_{F,C}$ = 21.3 Hz), 57.9, 41.5, 33.2, 33.1, 31.2, 28.4, 28.2, 26.7, 24.2, 22.1, 14.0, 10.7. $^{19}$F NMR (376 MHz, DMSO) $\delta$ -116.1. MS *m/z* 593.5 $(M + Na)^+$.

**Figure S7**. Electrospray mass spectrum of **3** acquired in positive-ion mode.

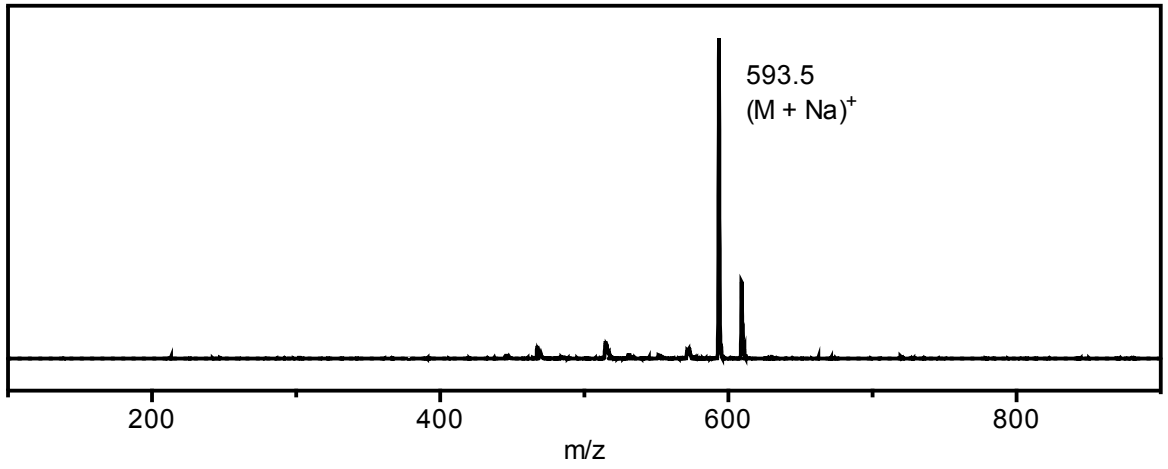
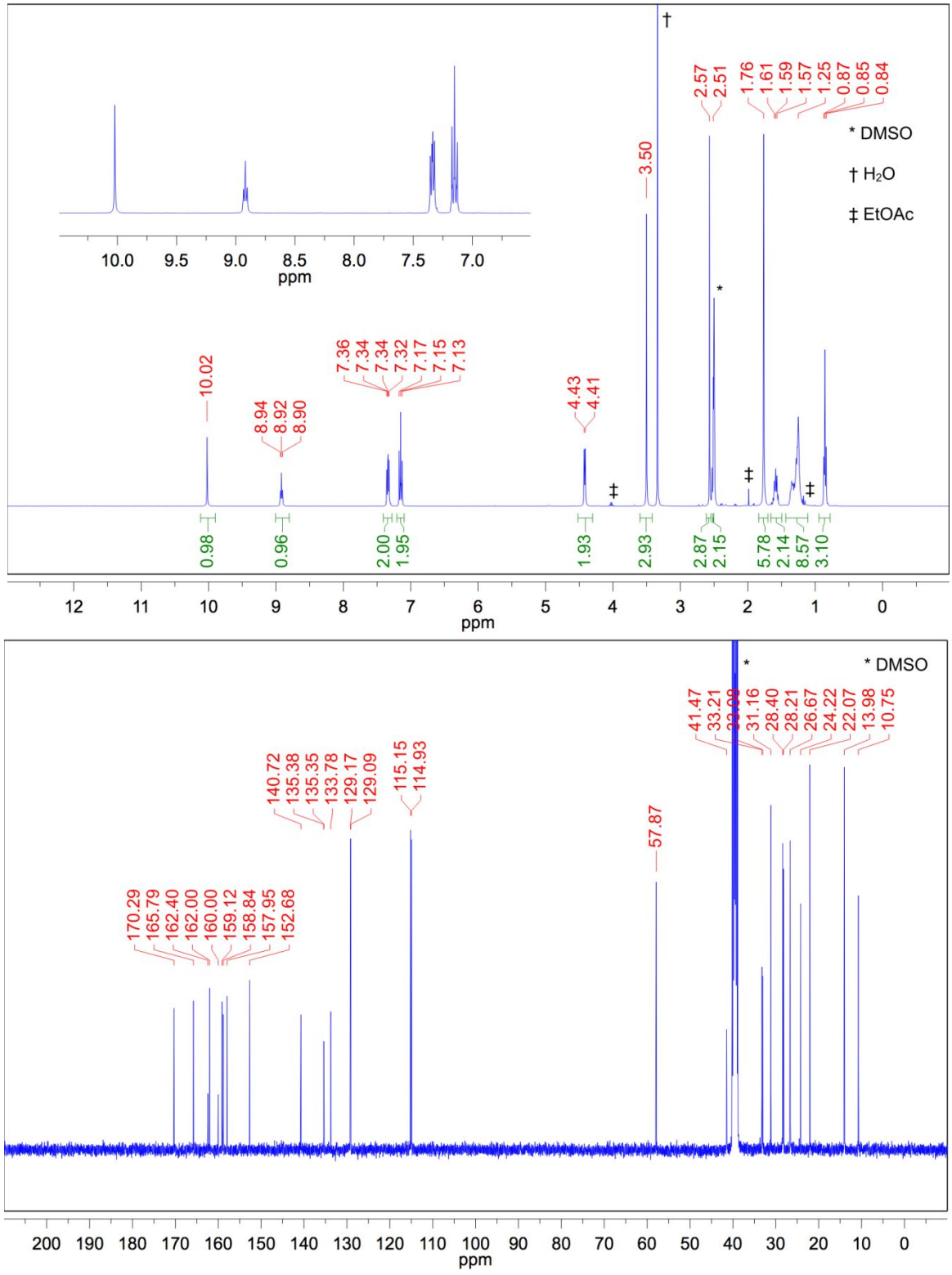
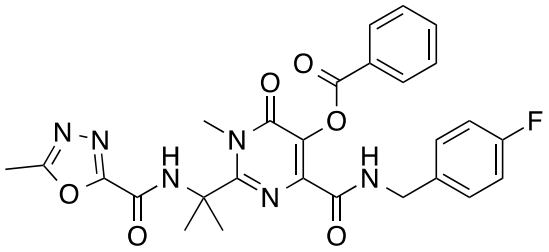


**Figure S8**. $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (101 MHz) of **3** in DMSO-$d_6$.





**4**
Chemical Formula: $C_{27}H_{25}FN_6O_6$
Exact Mass: 548.18
Molecular Weight: 548.53

**5-(Benzoyloxy)-*N*-[(4-fluorophenyl)methyl]-1,6-dihydro-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]}ethyl)-6-oxo-4-pyrimidinecarboxamide (4).** Benzoyl chloride (0.157 mL, 1.35 mmol, 1.5 equiv) was added dropwise to a solution of raltegravir (0.400 g, 0.90 mmol) and triethylamine (0.353 mL, 2.53 mmol, 2.8 equiv) in dichloromethane (6.0 mL) and stirred at room temperature. After 3 h the reaction was diluted with dichloromethane (25 mL), washed with saturated aq. $NaHCO_3$ (1 x 45 mL) and brine (1 x 45 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (ethyl acetate) to provide compound **4** as a white solid (0.316 mg, 64.0 % yield). $R_f$ = 0.39 (ethyl acetate). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.06 (s, 1H), 9.00 (t, *J* = 6.4 Hz, 1H), 8.05 (d, *J* = 7.0 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.30 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.09 (t, *J* = 8.9 Hz, 2H), 4.39 (d, *J* = 6.3 Hz, 2H), 3.54 (s, 3H), 2.58 (s, 3H), 1.80 (s, 6H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 165.8, 163.2, 161.9, 161.2 (d, *J* = 242.2 Hz), 159.5, 158.9, 158.0, 152.8, 141.0, 135.3 (d, *J* = 3.0 Hz), 134.2, 134.0, 130.0, 129.1 (d, *J* = 8.3 Hz), 129.0, 128.4, 115.0 (d, *J* = 21.3 Hz), 58.0, 41.5, 33.3, 26.7, 10.8. $^{19}$F NMR (376 MHz, DMSO) $\delta$ -116.1. MS *m/z* 571.6 $(M + Na)^+$.

**Figure S9**. Electrospray mass spectrum of **4** acquired in positive-ion mode.

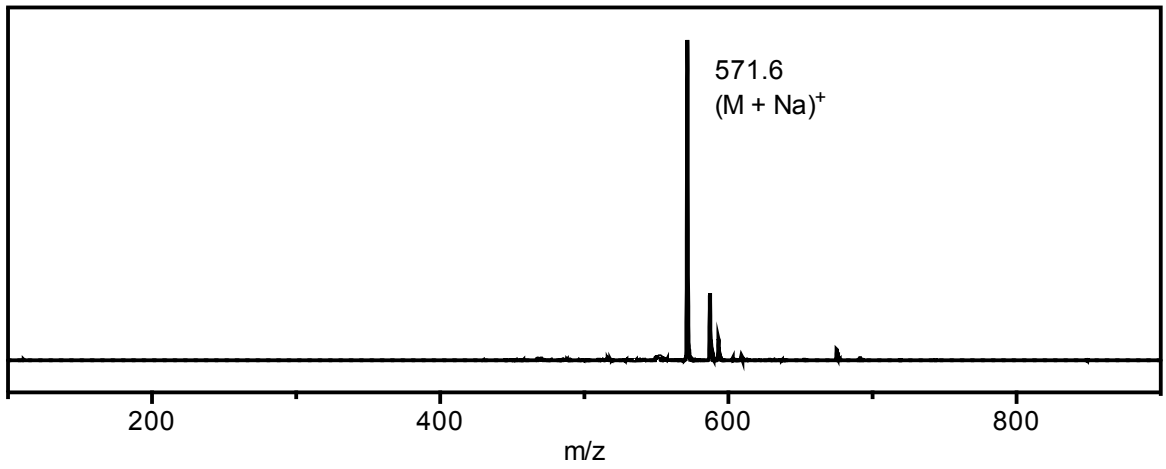
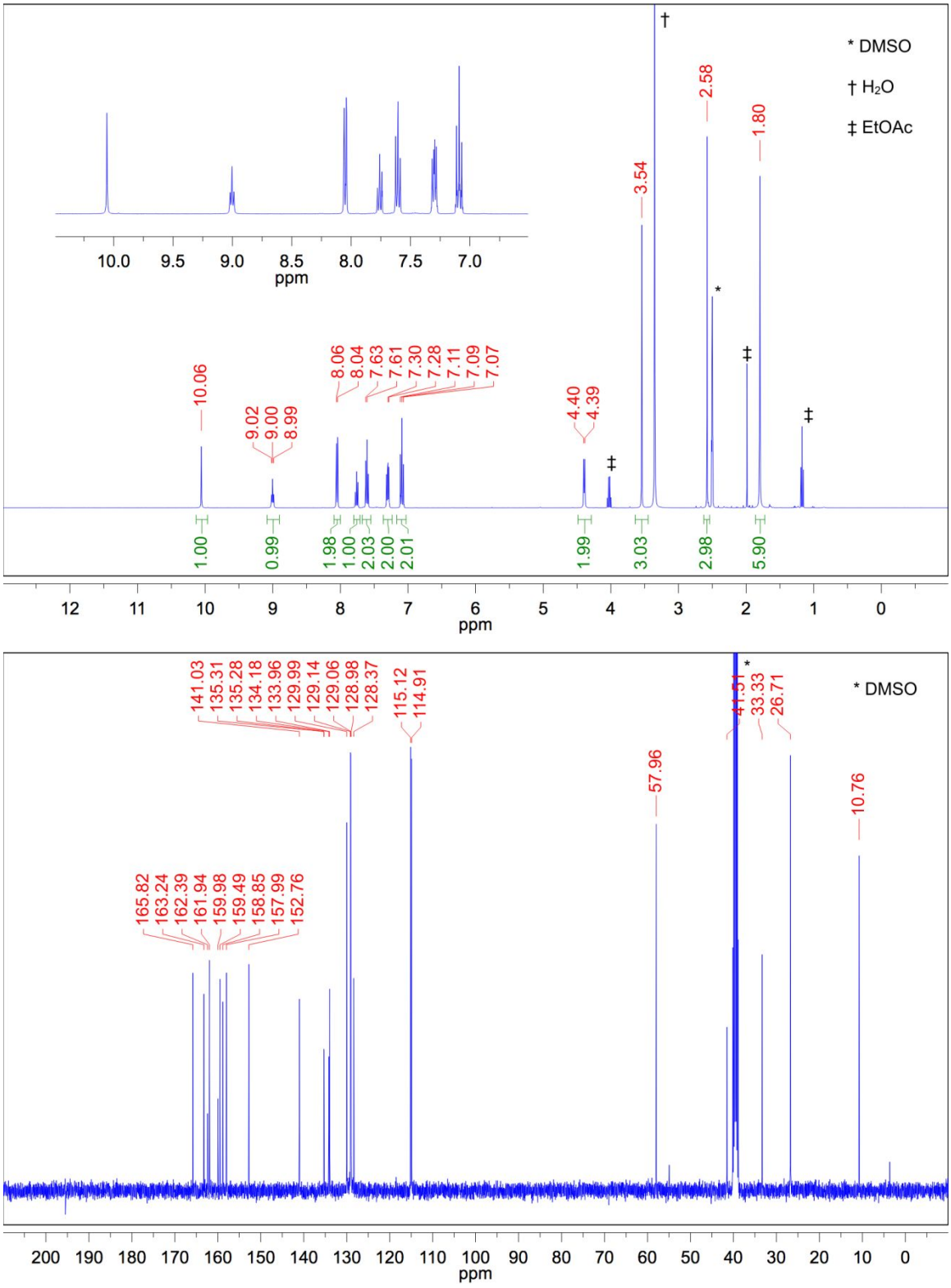
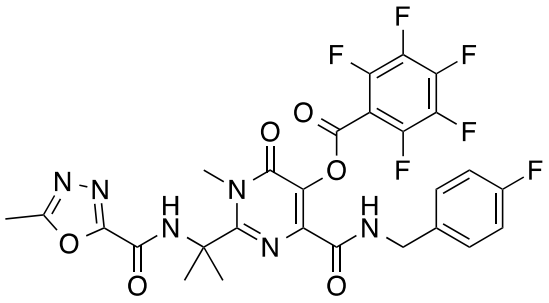


**Figure S10**. $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (101 MHz) of **4** in DMSO-$d_6$.





**5**
Chemical Formula: $C_{27}H_{20}F_6N_6O_6$
Exact Mass: 638.13
Molecular Weight: 638.48

**5-(Pentafluorobenzoyloxy)-*N*-[(4-fluorophenyl)methyl]-1,6-dihydro-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]}ethyl)-6-oxo-4-pyrimidinecarboxamide (5).** Pentafluorbenzoyl chloride (0.069 mL, 0.48 mmol, 1.1 equiv) was added dropwise to a solution of raltegravir (0.200 g, 0.45 mmol) and triethylamine (0.180 mL, 1.29 mmol, 2.9 equiv) in dichloromethane (3.0 mL) and stirred at room temperature. After 3 h the reaction was diluted with dichloromethane (25 mL), washed with saturated aq. $NaHCO_3$ (1 x 45 mL) and brine (1 x 45 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (ethyl acetate) to provide compound **5** as a white solid (0.025 g, 8.6 % yield). $R_f$ = 0.39 (ethyl acetate). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.08 (s, 1H), 9.04 (t, $J$ = 6.4 Hz, 1H), 7.33 (dd, $J$ = 8.7, 5.5 Hz, 2H), 7.14 (t, $J$ = 8.9 Hz, 2H), 4.42 (d, $J$ = 6.3 Hz, 2H), 3.55 (s, 3H), 2.57 (s, 3H), 1.79 (s, 6H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 165.8 , 161.6 , 161.2 (d, $J_{F,C}$ = 242.3 Hz), 160.3 , 158.2 , 157.9 , 155.8 , 152.7 , 141.0 , 135.2 (d, $J_{F,C}$ = 3.0 Hz), 132.9 , 129.1 (d, $J_{F,C}$ = 8.1 Hz), 115.0 (d, $J_{F,C}$ = 21.3 Hz), 58.0 , 41.5 , 33.4 , 26.6 , 10.7 (resonances from pentafluorobenzoyl group below limit of detection due to large $^{19}$F-$^{13}$C couplings). $^{19}$F NMR (376 MHz, DMSO) $\delta$ -116.0, -137.0, -146.3, -160.6. MS *m/z* 661.3 $(M + Na)^+$.

**Figure S11**. Electrospray mass spectrum of **5** acquired in positive-ion mode.

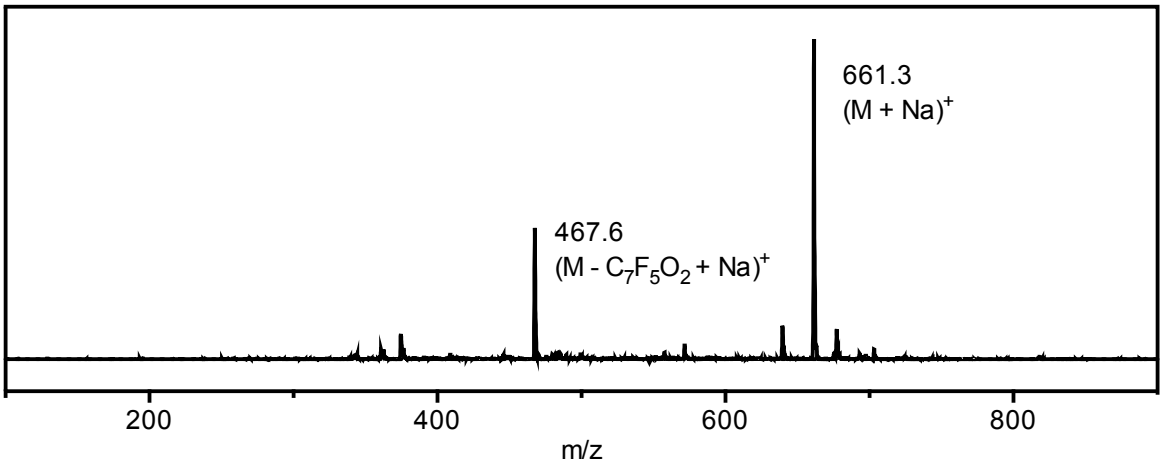
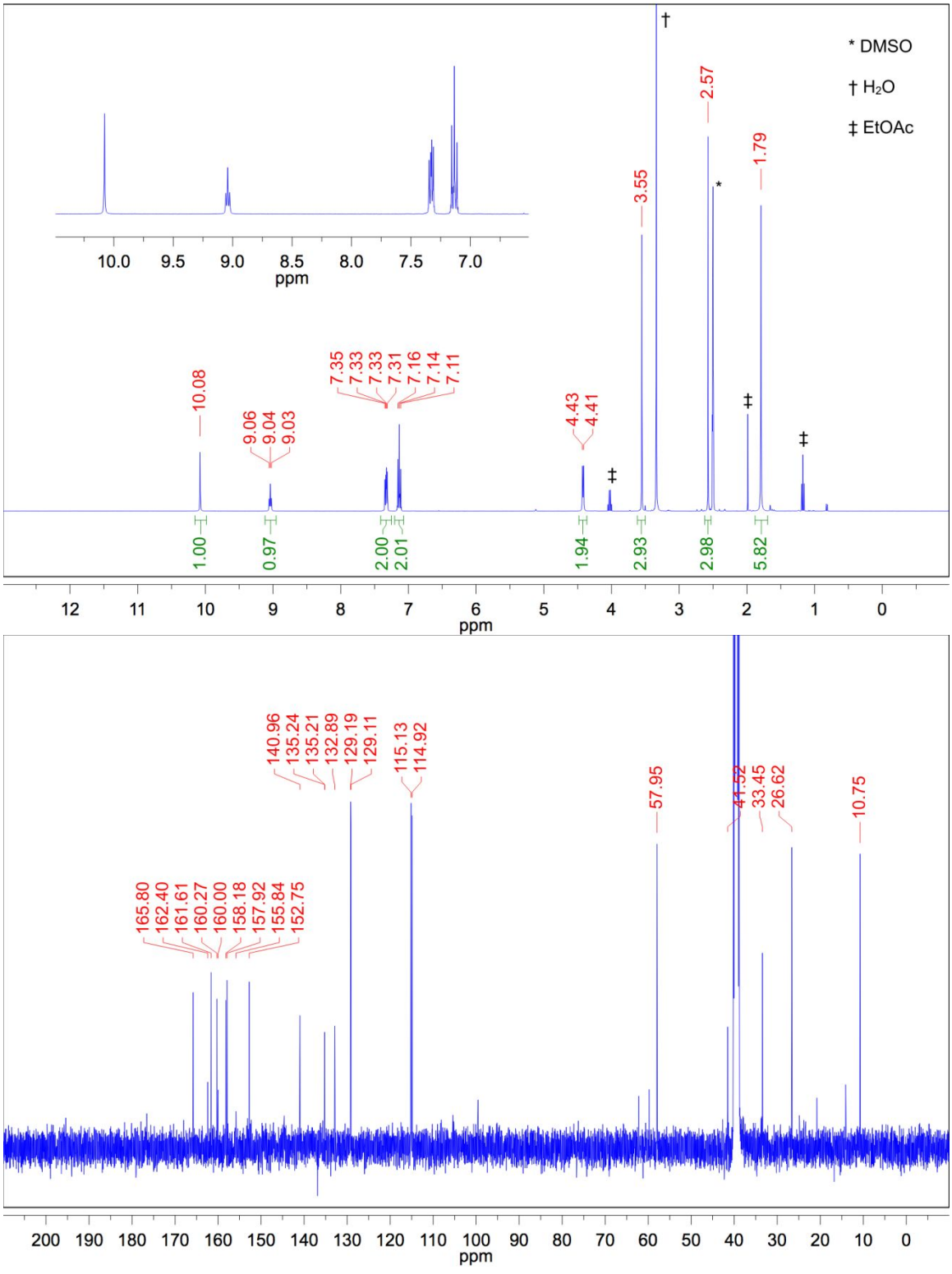
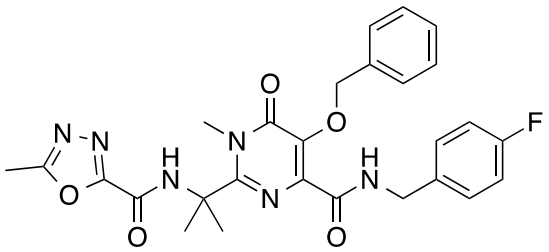


**Figure S12**. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) of **5** in DMSO-$d_6$.





**6**

Chemical Formula: $C_{27}H_{27}FN_6O_5$
Exact Mass: 534.20
Molecular Weight: 534.55

***N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]}ethyl)-6-oxo-5-(phenylmethoxy)-4-pyrimidinecarboxamide (6).** Potassium iodide (0.053 g, 0.32 mmol, 1.4 equiv), potassium carbonate (0.044 g, 0.32 mmol, 1.4 equiv) and 1,4,7,10,13,16-hexaoxacyclooctadecane (0.003 g, 0.01 mmol, 0.05 equiv) were dissolved in DMF (2.0 mL) and added to raltegravir (0.100 g, 0.23 mmol) under $N_2$. Following raltegravir dissolution benzyl chloride (0.037 mL, 0.32 mmol, 1.4 equiv) was added and the reaction was stirred at 60 ºC. After 4 h the reaction was cooled to room temperature and diluted with ethyl acetate (20 mL), washed with water (3 x 20 mL) and brine (3 x 20 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (1:1 acetone:hexanes) to provide compound **6** as a white solid (0.044 g, 36.6 % yield). $R_f$ = 0.18 (1:1 acetone:hexanes). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.94 (s, 1H), 8.86 (t, $J$ = 6.2 Hz, 1H), 7.43 (dd, $J$ = 7.7, 1.8 Hz, 2H), 7.39 – 7.30 (m, 5H), 7.08 (t, $J$ = 8.9 Hz, 2H), 5.08 (s, 2H), 4.43 (d, $J$ = 6.2 Hz, 2H), 3.52 (s, 3H), 2.57 (s, 3H), 1.73 (s, 6H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 165.8, 163.7, 161.1 (d, $J_{F,C}$ = 242.1 Hz), 160.2, 158.0, 156.9, 152.6, 142.7, 139.7, 137.0, 135.4 (d, $J_{F,C}$ = 3.0 Hz), 129.1 (d, $J_{F,C}$ = 8.1 Hz), 128.2, 128.1, 128.0, 115.0 (d, $J_{F,C}$ = 21.3 Hz), 73.4, 57.7, 41.4, 32.8, 26.8, 10.7 . $^{19}$F NMR (376 MHz, DMSO) $\delta$ -116.2. MS *m/z* 557.6 $(M + Na)^+$.

**Figure S13**. Electrospray mass spectrum of **6** acquired in positive-ion mode.

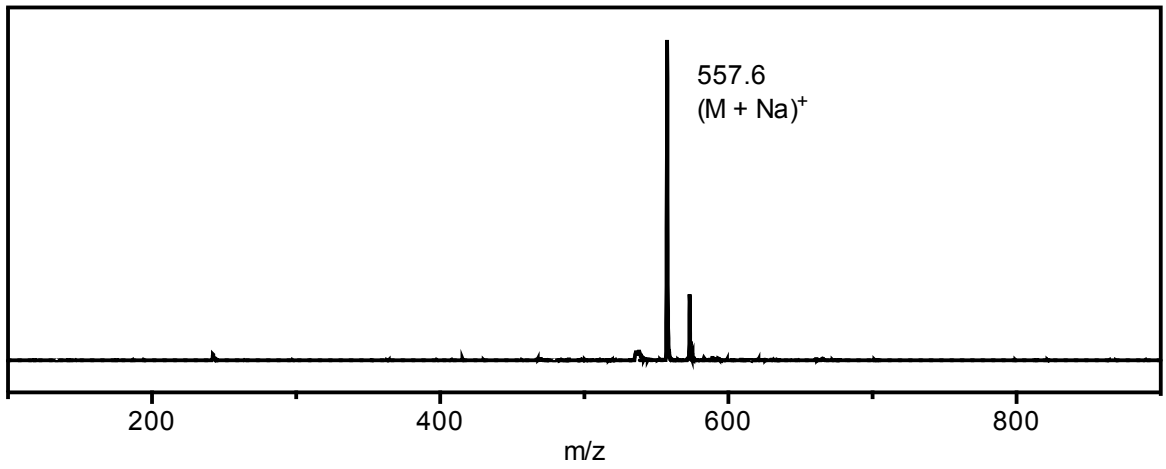
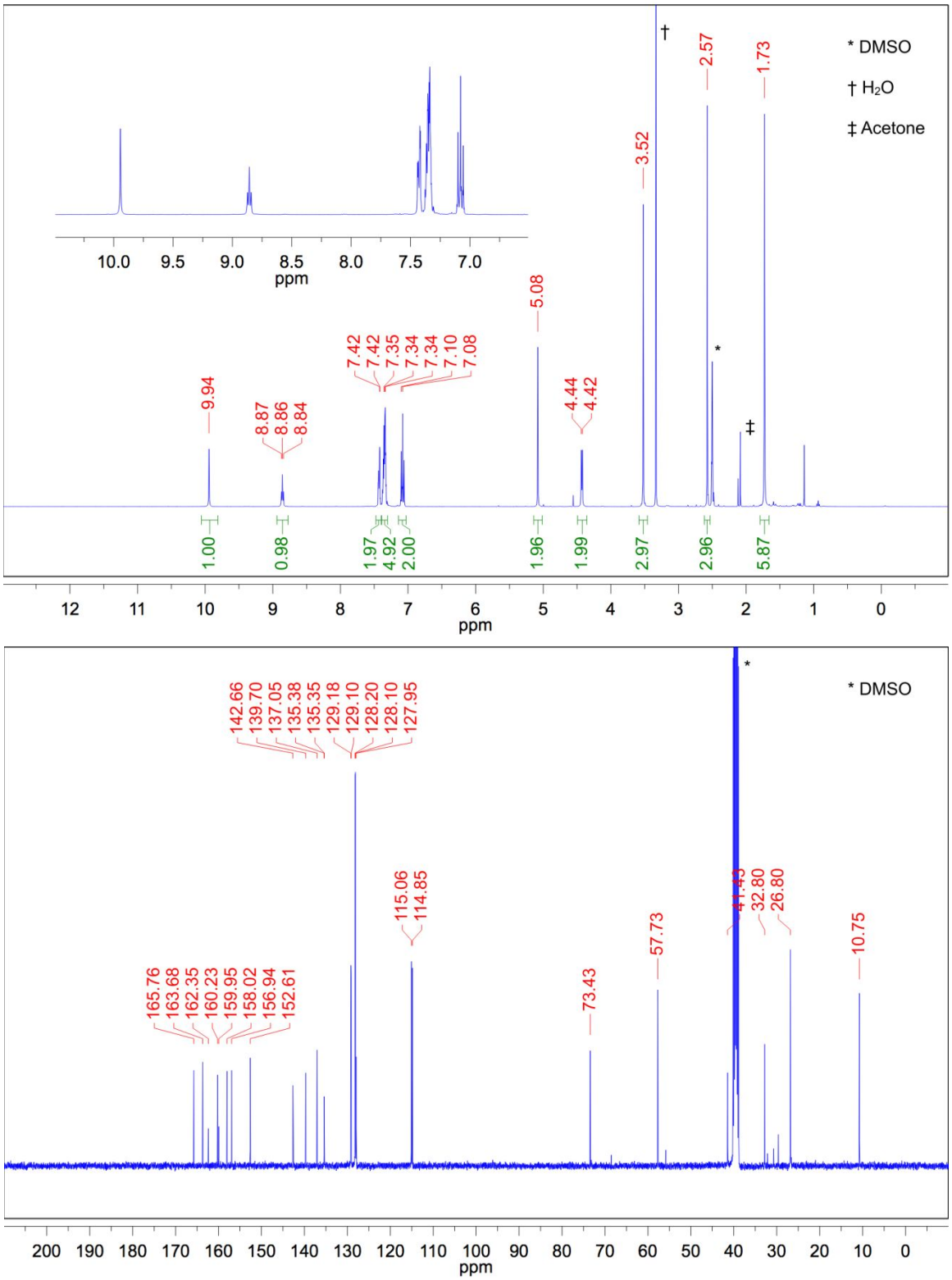
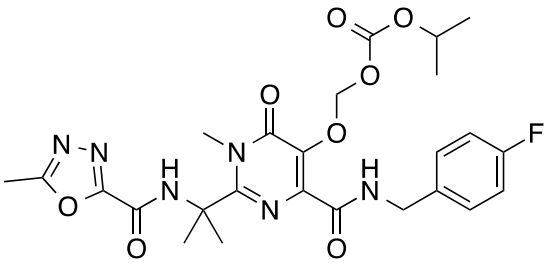


**Figure S14**. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) of **6** in DMSO-$d_6$.





**7**
Chemical Formula: $C_{25}H_{29}FN_6O_8$
Exact Mass: 560.20
Molecular Weight: 560.54

**{[4-({[(4-Fluorophenyl)methyl]amino]}carbonyl)-1,6-dihydro-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino}ethyl)-6-oxo-5-pyrimidinyl]oxy}methyl isopropyl carbonate (7).** Potassium iodide (0.246 g, 1.48 mmol, 1.3 equiv), potassium carbonate (0.223 g, 1.61 mmol, 1.4 equiv) and 1,4,7,10,13,16-hexaoxacyclooctadecane (0.014 g, 0.05 mmol, 0.05 equiv) were dissolved in DMF (10.0 mL) and added to raltegravir (0.500 g, 1.13 mmol) under $N_2$. Following raltegravir dissolution chloromethyl isopropyl carbonate (0.251 mL, 1.88 mmol, 1.7 equiv) was added and the reaction was stirred at 60 ºC. After 4 h the reaction was cooled to room temperature and diluted with ethyl acetate (100 mL), washed with water (3 x 100 mL) and brine (3 x 100 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (1:1 acetone:hexanes) to provide compound **7** as a white solid (0.275 g, 54.9 % yield). $R_f$ = 0.27 (1:1 acetone:hexanes). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.95 (s, 1H), 8.78 (t, $J$ = 6.3 Hz, 1H), 7.37 (dd, $J$ = 8.3, 5.6 Hz, 2H), 7.15 (t, $J$ = 8.9 Hz, 2H), 5.66 (s, 2H), 4.76 (hept, $J$ = 6.3 Hz, 1H), 4.41 (d, $J$ = 6.2 Hz, 2H), 3.49 (s, 3H), 2.57 (s, 3H), 1.73 (s, 6H), 1.20 (d, $J$ = 6.3 Hz, 6H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 165.7, 162.7, 161.2 (d, $J$ = 242.1 Hz), 159.9, 158.0, 157.6, 153.1, 152.6, 141.7, 138.0, 135.4 (d, $J$ = 2.9 Hz), 129.1 (d, $J$ = 8.1 Hz), 115.0 (d, $J$ = 21.2 Hz), 89.5, 72.0, 57.8, 41.4, 32.9, 26.7, 21.4, 10.7. $^{19}$F NMR (376 MHz, DMSO) $\delta$ -116.2. MS *m/z* 583.5 $(M + Na)^+$.

**Figure S15**. Electrospray mass spectrum of **7** acquired in positive-ion mode.

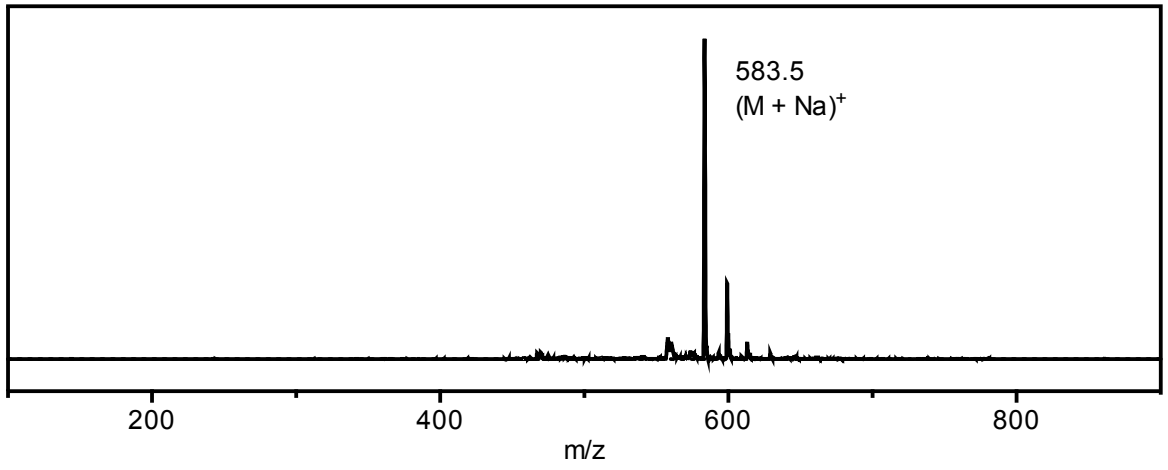


**Figure S16**. $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (101 MHz) of **7** in DMSO-$d_6$.