Supporting information for

Design and catalyzed activation of Tak-242 prodrugs for localized inhibition of TLR4-induced inflammation

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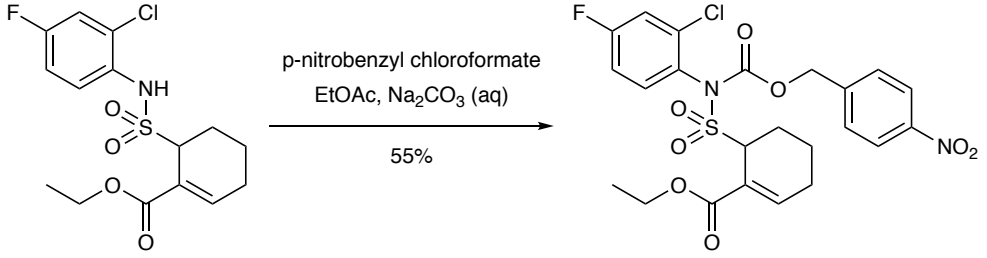
Materials. Chemicals and solvents were purchased from Sigma-Aldrich and Fisher Scientific. Racemic Tak-242 was synthesized using a known procedure.[1] Pd^0-resins were obtained from the Edinburgh Cancer Research UK Centre, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh (UK).

Instrumentation. NMR spectra were recorded at ambient temperature on a Bruker Ascend 600 MHz or at 55 °C on a Bruker Ascend 400 MHz. HRMS was performed using a Thermo LTQ Orbitrap Discovery MS with ESI probe in positive ion mode. Liquid chromatographic analysis for *p*-nitrobenzyl prodrugs **2** and **3** was performed on a Thermo Ultimate 3000 UHPLC instrument (Waltham, MA, USA) equipped with an Agilent Eclipse Plus C^{18} column (3.0 x 100 mm, 3.5 μm) maintained at 30 °C. The mobile phase consisted of solvent A (0.1% formic acid in water) and solvent C (acetonitrile). For compound **2**, the initial gradient was set to 50% solvent A with a linear gradient increasing to 100% C over 10 minutes. The gradient was allowed to return to initial conditions to re-equilibrate the column for 5 minutes. For compound **3**, the initial gradient was set to 50% solvent A and held at this gradient for 4 minutes. This was to allow for the separation of compound **1** from the reduced intermediate. After the 4 minute hold, the gradient increased linearly to 100% C over 6 minutes. The gradient was allowed to return to initial conditions to re-equilibrate the column for 5 minutes. The flow rate was 0.600 mL/min, and the injection loop was 20 μL. Detection was carried out by a UV/Vis detector set to 210 nm, 254 nm, and 280 nm wavelengths. Liquid chromatographic analysis for propargyl prodrugs **4** and **5** was performed on a Thermo Accela HPLC instrument (Waltham, MA, USA) equipped with an Agilent Poroshell 300SB-C^{18} column (2.1 x 75 mm, 5 μm) maintained at 30 °C. The mobile phase consisted of solvent A (0.1% formic acid in water) and solvent B (methanol). The initial gradient was set to 50% solvent A with a linear gradient increasing to 98% B over 4 minutes and maintained for an additional 2.5 minutes. The gradient was allowed to return to initial conditions to re-equilibrate the column for 1 minute. The flow rate was 0.350 mL/min, and the injection volume was 10 μL in full loop injection mode. Detection was carried out by a Thermo LTQ Orbitrap Discovery MS with ESI probe in positive ion mode. Determination of TLR4 antagonism was carried out on a Fisherbrand™ accuSkan™ GO UV/Vis Microplate Spectrophotometer.

Synthesis of ethyl 6-(*N*-(2-chloro-4-fluorophenyl)-*N*-(((4-nitrobenzyl)oxy)carbonyl)sulfamoyl)cyclohex-1-ene-1-carboxylate (2).



1 **2**

Ethyl 6-(*N*-(2-chloro-4-fluorophenyl)sulfamoyl)cyclohex-1-ene-1-carboxylate (64.5 mg, 0.178 mmol) stirred vigorously in 0.37 mL ethyl acetate, 0.26 mL saturated sodium carbonate, 0.11 mL water at 0 °C. *p*-nitrobenzylchloroformate (83.1 mg, 0.385 mmol) was added slowly. After stirring for 4 hours, the reaction mixture was diluted with ethyl acetate and water, and the aqueous phase was extracted three times with ethyl acetate. The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated completely, and column chromatography (0% - 20% ethyl acetate/hexanes) afforded the product as an amorphous white solid in 55% yield.

HRMS (+ESI) calcd for $C_{23}H_{22}ClFN_2O_8S$ [M + Na]+ 563.0662, found 563.0660

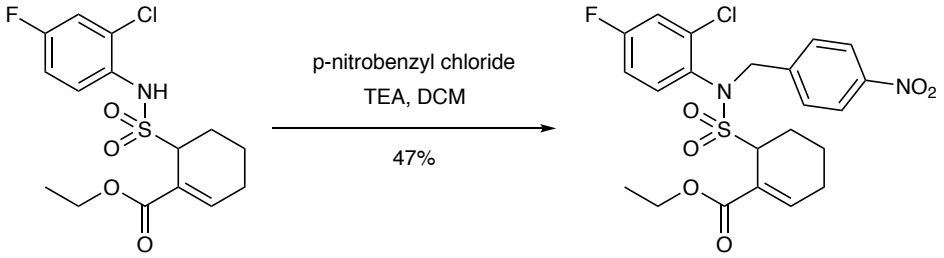
^{1}H NMR (600 MHz, $CDCl_3$) Rotamer A: δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.43 (m, 1H), 7.21 – 7.27 (m, 2H), 6.97 – 7.00 (m, 1H), 5.40 (m, 1H), 5.34 – 5.38 (m, 2H), 4.19 – 4.31 (m, 2H), 2.80 – 2.83 (m, 1H),

2.46 – 2.55 (m, 2H), 2.27 – 2.32 (m, 1H), 2.01 – 2.10 (m, 1H), 1.76 – 1.83 (m, 2H), 1.32 (t, *J* = 7.1 Hz) Rotamer B: δ 8.19 – 8.21 (m, 2H), 7.70 (dd, *J* = 8.7, 5.5 Hz, 1H), 7.41 – 7.43 (m, 2H), 7.36 – 7.37 (m, 1H), 7.21 – 7.27 (m, 1H), 7.06 – 7.10 (m, 1H), 5.26 (s, 2H), 5.01 – 5.02 (m, 1H), 4.06 – 4.18 (m, 2H), 2.68 – 2.71 (m, 1H), 2.46 – 2.55 (m, 1H), 2.27 – 2.32 (m, 1H), 2.16 – 2.24 (m, 1H), 1.76 – 1.83 (m, 2H), 1.24 (t, *J* = 7.0 Hz)

^{1}H NMR (400 MHz, DMSO, 55 °C) δ 8.12 (d, *J* = 8.9 Hz, 2 H), 7.48 – 7.53(m, 3 H), 7.46 (dd, *J* = 8.4, 3.0 Hz, 1 H), 7.15 – 7.21 (m, 2 H), 4.91 – 5.00 (m, 2 H), 4.73 (bs, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 2.15 – 2.38 (m, 3H), 1.90 – 2.01 (m, 1H), 1.78 – 1.87 (m, 1H), 1.58 – 1.67 (m, 1H), 1.09 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 162.6 (d, *J* = 253.9 Hz), 151.9, 149.1, 148.0 (d, *J* = 14.4 Hz), 142.2, 132.4 (d, *J* = 9.8 Hz), 128.3, 128.1, 123.9, 123.9 (d, *J* = 8.3 Hz), 117.8 (d, *J* = 25.9 Hz), 115.0 (d, *J* = 22.4 Hz), 67.7, 61.5, 59.1, 25.4, 23.9, 16.9, 14.4.

Synthesis of ethyl 6-(*N*-(2-chloro-4-fluorophenyl)-*N*-((4-nitrobenzyl)sulfamoyl)cyclohex-1-ene-1-carboxylate (3).



1 **3**

Ethyl 6-(*N*-(2-chloro-4-fluorophenyl)sulfamoyl)cyclohex-1-ene-1-carboxylate (80.0 mg, 0.221 mmol), *p*-nitrobenzylchloride (138.1 mg, 0.805 mmol) was stirred in dichloromethane (1.9 mL) at 0 °C. Triethylamine (0.171 mL, 1.22 mmol) was added slowly. After stirring for 50 hours, the reaction mixture was partitioned between dichloromethane and water. The aqueous phase was extracted three times with dichloromethane. The combined organic phase was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated completely, and column chromatography (0% - 20% ethyl acetate/hexanes) afforded the product as an amorphous white solid in 47% yield.

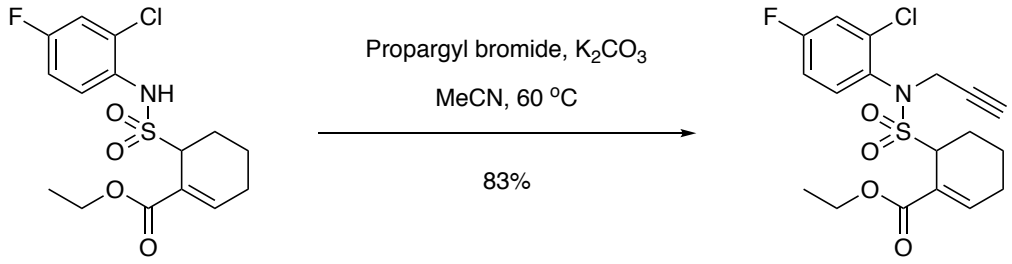
HRMS (+ESI) calcd for $C_{22}H_{22}ClFN_2O_6S$ [M + Na]+ 519.0763, found 519.0762

^{1}H NMR (600 MHz, DMSO-d6) δ 8.15 (d, *J* = 8.7 Hz, 2H), 7.53 – 7.61 (m, 4H), 7.24 (ddd, *J* = 8.3, 8.3, 3.3 Hz, 1H), 7.17 (m, 1H), 4.70 – 4.99 (m, 3H), 4.08 (bs, 2H), 2.33 – 2.37 (m, 1H), 2.17 – 2.26 (m, 2H), 1.95 (bs, 1H), 1.80 – 1.86 (m, 1H), 1.63 (bs, 1H), 1.09 (bs, 3H)

^{1}H NMR (400 MHz, DMSO-d6, 55 °C) δ 8.14 (d, *J* = 8.8 Hz, 2H), 7.49 – 7.55(m, 4H), 7.22 (ddd, *J* = 8.9, 8.0, 2.9 Hz, 1 H), 7.16 – 7.18 (m, 1H), 4.93 – 5.02 (m, 2 H), 4.76 (bs, 1H), 4.09 (q, *J* = 7.0 Hz, 2H), 2.17 – 2.40 (m, 3H), 1.93 – 2.04 (m, 1H), 1.79 – 1.91 (m, 1H), 1.61 – 1.66 (m, 1H), 1.12 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, DMSO-d6) δ 165.8, 162.0, 160.4, 147.1, 145.5, 143.3, 132.3, 130.2, 124.1, 123.5, 60.4, 40.1, 31.3, 24.2, 22.1, 16.1, 13.8.

Synthesis of ethyl 6-(*N*-(2-chloro-4-fluorophenyl)-*N*-(prop-2-yn-1-yl)sulfamoyl)cyclohex-1-ene-1-carboxylate (4).



1 **4**

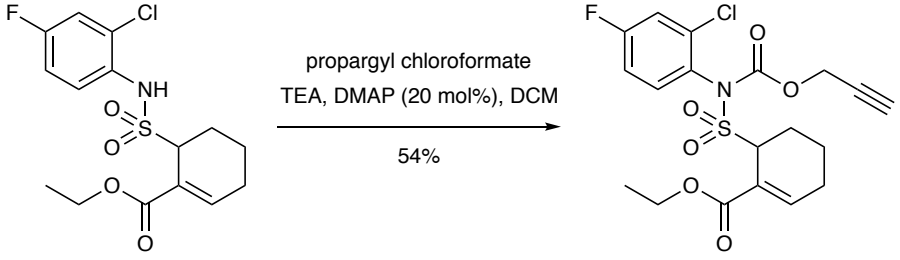
Ethyl 6-(*N*-(2-chloro-4-fluorophenyl)sulfamoyl)cyclohex-1-ene-1-carboxylate (376.0 mg, 1.04 mmol), potassium carbonate (296.4 mg, 2.14 mmol) was stirred in acetonitrile (9.5 mL) at 60 °C. Propargyl bromide 20 wt% in toluene (235 µL, 3.30 mmol) was added. After stirring for 20 hours at 60 °C, the reaction mixture was concentrated and partitioned between water (50 mL) and dichloromethane (50 mL). The aqueous phase was extracted with dichloromethane (2 x 50 mL), and the combined organic phase was washed with brine, dried over sodium sulfate, and concentrated. The resulting residue was purified via column chromatography (100% dichlormethane) to afford the product as an amorphous white solid in 83% yield.

HRMS (+ESI) calcd for $C_{18}H_{19}ClFNO_4S$ [M + Na]+ 422.0600, found 422.0608

^{1}H NMR (600 MHz, DMSO-d6) δ 7.66 – 7.69 (m, 1H), 7.59 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.34 (ddd, *J* = 8.8, 8.8, 2.9 Hz, 1H), 7.13 – 7.15 (m, 1H), 4.62 (bs, 1H), 4.44 (bs, 2H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.25 – 3.26 (m, 1H), 2.31 – 2.38 (m, 2H), 2.15 – 2.25 (m, 1H), 1.92 – 2.03 (m, 1H), 1.76 – 1.86 (m, 1H), 1.60 – 1.65 (m, 1H), 1.12 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (150 MHz, DMSO-d6) δ 165.7, 161.6 (d, *J* = 250.1 Hz), 145.6, 135.6 (d, *J* = 11.8 Hz), 134.4 (d, *J* = 11.4 Hz), 132.4, 123.9, 117.6 (d, *J* = 28.6 Hz), 115.1 (d, *J* = 23.4 Hz), 78.2, 76.7, 60.4, 56.7, 40.1, 24.3, 16.0, 13.8.

Synthesis of ethyl 6-(*N*-(2-chloro-4-fluorophenyl)-*N*-((prop-2-yn-1-yloxy)carbonyl)sulfamoyl)cyclohex-1-ene-1-carboxylate (5).



1 **5**

Triphosgene (2.4990 g, 8.42 mmol) and potassium carbonate (3.75 g, 27.1 mmol) were stirred in acetonitrile (27.5 mL) at 0 °C. Propargyl alcohol (500 mg, 8.92 mmol) was added dropwise. The solution was allowed to rise to room temperature and stir for 7.5 hours. The solution was filtered, and the solvent was distilled under reduced pressure to yield the crude chloroformate (932.8 mg, 7.87 mmol) which was used without further purification. To a solution of ethyl 6-(*N*-(2-chloro-4-fluorophenyl)sulfamoyl)cyclohex-1-ene-1-carboxylate (49.9 mg, 0.138 mmol) in dichloromethane (0.5 mL) at 0 °C was added triethylamine (59 µL, 0.420 mmol), 4-dimethylaminopyridine (20 mol%), and the crude chloroformate (95.6 mg, 0.807 mmol). The solution was allowed to rise to room temperature and stir for 45 minutes. The reaction mixture was diluted with dichloromethane and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified via column chromatography (25% ethyl acetate/hexanes) to afford the product as an amorphous white solid in 54% yield.

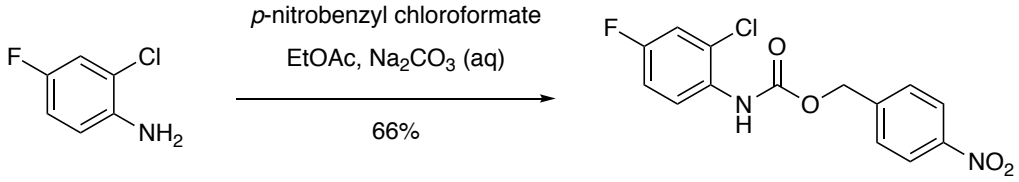
HRMS (+ESI) calcd for $C_{19}H_{19}ClFNO_6S$ [M + Na]+ 466.0498, found 466.0499

^{1}H NMR (600 MHz, $CDCl_3$) Rotamer A: δ 7.40 – 7.24 (m, 1H), 7.24 – 7.28 (m, 1H), 7.21 (dd, *J* = 8.0, 2.8 Hz, 1 H), 6.98 (ddd, *J* = 8.8, 7.7, 2.8 Hz, 1H), 5.43 (d, *J* = 4.5 Hz, 1H), 4.85 (dd, *J* = 15.5, 2.4 Hz, 1H), 4.79 (dd, *J* = 15.5, 2.4 Hz, 1H), 4.18 – 4.26 (m, 2H), 2.84 – 2.86 (m, 1H), 2.45 – 2.55 (m, 2H), 2.26 – 2.32 (m, 1H), 2.01 – 2.09 (m, 1H),

1.76 – 1.85 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H) Rotamer B: δ 7.62 (dd, *J* = 8.8, 5.5 Hz, 1H), 7.40 – 7.41 (m, 1H), 7.24 – 7.28 (m, 1H), 7.04 – 7.07 (m, 2H), 5.06 (d, *J* = 4.6 Hz), 4.75 (dd, *J* = 15.5, 2.4 Hz, 1H), 4.71 (dd, *J* = 15.5, 2.4 Hz, 1H), 4.29 – 4.34 (m, 2H), 2.72 – 2.74 (m, 1H), 2.45 – 2.55 (m, 2H), 2.24 – 2.32 (m, 1H), 2.17 – 2.24 (m, 1H), 1.76 – 1.85 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (150 MHz, $CDCl_3$) δ 166.14, 162.6 (d, *J* = 253.3 Hz), 151.8, 148.7, 136.3 (d, *J* = 11.4 Hz), 132.5 (d, *J* = 9.8 Hz), 129.4 (d, *J* = 4.3 Hz), 124.0, 117.7 (d, *J* = 26.1 Hz), 114.9 (d, *J* = 22.5 Hz), 76.5, 76.2, 61.5, 59.4, 55.1, 25.3, 24.0, 16.9, 14.4.

Synthesis of 4-nitrobenzyl (2-chloro-4-fluorophenyl)carbamate (6).



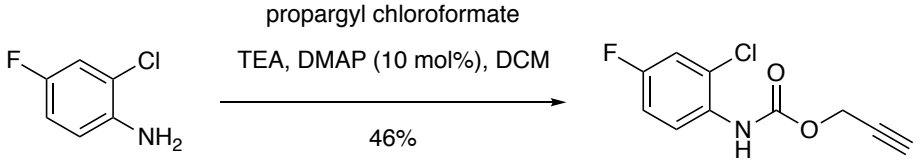
6

2-chloro-4-fluoroaniline (99.1 mg, 0.681 mmol) stirred vigorously in 1.43 mL ethyl acetate, 1.00 mL saturated sodium carbonate, 0.43 mL water at 0 °C. *p*-nitrobenzylchloroformate (162.7 mg, 0.755 mmol) was added slowly. After stirring for 2 hours, the reaction mixture was diluted with ethyl acetate (5 mL) and water (5 mL), and the aqueous phase was extracted with dichloromethane (2 x 5 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Recrystallization in ethyl acetate afforded the product as an amorphous white solid in 66% yield.

HRMS (+ESI) calcd for $C_{14}H_{10}ClFN_2O_4$ [M + Na]+ 347.0205, found 347.0205

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.7 Hz, 2H), 8.09 (bs, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.08 – 7.15 (m, 2H), 7.02 (ddd, *J* = 9.1, 7.9, 2.8 Hz, 1H), 5.31 (s, 2H)

Synthesis of prop-2-yn-1-yl (2-chloro-4-fluorophenyl)carbamate (7).



7

2-chloro-4-fluoroaniline (128.9 mg, 0.886 mmol) was stirred in 0.5 mL dichloromethane, triethylamine (159 μL, 1.13 mmol), and dimethylaminopyridine (10 mol%) at 0 °C. Propargyl chloroformate (87.5 mg, 0.738 mmol) was added slowly. After stirring for 1 hour, the reaction mixture was diluted with water and extracted with ethyl acetate (x3). The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Recrystallization in chloroform afforded the product as an amorphous white solid in 46% yield.

HRMS (+ESI) calcd for $C_{10}H_7ClFNO_2$ [M + Na]+ 250.0042, found 250.0042

^{1}H NMR (600 MHz, DMSO-*d6*) δ 8.95 (s, 1H), 8.02 (dd, J = 9.2, 5.8 Hz, 1H), 7.49 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.21 (ddd, *J* = 9.0, 8.3, 2.6 Hz, 1H), 3.31 (s, 2H), 2.52 (m, 1H).

Computational Details. Initial geometries of the Tak-242 prodrugs **2**, **3**, **4**, and **5** structures were obtained from a set of relaxed torsional energy scans using the hybrid B3LYP density functional in conjunction with a split-valence triple-ξ quality 6-311G(2*df*, 2*pd*) basis set. The stationary points identified from this initial set of computations were

subsequently subjected to full geometry optimizations and harmonic vibrational frequency computations using the same level of theory in order to quantify the energetic barrier of rotation (ΔE_{rot}) and the Gibb's free energetic barrier of rotation at room temperature (ΔG_{rot}).
All computations were performed using the Gaussian 09 software package and the analytic gradients and Hessians available therein. All computations were carried out using a pruned numerical integration grid composed of 175 radial shells (250 radial shells for sulfur atoms) and 974 angular points per shell along with a threshold $< 10^{-9}$ for the RMS change in the density matrix during the self-consistent field procedure. The threshold for removing linear dependent basis functions (magnitude of the eigenvalues of the overlap matrix) was tightened from 10^{-6} to 10^{-7}. All electronic energies have been converged to at least 10^{-9} E_h while the Cartesian forces of the gradient did not exceed 10^{-6} E_h Bohr^{-1} for all geometry optimizations. Pure angular momentum basis functions (i.e., 5*d*, 7*f*, etc.) were used instead of their Cartesian counterparts (i.e., 6*d*, 10*f*, etc.). The results from the set of relaxed torsional energy scans, the nature of each stationary point on the potential energy surface (n_i), and the corresponding Cartesian coordinates from the fully geometry optimizations are reported in the subsequent plots and tables.

HPLC Measurement of Nitroreductase-activated Prodrugs. *p*-nitrobenzyl prodrugs (**2** and **3**) were dissolved in DMSO and diluted with enzyme solution containing PBS (pH 7.4), nitroreductase (2 units/mL), and NADH (1 mg/mL) to a final concentration of 0.01 mg/mL prodrug in DMSO:PBS (1:19). The samples were incubated at 37 °C and were analyzed by HPLC at various timepoints. One phase exponential decay was performed using GraphPad Prism version 8.1.2 for MacOS, GraphPad Software, La Jolla California USA, www.graphpad.com.

HPLC Measurement of Prodrugs Activated By Pd^0-Resins. Propargyl prodrugs (**4** and **5**) were dissolved in DMSO and diluted with PBS (pH 7.4) containing Pd^0-resins (1 mg/mL) to a final concentration of 0.05 mg/mL prodrug in DMSO:PBS (1:19). The samples were incubated at 37 °C and were analyzed by LC-MS at various timepoints. One phase exponential decay was performed using GraphPad Prism version 8.1.2 for MacOS, GraphPad Software, La Jolla California USA, www.graphpad.com.

HPLC Measurement of Carbamate Stability. Carbamates **2** and **5** were dissolved in DMSO and diluted with PBS (pH 7.4) in the absence of catalyst to a final concentration of 0.01 mg/mL prodrug in DMSO:PBS (1:19). The samples were incubated at 37 °C and were analyzed by HPLC at various timepoints. One phase exponential decay was performed using GraphPad Prism version 8.1.2 for MacOS, GraphPad Software, La Jolla California USA, www.graphpad.com.

TLR4 Reporter Cell Assay. HEK-Blue™ hTLR4 Cells (InvivoGen) were cultured in Growth Medium: DMEM, 4.5 g/l glucose, 10% (v/v) fetal bovine serum, 100 U/mL penicillin, 100 µg/mL streptomycin, 100 µg/mL Normocin™, 2 mM L-glutamine.

A stock solution of 140,000 HEK TLR4 cells (InvivoGen) per 1 mL of HEK-Blue™Detection (InvivoGen) was created. 90 µL/well of the stock solution was added to a 96 well plate. To each of the wells was added 10 µL of 10% DMSO stock solutions of the desired drugs at varying concentrations (15 µM, 10 µM, 1 µM, 0.1 µM, 0.01 µM, 0.001 µM) plus a negative and positive control. The cells plus drug solutions were allowed to incubate for 1 hour at 37 °C in 5% CO_2. After 1 hour, 10 µL of LPS was incorporated into each well with a final concentration of 10 ng/mL per well. Plates were incubated for 22 hours at 37 °C in 5% CO_2. After 22 hours, the plates were read on a plate reader (AccuSkan GO Fisher Scientific) by shaking for 10 seconds prior to reading the plate at 650 nm. Log(inhibitor) vs response – variable slope was performed using GraphPad Prism version 8.1.2 for MacOS, GraphPad Software, La Jolla California USA, www.graphpad.com.

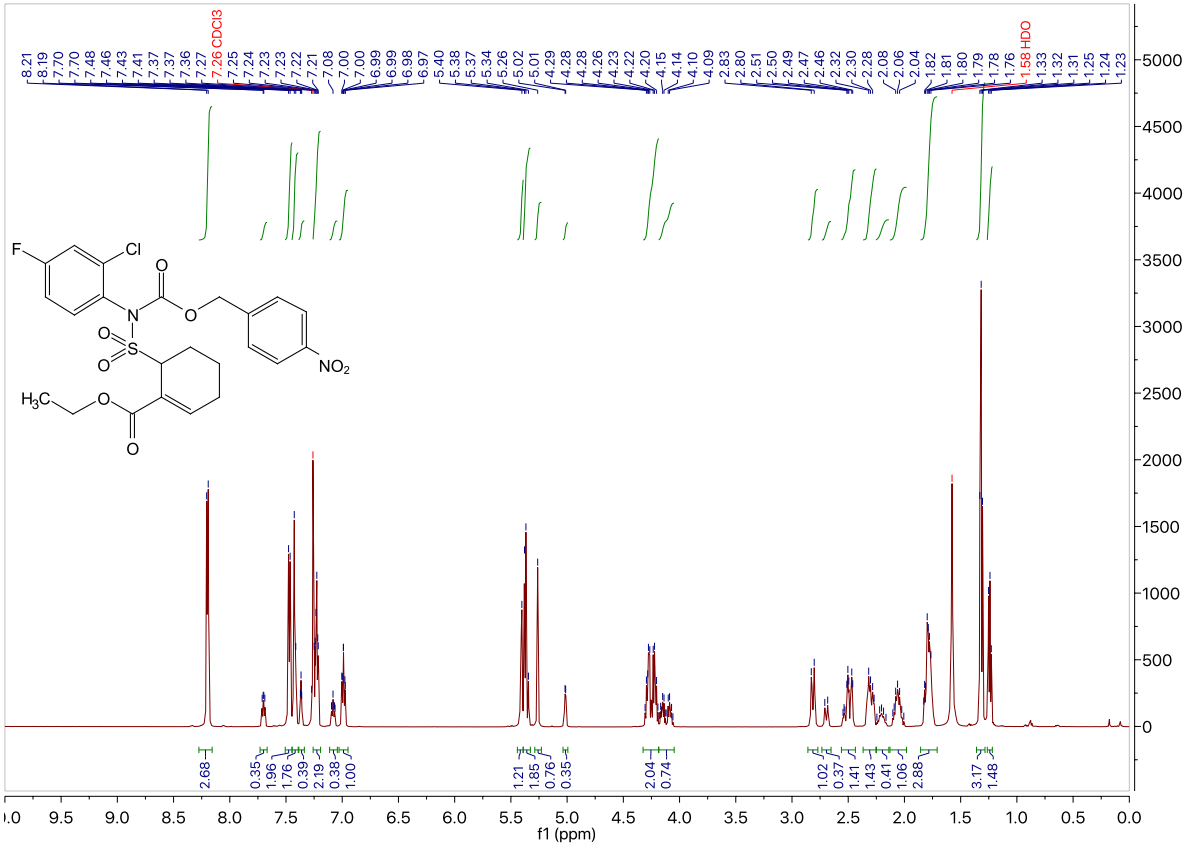


Figure S1. Proton NMR of compound **2** ($CDCl_3$).

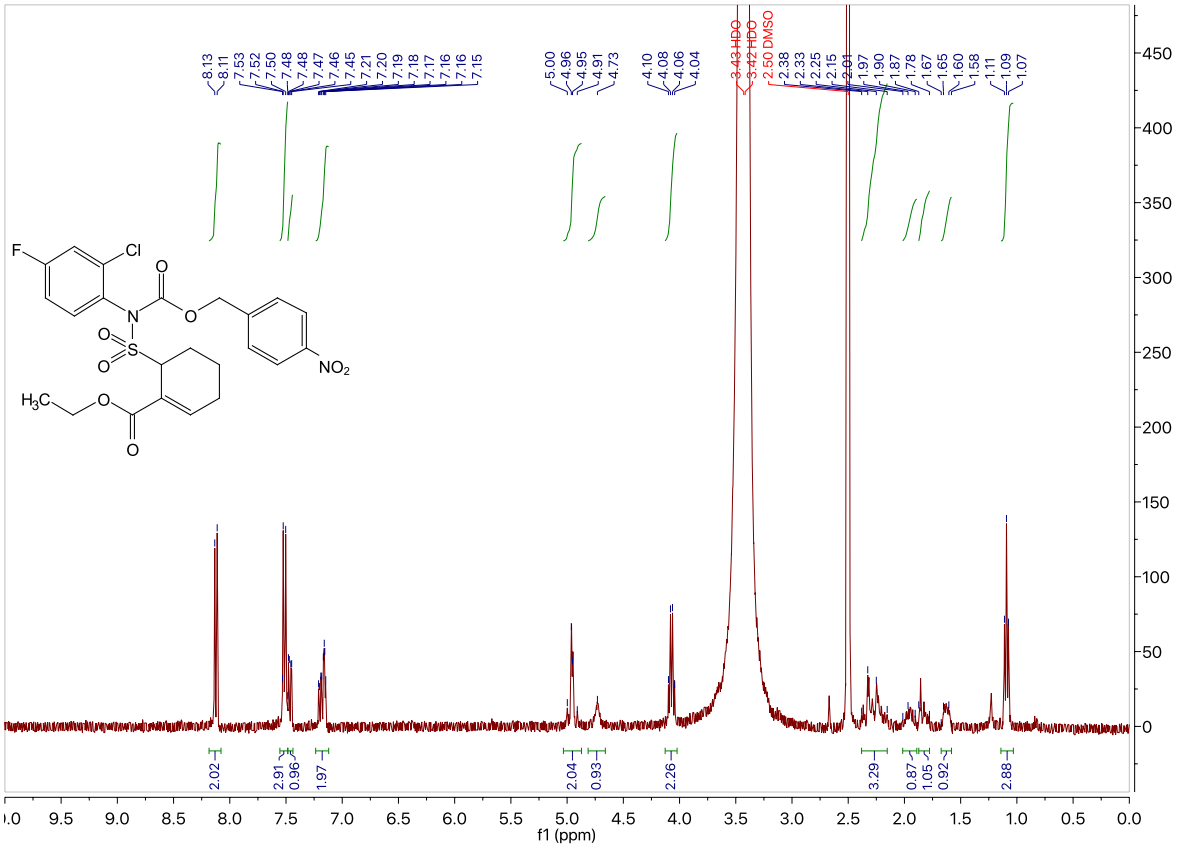


Figure S2. Proton NMR at 55 °C of compound **2** (DMSO-d6).

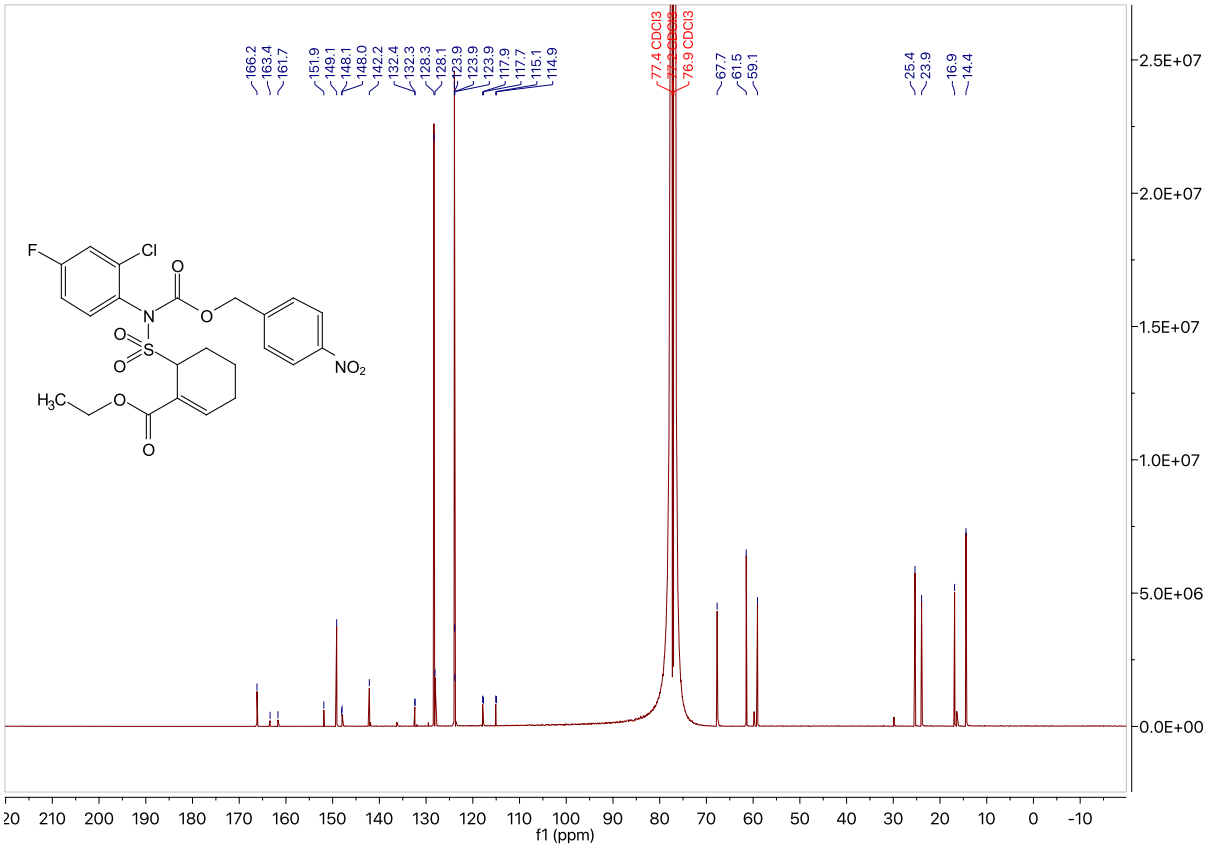


Figure S3. Carbon NMR of compound **2**.

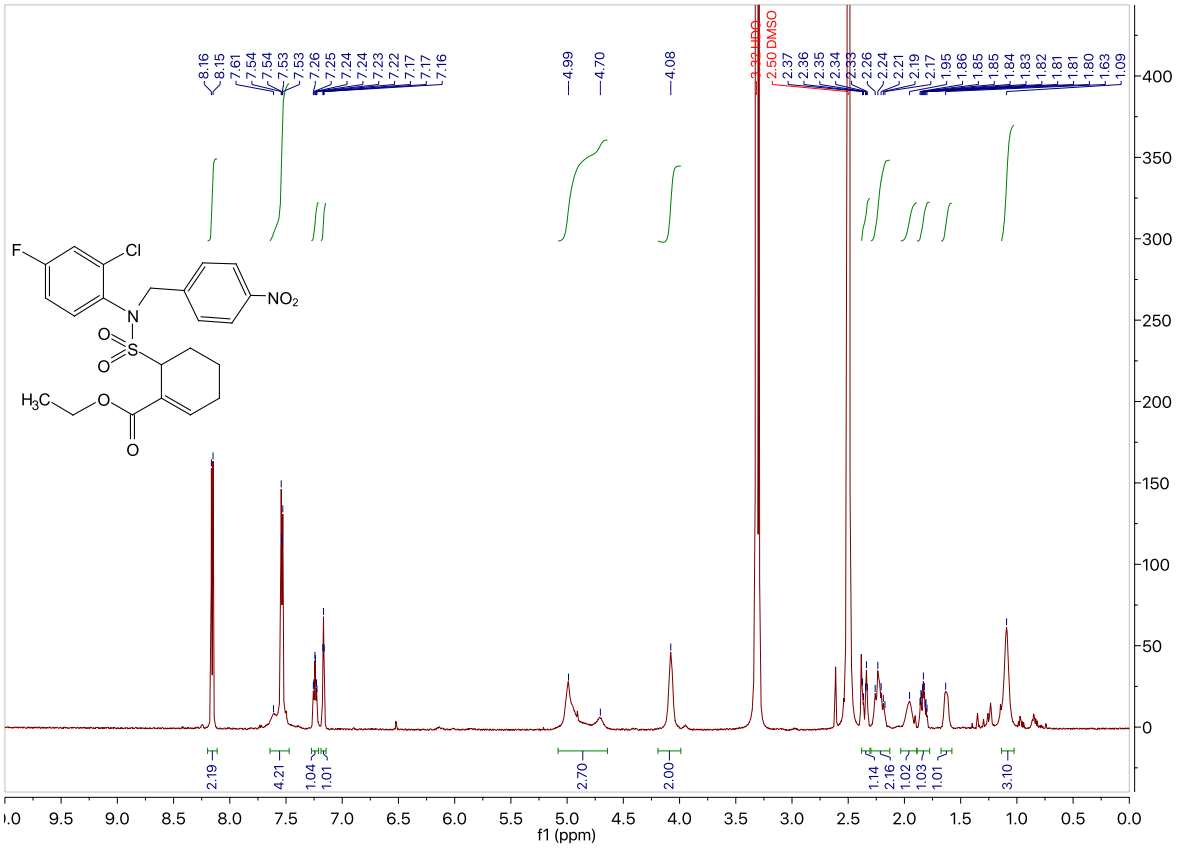


Figure S4. Proton NMR of compound **3**.

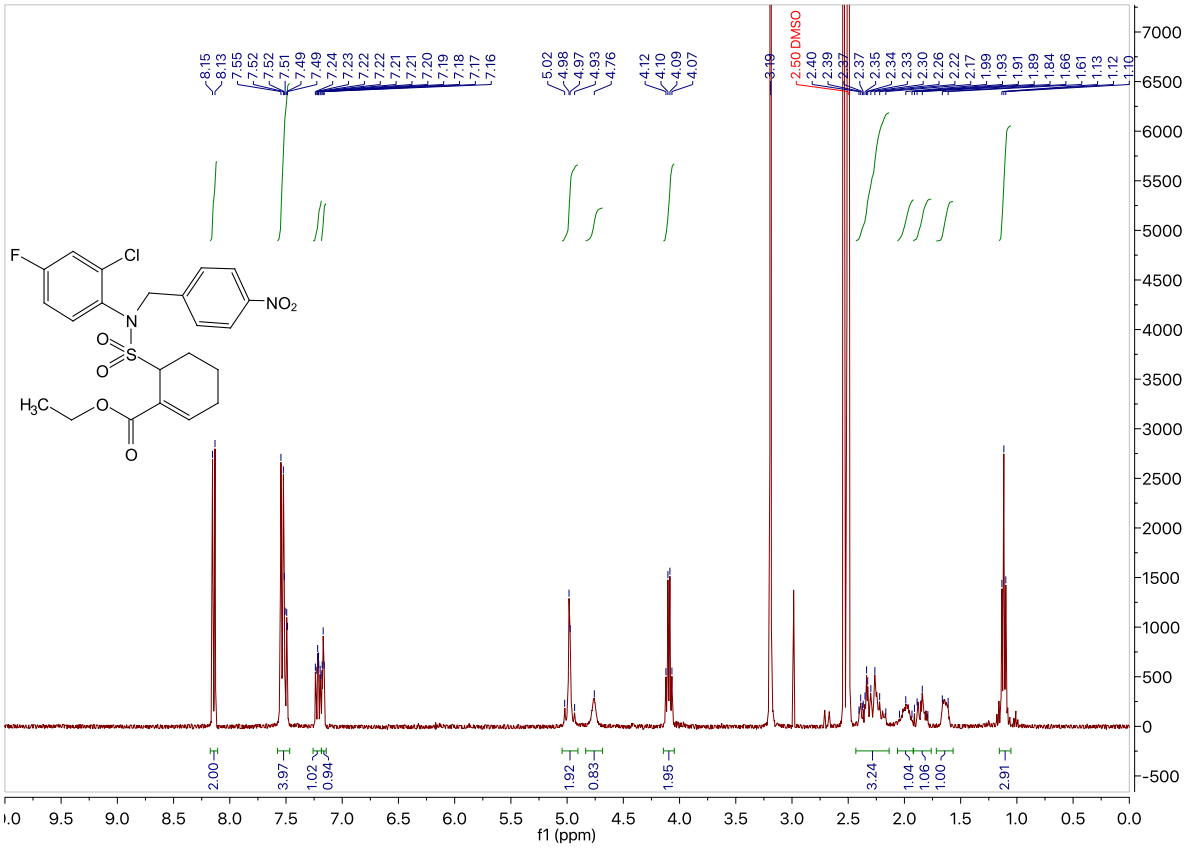


Figure S5. Proton NMR at 55 °C of compound **3**.

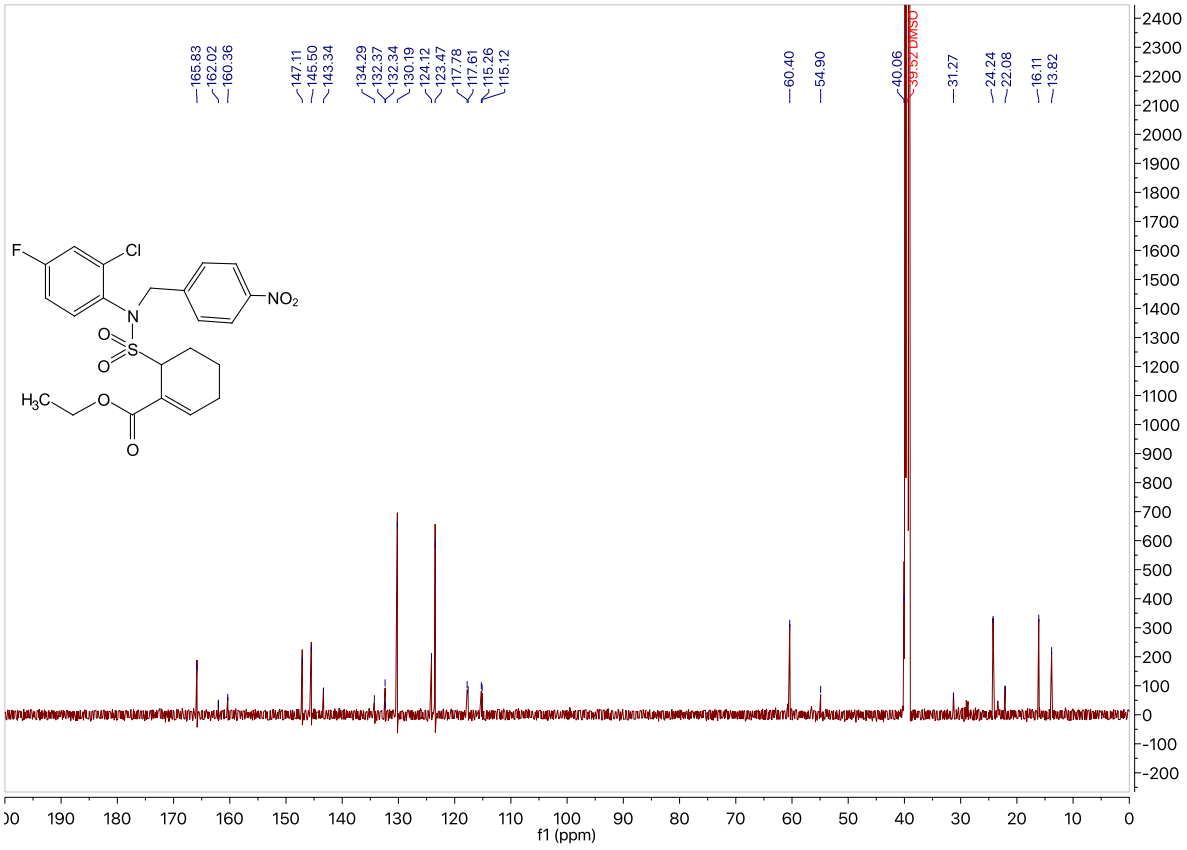


Figure S6. Carbon NMR of compound **3**.

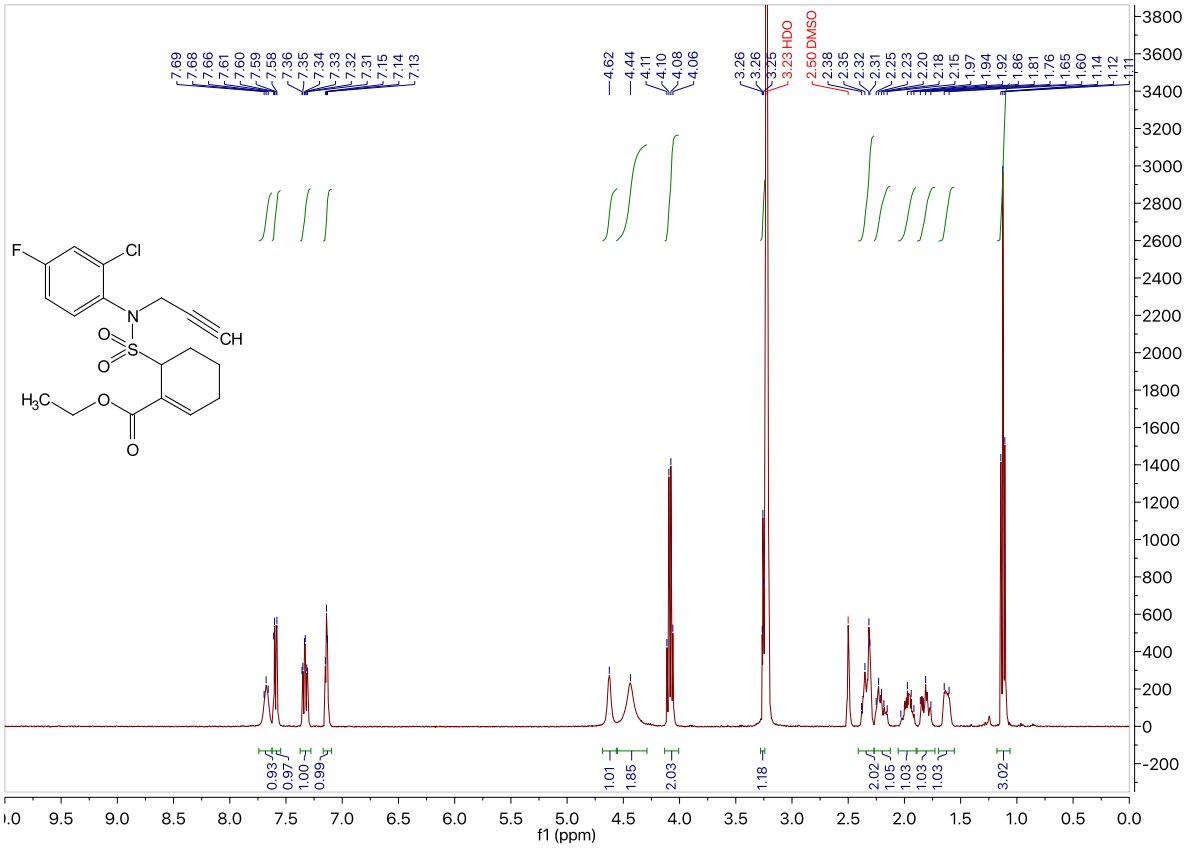


Figure S7. Proton NMR of compound **4**.

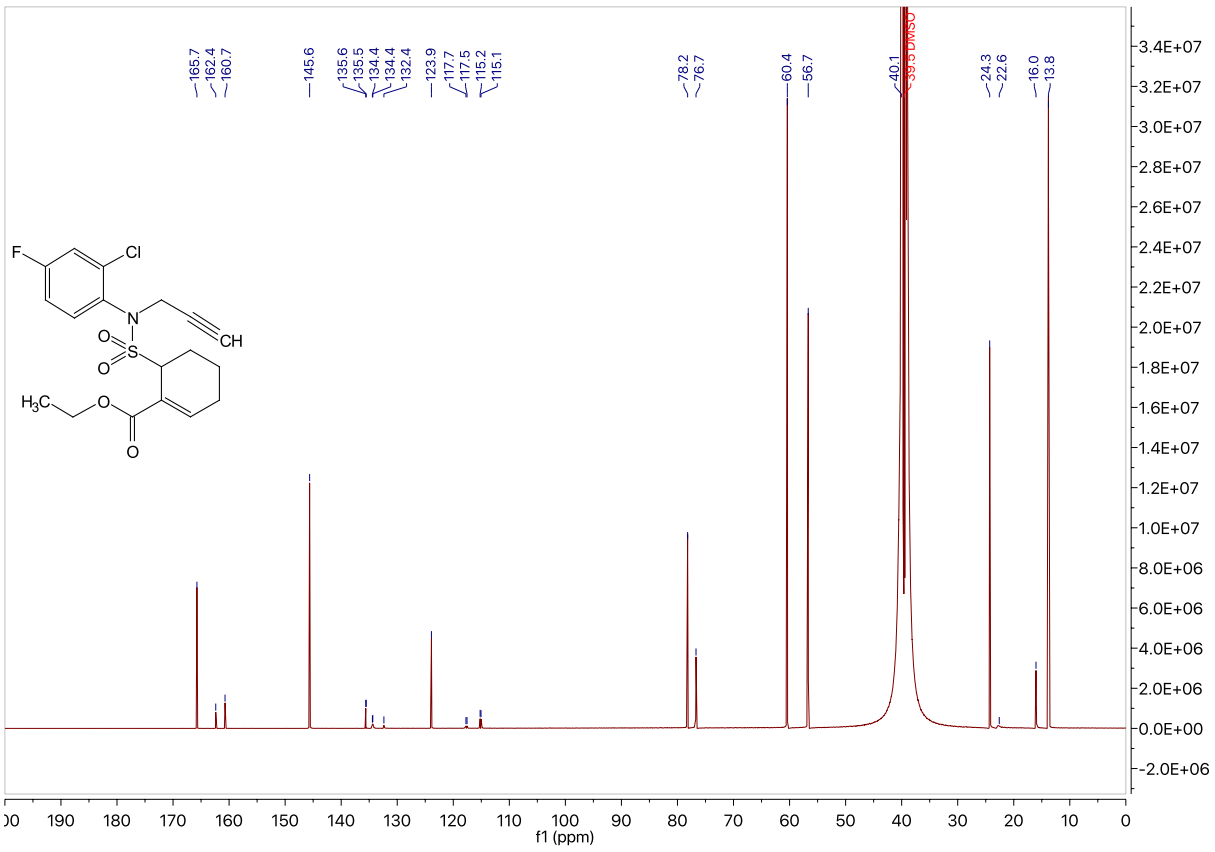


Figure S8. Carbon NMR of compound **4**.

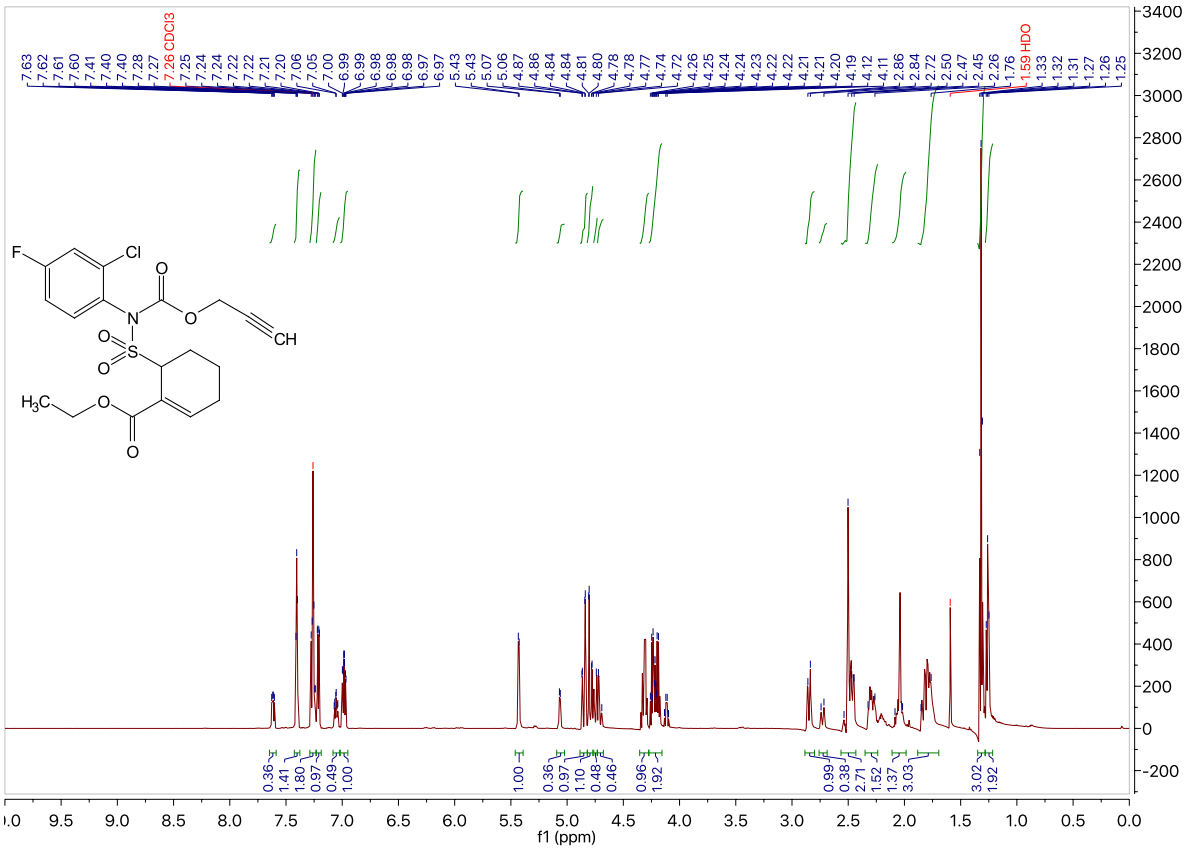


Figure S9. Proton NMR of compound **5**.

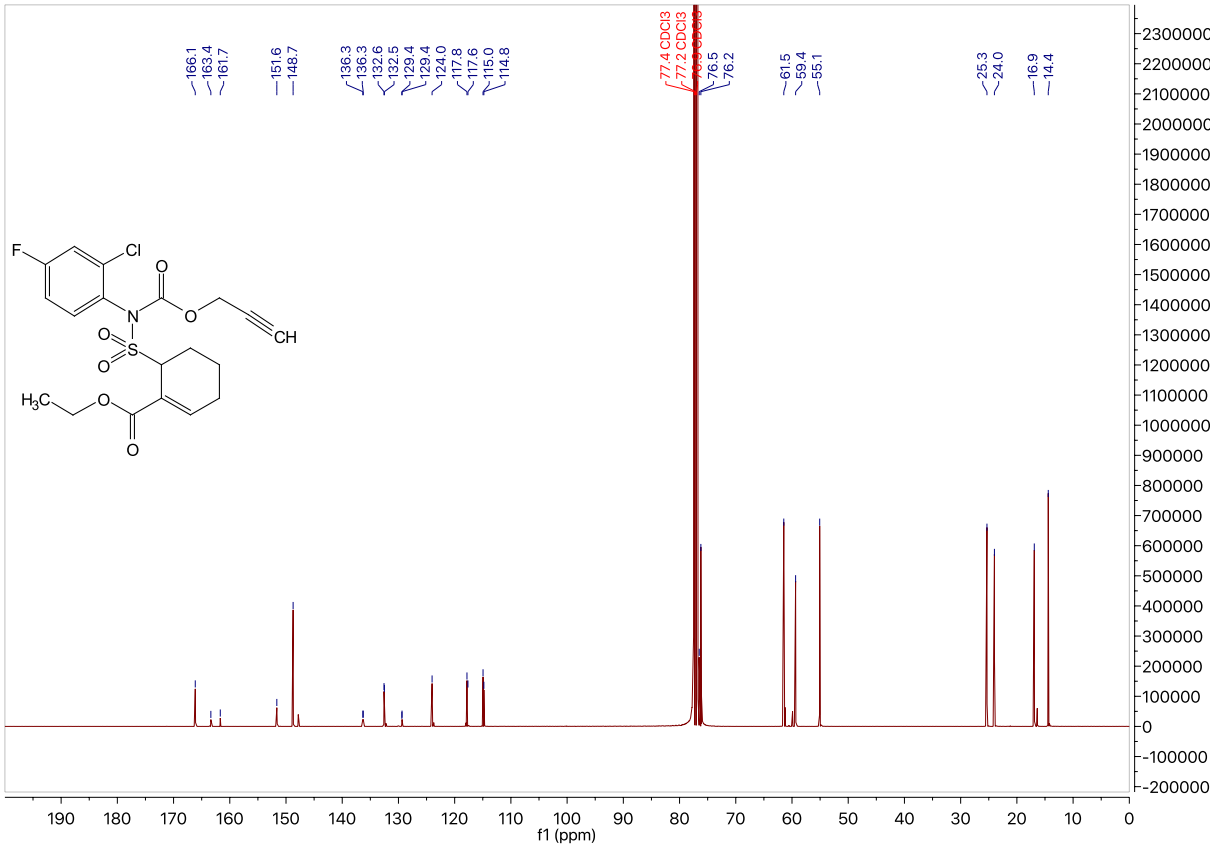


Figure S10. Carbon NMR of compound **5**.

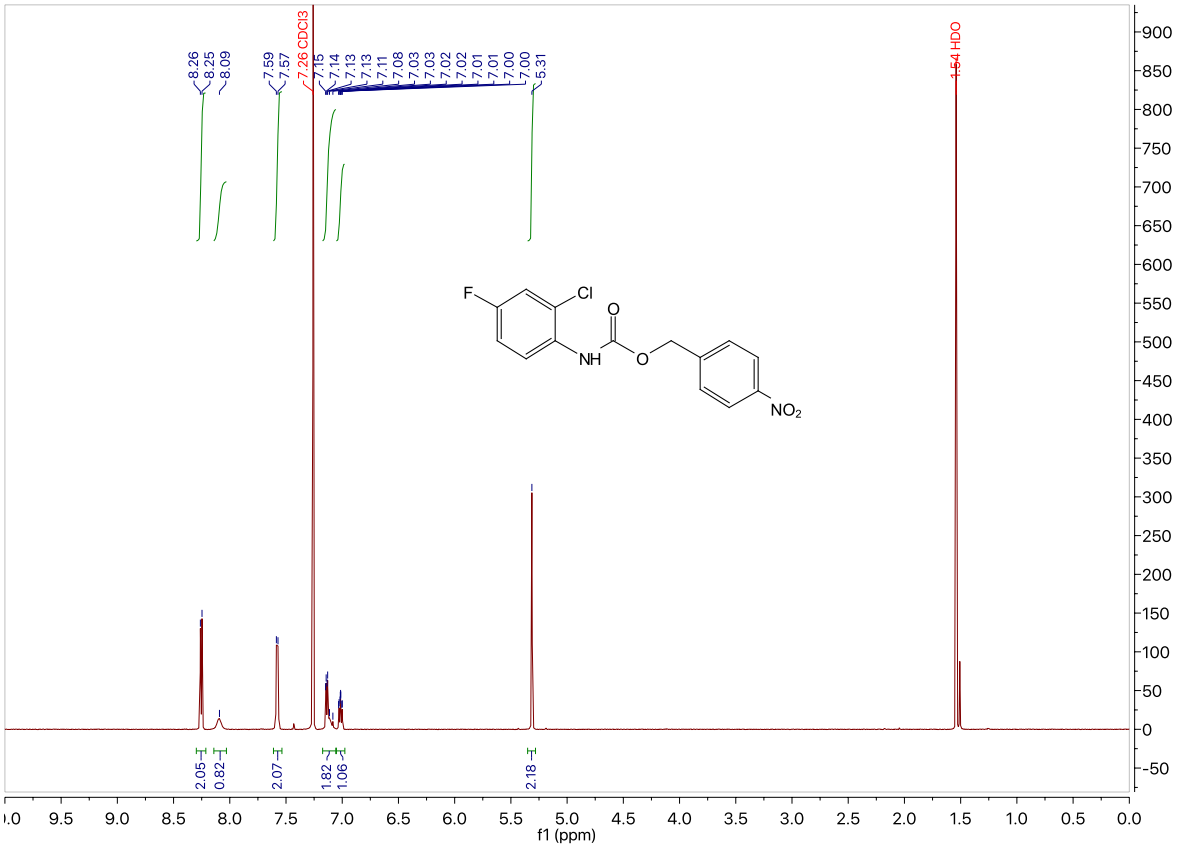


Figure S11. Proton NMR of compound **6**.

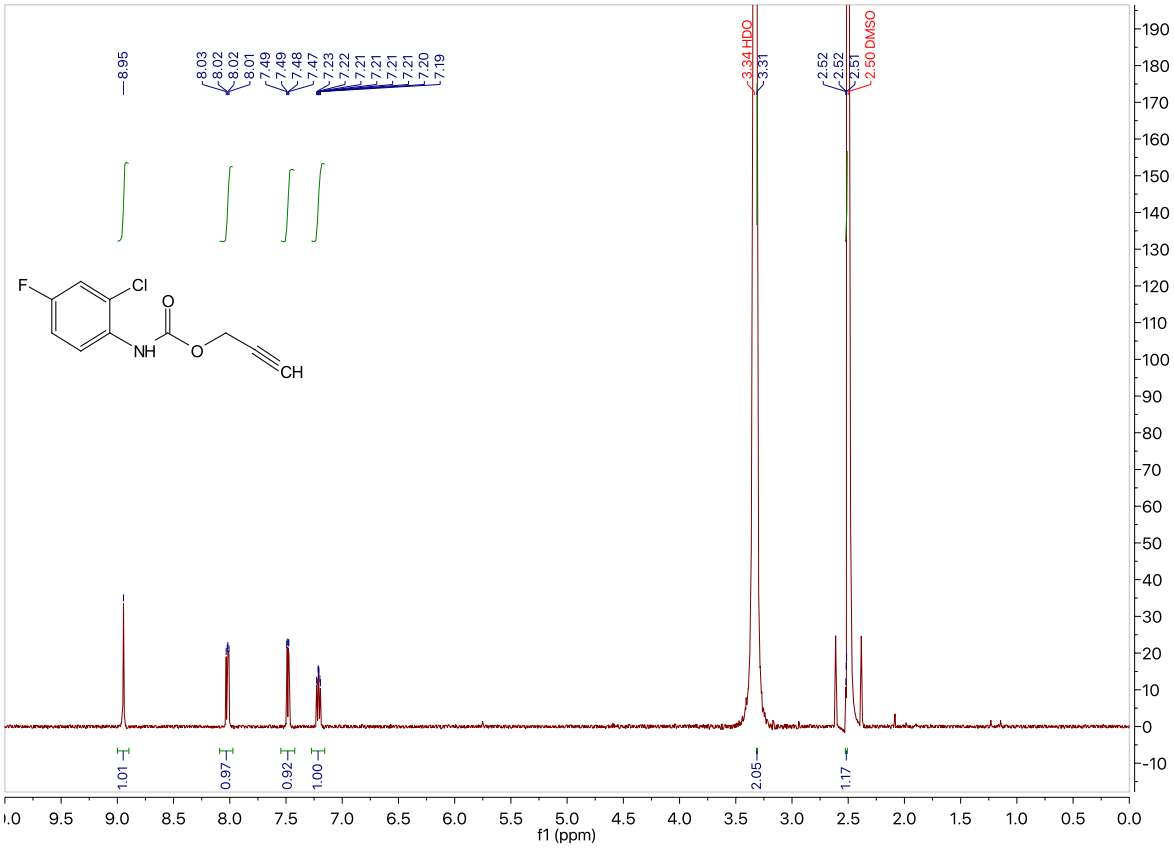


Figure S12. Proton NMR of compound **7**.

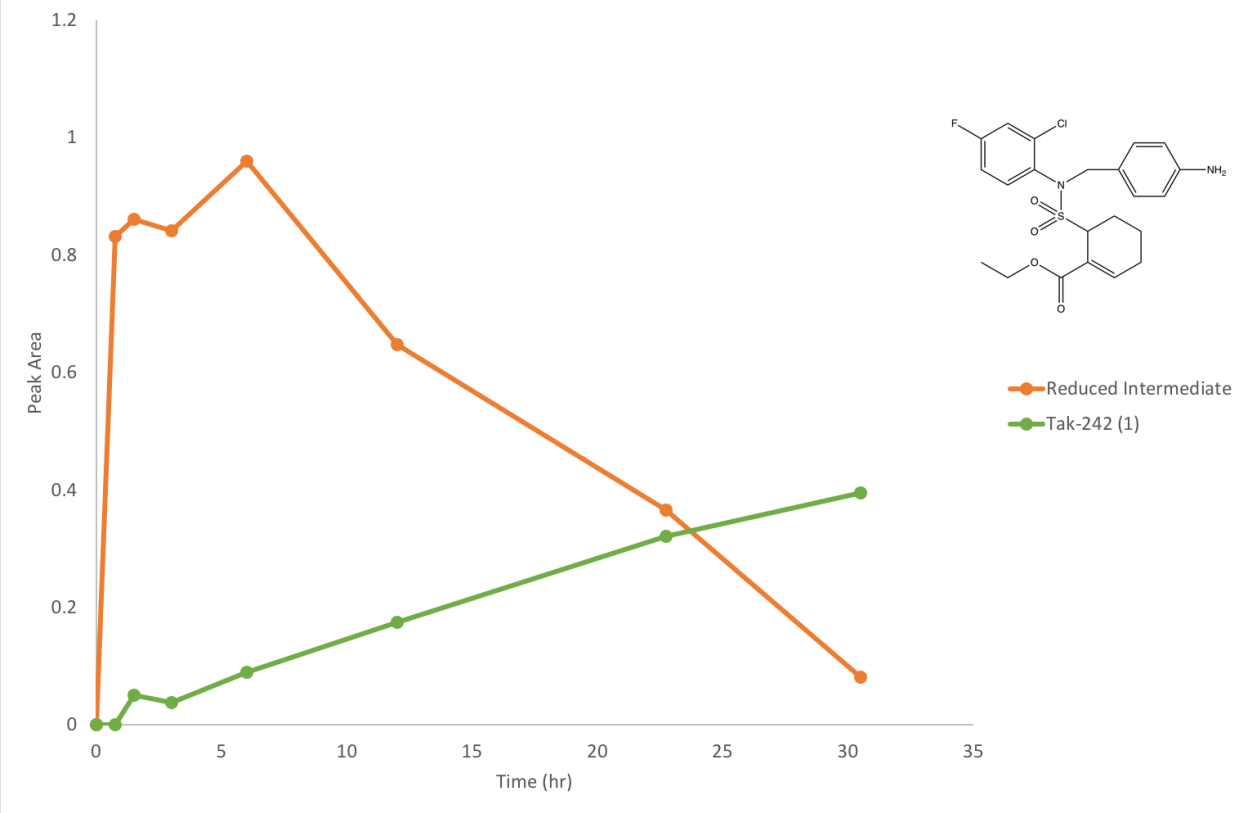


Figure S13. Appearance and disappearance of prodrug **3** reduced intermediate and the release of Tak-242 (**1**)

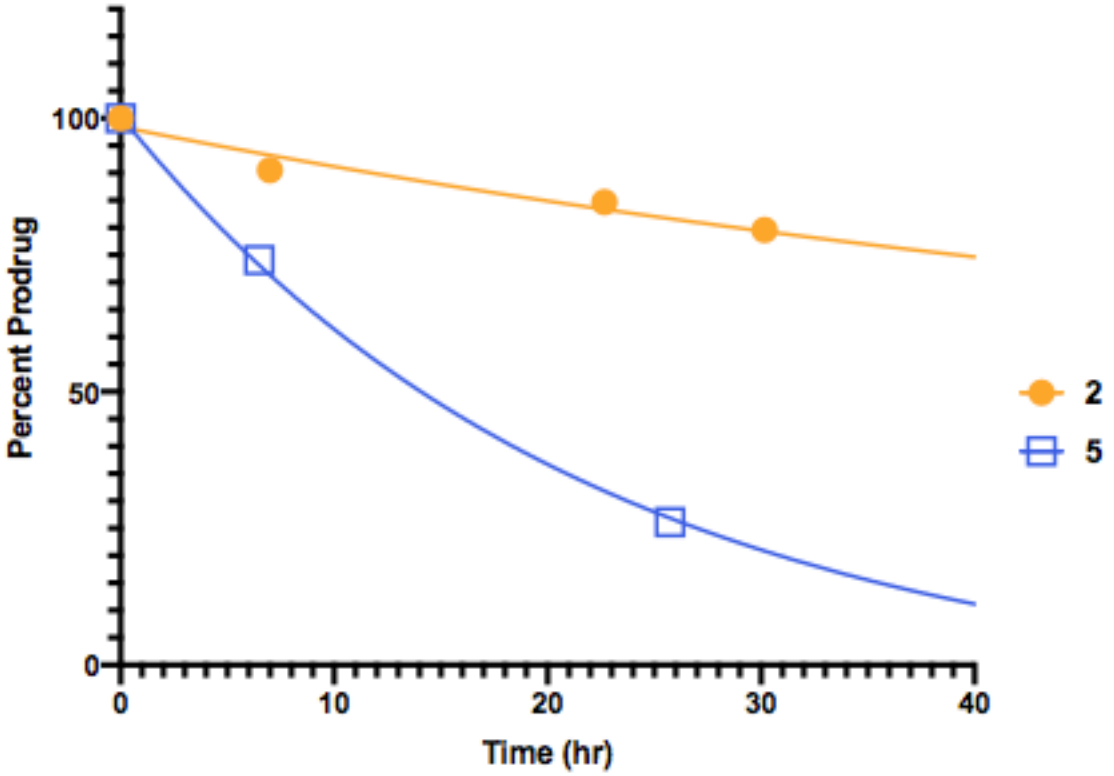


Figure S14. Stability of carbamates **2** and **5**.

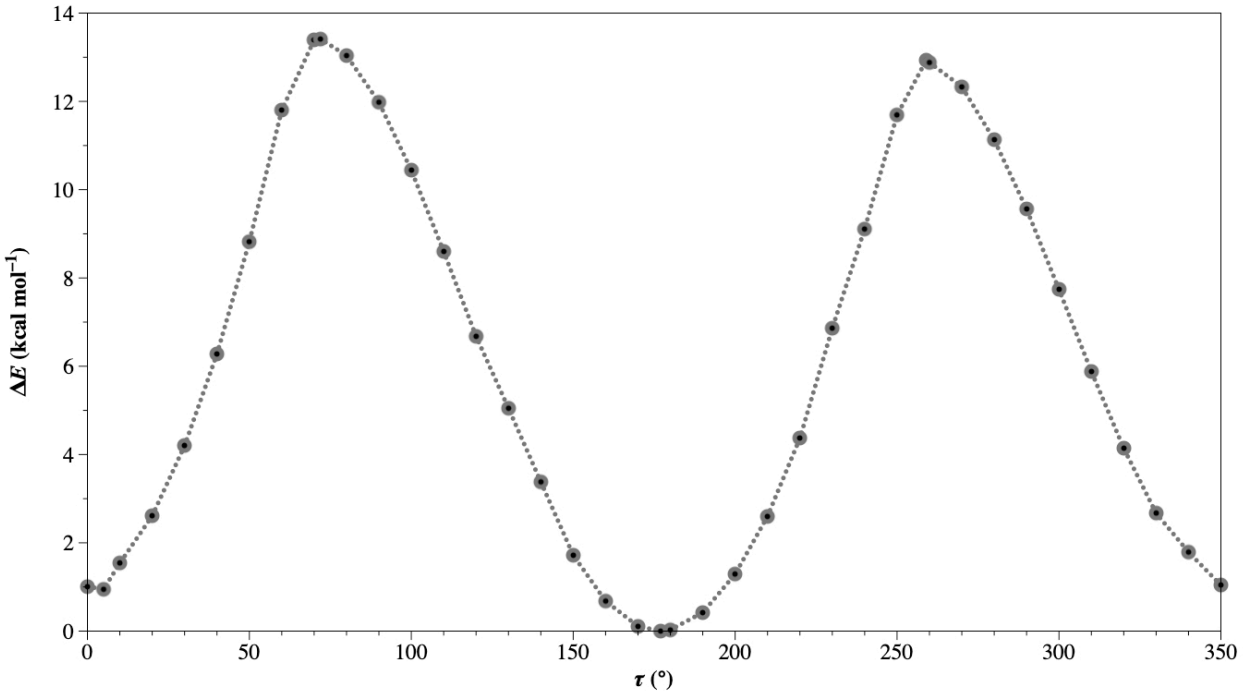


Figure S15. Cross section of the potential energy surface about torsional angle ($\tau_{C\text{-}N\text{-}C\text{-}O}$ = 0º - 350º) of prodrug **2** computed at the B3LYP/6-311G(2*df*,2*pd*) level of theory.

Table S1. Optimized Cartesian coordinates (in Å) of the global minimum energy structure (n_i = 0) of prodrug **2** ($\tau_{C\text{-}N\text{-}C\text{-}O}$ = 177º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	*y*	*z*
C	-1.010592	2.192351	-2.322442
C	-2.057334	2.875339	-1.730775
C	-2.569418	2.508844	-0.498885
C	-2.008471	1.421502	0.150994
C	-0.958745	0.692363	-0.410481
C	-0.468296	1.102480	-1.656716
H	-0.628269	2.508551	-3.280860
H	-3.383407	3.070376	-0.064584
H	-2.386714	1.115393	1.115175
F	-2.583211	3.926474	-2.375376
Cl	0.858900	0.258065	-2.408460
N	-0.429324	-0.437785	0.269312
S	-1.330301	-2.040666	0.501055
O	-2.572916	-1.412834	1.278330
O	-2.843516	-2.892512	1.077013
C	-3.211991	-1.629560	-1.581819
C	-1.832373	-2.247464	-1.306486
C	-1.729682	-3.723938	-1.604052
C	-2.765747	-4.441172	-2.047694
C	-4.104261	-3.854156	-2.352352
C	-3.972591	-2.367766	-2.685255
H	-3.806783	-1.665525	-0.671469
H	-2.595220	-5.494555	-2.232965

H	-4.566483	-4.402339	-3.175348
H	-4.956542	-1.912585	-2.805406
C	-0.414376	-4.419168	-1.469377
O	0.557895	-3.549223	-1.125457
O	-0.229407	-5.595238	-1.656460
C	1.892670	-4.081949	-0.931690
H	2.547372	-3.237259	-1.132164
H	2.061200	-4.859552	-1.673714
C	2.076970	-4.604757	0.478706
H	1.422228	-5.454641	0.664276
H	3.108260	-4.937256	0.608934
H	1.868811	-3.822252	1.206828
C	0.708622	-0.345197	1.041957
O	1.179421	-1.250620	1.691427
O	1.234186	0.901159	0.993808
C	2.448240	1.104747	1.751183
H	2.383825	0.550658	2.684024
H	2.451294	2.172407	1.959618
C	4.363776	-0.464095	1.275585
C	3.673447	0.708109	0.969175
C	4.126402	1.513960	-0.076903
C	5.249525	1.163006	-0.807342
C	5.917775	-0.006308	-0.475101
C	5.493464	-0.827592	0.557592
H	4.003744	-1.099191	2.072334
H	3.593312	2.422749	-0.322398
H	5.616802	1.772625	-1.617643
H	6.044155	-1.727769	0.780572
N	7.118711	-0.386617	-1.245202
H	-4.763373	-3.991971	-1.487499
H	-3.453733	-2.261590	-3.641405
H	-3.088139	-0.581048	-1.845270
H	-1.037316	-1.719854	-1.826594
O	7.473939	0.359644	-2.144320
O	7.683321	-1.424634	-0.936981

Table S2. Optimized Cartesian coordinates (in Å) of the local minimum energy structure ($n_i = 0$) of prodrug **2** ($\tau_{\text{C-N-C-O}}$ = 5º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	-2.472321	-3.377783	1.489407
C	-2.123735	-4.321739	0.540980
C	-1.214317	-4.050799	-0.465719
C	-0.643219	-2.789406	-0.514869
C	-0.974651	-1.800128	0.410590
C	-1.892473	-2.119534	1.417160
H	-3.176106	-3.624969	2.269209
H	-0.958813	-4.817071	-1.182595
H	0.076557	-2.552320	-1.284458
F	-2.685704	-5.536743	0.609334

Cl	-2.333982	-0.940522	2.622593
N	-0.376516	-0.510030	0.323074
S	-0.748909	0.714036	-0.998804
O	-0.190503	-0.160840	-2.208282
O	-0.790595	1.103821	-2.794829
C	-3.099872	-0.558913	-1.953524
C	-2.626210	0.509630	-0.952775
C	-3.196731	1.889148	-1.174684
C	-3.977396	2.183857	-2.218626
C	-4.415397	1.172475	-3.224808
C	-4.448131	-0.219120	-2.591636
H	-2.361992	-0.657310	-2.746866
H	-4.338838	3.201797	-2.296065
H	-5.393128	1.447975	-3.623498
H	-4.687262	-0.976081	-3.339636
C	-2.948580	2.968343	-0.174521
O	-2.214384	2.511836	0.863662
O	-3.357399	4.099381	-0.256348
C	-1.913191	3.450328	1.923212
H	-1.749222	2.822934	2.796388
H	-2.786359	4.078965	2.085662
C	-0.688531	4.282000	1.596834
H	-0.873139	4.920969	0.735378
H	-0.441110	4.918350	2.447894
H	0.164854	3.638629	1.385657
C	0.719652	-0.290114	1.137365
O	1.131168	-1.081654	1.949734
O	1.268464	0.927522	0.916227
C	2.477301	1.218082	1.657734
H	2.392542	0.789578	2.652833
H	2.493436	2.303319	1.725361
C	4.275132	-0.513968	1.300245
C	3.703029	0.708493	0.945370
C	4.272163	1.455262	-0.087521
C	5.394173	0.997710	-0.759080
C	5.941572	-0.219020	-0.381130
C	5.399563	-0.984572	0.639483
H	3.824150	-1.102354	2.086346
H	3.833289	2.403452	-0.368751
H	5.849792	1.560320	-1.558438
H	5.858599	-1.925598	0.898348
N	7.140848	-0.712978	-1.087313
H	-3.722254	1.185046	-4.073571
H	-5.243108	-0.249370	-1.842230
H	-3.154721	-1.519515	-1.445556
H	-2.799613	0.210034	0.077007
O	7.601469	-0.014259	-1.976667
O	7.599097	-1.789888	-0.738932

Table S3. Optimized Cartesian coordinates (in Å) of the transition state structure (n_i = 1) of prodrug **2** ($\tau_{C\text{-}N\text{-}C\text{-}O}$ = 72º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	*y*	*z*
C	-3.722253	0.301650	2.113735
C	-4.031830	-0.985720	2.511287
C	-3.219150	-2.064385	2.209208
C	-2.066285	-1.836454	1.476387
C	-1.717741	-0.555408	1.037538
C	-2.560688	0.509808	1.382233
H	-4.371604	1.122439	2.376832
H	-3.490242	-3.054413	2.545267
H	-1.407525	-2.656274	1.233020
F	-5.153708	-1.185735	3.217131
Cl	-2.173664	2.143579	0.911141
N	-0.528745	-0.329174	0.275981
S	-0.264868	-0.971234	-1.397311
O	-0.676094	-2.500773	-1.182886
O	-0.377121	-2.315493	-2.657016
C	-2.996062	-0.988005	-2.116969
C	-1.750715	-0.087101	-2.160025
C	-1.347704	0.365562	-3.541671
C	-2.004170	-0.014632	-4.641913
C	-3.222987	-0.875600	-4.618640
C	-3.951343	-0.727497	-3.282737
H	-2.683146	-2.029160	-2.157445
H	-1.645418	0.368846	-5.589048
H	-3.874059	-0.614347	-5.454788
H	-4.786992	-1.425864	-3.220877
C	-0.230001	1.339230	-3.716391
O	0.307537	1.685306	-2.527507
O	0.144003	1.784644	-4.772608
C	1.393362	2.642077	-2.546639
H	1.381881	3.072480	-1.548054
H	1.160018	3.412049	-3.279668
C	2.721810	1.978689	-2.852106
H	2.719739	1.551089	-3.852596
H	3.519709	2.720935	-2.800434
H	2.940128	1.194049	-2.128669
C	0.670435	-0.430659	1.046189
O	1.134778	-1.452413	1.479399
O	1.206683	0.784590	1.219607
C	2.386289	0.867666	2.065060
H	2.360704	0.044919	2.775490
H	2.274484	1.812567	2.590338
C	4.185336	-0.350902	0.783368
C	3.655902	0.852826	1.256817
C	4.320727	2.046823	0.977604
C	5.493506	2.051779	0.237877
C	5.990503	0.843037	-0.221896

C	5.354156	-0.361506	0.038965
H	3.674479	-1.278425	0.999622
H	3.920468	2.982006	1.346591
H	6.024169	2.963920	0.015132
H	5.780332	-1.278979	-0.335163
N	7.239665	0.838556	-1.010740
H	-2.928653	-1.919808	-4.774786
H	-4.371451	0.279323	-3.215119
H	-3.508780	-0.842578	-1.168015
H	-1.847145	0.777029	-1.508503
O	7.764875	1.916580	-1.242036
O	7.668957	-0.241637	-1.382481

Table S4. Optimized Cartesian coordinates (in Å) of the transition state structure (n_i = 1) of prodrug **2** ($\tau_{C\text{-}N\text{-}C\text{-}O}$ = 259º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	0.368020	3.034495	-1.766575
C	0.840030	3.815059	-0.727793
C	0.885507	3.354663	0.576419
C	0.439212	2.069573	0.836881
C	-0.059406	1.245907	-0.176501
C	-0.079701	1.750807	-1.484921
H	0.354117	3.421707	-2.773780
H	1.266229	3.992752	1.360284
H	0.468194	1.680752	1.843566
F	1.268720	5.054798	-1.001267
Cl	-0.665944	0.779270	-2.805458
N	-0.531308	-0.070887	0.109082
S	-1.943386	-0.464498	1.135060
O	-1.596796	0.385667	2.442642
O	-2.957751	-0.241652	2.674200
C	-3.393495	1.935477	0.707341
C	-3.198584	0.524588	0.124366
C	-4.442695	-0.323498	0.051709
C	-5.606528	0.065661	0.579827
C	-5.798047	1.393794	1.234122
C	-4.842439	2.420898	0.623336
H	-3.091750	1.936279	1.752247
H	-6.448948	-0.607573	0.480215
H	-6.836726	1.712403	1.133952
H	-4.927413	3.378486	1.138775
C	-4.408281	-1.625411	-0.678588
O	-3.182669	-1.857301	-1.192762
O	-5.345373	-2.372299	-0.812157
C	-2.992102	-3.074165	-1.952677
H	-2.174898	-2.838863	-2.630102
H	-3.899107	-3.270311	-2.520964
C	-2.642495	-4.241500	-1.051404
H	-3.457279	-4.457762	-0.362614

H	-2.465112	-5.129939	-1.659537
H	-1.736708	-4.031516	-0.483943
C	0.453718	-1.102178	0.132472
O	0.649853	-1.875924	-0.762862
O	1.116729	-1.105458	1.303320
C	2.145774	-2.117195	1.480593
H	1.849731	-3.013354	0.941537
H	2.144865	-2.311913	2.549786
C	3.917269	-1.829383	-0.290124
C	3.489019	-1.617225	1.021824
C	4.316329	-0.924766	1.907064
C	5.551993	-0.448683	1.498864
C	5.948403	-0.673890	0.189674
C	5.149854	-1.357503	-0.714106
H	3.275218	-2.357590	-0.980442
H	3.992132	-0.759959	2.926193
H	6.208191	0.084156	2.168808
H	5.500557	-1.510296	-1.722502
N	7.265352	-0.172952	-0.254250
H	-5.604741	1.295159	2.308149
H	-5.126317	2.592722	-0.417976
H	-2.734204	2.625736	0.182618
H	-2.720959	0.547392	-0.850203
O	7.959617	0.398739	0.572062
O	7.578295	-0.360964	-1.418878

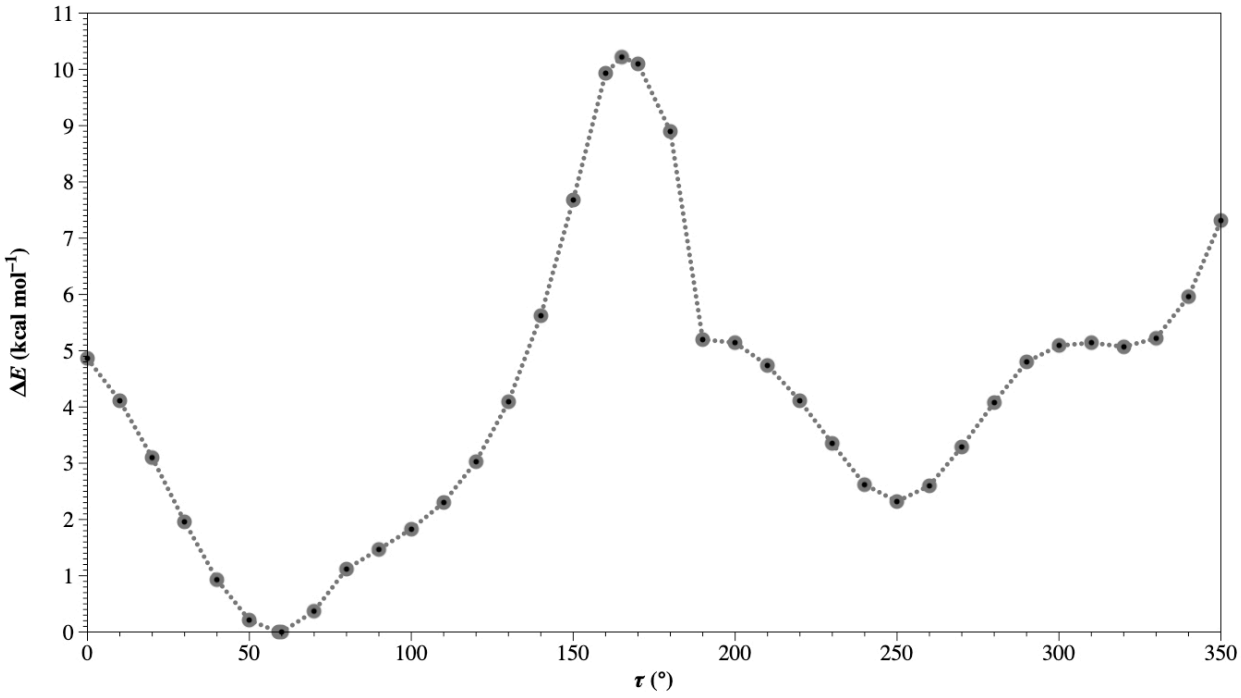


Figure S16. Cross section of the potential energy surface about torsional angle ($\tau_{C\text{-}N\text{-}C\text{-}C}$ = 0º - 350º) of prodrug **3** computed at the B3LYP/6-311G(2*df*,2*pd*) level of theory.

Table S5. Optimized Cartesian coordinates (in Å) of the global minimum energy structure (n_i = 0) of prodrug **3** ($\tau_{C\text{-}N\text{-}C\text{-}C}$ = 59º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	*y*	*z*
C	-0.636452	0.929699	0.084813
C	-0.793162	1.989128	-0.817663
C	-0.069895	3.166945	-0.690901
C	0.812401	3.290348	0.364720
C	1.003309	2.271131	1.279917
C	0.285977	1.098252	1.121642
H	-0.193642	3.975471	-1.394640
H	1.708179	2.396540	2.088414
H	0.427988	0.288217	1.819027
F	1.503751	4.430731	0.493621
Cl	-1.902343	1.876445	-2.164745
N	-1.338190	-0.304009	-0.070978
S	-2.301429	-0.902110	1.168570
C	-0.913592	-1.216939	-1.161304
H	-1.565183	-2.085909	-1.142954
H	-1.084999	-0.711654	-2.109966
C	0.534545	-1.649681	-1.068786
C	0.968817	-2.498637	-0.046720
C	1.452814	-1.213355	-2.022942
C	2.292356	-2.900544	0.021790
H	0.260246	-2.844558	0.692486
C	2.781617	-1.608448	-1.969669
H	1.126026	-0.557845	-2.819485
C	3.181432	-2.447388	-0.942993
H	2.645478	-3.558668	0.800036
H	3.503914	-1.279613	-2.700032
N	4.592532	-2.872239	-0.874506
O	4.918567	-3.608279	0.044138
O	5.350793	-2.461810	-1.739996
O	-2.121644	-0.041852	2.313017
O	-2.031693	-2.320828	1.266486
C	-4.071053	-0.716758	0.664733
C	-4.414784	0.776107	0.552713
C	-4.395117	-1.520122	-0.566165
C	-5.665260	1.005451	-0.295833
H	-3.584323	1.307180	0.088039
C	-4.975824	-0.980966	-1.641052
C	-5.475918	0.429268	-1.701094
H	-5.881593	2.073105	-0.346368
H	-5.158431	-1.625804	-2.492557
H	-4.777653	1.047817	-2.274294
H	-4.532146	1.189904	1.552039
H	-6.528654	0.527810	0.174695
H	-6.415179	0.450088	-2.258118
C	-4.171067	-3.001360	-0.570532
O	-3.712203	-3.621259	-1.498990

O	-4.600058	-3.557822	0.569613
C	-4.360612	-4.975520	0.722334
H	-4.865080	-5.504281	-0.086195
H	-3.289989	-5.151064	0.622560
C	-4.878107	-5.382413	2.082549
H	-4.717610	-6.450538	2.232182
H	-4.356628	-4.843266	2.872524
H	-5.945728	-5.181842	2.171452
H	-4.552029	-1.170689	1.534543

Table S6. Optimized Cartesian coordinates (in Å) of the local minimum energy structure ($n_i = 0$) of prodrug **3** ($\tau_{C\text{-}N\text{-}C\text{-}C}$ = 250º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	-1.919656	-0.809268	0.680693
C	-0.997430	-0.951820	1.722831
C	-1.234909	-1.819063	2.782219
C	-2.407628	-2.547879	2.794236
C	-3.345473	-2.444997	1.781548
C	-3.085547	-1.578459	0.734819
H	-0.519203	-1.928484	3.582217
H	-4.253795	-3.027575	1.824517
H	-3.808660	-1.474477	-0.061006
F	-2.635709	-3.381212	3.818107
Cl	0.504751	-0.069140	1.737872
N	-1.672140	0.047306	-0.443125
S	-2.756259	1.339941	-0.676212
C	-1.209921	-0.648907	-1.682485
H	-1.908607	-1.455614	-1.917212
H	-1.254953	0.065773	-2.495958
C	0.190898	-1.201611	-1.572481
C	0.414404	-2.488763	-1.082045
C	1.278988	-0.437641	-1.999925
C	1.698791	-3.001122	-0.986385
H	-0.423584	-3.099198	-0.773225
C	2.568694	-0.937036	-1.913822
H	1.107987	0.542986	-2.423247
C	2.759770	-2.210565	-1.398810
H	1.890428	-3.992275	-0.606892
H	3.421683	-0.365110	-2.243564
N	4.130816	-2.746140	-1.300048
O	4.267503	-3.877414	-0.859359
O	5.048391	-2.025850	-1.662737
O	-3.730622	1.296892	0.388003
O	-3.182983	1.301245	-2.058159
C	-1.808635	2.908628	-0.429464
C	-1.460704	3.064518	1.058607
C	-0.628497	3.023878	-1.355774
C	-0.319060	4.057315	1.273520
H	-1.156669	2.100588	1.463694

C	0.602956	3.295919	-0.915813
C	0.930649	3.614136	0.509424
H	-0.105222	4.141417	2.339522
H	1.399491	3.358241	-1.647831
H	1.378970	2.737584	0.988488
H	-2.354456	3.364811	1.601130
H	-0.616513	5.051433	0.929345
H	1.698027	4.390728	0.534936
C	-0.831603	2.952373	-2.836364
O	-0.106948	2.354548	-3.598436
O	-1.887393	3.676883	-3.219165
C	-2.241839	3.617215	-4.620496
H	-1.394857	3.967714	-5.209860
H	-2.425402	2.575004	-4.879286
C	-3.470774	4.474201	-4.816348
H	-3.767271	4.456116	-5.865516
H	-4.301288	4.101347	-4.218275
H	-3.275759	5.508774	-4.534427
H	-2.578552	3.622652	-0.732648

Table S7. Optimized Cartesian coordinates (in Å) of the transition state structure (n_i = 1) of prodrug **3** ($\tau_{C\text{-}N\text{-}C\text{-}C}$ = 165º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	2.572725	-1.048068	0.150235
C	3.370347	-0.799187	-0.974730
C	4.712424	-1.152974	-1.009265
C	5.264358	-1.760570	0.101596
C	4.514362	-2.038265	1.230274
C	3.174118	-1.691314	1.236670
H	5.317568	-0.959684	-1.881531
H	4.975057	-2.523963	2.077844
H	2.571144	-1.898073	2.106210
F	6.561358	-2.095660	0.072893
Cl	2.707773	-0.035347	-2.399574
N	1.170190	-0.754990	0.156025
S	0.545530	0.270605	1.337508
C	0.391526	-1.761636	-0.651596
H	0.635529	-1.572843	-1.695916
H	0.814899	-2.731472	-0.387041
C	-1.107963	-1.860070	-0.527360
C	-1.938514	-1.098961	-1.345729
C	-1.676881	-2.802395	0.331143
C	-3.315912	-1.240494	-1.285935
H	-1.516167	-0.367117	-2.018931
C	-3.048370	-2.969222	0.393796
H	-1.038932	-3.405437	0.963270
C	-3.850491	-2.175181	-0.413783
H	-3.969158	-0.636771	-1.894898
H	-3.505375	-3.690900	1.052035

N	-5.314509	-2.331592	-0.339447
O	-6.001857	-1.558729	-0.990235
O	-5.755046	-3.222312	0.371969
O	1.435648	0.225028	2.475597
O	-0.845201	-0.069043	1.494430
C	0.657977	2.036203	0.766464
C	2.137782	2.422486	0.597048
C	-0.206893	2.376024	-0.416438
C	2.302194	3.696821	-0.228937
H	2.673352	1.621242	0.090473
C	0.276784	2.999223	-1.497137
C	1.675816	3.517797	-1.613778
H	3.361288	3.942640	-0.315307
H	-0.421250	3.221595	-2.295203
H	2.282644	2.837592	-2.219457
H	2.589729	2.525322	1.581070
H	1.820497	4.536976	0.278073
H	1.657463	4.464320	-2.158254
C	-1.696969	2.234867	-0.348919
O	-2.407563	2.029795	-1.304217
O	-2.152292	2.452464	0.890073
C	-3.578571	2.318279	1.089248
H	-4.088620	3.042279	0.453758
H	-3.877391	1.321775	0.767509
C	-3.856716	2.546413	2.556843
H	-4.926294	2.451283	2.746312
H	-3.331967	1.812590	3.167148
H	-3.542642	3.543656	2.865107
H	0.238369	2.505984	1.659267

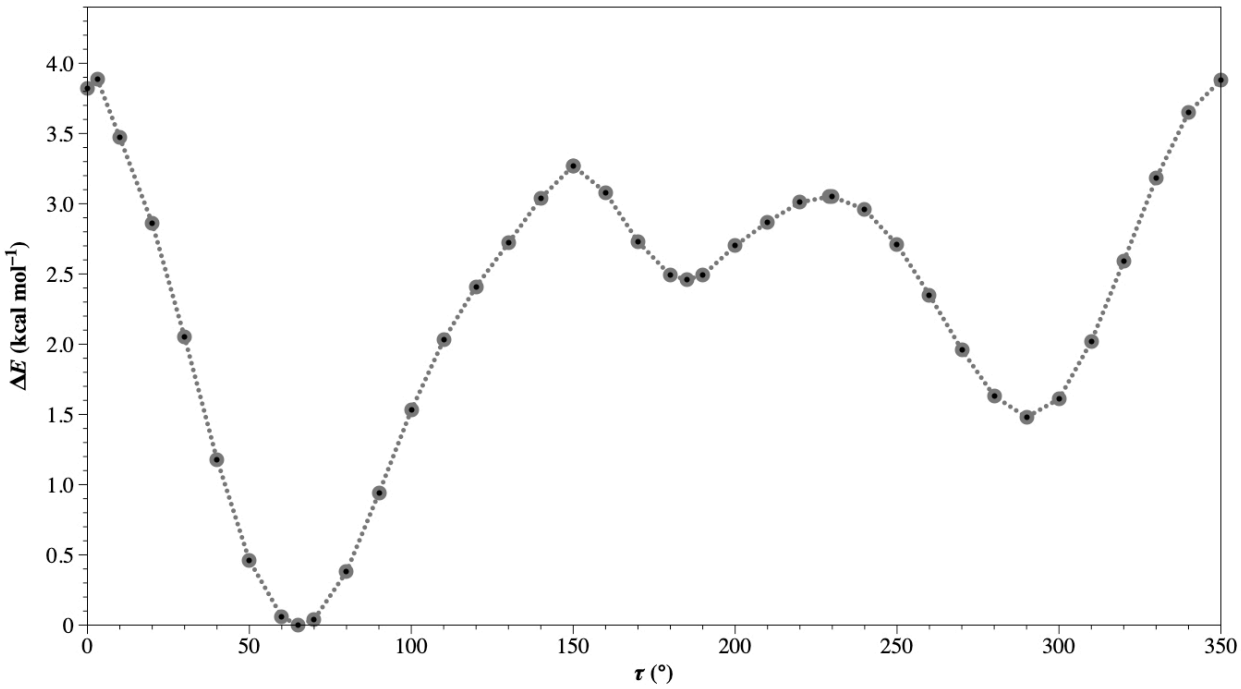


Figure S17. Cross section of the potential energy surface about torsional angle ($\tau_{C\text{-}N\text{-}C\text{-}C}$ = 0º - 350º) of prodrug **4** computed at the B3LYP/6-311G(2*df*,2*pd*) level of theory.

Table S11. Optimized Cartesian coordinates (in Å) of the global minimum energy structure (n_i = 0) of prodrug **4** ($\tau_{C\text{-}N\text{-}C\text{-}C}$ = 65º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	*y*	*z*
C	2.624419	-0.641972	0.653882
C	2.445302	-1.295213	1.859465
C	1.225366	-1.831813	2.229178
C	0.155763	-1.707445	1.356381
C	0.279073	-1.042925	0.132547
C	1.536988	-0.519886	-0.198641
H	3.589932	-0.237076	0.392260
H	1.126179	-2.341608	3.176253
H	-0.804858	-2.124750	1.617460
F	3.493507	-1.410165	2.688100
Cl	1.774334	0.311999	-1.716758
N	-0.821770	-0.912989	-0.756300
S	-2.307870	-0.083883	-0.392956
O	-2.804521	-0.856440	0.911525
O	-3.823034	0.248001	0.711289
C	-1.348995	1.556304	1.714271
C	-1.543777	1.546663	0.187027
C	-2.413117	2.654219	-0.353324
C	-3.073993	3.500288	0.442620
C	-2.968430	3.470129	1.930543
C	-1.599922	2.927103	2.344774
H	-2.038823	0.844655	2.161984
H	-3.677496	4.262989	-0.033329

H	-3.137417	4.468993	2.336086
H	-1.534675	2.836288	3.429994
C	-2.517970	2.879331	-1.823628
O	-1.765950	1.994402	-2.517798
O	-3.169304	3.748195	-2.348708
C	-1.752755	2.136079	-3.956813
H	-0.809359	1.687903	-4.261486
H	-1.744848	3.196827	-4.199574
C	-2.934940	1.439170	-4.601969
H	-3.870358	1.903173	-4.295920
H	-2.854817	1.513856	-5.687603
H	-2.961276	0.382718	-4.335142
H	-3.762291	2.830222	2.331867
H	-0.828460	3.637835	2.037117
H	-0.340529	1.215226	1.943108
H	-0.594784	1.544338	-0.342598
C	-0.943759	-1.921065	-1.820816
H	-1.750189	-1.600722	-2.483270
H	-0.028107	-1.909105	-2.416616
C	-1.206364	-3.285176	-1.357859
C	-1.415192	-4.402534	-0.981047
H	-1.608221	-5.391475	-0.647183

Table S12. Optimized Cartesian coordinates (in Å) of the local minimum energy structure (n_i = 0) of prodrug **4** ($\tau_{C\text{-}N\text{-}C\text{-}C}$ = 229°) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	0.655024	2.324562	-2.437903
C	2.014453	2.113572	-2.301909
C	2.525037	0.956885	-1.740296
C	1.635441	-0.010336	-1.299790
C	0.250641	0.158432	-1.401820
C	-0.217796	1.342698	-1.988610
H	0.288762	3.234100	-2.888784
H	3.593711	0.825364	-1.654420
H	2.011136	-0.917107	-0.848654
F	2.857703	3.061733	-2.735074
Cl	-1.928431	1.612888	-2.184459
N	-0.660445	-0.841469	-0.955472
S	-0.803567	-1.347214	0.715099
O	0.693400	-1.823960	1.013415
O	-0.020365	-1.972317	2.341310
C	0.363339	0.962234	1.864787
C	-1.005883	0.371999	1.477418
C	-1.988045	0.252033	2.616396
C	-1.657525	0.525991	3.881815
C	-0.311199	1.024346	4.286917
C	0.317567	1.810657	3.136489
H	1.065101	0.146897	2.026373
H	-2.431529	0.415068	4.630841

H	-0.395802	1.636780	5.186110
H	1.331798	2.122041	3.390900
C	-3.408321	-0.119567	2.351766
O	-3.617583	-0.373253	1.043682
O	-4.277046	-0.173356	3.187622
C	-4.965705	-0.722444	0.650797
H	-4.992008	-0.505232	-0.414154
H	-5.657437	-0.065895	1.175901
C	-5.277040	-2.180303	0.928908
H	-5.265923	-2.381429	1.997942
H	-6.272072	-2.417623	0.547797
H	-4.555522	-2.829518	0.434788
H	0.323362	0.170036	4.548271
H	-0.263475	2.721305	2.969224
H	0.741959	1.554123	1.033661
H	-1.468832	0.918142	0.659072
C	-0.898063	-1.957511	-1.904061
H	-0.446455	-1.674319	-2.855181
H	-0.378022	-2.865121	-1.579561
C	-2.306492	-2.270284	-2.130399
C	-3.441613	-2.571850	-2.363613
H	-4.448744	-2.835274	-2.569814

Table S13. Optimized Cartesian coordinates (in Å) of the local minimum energy structure (n_i = 0) of prodrug **4** ($\tau_{C\text{-}N\text{-}C\text{-}C}$ = 290°) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	-0.775674	2.611135	-2.344652
C	0.527751	2.673354	-2.820118
C	1.414736	1.611249	-2.685356
C	0.967471	0.454632	-2.054042
C	-0.340272	0.338881	-1.551194
C	-1.202250	1.440696	-1.715701
H	-1.441508	3.456423	-2.467552
H	2.426113	1.698925	-3.065672
H	1.646200	-0.381957	-1.925106
F	0.938714	3.802068	-3.426928
Cl	-2.848582	1.390072	-1.121490
N	-0.788886	-0.859932	-0.914188
S	-0.130309	-1.403301	0.660176
O	1.462403	-1.473491	0.336187
O	1.316747	-1.814376	1.816076
C	0.817786	1.102321	1.584801
C	-0.440250	0.210717	1.601141
C	-0.927623	-0.163051	2.984104
C	-0.299329	0.231714	4.105213
C	0.906367	1.119962	4.103117
C	0.925574	1.983609	2.835663
H	1.700430	0.460727	1.541415
H	-0.730411	-0.081012	5.053057

H	0.912048	1.739938	5.006865
H	1.849983	2.568776	2.783168
C	-2.196615	-0.932455	3.150803
O	-2.767135	-1.202868	1.951275
O	-2.681632	-1.262785	4.215261
C	-4.023308	-1.925204	1.970446
H	-4.498861	-1.657207	1.024663
H	-4.624133	-1.551018	2.802724
C	-3.804259	-3.426080	2.083879
H	-3.333730	-3.675263	3.037646
H	-4.767877	-3.943586	2.029395
H	-3.172925	-3.792515	1.269200
H	1.812188	0.497309	4.149326
H	0.094986	2.699572	2.875928
H	0.809754	1.718088	0.682228
H	-1.263734	0.648405	1.034351
C	-0.961960	-2.016075	-1.822800
H	-0.051746	-2.209848	-2.410930
H	-1.122000	-2.901848	-1.194878
C	-2.096390	-1.862326	-2.734972
C	-3.015029	-1.755719	-3.510394
H	-3.833537	-1.652655	-4.184596

Table S14. Optimized Cartesian coordinates (in Å) of the transition state structure (n_i = 1) of prodrug **4** ($\tau_{C\text{-}N\text{-}C\text{-}C}$ = 3º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	-0.449548	-1.551240	2.746659
C	-1.757419	-1.428144	3.177944
C	-2.790590	-1.120125	2.311343
C	-2.493402	-0.933437	0.970630
C	-1.187068	-1.034740	0.484413
C	-0.175276	-1.350493	1.401638
H	0.333256	-1.798012	3.447289
H	-3.800827	-1.038072	2.684651
H	-3.282998	-0.696711	0.272899
F	-2.024467	-1.618537	4.478697
Cl	1.478166	-1.506664	0.867899
N	-0.889190	-0.824735	-0.887796
S	-1.121868	0.675870	-1.725842
O	-2.687830	0.908917	-1.525247
O	-2.224561	2.146710	-2.268502
C	-1.207960	2.408513	0.516095
C	-0.225987	1.805165	-0.504500
C	0.543064	2.811485	-1.323456
C	0.304138	4.124530	-1.255474
C	-0.698192	4.724021	-0.327039
C	-0.853885	3.842611	0.913126
H	-2.206457	2.411348	0.085211
H	0.904371	4.772618	-1.881731

H	-0.395928	5.737278	-0.057254
H	-1.635089	4.233208	1.566834
C	1.657384	2.365561	-2.208154
O	1.832962	1.025287	-2.149393
O	2.342066	3.093100	-2.883877
C	2.913100	0.472485	-2.936290
H	3.167352	-0.455031	-2.427634
H	3.759313	1.155007	-2.889097
C	2.493376	0.224498	-4.372236
H	2.253022	1.161228	-4.871009
H	3.311530	-0.252099	-4.914504
H	1.625410	-0.433105	-4.419719
H	-1.658727	4.811767	-0.847129
H	0.078839	3.863637	1.482814
H	-1.237610	1.769746	1.397233
H	0.471051	1.114660	-0.037210
C	-0.856103	-1.976423	-1.832594
H	-1.659001	-1.873614	-2.569438
H	0.088229	-1.953342	-2.381926
C	-0.993438	-3.275029	-1.192748
C	-1.105749	-4.362222	-0.705037
H	-1.203826	-5.324070	-0.267049

Table S15. Optimized Cartesian coordinates (in Å) of the transition state structure (n_i = 1) of prodrug **4** ($\tau_{C\text{-}N\text{-}C\text{-}C}$ = 150°) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	2.450447	0.932754	-1.350147
C	3.291211	0.299448	-0.453807
C	2.857950	-0.741920	0.347330
C	1.540488	-1.157049	0.236559
C	0.643215	-0.542121	-0.643625
C	1.131690	0.508853	-1.433629
H	2.818487	1.740868	-1.963536
H	3.545061	-1.216419	1.032509
H	1.177724	-1.971010	0.846818
F	4.564501	0.710749	-0.367732
Cl	0.077657	1.333456	-2.557478
N	-0.699063	-0.989653	-0.737749
S	-1.871128	-0.886923	0.541369
O	-1.151610	-1.753685	1.667850
O	-2.403542	-1.241167	2.350531
C	-0.562196	1.077474	2.128449
C	-1.601295	0.930357	1.002262
C	-2.962513	1.502254	1.308453
C	-3.287917	1.973808	2.515643
C	-2.322776	2.034887	3.651856
C	-0.898656	2.195242	3.117288
H	-0.505254	0.141464	2.679122
H	-4.290695	2.360979	2.645967

H	-2.587950	2.853404	4.323053
H	-0.176592	2.175602	3.934972
C	-3.991020	1.606196	0.233862
O	-3.522741	1.145348	-0.948693
O	-5.100169	2.058747	0.375128
C	-4.422974	1.211732	-2.079241
H	-3.763807	1.240683	-2.944466
H	-4.983046	2.142884	-2.019920
C	-5.352637	0.014769	-2.127667
H	-6.018180	0.010009	-1.266611
H	-5.963104	0.064818	-3.030914
H	-4.788900	-0.917500	-2.145235
H	-2.400910	1.111037	4.235834
H	-0.808978	3.172631	2.635914
H	0.417150	1.251176	1.684897
H	-1.242599	1.345544	0.064424
C	-1.020867	-1.846505	-1.901748
H	-1.277543	-1.226383	-2.765802
H	-0.117306	-2.400823	-2.169090
C	-2.092040	-2.809235	-1.675469
C	-2.955360	-3.628634	-1.544966
H	-3.722081	-4.349588	-1.406222

Table S16. Optimized Cartesian coordinates (in Å) of the transition state structure (n_i = 1) of prodrug **4** ($\tau_{C\text{-}N\text{-}C\text{-}C}$ = 229°) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	0.655024	2.324562	-2.437903
C	2.014453	2.113572	-2.301909
C	2.525037	0.956885	-1.740296
C	1.635441	-0.010336	-1.299790
C	0.250641	0.158432	-1.401820
C	-0.217796	1.342698	-1.988610
H	0.288762	3.234100	-2.888784
H	3.593711	0.825364	-1.654420
H	2.011136	-0.917107	-0.848654
F	2.857703	3.061733	-2.735074
Cl	-1.928431	1.612888	-2.184459
N	-0.660445	-0.841469	-0.955472
S	-0.803567	-1.347214	0.715099
O	0.693400	-1.823960	1.013415
O	-0.020365	-1.972317	2.341310
C	0.363339	0.962234	1.864787
C	-1.005883	0.371999	1.477418
C	-1.988045	0.252033	2.616396
C	-1.657525	0.525991	3.881815
C	-0.311199	1.024346	4.286917
C	0.317567	1.810657	3.136489
H	1.065101	0.146897	2.026373
H	-2.431529	0.415068	4.630841

H	-0.395802	1.636780	5.186110
H	1.331798	2.122041	3.390900
C	-3.408321	-0.119567	2.351766
O	-3.617583	-0.373253	1.043682
O	-4.277046	-0.173356	3.187622
C	-4.965705	-0.722444	0.650797
H	-4.992008	-0.505232	-0.414154
H	-5.657437	-0.065895	1.175901
C	-5.277040	-2.180303	0.928908
H	-5.265923	-2.381429	1.997942
H	-6.272072	-2.417623	0.547797
H	-4.555522	-2.829518	0.434788
H	0.323362	0.170036	4.548271
H	-0.263475	2.721305	2.969224
H	0.741959	1.554123	1.033661
H	-1.468832	0.918142	0.659072
C	-0.898063	-1.957511	-1.904061
H	-0.446455	-1.674319	-2.855181
H	-0.378022	-2.865121	-1.579561
C	-2.306492	-2.270284	-2.130399
C	-3.441613	-2.571850	-2.363613
H	-4.448744	-2.835274	-2.569814

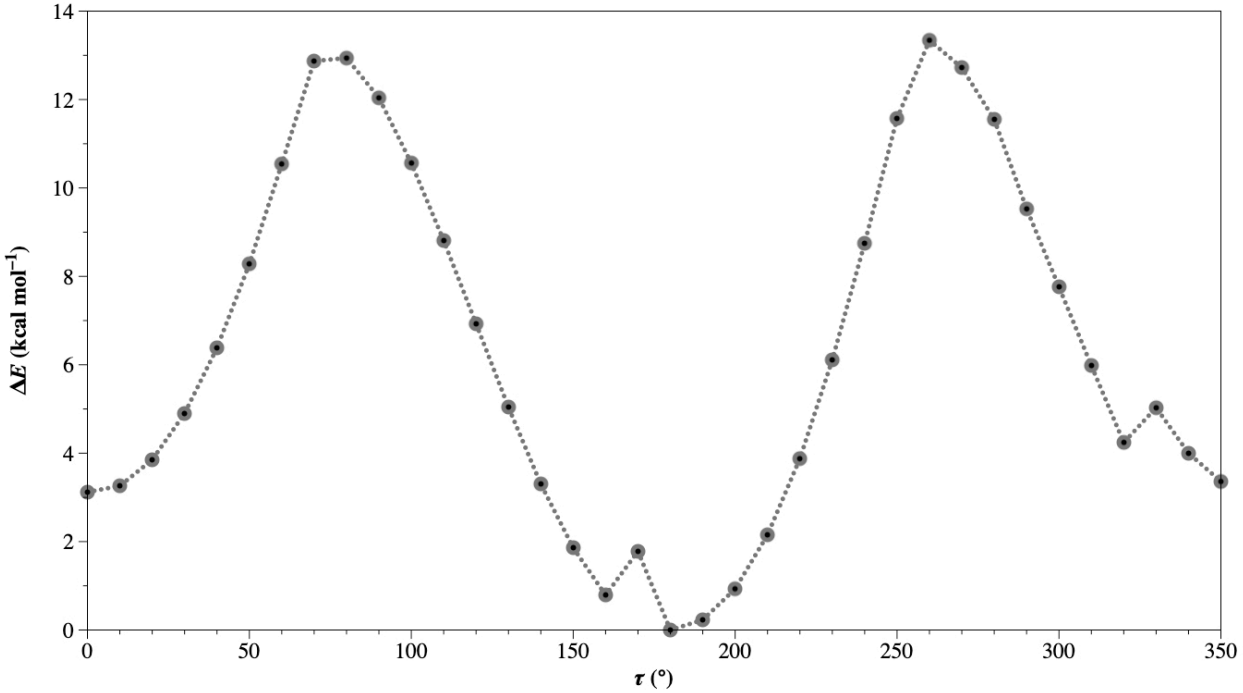


Figure S18. Cross section of the potential energy surface about torsional angle ($\tau_{C\text{-}N\text{-}C\text{-}O}$ = 0º - 350º) of prodrug **5** computed at the B3LYP/6-311G(2*df*,2*pd*) level of theory.

Table S17. Optimized Cartesian coordinates (in Å) of the global minimum energy structure (n_i = 0) of prodrug **5** ($\tau_{C\text{-}N\text{-}C\text{-}O}$ = 179º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	*y*	*z*
C	-1.528716	0.575241	-2.367101
C	-2.034937	-0.697700	-2.131861
C	-1.482659	-1.548804	-1.181924
C	-0.389398	-1.100126	-0.446493
C	0.166101	0.171672	-0.653147
C	-0.426689	0.998771	-1.626989
H	-1.986951	1.216247	-3.110106
H	-1.909963	-2.532239	-1.023098
H	0.058726	-1.739184	0.305957
F	-3.094572	-1.110609	-2.850847
Cl	0.203315	2.605133	-1.930937
N	1.307880	0.583163	0.087736
S	3.018745	-0.158341	-0.104473
O	2.575594	-1.686732	0.191925
O	4.058140	-1.680717	-0.173447
C	2.600959	-1.224447	-2.707048
C	3.093823	0.044628	-1.988729
C	4.514553	0.441160	-2.327157
C	5.262303	-0.233321	-3.217460
C	4.757204	-1.404401	-4.003877
C	3.226800	-1.370119	-4.100710
H	2.878292	-2.096749	-2.110618
H	6.269626	0.134152	-3.398309
H	5.216340	-1.403845	-4.999332
H	2.851442	-2.285983	-4.569352
C	5.105264	1.673976	-1.722330
O	4.195658	2.306799	-0.944105
O	6.236953	2.073374	-1.908672
C	4.631677	3.503762	-0.245061
H	3.712739	4.074977	-0.100040
H	5.309961	4.053683	-0.901195
C	5.285588	3.155577	1.082008
H	6.199414	2.577404	0.922112
H	5.553848	4.077824	1.608766
H	4.593481	2.585265	1.705744
C	1.206486	1.432797	1.173358
O	2.144979	1.812764	1.852017
O	-0.079353	1.798270	1.399466
C	-0.244329	2.722495	2.498881
H	0.300869	3.646898	2.278541
H	0.199277	2.292212	3.402842
H	5.087127	-2.335113	-3.518327
H	2.925267	-0.534558	-4.744824
H	1.511064	-1.202073	-2.775750
H	2.429212	0.894899	-2.153175
C	-1.666554	2.980791	2.678219

C	-2.834674	3.220723	2.859645
H	-3.868727	3.426672	3.013835

Table S18. Optimized Cartesian coordinates (in Å) of the local minimum energy structure (n_i = 0) of prodrug **5** ($\tau_{C\text{-}N\text{-}C\text{-}O}$ = 2º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	4.621385	-0.048165	0.277264
C	5.051041	-0.188153	-1.036340
C	4.193170	-0.012373	-2.114643
C	2.866053	0.317121	-1.857168
C	2.374329	0.449127	-0.549860
C	3.283467	0.263855	0.510677
H	5.317491	-0.180433	1.096261
H	4.565876	-0.119729	-3.126750
H	2.181620	0.472919	-2.682895
F	6.341209	-0.499041	-1.262130
Cl	2.766790	0.441481	2.175939
N	1.008496	0.767028	-0.318106
S	-0.473175	-0.290818	-1.009795
O	0.494218	-1.304581	-1.828484
O	-0.955175	-1.777158	-1.928497
C	0.263636	-2.122032	0.966590
C	-0.843618	-1.106521	0.651735
C	-2.223348	-1.737038	0.680777
C	-2.434982	-2.942919	1.239773
C	-1.381043	-3.787501	1.886000
C	-0.112752	-2.980123	2.180306
H	0.400296	-2.771755	0.096577
H	-3.459145	-3.308285	1.235648
H	-1.786782	-4.238911	2.800034
H	0.719172	-3.646893	2.429400
C	-3.439208	-1.024731	0.182537
O	-3.137436	0.212151	-0.271383
O	-4.565106	-1.482523	0.189913
C	-4.231874	1.002745	-0.803531
H	-3.914564	2.035059	-0.649879
H	-5.121586	0.803844	-0.202253
C	-4.475702	0.686242	-2.270635
H	-4.802774	-0.349129	-2.392506
H	-5.259854	1.342371	-2.663138
H	-3.569095	0.842073	-2.862365
C	0.714464	2.042161	0.095541
O	1.498320	2.955739	0.262281
O	-0.635073	2.145087	0.322237
C	-1.083564	3.462333	0.705312
H	-1.263223	4.054125	-0.200586
H	-0.285682	3.955816	1.267821
H	-1.151524	-4.632361	1.218393
H	-0.278210	-2.338678	3.055006

H	1.201414	-1.597013	1.146679
H	-0.796234	-0.237173	1.315028
C	-2.302066	3.348737	1.496957
C	-3.312349	3.304677	2.155923
H	-4.196857	3.257728	2.748582

Table S19. Optimized Cartesian coordinates (in Å) of the transition state structure (n_i = 0) of prodrug **5** ($\tau_{C\text{-}N\text{-}C\text{-}O}$ = 80º) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	-0.214241	-1.406115	2.293947
C	1.028711	-1.926592	2.632545
C	2.191024	-1.562884	1.961960
C	2.092720	-0.654914	0.912530
C	0.857391	-0.110648	0.519979
C	-0.290762	-0.494222	1.240901
H	-1.097594	-1.699997	2.847348
H	3.143249	-1.986117	2.260696
H	2.980653	-0.346268	0.372365
F	1.101350	-2.806984	3.647536
Cl	-1.860020	0.180245	0.855265
N	0.768704	0.815342	-0.568322
S	1.142923	0.303326	-2.319343
O	2.392374	-0.705204	-2.079139
O	2.048406	-0.720412	-3.566198
C	-0.086368	-2.247059	-2.217794
C	-0.411556	-0.765768	-2.481330
C	-1.013806	-0.486792	-3.840714
C	-1.280737	-1.461373	-4.727427
C	-1.055242	-2.916318	-4.447364
C	-1.067530	-3.182772	-2.936228
H	0.921442	-2.457386	-2.582324
H	-1.730981	-1.164913	-5.671823
H	-1.819682	-3.511614	-4.960081
H	-0.792085	-4.222135	-2.728330
C	-1.434046	0.902819	-4.195731
O	-1.166324	1.759975	-3.180922
O	-1.964901	1.233553	-5.237261
C	-1.538576	3.149979	-3.362083
H	-1.605370	3.538283	-2.343831
H	-2.522164	3.183243	-3.837070
C	-0.505076	3.905599	-4.183483
H	-0.454399	3.510157	-5.200295
H	-0.783065	4.963411	-4.237864
H	0.485884	3.836183	-3.725278
C	1.419397	2.059971	-0.320063
O	2.609441	2.275525	-0.409169
O	0.507740	2.989914	0.021903
C	1.058526	4.295969	0.330831
H	1.798180	4.562334	-0.430711

H	1.583569	4.240759	1.291414
H	-0.090780	-3.223139	-4.879122
H	-2.085678	-3.038572	-2.553532
H	-0.095581	-2.431570	-1.140423
H	-1.051633	-0.342226	-1.706484
C	-0.032564	5.258774	0.378590
C	-0.912848	6.082675	0.420482
H	-1.694229	6.806246	0.461703

Table S20. Optimized Cartesian coordinates (in Å) of the the local minimum energy structure ($n_i = 0$) of prodrug **5** ($\tau_{C\text{-}N\text{-}C\text{-}O} = 260°$) on the B3LYP/6-311G(2*df*,2*pd*) potential energy surface.

	x	***y***	***z***
C	2.351974	1.810823	-3.096372
C	1.472011	1.118982	-3.919490
C	0.410144	0.378894	-3.412052
C	0.234502	0.333778	-2.032370
C	1.103949	1.004576	-1.155178
C	2.160519	1.750533	-1.715943
H	3.162880	2.385938	-3.526040
H	-0.257801	-0.142648	-4.088038
H	-0.588173	-0.229375	-1.606776
F	1.659085	1.174969	-5.250700
Cl	3.265807	2.642430	-0.694238
N	0.925035	0.939806	0.262495
S	1.076834	-0.616339	1.232397
O	0.263563	-1.653493	0.284501
O	0.840376	-2.445750	1.454591
C	3.123674	-1.841490	-0.302954
C	2.920727	-0.846814	0.854063
C	3.594134	-1.239467	2.150066
C	4.331658	-2.356440	2.272814
C	4.601974	-3.293514	1.134748
C	4.476225	-2.560227	-0.207541
H	2.331365	-2.592057	-0.265649
H	4.789307	-2.547048	3.240671
H	5.597853	-3.736346	1.251396
H	4.568132	-3.266181	-1.039766
C	3.531844	-0.316083	3.323887
O	2.826933	0.798472	3.015691
O	4.053924	-0.512075	4.403179
C	2.692990	1.816641	4.039542
H	2.499925	2.730797	3.475339
H	3.644740	1.898025	4.569991
C	1.553068	1.499471	4.994652
H	1.750875	0.574732	5.541718
H	1.445899	2.312883	5.719978
H	0.608866	1.400651	4.451627
C	-0.102224	1.773729	0.793398
O	0.079024	2.844179	1.324188

O	-1.318623	1.194982	0.666032
C	-2.418888	1.963904	1.219780
H	-2.428212	2.954349	0.752631
H	-2.244068	2.110729	2.291163
H	3.889063	-4.130524	1.177619
H	5.300622	-1.842580	-0.303754
H	3.034501	-1.310089	-1.254142
H	3.219112	0.166752	0.583695
C	-3.660470	1.245598	0.975929
C	-4.708124	0.677567	0.790425
H	-5.628741	0.166712	0.625350

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