## Structure-based Design, Synthesis, and Biological Evaluation of Non-Acyl Sulfamate Inhibitors of the Adenylate-forming Enzyme MenE

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## A. Supplementary Tables and Figures

Table S1. Docking scores of OSB-AMS linker analogue virtual library.
Entry

Table S1. Docking scores of OSB-AMS linker analogue virtual library (continued).
Entry

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Entry

Table S2. Data collection and refinement statistics for m-phenyl ether analogue 5 bound to wildtype $E$. coli MenE.

| Property | Value |
| :---: | :---: |
| Space group | P 212121 |
| Cell constants | $71.15 \AA 74.42 \AA 79.03 \AA$ |
| $a, b, c, a, \beta, \gamma$ | $90.00^{\circ} 90.00^{\circ} \quad 90.00^{\circ}$ |
| Resolution ( $\AA$ ) | 54.181 .83 |
| \% Data completeness (in resolution range) | 99.3 (54.18-1.83) |
| $\mathrm{R}_{\text {merge }}$ | 0.15 |
| $<I / \sigma(I)>$ | 1.12 (at 1.83Å) |
| Refinement program | REFMAC 5.8.0158 |
| $\mathrm{R}^{\boldsymbol{a}}, \mathrm{R}_{\text {free }}{ }^{\text {b }}$ | 0.196, 0.244 |
| $\mathrm{R}_{\text {free }}$ test set | 1803 reflections (4.84\%) |
| Wilson B-factor ( $\AA^{2}$ ) | 26.1 |
| Anisotrpy | 0.031 |
| Bulk solvent $k_{\text {sol }}\left(\mathrm{e} / \AA^{3}\right), B_{\text {sol }}\left(\AA^{2}\right)$ | 0.33, 51.0 |
| L-test for twinning | $\langle \| L\left\rangle=0.45,\left\langle L^{2}\right\rangle=0.28\right.$ |
| Estimated twinning fraction | 0.035 for k,h,-1 |
| $\mathrm{F}_{\text {obs }}, \mathrm{F}_{\text {calc }}$ correlation | 0.95 |
| Total number of atoms | 3583 |
| Average B, all atoms ( $\AA^{2}$ ) | 28.0 |

[^0]

Figure S1. Thermographs of inhibitors titrated into E.coli MenE using isothermal calorimetry. (a) $m$-Phenyl ether analogue 5 titrated into wild-type E. coli MenE, (b) $p$-Phenyl ether analogue 6 titrated into wild-type E. coli MenE, (c) m-3-Pyridyl ether analogue 9 titrated into wild-type E. coli MenE. (d) m-Phenyl ether analogue 5 titrated into E. coli MenE (K437A mutant). The data were fit to a single binding site model with the Origin software.


Figure S2. Overlays of docked and cocrystallized m-phenyl ether analogue 5 and OSB-AMS (1) in complex with E. coli MenE. Structures were obtained by alignment of large N -terminal domains (residues 1-351) of MenE (R195K) (light blue) with m-phenyl ether analogue 5 docked (blue), wild-type MenE (salmon) with m-phenyl ether analogue 5 cocrystallized (purple), and MenE (R195K) (white) with OSB-AMS (1) cocrystallized (beige). (a) Overlay of ligands. (b) Comparison of binding positions of docked and cocrystallized $m$-phenyl ether analogue 5 (rmsd $=1.26 \AA$ ) with putative active-site interactions (dashed lines). (c) Comparison of binding positions of docked m-phenyl ether analogue 5 and cocrystallized OSB-AMS (1), illustrating predicted protusion of aryl ether linker of 5 away from adenosine binding pocket. (d) Comparison of binding positions of cocrystallized $m$-phenyl ether analogue 5 and cocrystallized OSB-AMS (1), illustrating observed $\approx 1.5 \AA$ translation of ribose motif of 5 into adenosine binding pocket.

## B. Materials and Methods

Reagents were obtained from Aldrich Chemical (www.sigma-aldrich.com) or Acros Organics (www.fishersci.com) and used without further purification. Optima or HPLC grade solvents were obtained from Fisher Scientific (www.fishersci.com), degassed with Ar, and purified on a solvent drying system. ${ }^{1}$ Reactions were performed in flame-dried glassware under positive Ar pressure with magnetic stirring.

TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light ( 254 nm ) or by staining with potassium permanganate ( KMnO ), cerium ammonium molybdenate (CAM), or iodine ( $\mathrm{I}_{2}$ ). Silica flash chromatography was performed on E. Merck 230-400 mesh silica gel 60. Preparative scale HPLC purification was carried out on a Waters 2545 HPLC with 2996 diode array detector using a Sunfire Prep C18 reverse phase column ( $10 \AA, 150 \mathrm{~mm} \times 19 \mathrm{~mm}$ ) with UV detection at 254 nm . Samples were lyophilized using a Labconco Freezone 2.5 instrument.

IR spectra were recorded on a Bruker Optics Tensor 27 FTIR spectrometer with Pike Technologies MIRacle ATR (attenuated total reflectance, ZnSe crystal) accessory and peaks reported in $\mathrm{cm}_{-1}$. NMR spectra were recorded on a Bruker Avance III 500 instrument or Bruker Avance III 600 instrument at $24^{\circ} \mathrm{C}$ in $\mathrm{CDCl}_{3}$ unless otherwise indicated. Spectra were processed using Bruker TopSpin or nucleomatica iNMR (www.inmr.net) software, and chemical shifts are expressed in ppm relative to TMS ( $1 \mathrm{H}, 0 \mathrm{ppm}$ ) or residual solvent signals: $\mathrm{CDCl}_{3}(1 \mathrm{H}, 7.24 \mathrm{ppm}$; $\left.{ }_{13} \mathrm{C}, 77.23 \mathrm{ppm}\right), \mathrm{CD}_{3} \mathrm{OD}\left({ }_{1} \mathrm{H}, 3.31 \mathrm{ppm} ;{ }_{13} \mathrm{C}, 49.15 \mathrm{ppm}\right), \mathrm{D}_{2} \mathrm{O}\left({ }_{1} \mathrm{H}, 4.80 \mathrm{ppm}\right)$; coupling constants are expressed in Hz . Mass spectra were obtained at the MSKCC Analytical Core Facility on a Waters Acuity SQD LC-MS by electrospray (ESI) ionization or atmospheric pressure chemical ionization (AP-CI).

[^1]
## C. Synthesis of $\boldsymbol{\alpha}$-Hydroxytetrazole Analogue 7






Figure S3. Synthesis of $\alpha$-hydroxytetrazole analogue 7. DIAD = diisopropyl azodicarboxylate, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMS = trimethylsilyl.


Methyl 2-(4-hydroxybutanoyl)benzoate (11). In a $25-\mathrm{mL}$ roundbottom flask, aryl bromide $\mathbf{1 0}$ ( $3 \mathrm{~g}, 11.66 \mathrm{mmol}, 1$ equiv), prepared as previously described, ${ }^{2}$ was suspended in THF ( 10 mL ) and cooled to $-78{ }^{\circ} \mathrm{C}$. A solution of $n-\operatorname{BuLi}(5.127 \mathrm{~mL}, 12.82 \mathrm{mmol}, 2.5 \mathrm{M}$ in hexanes, 1.1 equiv) was added and the reaction stirred for 1 h . The mixture was then transferred via cannula over 5 min to a solution of dimethyl carbonate ( $2.1 \mathrm{~g}, 23.32 \mathrm{mmol}, 2$ equiv) in THF ( 5 mL ) at $-78^{\circ} \mathrm{C}$, and stirred for 2 h with warming to rt . The reaction was quenched with $1 \mathrm{M} \mathrm{aq} \mathrm{HCl}(20$ mL ) and stirred for 10 min , then extracted with EtOAc ( $4 \times 25 \mathrm{~mL}$ ). The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography $(25 \% \rightarrow 100 \%$ EtOAc in hexanes) yielded methyl ester $\mathbf{1 1}$ as a clear oil ( $1.95 \mathrm{~g}, 75 \%$ ).

IR (ATR): 3400, 2954, 2883, 1720, 1597, 1575, 1486, 1436, 1406, 1370, 1285, 1195, 1136, 1098, 1054, 963, 914, 830, 764, 737, 709, 781, 647. ${ }^{1} \mathbf{H}-\mathbf{N M R}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 7.92$ (dt, $J$ $=7.8,0.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.58(\mathrm{td}, J=7.5,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.50(\mathrm{td}, J=7.7,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.35(\mathrm{dt}, J=7.6$, $0.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.90(\mathrm{~s}, 3 \mathrm{H}), 3.79(\mathrm{t}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 2.94(\mathrm{t}, J=6.7 \mathrm{~Hz}, 2 \mathrm{H}), 2.02$ (quintet, $J=6.3$ $\mathrm{Hz}, 2 \mathrm{H}$ ). ${ }^{13} \mathbf{C}$-NMR ( $151 \mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): $\delta 206.2,167.2,143.7,132.5,130.0,129.7,128.0,126.2$, 61.8, 52.7, 39.4, 26.7. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$223.0970; found 223.0966.


Methyl 2-(4-cyano-4-hydroxybutanoyl)benzoate (12). In a $25-\mathrm{mL}$ roundbottom flask, primary alcohol 11 ( $900 \mathrm{mg}, 4.049 \mathrm{mmol}$, 1 equiv) was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(15 \mathrm{~mL})$. Solid $\mathrm{NaHCO}_{3}$ ( $1.36 \mathrm{~g}, 16.19 \mathrm{mmol}, 4.0$ equiv) and Dess-Martin periodinane ( $2.146 \mathrm{~g}, 5.061 \mathrm{mmol}, 1.25$ equiv) were added and the mixture was stirred for 1 h . The mixture was poured into a solution of satd aq sodium thiosulfate $(50 \mathrm{~mL})$ and satd aq $\mathrm{NaHCO}_{3}(25 \mathrm{~mL})$, stirred vigorously for 10 min , then extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(4 \times 50 \mathrm{~mL})$. The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation to afford the crude aldehyde $\mathbf{S 1}$, which was carried forward without further purification.

In a $4-\mathrm{mL}$ borosilicate vial, $\mathrm{TMSCN}(421.6 \mathrm{mg}, 4.250 \mathrm{mmol}, 1.05$ equiv) and $\mathrm{LiCl}(17.16 \mu \mathrm{~g}$, $0.405 \mu \mathrm{~mol}, 0.0001$ equiv 0.3 M in THF) were added to the neat crude aldehyde $\mathbf{S} 1$ above and the mixture was stirred vigorously for 2 h . The reaction was quenched by addition of 6 M HCl $(20 \mathrm{~mL})$ and stirred for 10 min , then extracted with EtOAc $(4 \times 25 \mathrm{~mL})$. The combined organic

[^2]extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography $(30 \% \rightarrow 50 \%$ EtOAc in hexanes) yielded cyanohydrin 12 as a clear oil (790 mg, 79\%).

IR (ATR): 3434, 3070, 3002, 2954, 2848, 2253, 1793, 1711, 1597, 1576, 1487, 1436, 1409, 1371, 1285, 1203, 1165, 1138, 1093, 994, 960, 913, 830, 802, 761, 736, 708, 681, 648. ${ }^{1} \mathbf{H}-\mathrm{NMR}\left(600 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 7.97(\mathrm{dd}, J=7.8,0.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.62(\mathrm{td}, J=7.5,1.2 \mathrm{~Hz}, 1 \mathrm{H})$, $7.53(\mathrm{td}, J=7.7,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{dd}, J=7.6,0.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.81(\mathrm{~s}, 1 \mathrm{H}), 4.03(\mathrm{~s}, 1 \mathrm{H}), 3.92(\mathrm{~s}$, 3 H ), 3.14 (ddd, $J=18.8,8.9,4.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.98$ (ddd, $J=18.8,6.3,5.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.43 (ddt, $J=$ $14.2,9.3,4.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.25 (dddd, $J=14.4,7.8,6.5,5.0 \mathrm{~Hz}, 1 \mathrm{H}$ ). ${ }^{13} \mathbf{C}-\mathbf{N M R}$ ( 151 MHz ; $\mathrm{CDCl}_{3}$ ): $\delta 205.9,167.1,143.3,133.0,130.21,130.03,127.5,125.9,119.8,60.2,53.0,38.3,29.4$. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{17} \mathrm{O}_{4} \mathrm{Na}\left([\mathrm{M}+\mathrm{Na}]^{+}\right) 346.1055$; found 346.1041.


Methyl 2-(5-cyano-2-methoxytetrahydrofuran-2-yl)benzoate (13). In a $50-\mathrm{mL}$ roundbottom flask, cyanohydrin 12 ( $500 \mathrm{mg}, 2.022 \mathrm{mmol}, 1$ equiv) was dissolved in $\mathrm{MeOH}(20 \mathrm{~mL})$. Trimethyl orthoformate ( $858 \mathrm{mg}, 8.088 \mathrm{mmol}, 4.0$ equiv) and conc $\mathrm{H}_{2} \mathrm{SO}_{4}(19.8 \mathrm{mg}, 0.202$ mmol, 0.1 equiv) were and the reaction heated to reflux for 12 h . The reaction was cooled to rt , poured into satd aq $\mathrm{NaHCO}_{3}(50 \mathrm{~mL})$, and extracted with EtOAc ( $4 \times 50 \mathrm{~mL}$ ). The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography $\left(10 \% \rightarrow 30 \% \mathrm{EtOAc}\right.$ in hexanes with $1 \% \mathrm{Et}_{3} \mathrm{~N}$ ) yielded cyclic acetal 13 as a clear oil ( $425 \mathrm{mg}, 80 \%$ ).

IR (ATR): 2999, 2948, 2837, 1729, 1434, 1295, 1268, 1191, 1131, 1099, 1076, 1031, 960, 928, 874, 827, 784, 762, 738, 703, 651. ${ }^{1}$ H-NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.54$ (dt, $J=7.9,0.6 \mathrm{~Hz}$, $1 \mathrm{H}), 7.48-7.43(\mathrm{~m}, 1 \mathrm{H}), 7.42-7.36(\mathrm{~m}, 2 \mathrm{H}), 4.89-4.86(\mathrm{~m}, 1 \mathrm{H}), 3.88(\mathrm{~d}, J=11.6 \mathrm{~Hz}, 3 \mathrm{H}), 3.15(\mathrm{~s}$, $3 \mathrm{H}), 2.63-2.49(\mathrm{~m}, 3 \mathrm{H}), 2.38-2.20(\mathrm{~m}, 1 \mathrm{H}) .{ }^{13} \mathbf{C}-\mathbf{N M R}\left(151 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 170.5,136.4$, 132.4, 130.1, 128.5, 128.1, 127.2, 119.3, 110.9, 66.0, 52.4, 50.7, 40.1, 30.8. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{14} \mathrm{H}_{15} \mathrm{O}_{4} \mathrm{NNa}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$284.0899; found 284.0903.


6- N - $\boldsymbol{t}$-Butoxycarbonyl- $\mathbf{2}^{\prime}, 3^{\prime}-\mathrm{O}$-isopropylidene-5' N -( $\mathrm{N}-\mathbf{2}^{\prime \prime}$-[methyloxycarbonyl] [benzyl-(2-methoxy-5-[2H-tetrazol-5-yl]tetrahydrofuran-2-yl)])aminodeoxyadenosine (18). In a $25-\mathrm{mL}$ roundbottom flask, nitrile $13(206 \mathrm{mg}, 0.788 \mathrm{mmol}, 1$ equiv), sodium azide ( $153.7 \mathrm{mg}, 2.365$
mmol, 3.0 equiv), and triethylammonium hydrochloride ( $325.5 \mathrm{mg}, 2.365 \mathrm{mmol}, 3.0$ equiv) were suspended in toluene ( 15 mL ) and stirred at $100^{\circ} \mathrm{C}$ for 4 h . The reaction was cooled to rt , diluted with acetone ( 30 mL ), filtered through a pad of celite, and the filtrate concentrated by rotary evaporation. The residue was dissolved in $\mathrm{EtOAc}(50 \mathrm{~mL})$ and washed with satd aq $\mathrm{NH}_{4} \mathrm{Cl}(2 \mathrm{x}$ $25 \mathrm{~mL})$. The organic layer was dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation to afford the crude tetrazole $\mathbf{1 4}$, which was carried forward without further purification.

In a $25-\mathrm{mL}$ roundbottom flask, the crude tetrazole $\mathbf{1 4}$, protected adenosine $16(321 \mathrm{mg}, 0.789$ $\mathrm{mmol}, 1$ equiv), prepared as previously described, ${ }^{3}$ and resin-bound $\mathrm{PPh}_{3}(969 \mathrm{mg}, 1.182 \mathrm{mmol}$, 1.5 equiv, $32 \% \mathrm{w} / \mathrm{w}$ ) were suspended in THF ( 15 mL ) and cooled to $0{ }^{\circ} \mathrm{C}$. Diisopropyl azodicarboxylate ( $239 \mathrm{mg}, 1.182 \mathrm{mmol}, 1.5$ equiv) was added and the reaction was stirred for 14 h with warming to rt . The reaction was quenched with water $(1 \mathrm{~mL})$, filtered through a pad of celite, and the filtrate concentrated by rotary evaporation to yield the crude tetrazole-adenosine intermediate 18 as a yellow solid ( 680 mg ), which was carried forward without further purification.

$5^{\prime}-\mathrm{N}$-( N -[4"-([2"-(Carboxyl)phenyl]4-hydroxy)2H-tetrazol-5-yl]butanoyl)aminodeoxy-
adenosine (7). In a $50-\mathrm{mL}$ roundbottom flask, tetrazole-adenosine intermediate $\mathbf{1 8}$ was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20 \mathrm{~mL})$ and cooled to $0{ }^{\circ} \mathrm{C}$. TFA ( 20 mL ) and water ( 1 mL ) were added, and the reaction was stirred for 4 h with warming to rt . The mixture was concentrated by rotary evaporation and dried under high vacuum for 4 h to afford the crude spirolactone 19, which was carried forward without further purification.

The crude sprirolactone 19 above was dissolved in $\mathrm{MeOH}(25 \mathrm{~mL}$ ) and water ( 3 mL ), then LiOH ( $75 \mathrm{mg}, 3.152 \mathrm{mmol}, 4.0$ equiv) was added and the reaction stirred at rt for 12 h . The mixture was concentrated by rotary evaporation. Purification by preparative HPLC ( $5 \% \rightarrow 45 \% \mathrm{CH}_{3} \mathrm{CN}$ in $\mathrm{H}_{2} \mathrm{O}$ with $0.1 \%$ TFA) yielded the $\alpha$-hydroxytetrazole analogue 7 as a fluffy white solid (145 $\mathrm{mg}, 35 \%$ over 4 steps).

IR (ATR): 3350, 1751, 1694, 1509, 1468, 1428, 1324, 1289, 1202, 1138, 1062, 1033, 898, 831, 801, 767, 723, 700, 643. ${ }^{1} \mathbf{H}-\mathrm{NMR}\left(600 \mathrm{MHz} ; \mathrm{D}_{2} \mathrm{O}\right): \delta 8.00(\mathrm{~d}, J=4.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.84(\mathrm{~s}, 1 \mathrm{H})$, $7.46(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.39(\mathrm{q}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.30-7.25(\mathrm{~m}, 1 \mathrm{H}), 7.19(\mathrm{dd}, J=23.4,7.7 \mathrm{~Hz}$, $1 \mathrm{H}), 5.92(\mathrm{t}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.11(\mathrm{dtd}, J=29.2,12.4,4.7 \mathrm{~Hz}, 2 \mathrm{H}), 5.01(\mathrm{dt}, J=15.2,6.6 \mathrm{~Hz}$, $\left.{ }_{13} \mathrm{H}\right), ~ 4.59-4.56(\mathrm{~m}, 1 \mathrm{H}), 4.50(\mathrm{dq}, J=9.7,4.8 \mathrm{~Hz}, 2 \mathrm{H}), 2.79-2.72(\mathrm{~m}, 2 \mathrm{H}), 2.19-2.09(\mathrm{~m}, 2 \mathrm{H})$. ${ }^{13}$ C-NMR ( $151 \mathrm{MHz} ; \mathrm{D}_{2} \mathrm{O}$ ): $\delta 208.3$, 175.96, 175.80, 167.51, 167.48, 163.1, 162.9, 160.2, 155.29 , 155.29, 152.6, 148.4, 139.5, 138.34, 138.30, 138.15, 138.13, 137.18, 137.17, 137.16, $137.01,136.98$, 131.09, 131.08, 131.01, 131.00, 130.99, 129.35, 129.31, 127.80, 127.76, 126.51, $126.49,126.36,126.34,126.34,119.2,118.60,118.57,117.3,115.3,113.4,88.30,88.24,80.63$,

[^3]80.55, 73.07, 73.02, 70.05, 69.98, 64.5, 53.25, 53.12, 29.82, 29.76. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{22} \mathrm{O}_{7} \mathrm{~N}_{9}\left([\mathrm{M}+\mathrm{H}]^{+}\right) 524.1642$; found 524.1630.

## D. Synthesis of Acyl Squaramide Analogue 3



Figure S4. Synthesis of acyl squaramide analogue 3. DMAP = 4-dimethylaminopyridine, $\mathrm{DMF}=$ dimethylformamide, EDCI $=N$-ethyl- $N^{\prime}$-(3-dimethylaminopropyl)carbodiimide hydrochloride, TASF = tris(dimethylamino)sulfur trimethylsilyl difluoride, TFA = trifluoroacetic acid .


Benzyl 2-(4'-t-butoxy-4'-oxobutanoyl)benzoate (S3). In a $25-\mathrm{mL}$ roundbottom flask, diester $\mathbf{S 2}\left(1.64 \mathrm{~g}, 5.610 \mathrm{mmol}, 1\right.$ equiv), prepared as previously described, ${ }^{3}$ was dissolved in MeOH $(5 \mathrm{~mL})$ and water ( 0.5 mL ). $\mathrm{LiOH}(136 \mathrm{mg}, 5.66 \mathrm{mmol}, 1.01$ equiv) was added and the reaction stirred at rt for 5 h . The mixture was concentrated by rotary evaporation and dried under high
vacuum to afford the crude monocarboxylic acid, which was carried forward without further purification.

The crude monocarboxylic acid above was suspended in $\mathrm{CH}_{3} \mathrm{CN}(10 \mathrm{~mL}) . \mathrm{K}_{2} \mathrm{CO}_{3}(1.162 \mathrm{~g}$, $8.413 \mathrm{mmol}, 1.5$ equiv) and benzyl bromide ( $1.438 \mathrm{~g}, 8.413 \mathrm{mmol}, 1.5$ equiv) were added and the reaction stirred at rt for 12 h . The reaction was quenched with water ( 50 mL ) and extracted with EtOAc ( $4 \times 50 \mathrm{~mL}$ ). The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography ( $10 \% \rightarrow 25 \%$ EtOAc in hexanes) yielded diester $\mathbf{S 3}$ as a clear oil ( $1.9 \mathrm{~g}, 92 \%$ ).

IR (ATR): 2979, 1719, 1575, 1456, 1367, 1270, 1151, 1092, 991, 949, 912, 848, 732, 698, 648.
${ }^{1} \mathbf{H}-\mathrm{NMR}\left(600 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 7.92(\mathrm{dd}, J=7.8,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.55(\mathrm{td}, J=7.5,1.2 \mathrm{~Hz}, 1 \mathrm{H})$, 7.46 (td, $J=7.6,1.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.43 (dd, $J=7.6,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.41-7.39$ (m, 2H), 7.38-7.36 (m, $2 \mathrm{H}), 7.35-7.32(\mathrm{~m}, 1 \mathrm{H}), 5.29(\mathrm{~s}, 2 \mathrm{H}), 3.03(\mathrm{t}, J=6.8 \mathrm{~Hz}, 2 \mathrm{H}), 2.57(\mathrm{t}, J=6.8 \mathrm{~Hz}, 2 \mathrm{H}), 1.45(\mathrm{~s}$, 9H). ${ }^{13} \mathbf{C}-\mathbf{N M R}\left(151 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 203.9,172.0,166.4,143.2,135.3,132.3,130.0,129.7$, 128.63, 128.54, 128.48, 128.1, 126.4, 80.5, 67.5, 37.7, 29.4, 28.1 HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{24} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right) 369.1702$; found 369.1711.


4-(2'-[Benzyloxycarbonyl]phenyl)-4-oxobutanoic acid (22). In a $25-\mathrm{mL}$ roundbottom flask, diester $\mathbf{S 3}\left(1.9 \mathrm{~g}, 5.157 \mathrm{mmol}, 1\right.$ equiv) was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \mathrm{~mL})$ and cooled to $0{ }^{\circ} \mathrm{C}$. Water $(0.5 \mathrm{~mL})$ and TFA $(5 \mathrm{~mL})$ were added and the reaction stirred for 3 h . The mixture was concentrated by rotary evaporation. Purification by silica flash chromatography ( $40 \% \rightarrow 60 \%$ EtOAc in hexanes) yielded the monocarboxylic acid 22 as a white solid ( $1.4 \mathrm{~g}, 87 \%$ ).

IR (ATR): 3035, 1706, 1597, 1575, 1498, 1400, 1377, 1272, 1136, 1094, 1041, 991, 956, 912, 735, 698, 648. ${ }^{1} \mathbf{H}-\mathrm{NMR}\left(500 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 7.96-7.94(\mathrm{~m}, 1 \mathrm{H}), 7.57(\mathrm{td}, J=7.5,1.2 \mathrm{~Hz}, 1 \mathrm{H})$, $7.49(\mathrm{td}, J=7.7,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.41-7.37(\mathrm{~m}, 5 \mathrm{H}), 7.36-7.33(\mathrm{~m}, 1 \mathrm{H}), 5.30(\mathrm{~s}, 2 \mathrm{H}), 3.06(\mathrm{t}, J=6.7$ $\mathrm{Hz}, 2 \mathrm{H}), 2.70(\mathrm{t}, J=6.7 \mathrm{~Hz}, 2 \mathrm{H}) .{ }^{13} \mathrm{C}-\mathrm{NMR}\left(126 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 203.6,178.8,166.3,142.9$, 135.2, 132.5, 130.1, 129.9, 128.69, 128.63, 128.59, 128.0, 126.3, 67.6, 37.4, 28.0. HRMS (ESI) $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{18} \mathrm{H}_{16} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right) 312.0998$; found 312.1005 .

$2^{\prime}, 3^{\prime}-O$ - $\boldsymbol{t}$-Butyldimethylsilyl-5'- $N$-(3-amino-cyclobut-3-ene-1,2-dione)aminodeoxyadenosine (21). In a $25-\mathrm{mL}$ roundbottom flask, protected amino-adenosine analogue $20(180 \mathrm{mg}, 0.364$
mmol, 1 equiv), prepared as previously described, ${ }^{4}$ was suspended in $\mathrm{MeOH}(5 \mathrm{~mL})$. Dimethyl squarate ( $103 \mathrm{mg}, 0.727 \mathrm{mmol}, 2.0$ equiv) was added and the reaction stirred at rt for 4 h . The mixture was cooled to $0^{\circ} \mathrm{C}$ and anhydrous ammonia was slowly bubbled into the solution for 15 min . The reaction was stirred for 1 h with warming to rt , then filtered through a pad of celite. The filtrate was concentrated by rotary evaporation, reconstituted in $15 \% \mathrm{MeOH}$ in EtOAc $(5 \mathrm{~mL})$, filtered though a pad of silica, and the pad washed with $15 \% \mathrm{MeOH}$ in EtOAc ( 100 mL ). The filtrate was concentrated by rotary evaporation to afford the crude squaramide-adenosine intermediate 21 as a yellow tinged solid ( 172 mg ), which was carried forward without further purification.

$\mathbf{2}^{\prime}, \mathbf{3}^{\prime}$-O-t-Butyldimethylsilyl-5'- $N$-( $N$-[4"-(2"-[benzyloxycarbonyl]phenyl)-4-oxobutanoyl]-(3-amino-cyclobut-3-ene-1,2-dione))aminodeoxy adenosine (S5). In a $25-\mathrm{mL}$ roundbottom flask, monocarboxylic acid 22 ( $87 \mathrm{mg}, 0.280 \mathrm{mmol}, 1.1$ equiv), protected squaramide-adenosine intermediate 21 ( $165 \mathrm{mg}, 0.280 \mathrm{mmol}, 1$ equiv), and DMAP ( $34 \mathrm{mg}, 0.280 \mathrm{mmol}, 1.0$ equiv) were dissolved in $1: 1 \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{CH}_{3} \mathrm{CN}(5 \mathrm{~mL})$. EDCI ( $214 \mathrm{mg}, 1.118 \mathrm{mmol}$, 4.0 equiv) was added and the reaction was stirred at rt for 12 h . The reaction was quenched with $1 \mathrm{M} \mathrm{KHSO}_{4}$ $(20 \mathrm{~mL})$, and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \times 20 \mathrm{~mL})$. The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. The residue was reconstituted in $5 \%$ MeOH in EtOAc ( $\approx 20 \mathrm{~mL}$ ), filtered though a pad of silica, and the pad washed with $5 \% \mathrm{MeOH}$ in EtOAc $(100 \mathrm{~mL})$. The filtrate was concentrated by rotary evaporation to afford the crude protected squaramide analogue $\mathbf{S 5}(125 \mathrm{mg})$, which was carried forward without further purification.

$5^{\prime}-\mathrm{N}$-( $N$-[4"-(2"(carboxyl)phenyl)-4"-oxobutanoyl]-(3-amino-cyclobut-3-ene-1,2-dione))aminodeoxyadenosine (3). In a $25-\mathrm{mL}$ roundbottom flask, crude protected squaramide analogue $\mathbf{S 5}$ ( $125 \mathrm{mg}, 0.538 \mathrm{mmol}, 1$ equiv) and $10 \% \mathrm{Pd} / \mathrm{C}(15 \mathrm{mg}, 0.014 \mathrm{mmol}, 0.1$ equiv) were suspended in $\mathrm{MeOH}(14 \mathrm{~mL})$ and stirred under $\mathrm{H}_{2}$ balloon for 4 h . The mixture was filtered through a celite pad, concentrated by rotary evaporation, and dried under high vacuum for 2 h to afford the crude carboxylate intermediate, which was carried forward without further purification.

[^4]In a $10-\mathrm{mL}$ roundbottom flask, the crude carboxylate intermediate above was suspended in $\mathrm{CH}_{3} \mathrm{CN}(3 \mathrm{~mL})$. TASF ( $108 \mathrm{mg}, 0.394 \mathrm{mmol}, 2.5$ equiv) was added and the reaction was stirred at $50{ }^{\circ} \mathrm{C}$ for 12 h . The mixture was concentrated by rotary evaporation. Purification by preparative $\operatorname{HPLC}\left(5 \% \rightarrow 95 \% \mathrm{CH}_{3} \mathrm{CN}\right.$ in $\mathrm{H}_{2} \mathrm{O}$ with $0.01 \%$ TFA) yielded acyl squaramide analogue $\mathbf{3}$ as a fluffy white solid ( $52 \mathrm{mg}, 23 \%$ over 4 steps).

IR (ATR): 3364, 2487, 1803, 1698, 1601, 1537, 1447, 1204, 1143, 1124, 980, 895, 801, 768, 724, 702, 638. ${ }^{1}$ H-NMR ( 600 MHz ; MeOD): $\delta 8.45(\mathrm{~s}, 1 \mathrm{H}), 8.33(\mathrm{~s}, 1 \mathrm{H}), 7.85-7.84(\mathrm{~m}, 1 \mathrm{H})$, 7.74-7.71 (m, 1H), 7.61-7.57 (m, 2H), $6.06(\mathrm{~d}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.72(\mathrm{t}, J=5.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.41(\mathrm{t}, J$ $=5.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.24(\mathrm{q}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.07(\mathrm{ddd}, J=46.9,14.3,4.9 \mathrm{~Hz}, 2 \mathrm{H}), 2.99-2.86(\mathrm{~m}$, 2H), 2.66-2.63 (m, 2H). 13C-NMR ( 151 MHz ; MeOD): $\delta 189.6,183.8,174.5,173.6,170.1$, $160.9,153.32,153.31,150.2,147.79,147.78,147.78,147.76,147.74,147.73,143.6,120.7,90.5$, 85.0, 75.4, 72.2, 49.6, 46.0, 38.7, 30.9. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{24} \mathrm{~N}_{7} \mathrm{O}_{9}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$ 566.1636; found 566.1627.

## E. Synthesis of Alkyl Sulfamide Analogue 4



Figure S5. Synthesis of alkyl sulfamide analogue 4. DIAD = diisopropyl azodicarboxylate, TFA = trifluoroacetic acid, THF = tetrahydrofuran.


Benzyl 2-(4-hydroxybutanoyl)benzoate (23). In a $25-\mathrm{mL}$ roundbottom flask, aryl bromide $\mathbf{S 6}$ ( $1 \mathrm{~g}, 3.889 \mathrm{mmol}, 1$ equiv) was suspended in THF ( 4 mL ) and cooled to $-78^{\circ} \mathrm{C}$. A solution of $n-\mathrm{BuLi}(3.038 \mathrm{~mL}, 4.861 \mathrm{mmol}, 1.6 \mathrm{M}$ in THF, 1.25 equiv) was added and the reaction stirred for 1 h . The mixture was transferred via cannula over 5 min to a stirring solution of benzyl chloroformate ( $1.326 \mathrm{~g}, 7.778 \mathrm{mmol}$, 2 equiv) in THF ( 5 mL ) at $-78^{\circ} \mathrm{C}$, then stirred for 2 h with warming to rt . The reaction was quenched with $1 \mathrm{M} \mathrm{HCl}(20 \mathrm{~mL})$ and stirred for 10 min , then extracted with EtOAc ( $4 \times 25 \mathrm{~mL}$ ). The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography $(40 \% \rightarrow 60 \%$ EtOAc in hexanes) yielded benzyl ester 23 as a clear oil ( $950 \mathrm{mg}, 82 \%$ ).

IR (ATR): 3393, 3068, 3036, 2954, 2886, 1716, 1599, 1577, 1500, 1457, 1406, 1378, 1274, 1139, 1101, 1079, 1004, 961, 915, 755, 701, 649. ${ }^{1} \mathbf{H}-N M R\left(600 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 7.95-7.94(\mathrm{~m}$, $1 \mathrm{H}), 7.57(\mathrm{td}, J=7.5,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.48(\mathrm{td}, J=7.7,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.40(\mathrm{dt}, J=13.8,7.0 \mathrm{~Hz}, 4 \mathrm{H})$, $7.36-7.33(\mathrm{~m}, 2 \mathrm{H}), 5.32(\mathrm{~s}, 2 \mathrm{H}), 3.70(\mathrm{t}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 2.88(\mathrm{t}, J=6.8 \mathrm{~Hz}, 2 \mathrm{H}), 2.19(\mathrm{~s}, 1 \mathrm{H})$, 1.92 (quintet, $J=6.4 \mathrm{~Hz}, 2 \mathrm{H}$ ). ${ }^{13} \mathbf{C}-\mathbf{N M R}\left(151 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 206.0,166.6,143.7$, 135.3, $132.5,130.1,129.7,128.67,128.55,128.54,128.0,126.2,67.6,61.7,39.4,26.6$. HRMS (ESI) $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{18} \mathrm{H}_{18} \mathrm{O}_{4} \mathrm{Na}\left([\mathrm{M}+\mathrm{H}]{ }^{+}\right) 321.1103$; found 321.1110.


6- $N$ - $t$-Butoxycarbonyl- $\mathbf{2}^{\prime}, \mathbf{3}^{\prime}-\mathrm{O}$-isopropylidene- $5^{\prime}-\mathrm{N}$-( N -[benzyloxycarbonyl]-[benzyl 2-(4hydroxybutanoyl)]sulfamoyl)aminodeoxyadenosine (25). In a $25-\mathrm{mL}$ roundbottom flask, DIAD ( $81 \mathrm{mg}, 0.402 \mathrm{mmol}, 1.5$ equiv) was suspended in THF ( 5 mL ) and cooled to $0{ }^{\circ} \mathrm{C}$. A solution of triphenylphosphine ( $105 \mathrm{mg}, 0.402 \mathrm{mmol}, 1.5$ equiv) in THF ( 1 mL ) was added dropwise and the reaction stirred for 10 min . A solution of primary alcohol $23(80 \mathrm{mg}, 0.268$ mmol, 1 equiv) in THF ( 1 mL ) was added dropwise, followed by a solution of Cbz-protected sulfamido-adenosine analogue 24 ( $266 \mathrm{mg}, 0.364 \mathrm{mmol}, 1$ equiv), prepared as previously described, ${ }^{3}$ in THF ( 1 mL ). The reaction was stirred for 14 h with warming to rt . $\mathrm{MeOH}(1 \mathrm{~mL})$ was added and the solvent was removed by rotary evaporation. The resulting residue was reconstituted in $\mathrm{Et}_{2} \mathrm{O}$, filtered through a pad of silica, the pad washed with $100 \mathrm{~mL} \mathrm{Et}_{2} \mathrm{O}$. The filtrate was concentrated by rotary evaporation to afford the crude protected alkyl sulfamide analogue $\mathbf{2 5}$ ( $350 \mathrm{mg}, 145 \%$ ), which was carried forward without further purification.

$5^{\prime}-N-(N-[4 "-(2$ "'-[Carboxyl]phenyl)-4-oxobutane]sulfamoyl)aminodeoxyadenosine (14). In a $10-\mathrm{mL}$ roundbottom flask, crude protected alkyl sulfamide analogue $\mathbf{2 5}$ (quantitative yield assumed) and $10 \% \mathrm{Pd} / \mathrm{C}(28 \mathrm{mg}, 0.027 \mathrm{mmol}, 0.1$ equiv) were suspended in $\mathrm{MeOH}(5 \mathrm{~mL})$. The reaction was stirred vigorously under $\mathrm{H}_{2}$ balloon for 12 h , then diluted with EtOAc ( 5 mL ), filtered through a celite pad. The filtrate was concentrated by rotary evaporation to afford the crude, partially protected sulfamide, which was carried forward without further purification.

The crude, partially protected sulfamide above was reconstituted in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(15 \mathrm{~mL})$ and cooled to $0^{\circ} \mathrm{C}$. Water $(0.5 \mathrm{~mL})$ and TFA $(15 \mathrm{~mL})$ were added and the reaction stirred for 3 h . The mixture was concentrated by rotary evaporation. Purification by preparative HPLC ( $5 \% \rightarrow 30 \%$ $\mathrm{CH}_{3} \mathrm{CN}$ in $\mathrm{H}_{2} \mathrm{O}$ with $0.1 \%$ TFA) yielded the alkyl sulfamide analogue 4 as a fluffy white solid ( $51 \mathrm{mg}, 38 \%$ over 3 steps).

IR (ATR): 3393, 3068, 3036, 2954, 2886, 1716, 1599, 1577, 1500, 1457, 1406, 1378, 1274, 1139, 1101, 1079, 1004, 961, 915, 755, 701, 649. ${ }^{1}$ H-NMR ((600 MHz; D $\left.{ }_{2} \mathrm{O}\right): \delta 8.13(\mathrm{~s}, 1 \mathrm{H})$, $8.05(\mathrm{~s}, 1 \mathrm{H}), 7.42(\mathrm{dd}, J=7.7,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.35(\mathrm{td}, J=7.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.23(\mathrm{td}, J=7.5,1.1$ $\mathrm{Hz}, 1 \mathrm{H}), 7.16$ (dd, $J=7.5,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.85(\mathrm{~d}, J=6.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.68$ (dd, $J=6.3,5.5 \mathrm{~Hz}, 1 \mathrm{H})$, 4.30 (dd, $J=5.4,3.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.25(\mathrm{q}, J=3.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.29-3.22(\mathrm{~m}, 3 \mathrm{H}), 2.96-2.88$ (m, 2H),
$2.73(\operatorname{td}, J=7.3,1.6 \mathrm{~Hz}, 2 \mathrm{H}), 1.72$ (quintet, $J=7.2 \mathrm{~Hz}, 2 \mathrm{H}) .{ }^{13} \mathbf{C}-\mathbf{N M R}\left(151 \mathrm{MHz} ; \mathrm{D}_{2} \mathrm{O}\right): \delta$ $175.8,155.6,152.4,148.3,141.1,138.6,137.0,131.0,129.5,127.8,126.4,119.3,117.3,115.4$, 88.8, 83.6, 72.8, 71.1, 48.9, 44.0, 41.8, 39.0, 23.6. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{26} \mathrm{~N}_{7} \mathrm{O}_{8} \mathrm{~S}$ $\left([\mathrm{M}+\mathrm{H}]^{+}\right) 536.1564$; found 536.1539.

## F. SYNTHESIS OF m-Phenyl ETHER ANALOGUE 5



Figure S6. Synthesis of m-phenyl ether analogue 5. DIAD, diisopropyl azodicarboxylate; DMA, dimethylacetamide; dtbpf, 1,1'-bis(di-t-butylphosphino)ferrocene; NMO, $N$-methylmorpholine- N -oxide; TBAF, tetrabutylammonium fluoride; TBSCI, $t$-butyldimethylsilyl chloride; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TPAP, tetrapropylammonium perruthenate.

(2-((tert-Butyldimethylsilyloxy)methyl)phenyl)methanol (27). In a $500-\mathrm{mL}$ roundbottom flask, $\mathrm{LiAlH}_{4}\left(4.880 \mathrm{~g}, 128.6 \mathrm{mmol}, 1.25\right.$ equiv) was suspended in $\mathrm{Et}_{2} \mathrm{O}(200 \mathrm{~mL})$ and cooled to $0{ }^{\circ} \mathrm{C}$. Dimethyl phthalate (26) ( $20 \mathrm{~g}, 102.9 \mathrm{mmol}, 1$ equiv) in THF ( 50 mL ) was added dropwise then the reaction was stirred for 36 h with warming to rt . The reaction was cooled to $0^{\circ} \mathrm{C}$, then water $(5 \mathrm{~mL}), 3.75 \mathrm{M} \mathrm{aq} \mathrm{NaOH}(5 \mathrm{~mL})$, and water ( 15 mL ) were added sequentially and the reaction stirred for 15 min . $\mathrm{MgSO}_{4}(5 \mathrm{~g})$ was then added and the reaction stirred for 15 min with warming to rt, filtered through a pad of celite, and the solvent removed by rotary evaporation to afford the crude diol, which was carried forward without further purification.

In a $250-\mathrm{mL}$ roundbottom flask, the crude diol ( $11.3 \mathrm{~g}, 81.78 \mathrm{mmol}$, 1 equiv) and TBSCl $(12.94 \mathrm{~g}, 85.86 \mathrm{mmol}, 1.05$ equiv) were dissolved in dichloromethane ( 150 mL ) and cooled to $0^{\circ} \mathrm{C}$. Triethylamine ( $45.64 \mathrm{~mL}, 327.1 \mathrm{mmol}, 4$ equiv) was added and the reaction returned to rt . After 14 h the reaction was quenched with satd aq $\mathrm{NH}_{4} \mathrm{Cl}(150 \mathrm{~mL})$, the organic layer removed, the aqueous layer extracted with dichloromethane ( $3 \times 150 \mathrm{~mL}$ ), the combined organic extracts
were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation to afford the crude alcohol $27(17.6 \mathrm{~g})$, which was carried forward without further purification.


1-(2-((tert-Butyldimethylsilyloxy)methyl)phenyl)prop-2-en-1-one (28). In a 1-L roundbottom flask, crude alcohol $27(17.6 \mathrm{~g}, 69.72 \mathrm{mmol}, 1$ equiv) was suspended in hexanes ( 500 mL ). $\mathrm{MnO}_{2}(90 \mathrm{~g}, 1.045 \mathrm{~mol}, 15$ equiv) was added and the reaction stirred vigorously for 14 h . The reaction was then filtered through a pad of celite and the solvent removed by rotary evaporation to afford the crude aldehyde, which was carried forward without further purification.

In a $100-\mathrm{mL}$ roundbottom flask, the crude aldehyde ( $15.3 \mathrm{~g}, 61.10 \mathrm{mmol}, 1$ equiv) was dissolved in 60 mL THF and cooled to $0^{\circ} \mathrm{C}$. Vinylmagnesium bromide $(91.65 \mathrm{~mL}, 91.65 \mathrm{mmol}, 1 \mathrm{M}$ in THF, 1.5 equiv) was added dropwise over 30 min . After 1 h , the reaction was quenched with satd aq $\mathrm{NH}_{4} \mathrm{Cl}(200 \mathrm{~mL})$, extracted with $\mathrm{EtOAc}(3 \mathrm{x} 200 \mathrm{~mL})$, the combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation to afford the crude allylic alcohol, which was carried forward without further purification.

In a 1-L roundbottom flask, the crude allylic alcohol was suspended in hexanes ( 500 mL ). $\mathrm{MnO}_{2}$ ( $53 \mathrm{~g}, 610.4 \mathrm{mmol}, 10$ equiv) was added and the reaction stirred vigorously for 8 h . The reaction was then filtered through a pad of celite and the solvent removed by rotary evaporation. Purification by silica flash chromatography $(0 \% \rightarrow 20 \%$ EtOAc in hexanes) yielded the vinyl ketone 28 as a clear oil ( $16.2 \mathrm{~g}, 58 \%$ over 5 steps).

IR (ATR): 2957, 2932, 2888, 2859, 1674, 1609, 1575, 1474, 1404, 1364, 1298, 1258, 1230, 197, 1130, 1081, 994, 966, 840, 817, 779, 755, 671. ${ }^{1} \mathbf{H}-\mathbf{N M R}\left(600 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 7.74$ (dd, $J=$ $7.8,0.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.56(\mathrm{dd}, J=7.7,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.51(\mathrm{td}, J=7.6,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.33-7.31(\mathrm{~m}, 1 \mathrm{H})$, $6.87(\mathrm{dd}, J=17.4,10.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.20(\mathrm{dd}, J=17.4,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.96(\mathrm{dd}, J=10.6,1.4 \mathrm{~Hz}, 1 \mathrm{H})$, $4.95(\mathrm{~s}, 2 \mathrm{H}), 0.94(\mathrm{~s}, 9 \mathrm{H}), 0.10(\mathrm{~s}, 6 \mathrm{H}) .{ }^{13} \mathbf{C}$-NMR ( $151 \mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): $\delta$ 195.2, 142.4, 135.7, 135.2, 131.5, 130.8, 128.8, 127.1, 126.3, 63.0, 26.0, 18.4, -5.4. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{O}_{2} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$277.1624; found 277.1631.

(E)-1-(2-((tert-Butyldimethylsilyloxy)methyl)phenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (30). In a $15-\mathrm{mL}$ sealed tube, vinyl ketone $28(300 \mathrm{mg}, 1.085 \mathrm{mmol}, 1.2$ equiv), 3-bromophenol (29) ( $156 \mathrm{mg}, 0.904 \mathrm{mmol}, 1$ equiv), $\mathrm{NBu}_{4} \mathrm{Cl}\left(25 \mathrm{mg}, 0.0904 \mathrm{mmol}, 0.1\right.$ equiv), and $\mathrm{PdCl}_{2}$ (dtbpf) $\left(59 \mathrm{mg}, 0.0904 \mathrm{mmol}, 0.1\right.$ equiv) were suspended in DMA $(2.7 \mathrm{~mL}) . \mathrm{NCy}_{2} \mathrm{Me}(265 \mathrm{mg}, 1.356$
mmol, 1.5 equiv) was added, the reaction vessel sealed, and the reaction stirred vigorously at 85 ${ }^{\circ} \mathrm{C}$ for 16 h . The reaction was cooled to rt then diluted with water ( 8 mL ) and extracted with $\mathrm{Et}_{2} \mathrm{O}(4 \times 8 \mathrm{~mL})$, the combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography $(10 \% \rightarrow 30 \%$ EtOAc in hexanes) yielded phenol $\mathbf{3 0}$ as a white solid ( $274 \mathrm{mg}, 82 \%$ ).

IR (ATR): 3354, 2955, 2929, 2892, 2857, 1625, 1600, 1472, 1452, 1361, 1257, 1160, 112, 1084, 1022, 997, 983, 839, 816, 778, 740, 677, 610. ${ }^{1}$ H-NMR ( $600 \mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): $\delta 7.75-7.74$ (m, $1 \mathrm{H}), 7.60(\mathrm{dd}, \mathrm{J}=7.6,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.53(\mathrm{td}, \mathrm{J}=7.6,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{~d}, \mathrm{~J}=16.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.35$ (t, J = 7.3 Hz, 1H), 7.28-7.25 (m, 1H), $7.18(\mathrm{~d}, \mathrm{~J}=16.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.13(\mathrm{~d}, \mathrm{~J}=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.05(\mathrm{t}$, $\mathrm{J}=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.89(\mathrm{ddd}, \mathrm{J}=8.1,2.5,0.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.41(\mathrm{~s}, 1 \mathrm{H}), 4.96(\mathrm{~s}, 2 \mathrm{H}), 0.92(\mathrm{~s}, 9 \mathrm{H}), 0.09$ (s, 6H). ${ }^{13}$ C-NMR ( $151 \mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): $\delta 195.4,156.1,145.6,142.0,136.30,136.20,131.3$, 130.2, 128.4, 127.2, 126.4, 126.2, 121.3, 117.9, 114.7, 63.0, 26.0, 18.4, -5.3. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{27} \mathrm{O}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right) 367.1729$; found 367.1743.


6- N - $\boldsymbol{t}$-Butoxycarbonyl-2', $\mathbf{3}^{\prime}$ - O -isopropylidene-5'-O-([E]-1-[2-([tert-butyldimethylsilyloxy]-methyl)phenyl]-3-(3-hydroxyphenyl) prop-2-en-1-one)adenosine (31). In a $10-\mathrm{mL}$ roundbottom flask, phenol $\mathbf{3 0}(125 \mathrm{mg}, 0.339 \mathrm{mmol}, 1$ equiv), protected adenosine $\mathbf{1 6}(138 \mathrm{mg}$, $0.339 \mathrm{mmol}, 1$ equiv), and resin-bound $\mathrm{PPh}_{3}(417 \mathrm{mg}, 0.509 \mathrm{mmol}, 32 \mathrm{wt} \%, 1.5$ equiv) were suspended in THF ( 4 mL ) and cooled to $0^{\circ} \mathrm{C}$. DIAD ( $103 \mathrm{mg}, 0.509 \mathrm{mmol}, 1.5$ equiv) was added dropwise, then the reaction was stirred for 14 h with warming to rt . The reaction was quenched with water $(0.2 \mathrm{~mL})$, filtered through a pad of celite, and the pad washed with EtOAc. The combined filtrates were concentrated by rotary evaporation. Purification by silica flash chromatography $(40 \% \rightarrow 60 \%$ EtOAc in hexanes) yielded the protected phenol-ademosine intermediate 31 as a white solid ( $205 \mathrm{mg}, 80 \%$ ).

IR (ATR): 2932, 2858, 1752, 1700, 1620, 1586, 1528, 1464, 1370, 1326, 1303, 1232, 1213, 1146, 1083, 1012, 945, 911, 840, 776, 734, 670, 646. ${ }^{1}$ H-NMR ( $600 \mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): $\delta 8.78(\mathrm{~s}$, $1 \mathrm{H}), 8.09(\mathrm{~s}, 1 \mathrm{H}), 7.92(\mathrm{~s}, 1 \mathrm{H}), 7.75(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.61(\mathrm{dd}, J=7.6,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.53$ (td, $J=7.6,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{t}, J=13.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.36(\mathrm{td}, J=7.5,0.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.27(\mathrm{t}, J=4.0 \mathrm{~Hz}$, $2 \mathrm{H}), 7.19-7.15(\mathrm{~m}, 2 \mathrm{H}), 7.01(\mathrm{t}, J=1.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.79(\mathrm{dd}, J=8.1,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.26(\mathrm{~d}, J=2.3$ $\mathrm{Hz}, 1 \mathrm{H}), 5.48(\mathrm{dd}, J=6.2,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.18(\mathrm{dd}, J=6.2,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.96(\mathrm{~s}, 2 \mathrm{H}), 4.75-4.66$ (m, 2H), 4.29 (dd, $J=10.2,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.18$ (dd, $J=10.1,4.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.67$ (s, 3H), 1.55 (s, 9H), $1.49(\mathrm{~s}, 3 \mathrm{H}), 1.43(\mathrm{~s}, 3 \mathrm{H}), 0.93(\mathrm{~s}, 9 \mathrm{H}), 0.09(\mathrm{~s}, 6 \mathrm{H}) .{ }^{13} \mathbf{C}-\mathrm{NMR}\left(151 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta$ $194.8,158.4,153.2,150.4,150.0,149.5,145.0,142.1,141.2,136.3,131.3,130.2,128.4,127.2$, $126.51,126.40,122.3,122.0,116.7,114.7,113.8,113.3,91.6,85.5,84.7,82.4,81.8,68.1,63.0$, 28.21, 28.16, 27.3, 26.0, 25.4, 18.4, -5.3. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{40} \mathrm{H}_{52} \mathrm{~N}_{5} \mathrm{O}_{8} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$ 758.3585 ; found 758.3561 .


6-N-t-Butoxycarbonyl-2', $\mathbf{3}^{\prime}-O$-isopropylidene-5'-O-(1-[2-(hydroxymethyl)phenyl]-3-(3-hydroxyphenyl)prop-2-en-1-one)adenosine (S7). In a $4-\mathrm{mL}$ scintillation vial, protected phenol-adenosine intermediate 31 ( $100 \mathrm{mg}, 131.9 \mu \mathrm{~mol}, 1$ equiv) and Stryker's reagent ( 23 mg , $11.9 \mu \mathrm{~mol}, 0.09$ equiv) were suspended in toluene ( 2 mL ), then phenylsilane ( $28.5 \mathrm{mg}, 263.8$ $\mu \mathrm{mol}, 2$ equiv) was added. After 16 h , the reaction was quenched with satd aq $\mathrm{NH}_{4} \mathrm{Cl}(5 \mathrm{~mL})$ and stirred for $5 \mathrm{~min}, 10 \%$ aq $\mathrm{NH}_{4} \mathrm{OH}(5 \mathrm{~mL})$ was added and the reaction stirred for an additional 5 min , then extracted with $\mathrm{Et}_{2} \mathrm{O}(4 \times 10 \mathrm{~mL})$. The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, concentrated by rotary evaporation, and dried under high vacuum for 1 $h$ to afford the crude reduced intermediate.

In a $10-\mathrm{mL}$ roundbottom flask, the crude reduced intermediate was reconstituted in THF ( 3 mL ) and cooled to $0^{\circ} \mathrm{C}$. TBAF ( $264 \mu \mathrm{~L}, 264 \mu \mathrm{~mol}, 1 \mathrm{M}$ in THF, 2 equiv) was added and the reaction stirred for $1 \mathrm{~h} . \mathrm{CaCO}_{3}(132 \mathrm{mg}, 1.315 \mathrm{mmol}, 10$ equiv) and $\mathrm{MeOH}(3 \mathrm{~mL})$ was added and the reaction stirred for 15 min . Sulfonic acid resin (Dowex $50 \mathrm{WX8}, 200 \mathrm{mg}$ ) was added and the reaction stirred for an additional 10 min . The reaction was then filtered through a pad of celite and concentrated by rotary evaporation to afford the crude benzyl alcohol $\mathbf{S 7}(86 \mathrm{mg}, 101 \%$ yield).

$5^{\prime}$-O-([2-(Carboxyl)phenyl]3-(3-hydroxyphenyl)propanoyl)adenosine (5). In a 5-mL roundbottom flask, crude benzyl alcohol $\mathbf{S} 7(86 \mathrm{mg}, 133.1 \mu \mathrm{~mol}$, 1 equiv) was dissolved in $\mathrm{CH}_{3} \mathrm{CN}(2 \mathrm{~mL})$. Water ( $24 \mathrm{mg}, 1.33 \mathrm{mmol}, 10$ equiv), $\mathrm{NMO}(156 \mathrm{mg}, 1.33 \mathrm{mmol}, 10$ equiv) and TPAP ( $4.8 \mathrm{mg}, 13 \mu \mathrm{~mol}, 0.1$ equiv) were then added. After 14 h the reaction was quenched with isopropanol and $1 \mathrm{M} \mathrm{KHSO}_{4}(1 \mathrm{~mL})$ was added before the reaction was diluted with water ( 10 $\mathrm{mL})$, extracted with EtOAc ( $4 \times 10 \mathrm{~mL}$ ), the combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation to afford the crude carboxylic acid, which was carried forward without further purification.

In a $25-\mathrm{mL}$ roundbottom flask, the crude carboxylic acid was reconstituted in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \mathrm{~mL})$ and cooled to $0^{\circ} \mathrm{C}$. TFA $(5 \mathrm{~mL})$ and water $(0.1 \mathrm{~mL})$ were added and the reaction stirred for 4 h with warming to rt . The mixture was concentrated by rotary evaporation. Purification by preparative
$\operatorname{HPLC}\left(5 \% \rightarrow 45 \% \mathrm{CH}_{3} \mathrm{CN}\right.$ in $\mathrm{H}_{2} \mathrm{O}$ with $0.1 \%$ TFA) yielded the $m$-phenyl ether analogue 5 as a fluffy white solid ( $30 \mathrm{mg}, 44 \%$ over 4 steps).

IR (ATR): 3320, 2946, 2837, 1757, 1697, 1607, 1492, 1447, 1424, 1290, 1262, 1204, 1141, 1103, 1030, 900, 842, 802, 771, 726, 701, 644. ${ }^{1}$ H-NMR ( 600 MHz ; MeOD): $\delta 8.40$ (s, 1H), $8.29(\mathrm{~s}, 1 \mathrm{H}), 7.80-7.77(\mathrm{~m}, 1 \mathrm{H}), 7.70-7.69(\mathrm{~m}, 1 \mathrm{H}), 7.58-7.55(\mathrm{~m}, 2 \mathrm{H}), 7.12-7.09(\mathrm{~m}, 1 \mathrm{H}), 6.73-$ $6.69(\mathrm{~m}, 2 \mathrm{H}), 6.10(\mathrm{~d}, J=4.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.67(\mathrm{t}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.44(\mathrm{dd}, J=5.9,3.7 \mathrm{~Hz}, 1 \mathrm{H})$, $4.35(\mathrm{dt}, J=4.7,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.28-4.26(\mathrm{~m}, 1 \mathrm{H}), 4.17-4.14(\mathrm{~m}, 1 \mathrm{H}), 2.69-2.28(\mathrm{~m}, 4 \mathrm{H})$. ${ }^{13}$ C-NMR (151 MHz; $\mathrm{CDCl}_{3}$ ): $\delta 160.1,153.1,150.2,147.36,147.33,144.27,144.25,144.25$, $143.0,130.74,130.72,122.45,122.42,122.37,120.4,115.66,115.63,113.2,90.5,85.1,76.4$, 71.9, 68.3, 49.9, 49.6, 31.1. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{26} \mathrm{~N}_{5} \mathrm{O}_{7}\left([\mathrm{M}+\mathrm{H}]^{+}\right) 520.1832$; found 520.1824 .

## G. Synthesis of p-Phenyl Ether Analogue 6



Figure S7. Synthesis of p-phenyl ether analogue 6. DIAD, diisopropyl azodicarboxylate; DMA, dimethylacetamide; dtbpf, 1,1'-bis(di-t-butylphosphino)ferrocene; NMO, $N$-methylmorpholine- $N$-oxide; TBAF, tetrabutylammonium fluoride; TBSCI, $t$-butyldimethylsilyl chloride; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TPAP, tetrapropylammonium perruthenate.

(E)-1-(2-((t-Butyldimethylsilyloxy)methyl)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (S8). In a $15-\mathrm{mL}$ sealed tube, vinyl ketone $28(300 \mathrm{mg}, 1.085 \mathrm{mmol}, 1.2$ equiv), 4-bromophenol ( $156 \mathrm{mg}, 0.904 \mathrm{mmol}, 1$ equiv), $\mathrm{NBu}_{4} \mathrm{Cl}\left(25 \mathrm{mg}, 0.0904 \mathrm{mmol}, 0.1\right.$ equiv), and $\mathrm{PdCl}_{2}$ (dtbpf) ( 59 $\mathrm{mg}, 0.0904 \mathrm{mmol}, 0.1$ equiv) were suspended in DMA ( 2.7 mL ). $\mathrm{NCy}_{2} \mathrm{Me}(265 \mathrm{mg}, 1.356$ $\mathrm{mmol}, 1.5$ equiv) was added, the reaction vessel sealed, and the reaction stirred vigorously at $85^{\circ} \mathrm{C}$ for 16 h . The reaction was cooled to rt , diluted with water ( 8 mL ), and extracted with $\mathrm{Et}_{2} \mathrm{O}$ $(4 \times 8 \mathrm{~mL})$. The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography ( $10 \% \rightarrow 30 \%$ EtOAc in hexanes) yielded phenol S8 as a white solid ( $270 \mathrm{mg}, 81 \%$ ).

IR (ATR): 3332, 2957, 2931, 2887, 2858, 1626, 1580, 1514, 1473, 1443, 1364, 1336, 1282, 1258, 1215, 1171, 1128, 1085, 1025, 985, 941, 911, 834, 777, 734, 671, 631. ${ }^{1}$ H-NMR ( 600 $\mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): $\delta 7.72(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.56(\mathrm{dd}, J=7.6,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.52(\mathrm{td}, J=7.6,1.0 \mathrm{~Hz}$, $1 \mathrm{H}), 7.47-7.43(\mathrm{~m}, 3 \mathrm{H}), 7.35(\mathrm{td}, J=7.5,0.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.05(\mathrm{~d}, J=15.9 \mathrm{~Hz}, 1 \mathrm{H}), 6.87-6.84(\mathrm{~m}$, $2 \mathrm{H}), 6.59(\mathrm{~s}, 1 \mathrm{H}), 4.94(\mathrm{~s}, 2 \mathrm{H}), 0.91(\mathrm{~s}, 9 \mathrm{H}), 0.08(\mathrm{~s}, 6 \mathrm{H}) .{ }^{13} \mathbf{C}-\mathrm{NMR}\left(151 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta$ $196.5,158.7,146.7,141.4,136.7,131.0,130.6,128.2,127.3,127.0,126.5,123.6,116.1,62.9$, 26.0, 18.4, -5.4. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{27} \mathrm{O}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right) 367.1729$; found 367.1727.


6- N - $\boldsymbol{t}$-Butoxycarbonyl-2', $\mathbf{3}^{\prime}$ - O -isopropylidene-5' -O -([E]-1-[2-([tert-butyldimethylsilyloxy]-methyl)phenyl]-3-(4-hydroxyphenyl)prop-2-en-1-one)adenosine (S9). In a $25-\mathrm{mL}$ roundbottom flask, phenol $\mathbf{S 8}(230 \mathrm{mg}, 0.624 \mathrm{mmol}, 1$ equiv), protected adenosine $\mathbf{1 6}(254 \mathrm{mg}, 0.624$ mmol , 1 equiv), and resin-bound $\mathrm{PPh}_{3}$ ( $767 \mathrm{mg}, 0.936 \mathrm{mmol}, 32 \mathrm{wt} \%$, 1.5 equiv) were suspended in THF ( 6 mL ) and cooled to $0^{\circ} \mathrm{C}$. DIAD ( $189 \mathrm{mg}, 0.936 \mathrm{mmol}, 1.5$ equiv) was added dropwise, then the reaction was stirred for 14 h with warming to rt . The reaction was quenched with water $(0.2 \mathrm{~mL})$, filtered through a pad of celite, and the pad was washed with EtOAc. The combined filtrates were concentrated by rotary evaporation. Purification by silica flash chromatography ( $40 \% \rightarrow 60 \%$ EtOAc in hexanes) yielded phenol-adenosine intermediate $\mathbf{S 9}$ as a white solid ( $310 \mathrm{mg}, 66 \%$ ).

IR (ATR): 2989, 2954, 2931, 2857, 2247, 1751, 1705, 1658, 1609, 1511, 1463, 1423, 1384, 1369, 1327, 1304, 1251, 1213, 1174, 1144, 1081, 1017, 982, 909, 836, 776, 729, 668, 645. ${ }^{1} \mathbf{H}-\mathbf{N M R}\left(\left(600 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 8.79(\mathrm{~s}, 1 \mathrm{H}), 8.09(\mathrm{~s}, 1 \mathrm{H}), 8.05(\mathrm{~s}, 1 \mathrm{H}), 7.74(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H})\right.$, $7.60(\mathrm{dd}, J=7.6,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.52(\mathrm{td}, J=7.6,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.49-7.44(\mathrm{~m}, 3 \mathrm{H}), 7.35(\mathrm{t}, J=7.5$ $\mathrm{Hz}, 1 \mathrm{H}), 7.09$ (d, $J=15.9 \mathrm{~Hz}, 1 \mathrm{H}), 6.79-6.76$ (m, 2H), 6.25 (d, $J=2.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 5.52 (dd, $J=6.2$, $2.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.19$ (dd, $J=6.2,2.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.95(\mathrm{~s}, 2 \mathrm{H}), 4.72(\mathrm{dd}, J=7.4,4.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.30(\mathrm{dd}$, $J=10.2,4.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.18(\mathrm{dd}, J=10.2,4.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.67(\mathrm{~s}, 3 \mathrm{H}), 1.56(\mathrm{~s}, 9 \mathrm{H}), 1.43(\mathrm{~s}, 3 \mathrm{H})$, 0.92 (s, 9H), $0.09(\mathrm{~s}, 6 \mathrm{H}) .{ }^{13} \mathbf{C}-\mathbf{N M R}\left(151 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 195.1,159.9,153.2,150.26,150.06$, $149.6,145.1,141.8,141.3,136.6,131.0,130.2,128.25,128.23,127.1,126.3,124.2,122.2$, 114.74, 114.66, 91.7, 85.5, 84.6, 82.4, 81.8, 68.0, 62.9, 28.1, 27.2, 26.0, 25.4, 18.4, -5.3. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{40} \mathrm{H}_{52} \mathrm{~N}_{5} \mathrm{O}_{8} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right) 758.3585$; found 758.3576.


6- N - $\boldsymbol{t}$-Butoxycarbonyl-2', $\mathbf{3}^{\prime}$ - O -isopropylidene-5'-O-(1-[2-(hydroxymethyl)phenyl]-3-(3hydroxyphenyl) propan-1-one)adenosine (S10). In a $10-\mathrm{mL}$ roundbottom flask, phenoladenosine intermediate $\mathbf{S} 9(265 \mathrm{mg}, 349.6 \mu \mathrm{~mol}, 1$ equiv) and Stryker's reagent ( $62 \mathrm{mg}, 31.5$ $\mu \mathrm{mol}, 0.09$ equiv) were dissolved in toluene ( 5 mL ). Phenylsilane ( $96 \mathrm{mg}, 699.2 \mu \mathrm{~mol}, 2$ equiv) was added and the reaction stirred for 16 h . The reaction was quenched with satd aq $\mathrm{NH}_{4} \mathrm{Cl}$ $(10 \mathrm{~mL})$ and the mixture stirred for 5 min , then $10 \%$ aq $\mathrm{NH}_{4} \mathrm{OH}(10 \mathrm{~mL})$ was added and the mixture stirred for an additional 5 min . The mixture was extracted with $\mathrm{Et}_{2} \mathrm{O}(4 \times 20 \mathrm{~mL})$. The
combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation, and dried under high vacuum for 1 h to afford the crude reduced phenol-adenosine intermediate, which was carried forward without further purification.

The crude reduced phenol-adenosine intermediate above was reconstituted in THF ( 5 mL ) and cooled to $0{ }^{\circ} \mathrm{C}$. TBAF ( $697 \mu \mathrm{M}, 697 \mu \mathrm{~mol}, 1 \mathrm{M}$ in THF, 2 equiv) was added and the reaction stirred for $1 \mathrm{~h} . \mathrm{CaCO}_{3}(349 \mathrm{mg}, 3.486 \mathrm{mmol}, 10$ equiv) and $\mathrm{MeOH}(3 \mathrm{~mL})$ were added and the reaction stirred for 15 min . Sulfonic acid resin (Dowex $50 \mathrm{WX8}, 500 \mathrm{mg}$ ) was added and the mixture stirred for an additional 10 min . The mixture was filtered through a pad of celite. The filtrate was concentrated by rotary evaporation to afford the crude benzyl alcohol $\mathbf{S 1 0}$ ( 202 mg , $90 \%$ yield), which was carried forward without further purification.

$5^{\prime}$-O-([2-(Carboxyl)phenyl]3-(3-hydroxyphenyl)propanoyl)adenosine (6). In a $10-\mathrm{mL}$ roundbottom flask, crude benzyl alcohol $\mathbf{S 1 0}(202 \mathrm{mg}, 312.8 \mu \mathrm{~mol}, 1$ equiv) was dissolved in $\mathrm{CH}_{3} \mathrm{CN}(5 \mathrm{~mL})$. Water ( $56 \mathrm{mg}, 3.128 \mathrm{mmol}, 10$ equiv), NMO ( $366 \mathrm{mg}, 3.128 \mathrm{mmol}, 10$ equiv) and TPAP ( $11 \mathrm{mg}, 31 \mu \mathrm{~mol}, 0.1$ equiv) were added and the reaction stirred at rt for 14 h . The reaction was quenched with $i-\mathrm{PrOH}$ and $1 \mathrm{M} \mathrm{KHSO}_{4}(1 \mathrm{~mL})$ was added, then the reaction was diluted with water $(20 \mathrm{~mL})$ and extracted with EtOAc $(4 \times 20 \mathrm{~mL})$. The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, concentrated by rotary evaporation, and dried under high vacuum 1 h to afford the crude carboxylic acid, which was carried forward without further purification.

In a $25-\mathrm{mL}$ roundbottom flask, the crude carboxylic acid was reconstituted in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(8 \mathrm{~mL})$ and cooled to $0^{\circ} \mathrm{C}$. TFA ( 8 mL ) and water ( 0.8 mL ) were added and the reaction stirred for 4 h with warming to rt . The mixture was concentrated by rotary evaporation. Purification by preparative HPLC $\left(5 \% \rightarrow 45 \% \mathrm{CH}_{3} \mathrm{CN}\right.$ in $\mathrm{H}_{2} \mathrm{O}$ with $\left.0.1 \% \mathrm{TFA}\right)$ yielded the $p$-phenyl ether analogue $\mathbf{6}$ as a fluffy white solid ( $65 \mathrm{mg}, 36 \%$ over 4 steps).

IR (ATR): 3323, 2921, 2869, 1750, 1690, 1614, 1512, 1424, 1292, 1242, 1203, 1140, 1050, 980, 898, 827, 801, 769, 724, 699, 642. ${ }^{1} \mathrm{H}-\mathrm{NMR}(600 \mathrm{MHz}$; MeOD): $\delta 8.45(\mathrm{~s}, 1 \mathrm{H}), 8.33(\mathrm{~s}, 1 \mathrm{H})$, 7.84-7.83 (m, 1H), 7.77-7.76 (m, 1H), 7.64-7.63 (m, 2H), 7.04-7.03 (m, 2H), 6.87-6.85 (m, 2H), $6.14(\mathrm{~d}, J=4.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.72(\mathrm{t}, J=4.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.49(\mathrm{t}, J=4.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.40(\mathrm{q}, J=3.9 \mathrm{~Hz}$, 1 H ), 4.32-4.30 (m, 1H), 4.20 (dd, $J=10.9,3.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.72-2.65(\mathrm{~m}, 1 \mathrm{H}), 2.48-2.29$ (m, 3H). ${ }^{13}$ C-NMR (151 MHz; $\mathrm{CDCl}_{3}$ ): $\delta 158.3,153.38,153.37,150.2,147.71,147.70,142.8,136.7$, $135.9,135.20,135.19,135.19,135.18$, 131.7, 130.5, 120.46, 120.45, 115.7, 90.5, 85.1, 76.4, 71.9, 68.5, 50.0, 49.6, 30.2. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{26} \mathrm{~N}_{5} \mathrm{O}_{7}\left([\mathrm{M}+\mathrm{H}]^{+}\right) 520.1832$; found 520.1809.

## H. SYNTHESIS OF $\boldsymbol{m}$-(3-TRIFLUOROMETHYLPHENYL) ETHER ANALOGUE 8



Figure S8. Synthesis of m-(3-trifluoromethylphenyl) ether analogue 8. DIAD, diisopropyl azodicarboxylate; DMA, dimethylacetamide; dtbpf, 1,1'-bis(di-t-butylphosphino)ferrocene; NMO, N-methylmorpholine- $N$-oxide; TBAF, tetrabutylammonium fluoride; TBSCI, $t$-butyldimethylsilyl chloride; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TPAP, tetrapropylammonium perruthenate.

(E)-1-(2-((t-Butyldimethylsilyloxy)methyl)phenyl)-3-(3-hydroxy-5-(trifluoromethyl)phenyl)-prop-2-en-1-one (S11). In a $15-\mathrm{mL}$ sealed tube, vinyl ketone $28(300 \mathrm{mg}, 1.085 \mathrm{mmol}, 1.2$ equiv), 3-bromo-5-trifluoromethylphenol ( $218 \mathrm{mg}, 0.904 \mathrm{mmol}, 1$ equiv), $\mathrm{Bu}_{4} \mathrm{NCl}(25 \mathrm{mg}$, $0.0904 \mathrm{mmol}, 0.1$ equiv), and $\mathrm{PdCl}_{2}$ (dtbpf) ( $59 \mathrm{mg}, 0.0904 \mathrm{mmol}, 0.1$ equiv) were suspended in DMA ( 2.7 mL ). $\mathrm{NCy}_{2} \mathrm{Me}(265 \mathrm{mg}, 1.356 \mathrm{mmol}, 1.5$ equiv) was added, the reaction vessel sealed, and the reaction stirred vigorously at $85^{\circ} \mathrm{C}$ for 16 h . The reaction was cooled to rt , diluted with water ( 8 mL ), and extracted with $\mathrm{Et}_{2} \mathrm{O}(4 \times 8 \mathrm{~mL})$. The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography $(10 \% \rightarrow 30 \%$ EtOAc in hexanes) yielded phenol S11 as a white solid (290 $\mathrm{mg}, 74 \%$ ).

IR (ATR): 3372, 2955, 291, 2885, 2858, 1601, 1449, 1369, 1310, 1258, 1219, 1173, 1130, 1098, 1024, 981, 911, 839, 815, 778, 736, 690, 669, 620. ${ }^{1}$ H-NMR ((500 MHz; CDCl $\left.)_{3}\right): \delta 7.73$ (d, $J=$ $7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.61(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.54(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{~d}, J=16.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.38-$ $7.35(\mathrm{~m}, 2 \mathrm{H}), 7.23(\mathrm{~d}, J=16.0 \mathrm{~Hz}, 2 \mathrm{H}), 7.12(\mathrm{~s}, 1 \mathrm{H}), 6.08(\mathrm{~s}, 1 \mathrm{H}), 4.96(\mathrm{~s}, 2 \mathrm{H}), 0.92(\mathrm{~s}, 9 \mathrm{H})$, $0.09(\mathrm{~s}, 6 \mathrm{H}) .{ }^{13} \mathbf{C}-\mathrm{NMR}\left(126 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 195.1,156.6,143.8,142.0,137.0,136.0,132.8$, 131.7, 128.5, 127.60, 127.52, 126.6, 123.5, 118.1, 117.3, 114.4, 63.1, 26.0, 18.4, -5.4 .
${ }^{19}$ F-NMR ( $126 \mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): $\delta$-63.0. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{28} \mathrm{O}_{3} \mathrm{~F} 3 \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$ 437.1760; found 437.1739.


6- N - $\boldsymbol{t}$-Butoxycarbonyl-2', $\mathbf{3}^{\prime}$ - O -isopropylidene-5'- O -([E]-1-[2-([tert-butyldimethylsilyloxy]-methyl)phenyl]-3-(3-hydroxy-5-(trifluoromethyl) phenyl) prop-2-en-1-one)adenosine (S12). In a $10-\mathrm{mL}$ roundbottom flask, phenol $\mathbf{S} 11(270 \mathrm{mg}, 0.619 \mathrm{mmol}, 1$ equiv), protected adenosine 16 ( $126 \mathrm{mg}, 0.309 \mathrm{mmol}, 1$ equiv), and resin-bound $\mathrm{PPh}_{3}$ ( $507 \mathrm{mg}, 0.619 \mathrm{mmol}, 32 \mathrm{wt} \%, 1.5$ equiv) were suspended in THF ( 6 mL ) and cooled to $0^{\circ} \mathrm{C}$. DIAD ( $125 \mathrm{mg}, 0.619 \mathrm{mmol}, 1.5$ equiv) was added dropwise, then the reaction was stirred for 14 h with warming to rt . The reaction was quenched with water $(0.2 \mathrm{~mL})$, filtered through a pad of celite, and the pad was washed with EtOAc. The combined filtrates were concentrated by rotary evaporation. Purification by silica flash chromatography ( $40 \% \rightarrow 60 \%$ EtOAc in hexanes) yielded the protected phenol-adenosine intermediate $\mathbf{S 1 2}$ as a white solid ( $215 \mathrm{mg}, 84 \%$ ).

IR (ATR): 2982, 2955, 2934, 2857, 2244, 1753, 1717, 1666, 1610, 1521, 1464, 1359, 1326, $1300,1233,1173,1133,1104,1080,1020,977,911,587,839,815,778,734,689,646$. ${ }^{1} \mathbf{H}-\mathbf{N M R}\left(\left(600 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 8.76(\mathrm{~s}, 1 \mathrm{H}), 8.04(\mathrm{~s}, 1 \mathrm{H}), 7.92(\mathrm{~s}, 1 \mathrm{H}), 7.76(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H})\right.$, 7.63 (d, $J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.55(\mathrm{td}, J=7.6,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.44(\mathrm{~d}, J=16.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.39$ (dd, $J=$ $13.8,5.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.26(\mathrm{~s}, 1 \mathrm{H}), 7.22(\mathrm{~d}, J=16.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.15(\mathrm{~s}, 1 \mathrm{H}), 7.03(\mathrm{~s}, 1 \mathrm{H}), 6.22(\mathrm{~d}, J=$ $2.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.52(\mathrm{dd}, J=6.2,2.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.21(\mathrm{dd}, J=6.2,3.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.96(\mathrm{~s}, 2 \mathrm{H}), 4.70-4.68$ $(\mathrm{m}, 1 \mathrm{H}), 4.29(\mathrm{ddd}, J=48.5,10.0,4.9 \mathrm{~Hz}, 2 \mathrm{H}), 1.67(\mathrm{~s}, 3 \mathrm{H}), 1.55(\mathrm{~s}, 9 \mathrm{H}), 1.44(\mathrm{~s}, 3 \mathrm{H}), 0.93(\mathrm{~s}$, 9H), 0.09 (s, 6H). ${ }^{13}$ C-NMR (126 MHz; $\mathrm{CDCl}_{3}$ ): $\delta 194.1,158.7,153.2,150.27,150.16,149.5$, $142.9,142.3,141.4,137.3,135.9,132.8,131.6,128.5,127.9,127.3,126.5,123.4,122.4,118.0$, $117.1,114.9,113.0,91.4,85.3,84.4,82.4,81.7,68.5,63.0,28.1,27.2,26.0,25.4,18.4,-5.3$. ${ }^{19}$ F-NMR ( $126 \mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): $\delta-63.0$. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{41} \mathrm{H}_{51} \mathrm{~N}_{5} \mathrm{O}_{8} \mathrm{~F}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$ 826.3459; found 826.3453.


6- N - $\boldsymbol{t}$-Butoxycarbonyl-2', $\mathbf{3}^{\prime}-\mathrm{O}$-isopropylidene-5'-O-(1-[2-(hydroxymethyl)phenyl]-3-(3-hydroxy-5-(trifluoromethyl)phenyl)propan-1-one) adenosine (S13). In a $25-\mathrm{mL}$ roundbottom flask, olefin S12 ( $215 \mathrm{mg}, 260.3 \mu \mathrm{~mol}, 1$ equiv) and Stryker's reagent ( $51 \mathrm{mg}, 26.0 \mu \mathrm{~mol}$, 0.09 equiv) were dissolved in toluene ( 5 mL ). Phenylsilane ( $56 \mathrm{mg}, 521 \mu \mathrm{~mol}, 2$ equiv) was
added and the reaction stirrwed for 16 h . The reaction was quenched with satd aq $\mathrm{NH}_{4} \mathrm{Cl}(10$ mL ) and stirred for 5 min , then $10 \% \mathrm{aq} \mathrm{NH}_{4} \mathrm{OH}(10 \mathrm{~mL})$ was added and the reaction stirred for an additional 5 min . The mixture was extracted with $\mathrm{Et}_{2} \mathrm{O}(4 \times 20 \mathrm{~mL})$. The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography $(50 \% \rightarrow 100 \%$ EtOAc in hexanes) yielded the reduced intermediate $\mathbf{S 1 3}$ as a white solid ( $207 \mathrm{mg}, 96 \%$ ).

IR (ATR): 2982, 2956, 2933, 2902, 2858, 2245, 1753, 1681, 1610, 1587, 1522, 1463, 1359, $1329,1233,1172,1144,1128,1105,1080,1107,972,911,854,839,814,777,734,702,670$, 646. ${ }^{1} \mathbf{H}-$ NMR ( $600 \mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): $\delta 8.78(\mathrm{~s}, 1 \mathrm{H}), 8.05(\mathrm{~s}, 1 \mathrm{H}), 7.95(\mathrm{~s}, 1 \mathrm{H}), 7.82(\mathrm{~d}, J=7.8$ $\mathrm{Hz}, 1 \mathrm{H}), 7.73-7.71(\mathrm{~m}, 1 \mathrm{H}), 7.55-7.52(\mathrm{~m}, 1 \mathrm{H}), 7.34-7.31(\mathrm{~m}, 1 \mathrm{H}), 7.10(\mathrm{~s}, 1 \mathrm{H}), 6.84(\mathrm{~s}, 2 \mathrm{H})$, $6.23(\mathrm{~d}, J=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.50(\mathrm{dd}, J=6.2,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.17(\mathrm{dd}, J=6.2,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.00(\mathrm{~s}$, $2 \mathrm{H}), 4.68(\mathrm{q}, J=3.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.23$ (ddd, $J=55.1,10.1,4.6 \mathrm{~Hz}, 2 \mathrm{H}), 3.25(\mathrm{t}, J=7.6 \mathrm{~Hz}, 2 \mathrm{H})$, $3.02(\mathrm{t}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 1.66(\mathrm{~s}, 3 \mathrm{H}), 1.55(\mathrm{~s}, 9 \mathrm{H}), 1.43(\mathrm{~s}, 3 \mathrm{H}), 0.95(\mathrm{~s}, 9 \mathrm{H}), 0.11(\mathrm{~s}, 6 \mathrm{H})$. ${ }^{13} \mathbf{C}-\mathbf{N M R}\left(126 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 201.4,158.3,153.2,150.3,150.1,149.5,144.2,143.3,141.3$, $134.5,132.3,132.1,128.7,126.9,126.4,123.8,122.3,118.4,118.2,114.8,109.0,91.6,85.3$, 84.5, 82.4, 81.7, 68.2, 63.5, 41.8, 30.0, 28.1, 27.3, 26.0, 25.4, 18.4, -5.3. ${ }^{19}$ F-NMR ( 126 MHz ; $\mathrm{CDCl}_{3}$ ): $\delta-62.7$. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{41} \mathrm{H}_{53} \mathrm{~N}_{5} \mathrm{O}_{8} \mathrm{~F}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right) 828.3610$; found 828.3616.


5'-O-([2-(Carboxyl)phenyl]3-(3-hydroxy-5-(trifluoromethyl)phenyl)propanoyl)-
adenosine (8). In a $25-\mathrm{mL}$ roundbottom flask, TBS-protected alcohol S13 ( $217 \mathrm{mg}, 260.3 \mu \mathrm{~mol}$, 1 equiv) was dissolved in THF ( 5 mL ) and cooled to $0^{\circ} \mathrm{C}$. TBAF ( $786 \mu \mathrm{~L}, 786.0 \mu \mathrm{~mol}, 1 \mathrm{M}$ in THF, 3 equiv) was and the reaction stirred for $1 \mathrm{~h} . \mathrm{CaCO}_{3}(349 \mathrm{mg}, 3.486 \mathrm{mmol}, 10$ equiv) and $\mathrm{MeOH}(3 \mathrm{~mL})$ were added and the reaction stirred for 15 min . Sulfonic acid resin (Dowex $50 \mathrm{WX} 8,500 \mathrm{mg}$ ) was added and the reaction stirred for an additional 10 min . The reaction was then filtered through a pad of celite. The filtrate was concentrated by rotary evaporation to afford the crude benzyl alcohol, which was carried forward without further purification.

In a $10-\mathrm{mL}$ roundbottom flask, the crude benzyl alcohol above was reconstituted in $\mathrm{CH}_{3} \mathrm{CN}$ ( 5 mL ). Water ( $45 \mathrm{mg}, 2.5 \mathrm{mmol}, 10$ equiv), NMO ( $295 \mathrm{mg}, 2.521 \mathrm{mmol}, 10$ equiv), and TPAP $(8.9 \mathrm{mg}, 25 \mu \mathrm{~mol}, 0.1$ equiv) were added and the reaction stirred at rt for 14 h . The reaction was quenched with $i-\mathrm{PrOH}$ and $1 \mathrm{M} \mathrm{KHSO}_{4}(1 \mathrm{~mL})$, diluted with water $(20 \mathrm{~mL})$, and extracted with EtOAc ( $4 \times 20 \mathrm{~mL}$ ). The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, concentrated by rotary evaporation, and dried under high vacuum 1 h to afford the crude carboxylic acid, which was carried forward without further purification.

In a $25-\mathrm{mL}$ roundbottom flask, the crude carboxylic acid above was reconstituted in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ $(8 \mathrm{~mL})$ and cooled to $0^{\circ} \mathrm{C}$. TFA $(8 \mathrm{~mL})$ and water $(0.8 \mathrm{~mL})$ were added and the reaction stirred
for 4 h with warming to rt . The mixture was concentrated by rotary evaporation. Purification by preparative HPLC ( $5 \% \rightarrow 45 \% \mathrm{CH}_{3} \mathrm{CN}$ in $\mathrm{H}_{2} \mathrm{O}$ with $0.1 \%$ TFA) yielded $m$-(3-trifluoromethylphenyl) ether analogue $\mathbf{8}$ as a fluffy white solid ( $46 \mathrm{mg}, 31 \%$ over 3 steps).

IR (ATR): 3346, 2509, 2247, 2076, 1756, 1693, 1608, 1455, 1353, 1320, 1289, 1245, 1205, 1126, 1055, 982, 898, 842, 802, 767, 726, 703, 644. ${ }^{1}$ H-NMR (( $\left.600 \mathrm{MHz} ; \mathrm{MeOD}\right): \delta 8.43$ (s, $1 \mathrm{H}), 8.34(\mathrm{~s}, 1 \mathrm{H}), 7.84-7.81(\mathrm{~m}, 1 \mathrm{H}), 7.72-7.68(\mathrm{~m}, 1 \mathrm{H}), 7.60-7.57(\mathrm{~m}, 2 \mathrm{H}), 7.05-6.96(\mathrm{~m}, 3 \mathrm{H})$, $6.14(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.76(\mathrm{t}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.53(\mathrm{t}, J=5.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.43-4.38(\mathrm{~m}, 2 \mathrm{H})$, 4.28 (dd, $J=10.8,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.89-2.50(\mathrm{~m}, 4 \mathrm{H}) .{ }^{13} \mathbf{C}-\mathrm{NMR}(126 \mathrm{MHz} ; \mathrm{MeOD}): \delta 160.4$, 153.13, 153.05, 153.03, 150.1, 147.1, 145.77, 145.71, 145.65, 143.22, 143.18, 132.9, 131.58, $131.43,125.4,124.1,120.5,119.4,118.9,110.4,90.7,84.8,76.0,71.8,68.8,49.3,31.0$. ${ }^{19}$ F-NMR ( 126 MHz ; MeOD): $\delta-64.07$. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{27} \mathrm{H}_{25} \mathrm{~N}_{5} \mathrm{O}_{7} \mathrm{~F}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$ 588.1706; found 588.1681.

## I. Synthesis of m-3-PyRidyl Ether Analogue 9





Figure S9. Synthesis of m-3-pyridyl ether analogue 9. DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DIAD, diisopropyl azodicarboxylate; DMA, dimethylacetamide; dtbpf, 1,1'-bis(di-t-butylphosphino)ferrocene; TBSCI, $t$-butyldimethylsilyl chloride; TFA, trifluoroacetic acid; THF tetrahydrofuran.


Methyl 2-(4-hydroxybut-1-en-2-yl)benzoate (34). In a $250-\mathrm{mL}$ roundbottom flask, 3-bromobut-3-en-1-ol (33) ( $1 \mathrm{~g}, 6.622 \mathrm{mmol}, 1$ equiv), (2-(methoxycarbonyl)phenyl)boronic acid (32) ( $1.787 \mathrm{~g}, 9.33 \mathrm{mmol}, 1.5$ equiv), $\mathrm{Pd}\left(\mathrm{PPh}_{3}\right)_{4}(765 \mathrm{mg}, 0.662 \mathrm{mmol}, 0.1$ equiv) and $\mathrm{K}_{3} \mathrm{PO}_{4}$ ( $5.62 \mathrm{~g}, 26.48 \mathrm{mmol}, 4.0$ equiv) were suspended in THF ( 40 mL ) and dioxane ( 40 mL ) and heated to reflux for 14 h . The reaction was cooled to rt , diluted with water ( 300 mL ) and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(4 \times 100 \mathrm{~mL})$. The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography $(25 \% \rightarrow 75 \%$ EtOAc in hexanes) yielded olefin intermediate 34 as a clear oil ( $863 \mathrm{mg}, 63 \%$ ).

IR (ATR): 3412, 3078, 2952, 2884, 1716, 1636, 1598, 1571, 1484, 1434, 1292, 1259, 1192, $1164,1123,1076,1050,991,964,910,860,830,772,729,658,624 .{ }^{1} \mathbf{H}-N M R((600 \mathrm{MHz}$; $\mathrm{CDCl}_{3}$ ): $\delta 7.76$ (dd, $\left.J=7.8,1.1 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.47(\mathrm{td}, J=7.6,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{td}, J=7.6,1.0 \mathrm{~Hz}$, $1 \mathrm{H}), 7.27-7.26(\mathrm{~m}, 1 \mathrm{H}), 5.25(\mathrm{~d}, J=1.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.94(\mathrm{~d}, J=1.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.88(\mathrm{~s}, 3 \mathrm{H}), 3.62$
$(\mathrm{q}, J=5.2 \mathrm{~Hz}, 2 \mathrm{H}), 3.34(\mathrm{~s}, 1 \mathrm{H}), 2.72(\mathrm{t}, J=5.4 \mathrm{~Hz}, 2 \mathrm{H}) .{ }^{13} \mathbf{C}-\mathrm{NMR}\left(126 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 169.2$, $145.8,143.2,131.4,130.6,129.9,128.9,127.1,117.1,59.9,52.5,41.6$. HRMS (ESI) $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$207.1021; found 207.1021.


Methyl 2-(3-hydroxypropanoyl)benzoate (S14). In a $100-\mathrm{mL}$ roundbottom flask, methyl 2-(4-hydroxybut-1-en-2-yl)benzoate (34) ( $850 \mathrm{mg}, 4.121 \mathrm{mmol}$, 1 equiv) was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ $(50 \mathrm{~mL})$ and cooled to $-78^{\circ} \mathrm{C}$. Ozone was bubbled through the solution until a persistent blue color was observed, then nitrogen was bubbled through the solution until the blue color disappeared. The ozonide was quenched by addition of $\mathrm{PPh}_{3}(1.167 \mathrm{~g}, 4.45 \mathrm{mmol}, 1.08$ equiv) and the reaction stirred for 3 h with warming to rt . The mixture was concentrated by rotary evaporation. Purification by silica flash chromatography ( $50 \% \rightarrow 100 \%$ EtOAc in hexanes) yielded keto alcohol intermediate $\mathbf{S 1 4}$ as a clear oil ( $732 \mathrm{mg}, 85 \%$ ).

IR (ATR): 3428, 2956, 2894, 1719, 1599, 1576, 1488, 1347, 1390, 1362, 1285, 1211, 1195, 1167, 1137, 1098, 1048, 991, 962, 914, 867, 832, 766, 741, 710, 681, 648. ${ }^{1}$ H-NMR ((600 $\left.\mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 8.40(\mathrm{~s}, 1 \mathrm{H}), 8.34-8.32(\mathrm{~m}, 2 \mathrm{H}), 8.22-8.22(\mathrm{~m}, 1 \mathrm{H}), 7.87-7.86(\mathrm{~m}, 2 \mathrm{H}), 7.74$ (t, $J=0.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.61(\mathrm{t}, J=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.11(\mathrm{~d}, J=4.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.79(\mathrm{t}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H})$, 4.58-4.54 (m, 2H), 4.48-4.42 (m, 2H), 3.03-2.94 (m, 2H), 2.68-2.36 (m, 2H). ${ }^{13}$ C-NMR (126 $\mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): $\delta 206.1,167.2,143.0,132.5,130.0$, 128.2, 126.4, 126.1, 58.2, 52.8, 45.1. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{11} \mathrm{H}_{13 \mathrm{O}} 4\left([\mathrm{M}+\mathrm{H}]^{+}\right)$209.0814; found 209.0809 .


Methyl 2-acryloylbenzoate (S35). In a $25-\mathrm{mL}$ roundbottom flask, DDQ ( $218 \mathrm{mg}, 0.960 \mathrm{mmol}$, 2.0 equiv) and $\mathrm{PPh}_{3}\left(264 \mathrm{mg}, 1.008 \mathrm{mmol}, 2.1\right.$ equiv) were dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$. Tetrabutylammonium iodide ( $355 \mathrm{mg}, 0.960 \mathrm{mmol}, 2.0$ equiv) was added and the reaction stirred for 10 min . Methyl 2-(3-hydroxypropanoyl)benzoate ( $\mathbf{S 1 4}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(1 \mathrm{~mL}$ ) was added and the reaction stirred at rt for 30 min . DBU ( $292 \mathrm{mg}, 1.920 \mathrm{mmol}, 4.0$ equiv) was added and the reaction stirred for 30 min . The mixture was poured into water ( 30 mL ) and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ (4 x 30 mL ). The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography $(0 \% \rightarrow 20 \%$ EtOAc in hexanes) yielded vinyl ketone 35 as a clear oil ( $74 \mathrm{mg}, 81 \%$ ).

IR (ATR): 2954, 1724, 1669, 1611, 1575, 1486, 1435, 1404, 1286, 1231, 1193, 1129, 1076, 1041, 997, 959, 912, 831, 801, 765, 746, 709, 678, 645. ${ }^{1}$ H-NMR (( $600 \mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): 7.98 $(\mathrm{dd}, \mathrm{J}=7.8,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.61(\mathrm{td}, \mathrm{J}=7.5,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.54(\mathrm{td}, \mathrm{J}=7.6,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.37$ (dd, J = 7.5, $0.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), $6.67(\mathrm{dd}, \mathrm{J}=17.7,10.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.99(\mathrm{dd}, \mathrm{J}=10.7,0.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.85$
(dd, $\mathrm{J}=17.7,0.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.84(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathbf{C}-\mathrm{NMR}\left(126 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 197.1,166.7,141.1$, $137.3,132.3,130.6,130.1,129.9,129.2,127.6,52.5$. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{11} \mathrm{H}_{11 \mathrm{O}}$ $\left([\mathrm{M}+\mathrm{H}]^{+}\right)$191.0708; found 191.0709.


Methyl (E)-2-(3-(5-hydroxypyridin-3-yl)acryloyl)benzoate (37). In a $15-\mathrm{mL}$ sealed tube, vinyl ketone 35 ( $185 \mathrm{mg}, 0.973 \mathrm{mmol}, 1.2$ equiv), aryl bromide 36 ( $141 \mathrm{mg}, 0.811 \mathrm{mmol}, 1$ equiv), $\mathrm{NBu}_{4} \mathrm{Cl}\left(23 \mathrm{mg}, 0.081 \mathrm{mmol}, 0.1\right.$ equiv), and $\mathrm{PdCl}_{2}$ (dtbpf) ( $53 \mathrm{mg}, 0.081 \mathrm{mmol}, 0.1$ equiv) were suspended in DMA ( 2.4 mL ). $\mathrm{NCy}_{2} \mathrm{Me}(237 \mathrm{mg}, 1.215 \mathrm{mmol}, 1.5$ equiv) was added, the reaction vessel sealed, and the reaction stirred vigorously at $85^{\circ} \mathrm{C}$ for 16 h . The reaction was cooled to rt , diluted with water $(8 \mathrm{~mL})$, and extracted with $\mathrm{Et}_{2} \mathrm{O}(4 \times 8 \mathrm{~mL})$. The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography $(50 \% \rightarrow 100 \%$ EtOAc in hexanes) yielded phenol 37 as an off-white solid ( $154 \mathrm{mg}, 67 \%$ ).

IR (ATR): 3066, 2953, 1719, 1653, 1609, 1576, 1486, 1434, 1282, 1217, 1186, 1138,1108, 1064, 1020, 977, 911, 859, 828, 792, 769, 729, 708, 690, 667, 648, 607. ${ }^{\mathbf{1}} \mathbf{H}$-NMR ( $(600 \mathrm{MHz}$; $\left.\mathrm{CDCl}_{3}\right): \delta 8.26(\mathrm{~d}, \mathrm{~J}=2.3 \mathrm{~Hz}, 1 \mathrm{H}), 8.16(\mathrm{~d}, \mathrm{~J}=0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.99(\mathrm{dd}, \mathrm{J}=7.8,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.63$ $(\mathrm{td}, \mathrm{J}=7.5,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.57(\mathrm{td}, \mathrm{J}=7.7,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.49(\mathrm{~d}, \mathrm{~J}=1.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.43(\mathrm{dd}, \mathrm{J}=7.5$, $1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.18(\mathrm{~d}, \mathrm{~J}=16.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.07(\mathrm{~d}, \mathrm{~J}=16.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.83(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathbf{C}-\mathbf{N M R}(126$ $\mathrm{MHz} ; \mathrm{CDCl}_{3}$ ): $\delta 196.0,166.9,155.0,141.3,140.2,139.2,137.8,132.5,132.3,130.29,130.23$, 129.8, 129.2, 127.6, 122.7, 52.7. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{16 \mathrm{H} 14 \mathrm{NO} 4\left([\mathrm{M}+\mathrm{H}]^{+}\right) \text {284.0923; }}^{\text {; }}$ found 284.0934.


5'-O-([2-(Carboxyl)phenyl]3-(5-hydroxypyridin-3-yl)propanoyl)adenosine (9). In a $10-\mathrm{mL}$ roundbottom flask, phenol $37(90 \mathrm{mg}, 0.317 \mathrm{mmol}, 1$ equiv), protected adenosine $\mathbf{1 6}(86 \mathrm{mg}$, $0.212 \mathrm{mmol}, 1$ equiv), and resin-bound $\mathrm{PPh}_{3}(260 \mathrm{mg}, 0.317 \mathrm{mmol}, 32 \mathrm{wt} \%, 1.5$ equiv) were suspended in THF ( 5 mL ) and cooled to $0^{\circ} \mathrm{C}$. DIAD ( $62 \mathrm{mg}, 0.317 \mathrm{mmol}, 1.5$ equiv) was added dropwise, then the reaction was stirred for 14 h with warming to rt . The reaction was quenched with water $(0.2 \mathrm{~mL})$, filtered through a pad of celite, and the pad washed with EtOAc. The combined filtrates were concentrated by rotary evaporation to afford the crude protected phenoladenosine intermediate 38, which was carried forward without further purification.

In a $10-\mathrm{mL}$ roundbottom flask, the crude phenol-adenosine intermediate $\mathbf{3 8}$ above was dissolved in toluene ( 5 mL ). Stryker's reagent ( $104 \mathrm{mg}, 319 \mu \mathrm{~mol}, 1.5$ equiv) was added and the reaction
stirred for 12 h . The reaction was quenched with satd aq $\mathrm{NH}_{4} \mathrm{Cl}(10 \mathrm{~mL})$ and stirred for 5 min , then $10 \%$ aq $\mathrm{NH}_{4} \mathrm{OH}(10 \mathrm{~mL})$ was added and the reaction stirred for an additional 5 min . The reaction was then extracted with EtOAc ( $4 \times 20 \mathrm{~mL}$ ). The combined organic extracts were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered, and concentrated by rotary evaporation to afford the crude reduced intermediate, which was carried forward without further purification.

In a $25-\mathrm{mL}$ roundbottom flask, the crude reduced intermediate above was dissolved in MeOH ( 5 $\mathrm{mL})$. Water ( 0.5 mL ) and $\mathrm{LiOH}(10 \mathrm{mg}, 0.423 \mathrm{mmol}, 2$ equiv) were added and the reaction stirred at rt for 6 h . Concentration by rotary evaporation afforded the crude carboxylate intermediate, which was carried forward without further purification.

In a $25-\mathrm{mL}$ roundbottom flask, the crude carboxylate intermediate above was suspended in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. Water $(0.5 \mathrm{~mL})$ and TFA $(5 \mathrm{~mL})$ were added and the reaction stirred at rt for 4 h . The mixture was concentrated by rotary evaporation. Purification by preparative HPLC ( $5 \% \rightarrow 45 \%$ $\mathrm{CH}_{3} \mathrm{CN}$ in $\mathrm{H}_{2} \mathrm{O}$ with $0.1 \%$ TFA) yielded $m$-3-pyridyl ether analogue 9 as a fluffy white solid (32 $\mathrm{mg}, 29 \%$ over 4 steps).

IR (ATR): 3397, 2521, 1681, 1577, 1428, 1290, 1202, 1138, 1046, 979, 899, 840, 800, 765, 723, 701, 680, 642, 611. ${ }^{1} \mathbf{H}-\mathbf{N M R}\left(\left(600 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 8.40(\mathrm{~s}, 1 \mathrm{H}), 8.34-8.32(\mathrm{~m}, 2 \mathrm{H}), 8.22-8.22\right.$ $(\mathrm{m}, 1 \mathrm{H}), 7.87-7.86(\mathrm{~m}, 2 \mathrm{H}), 7.74(\mathrm{t}, \mathrm{J}=0.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.61(\mathrm{t}, \mathrm{J}=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.11(\mathrm{~d}, \mathrm{~J}=4.3 \mathrm{~Hz}$, $1 \mathrm{H}), 4.79(\mathrm{t}, \mathrm{J}=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.58-4.54(\mathrm{~m}, 2 \mathrm{H}), 4.48-4.42(\mathrm{~m}, 2 \mathrm{H}), 3.03-2.94(\mathrm{~m}, 2 \mathrm{H}), 2.68-2.36$ $(\mathrm{m}, 2 \mathrm{H}) .{ }^{13} \mathbf{C}-\mathrm{NMR}\left(126 \mathrm{MHz} ; \mathrm{CDCl}_{3}\right): \delta 162.5,158.1,153.82,153.82,153.80,150.19,150.17$, $148.39,148.37,148.35,143.06,143.02,137.69,137.68,131.7,131.0,129.9,120.6,90.8,84.3$, 75.4, 71.7, 70.0, 49.6, 28.0. HRMS (ESI) $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{25} \mathrm{~N}_{6} \mathrm{O} 7\left([\mathrm{M}+\mathrm{H}]^{+}\right) 521.1785$; found 521.1772.

## J. ${ }^{1}$ H-NMR AND ${ }^{13} \mathbf{C}$-NMR Spectra

1. Synthesis of $\alpha$-Hydroxytetrazole Analogue 7 S38
2. Synthesis of Acyl Squaramide Analogue 3 S42
3. Synthesis of Alkyl Sulfamide Analogue 4 S45
4. Synthesis of $m$-Phenyl Ether Analogue 5 S47
5. Synthesis of $p$-Phenyl Ether Analogue $6 \quad$ S51
6. Synthesis of $m$-(3-Trifluoromethylphenyl) Ether Analogue 8 S54
7. Synthesis of $m$-3-Pyridyl Ether Analogue 9 S58





60.242
-52.993
$-\quad 38.288$
29.359


























[^0]:    ${ }^{a} R$ factor was calculated from the equation $\frac{\sum\left|\left|F_{\text {obs }}\right|-\left|F_{\text {calc }}\right|\right|}{\sum\left|F_{\text {obs }}\right|}$, where $F_{\text {obs }}$ and $F_{\text {calc }}$ are observed and calculated structure factors, respectively.
    ${ }^{b}$ For $\mathrm{R}_{\text {free }}$, the sum is extended over a subset of reflections (4.84 \%) excluded from all stages of refinement.

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