Supporting Information

Synthesis of 5′-carboxymethylsulfonyl-5′-deoxyribonucleosides under mild hydrolytic conditions: A new class of acidic nucleosides as inhibitors of ribonuclease A

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General experimental procedures:

All reagents were commercially purchased. Column chromatographic separations were done using silica gel (60-120 and 230-400 mesh). Solvents were dried and distilled following standard procedures. TLC was carried out on precoated plates (Merck silica gel 60, f254) and the spots were visualized with UV light or by charring the plates dipped in 5% H₂SO₄ in MeOH, 5% vanillin in MeOH and 5% ninhydrin in n-butanol solutions. ¹H-NMR (400 MHz) and ¹³C-NMR (100 MHz) spectra were recorded on Bruker NMR spectrometer unless stated otherwise. All ¹H and ¹³C NMR were recorded in CDCl₃, D₆-DMSO and D₂O (using HPLC grade acetonitrile as internal standard). Chemical shifts are reported in parts per million (ppm, δ scale). DEPT experiments have been carried out to identify the methylene carbons. Mass spectroscopy data were obtained from Xevo G2QTof mass spectrometer in ESI⁺ mode. Melting points were determined in open-end capillary tubes and are uncorrected. Bovine pancreatic RNase A, yeast tRNA, 2′, 3′-cCMP, 3′-CMP and human serum albumin (HSA) were purchased commercially. UV-Vis measurements were made using a UV-Vis spectrophotometer (Model Lambda 25). Concentrations of the solutions were estimated spectrophotometrically using the following data: 

\[ \varepsilon_{278.5} = 9800 \text{ M}^{-1}\text{cm}^{-1} \text{ (RNase A)} \] and 

\[ \varepsilon_{268} = 8500 \text{ M}^{-1}\text{cm}^{-1} \text{ (2′, 3′-cCMP)}. \]

Purity of chiral amino-acid coupled 5′-modified uridine 3 (U5′Asp) and most active RNase A inhibitor 14 (C5′SO₂CH₂COOH) in this series was analyzed for purity on Enable C18H reverse phase column (15 cm x 4.0 mm) having flow rate of 1.0 mL/min, λ= 254 nm. The mobile phase was a mixture of a buffer consisting of Na₂HPO₄, NaH₂PO₄, tetrabutylammonium sulphate whose pH was adjusted to 3.0 by H₃PO₄ and methanol. Applied gradient was 68% buffer in methanol over 40 minutes. The observed purities of these two compounds were more than 95%.
Synthesis of RNase A inhibitors:

5′-amino-acid modified nucleosides:

Amino-acid modified nucleoside was synthesized through a well established synthetic strategy starting from 5′ amino uridine 1S.³ Amide coupling⁴ of this amine with partially protected L-aspartic acid elicited amino-acid conjugate 2S. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) was used as coupling agent in dry DMF with activator N-hydroxybenzotriazole (HOBT). This protected amino-acid conjugate of uridine was efficiently turned into target inhibitor 3 by deprotection of benzyl ester and acid-labile groups in a single step. Choice of ester hydrolysis condition was important for compound 3, which was expected to be recemized largely under all other basic conditions except with TMTOH.⁵ Acidic hydrolysis were performed by 10% trifluoroacetic acid (TFA) in DCM to afford 3 (U5′Asp) in moderate yield.

Scheme S1: Synthesis of U5′Asp 3.
Experimental procedures:

5′-N-[N-tert-Butoxycarbonyl-4-(benzyloxy carbonyl)-L-aspartyl]-5′-amino-5′-deoxy-2′,3′-O-isopropylideneuridine 2S: A solution of L-boc-asp(Obzl)-OH (3.15 g, 9.75 mmol) in dry DMF (5 mL) was cooled to 0 °C. EDC·HCl (1.87 g, 9.75 mmol) and HOBT (0.97 g, 7.15 mmol) were added to this solution and the mixture was stirred at room temperature. After 0.2 h a solution of 5′-aminouridine 1S (1.84 g, 6.50 mmol) in DMF (7 mL), was added to the reaction mixture and the mixture was stirred further for 10 h. After completion of the reaction (TLC), the reaction mixture was diluted with EtOAc and the organic solution was washed with 5% HCl, 10% NaHCO₃, and finally with brine. Organic layers were combined, dried over anhyd. Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure. The crude product residue was purified over silica gel [Eluent: 60-70% of EtOAc in pet ether] to afford compound 2S as hygroscopic solid (2.48 g, 65% yield with respect to amine 1S). ¹H NMR (CDCl₃, 25°C, TMS): ¹H NMR (CDCl₃, 25°C, TMS): δ = 1.32 (s, 3H), 1.42 (s, 9H), 1.54 (s, 3H), 2.53 (bs, 2H), 2.81-2.97 (m, 2H), 3.49-3.55 (m, 1H), 3.66-3.72 (m, 1H), 4.19-4.20 (m, 1H), 4.56 (bs, 1H), 4.77 (bs, 1H), 5.04 (bs, 1H), 5.08-5.11 (m, 2H), 5.52 (bs, 1H), 5.72-5.76 (m, 2H), 7.25-7.37 (m, 5H), 9.87 ppm (bs, 1H); ¹³C NMR (CDCl₃, 25°C, TMS): δ = 25.4, 27.2, 28.4, 36.6 (CH₂), 41.0 (CH₂), 50.9, 66.8, 77.4, 80.5 (C), 81.0, 84.0, 85.2, 94.9, 102.9, 114.8 (C), 128.2, 128.4, 128.6, 135.5 (C),
143.1, 150.5 (C), 155.6 (C), 163.6 (C), 171.4 (C), 171.5 ppm (C); HRMS (ESI⁺), m/z calcd for (M+H)⁺ C₂₈H₃₇N₄O₁₀: 589.2510, found: 589.2534.

**5′-N-(4-Carboxy-L-aspartyl)-5′-amino-5′-deoxyuridine 3:** To a clear solution of compound 2S (0.40 g, 0.68 mmol) in DCE (20 mL), TMTOH (0.61 g, 3.40 mmol) was added and reaction mixture was heated at 70 °C for 8 h. After completion of reaction (TLC), volatile matters was removed under reduced pressure and the crude mass thus obtained was dissolved in 10% trifluoroacetic acid (TFA) in DCM (10 mL). The reaction mixture was stirred for 7 h at room temperature. Thereafter, all the volatile matters were removed. The crude residue was triturated with chilled diethyl ether (3x10 mL) to remove non-polar impurities and residual acid. Ether layer was decanted off each time to afford the compound 3 (0.11 g, 45%) as white hygroscopic solid. ¹H NMR (D₂O, 25°C, water suppressed): δ = 2.94-3.06 (m, 2H), 3.48-3.54 (m, 1H), 3.60-3.65 (m, 1H), 4.15 (bs, 2H), 4.27-4.30 (m, 1H), 4.34 (bs, 1H), 5.70-5.71 (m, 1H), 5.83 (d, J = 8.0 Hz, 1H), 7.60 ppm (d, J = 8.0 Hz, 1H); ¹³C NMR (D₂O, 25°C): δ = 35.4 (CH₂), 41.6 (CH₂), 50.2, 71.0, 73.5, 82.1, 91.6, 102.9, 143.2, 152.1 (C), 166.8 (C), 169.5 (C), 173.2 ppm (C); HRMS (ESI⁺), m/z calcd for (M+H)⁺ C₁₃H₁₉N₄O₈: 359.1203, found: 359.1206.
**5′-thio and sulfone-acetic acid modified nucleosides:**

![Chemical Structure](image)

**5′-Deoxy-5′-S-[(methoxycarbonyl)methylthio]-2′,3′-O-isopropylideneuridine 5:** To a suspension of NaH (60% in dispersed in mineral oil, 0.38 g, 9.5 mmol) in DMF (10 mL), methyl-2-mercaptoacetate (1.8 mL, 14.4 mmol) was added dropwisely at 0 °C under argon. The suspension was allowed to warm at room temperature while the solution turned yellow. The reaction mixture was cooled to 0 °C and 2′,3′-O-isopropylidene-5′-O-tosyluridine 4° (1.40 g, 3.2 mmol) in DMF (5 mL) was added to it. After 8 h, satd. aq NH₄Cl solution was added to the reaction mixture and was partitioned and washed with EtOAc (2x50 mL). Combined organic layers were washed with brine, separated, dried over anhyd Na₂SO₄ and filtered. The filtrate was removed under reduced pressure and the residue was purified over a silica gel column to afford compound 5 (0.97 g, 82%) [Eluent: 60-70% of EtOAc in pet ether]. White solid. M.p. 102-105 °C. ¹H NMR (CDCl₃, 25°C, TMS): δ = 1.35 (s, 3H), 1.57 (s, 3H), 2.99-3.01 (m, 2H), 3.27 (d, J = 14.8, 1H), 3.33 (d, J = 14.8, 1H), 3.73 (s, 3H), 4.27-4.32 (m, 1H), 4.79-4.82 (m, 1H), 4.97-4.99 (m, 1H), 5.64 (d, J = 2.0 Hz, 1H), 5.73-5.75 (m, 1H), 7.29 (d, J = 8.0 Hz, 1H), 8.30 ppm (bs, 1H); ¹³C NMR (CDCl₃, 25°C, TMS): δ = 25.1, 26.9, 33.6 (CH₂), 34.4 (CH₂), 52.4, 83.2, 84.3, 86.8, 94.5, 102.5, 114.4 (C), 142.9, 150.1 (C), 163.9 (C), 170.5 ppm (C). HRMS (ES⁺), m/z calculated for (M+H)⁺ C₁₅H₂₁N₂O₇S: 373.1069, found: 373.1078.
5'-Deoxy-5'-S-[(methoxycarbonyl)methylthio]uridine 6: Compound 5 (0.25 g, 0.67 mmol) was stirred with aq TFA (70%, 10 mL) at room temperature. After 3 h, the solvent was evaporated to dryness under reduced pressure, co-evaporated twice with toluene (2x10 mL) and the residue was chromatographed to obtain compound 6 (0.21 g, 78%). [Eluent: 0-5% of MeOH in CHCl₃]. Hygroscopic solid. ¹H NMR ([D₆]DMSO, 25 °C): δ = 2.80-2.93 (m, 2H), 3.34-3.43 (m, 2H), 3.60 (s, 3H), 3.83-3.91 (m, 2H), 4.07-4.11 (m, 1H), 5.23 (d, J = 5.2 Hz, 1H), 5.42 (d, J = 5.6 Hz, 1H), 5.63 (dd, J = 1.6 Hz, 8.0 Hz, 1H), 5.72 (d, J = 5.6 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 11.35 (s, 1H). ¹³C NMR ([D₆]DMSO, 25 °C): δ = 33.7 (CH₂), 34.6 (CH₂), 52.4, 72.5, 72.6, 83.3, 88.8, 102.5, 141.5, 151.1 (C), 163.4 (C), 170.9 (C). HRMS (ES⁺), m/z calculated for (M+Na)⁺ C₁₂H₁₆N₂O₇SNa: 355.0576, found: 355.0573.

5'-Deoxy-5'-S-(carboxymethylthio)uridine 7: Compound 6 (0.15 g, 0.45 mmol) was dissolved in a mixture of aq NaOH (1 M, 2.5 mL) and THF (5 mL) and the solution was stirred at room temperature for 2 h. Volatile matters were removed under reduced pressure and the solution was neutralized with 1 M HCl solution. The resulting solution was evaporated to dryness under reduced pressure and the crude mass thus obtained, was purified over silica gel column to obtain compound 7 (0.11 g, 75%) [Eluent: 10-25% of MeOH in CHCl₃]. Hygroscopic solid. ¹H NMR
([D6]DMSO, 25 °C): $\delta = 2.77\text{-}2.87$ (m, 2H), 3.04\text{-}3.14 (m, 2H), 3.87\text{-}3.93 (m, 2H), 4.05\text{-}4.08 (m, 1H), 5.64 (d, $J = 8.0$ Hz, 1H), 5.74 (d, $J = 5.6$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 11.34 (bs, 1H). $^{13}$C NMR ([D6]DMSO, 25 °C): $\delta = 34.4$ (CH$_2$), 37.5 (CH$_2$), 72.5, 72.9, 83.5, 88.4, 102.5, 141.4, 151.1 (C), 163.5 (C), 173.3 (C). HRMS (ES$^+$), m/z calculated for (M+Na)$^+$ C$_{11}$H$_{14}$N$_2$O$_7$SNa: 341.0420, found: 341.0411.

5′-Deoxy-5′-SO$_2$-[(methoxycarbonyl)methylsulfonyl]-2′,3′-O-isopropylideneuridine 8: MMPP (3.47 g, 7.02 mmol) was added to a solution of compound 5 (0.87 g, 2.34 mmol) in anhyd. MeOH (15 mL) and the mixture was stirred at room temperature and N$_2$ atmosphere. After 6 h, this reaction mixture was concentrated, treated with satd. aq NaHCO$_3$ and the solution was washed with EtOAc (2x25 mL). Organic layers were separated, dried over anhyd. Na$_2$SO$_4$, filtered and the filtrate was concentrated under reduced pressure. The residue thus obtained was purified over silica gel column [Eluent: 2-5% of MeOH in CHCl$_3$] to afford sulfone compound 8 (0.92 g, 85%) as white solid. M.p. 224-230°C (decomposes); $^1$H NMR, ([D6]DMSO, 25 °C): $\delta = 1.28$ (s, 3H), 1.47 (s, 3H), 3.62 (s, 3H), 3.71-3.76 (m, 1H), 3.83-3.89 (m, 1H), 4.32 (s, 2H), 4.40-4.43 (m, 1H), 4.86-4.88 (m, 1H), 5.12-5.14 (m, 1H), 5.62 (d, $J = 8.0$ Hz, 1H), 5.76 (s, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 11.45 ppm (s, 1H). $^{13}$C NMR, ([D6]DMSO, 25 °C): $\delta = 25.4, 27.3, 53.1, 56.5$ (CH$_2$), 58.2 (CH$_2$), 82.9, 83.9, 84.1, 95.0, 102.2, 113.6 (C), 144.6, 150.9 (C), 163.8 (C), 164.0 ppm (C). HRMS (ES$^+$), m/z calculated for (M+H)$^+$ C$_{15}$H$_{21}$N$_2$O$_9$S: 405.0968, found: 405.0955.
5’-Deoxy-5’-SO₂-[(methoxycarbonyl)methylsulfonyl]uridine 9: Compound 8 (0.4 g, 0.99 mmol) was dissolved in 80% acetic acid (10 mL) and heated to reflux for 2.5 h. The reaction mixture was cooled, volatile matters was removed under reduced pressure. The crude mass thus obtained was purified by column chromatography [Eluent: 3-15% of MeOH in DCM] to obtain compound 9 (0.27 g, 75%). Hygroscopic solid; ¹H NMR ([D₆]DMSO, 25 °C): δ = 3.57-3.66 (m, 4H), 3.81-3.87 (m, 1H), 3.94-3.98 (m, 1H), 4.09-4.19 (m, 2H), 4.29-4.38 (m, 2H), 5.42 (d, J = 5.6 Hz, 1H), 5.51 (d, J = 5.6 Hz, 1H), 5.62 (d, J = 8.0 Hz, 1H), 5.71-5.74 (m, 1H), 7.64 (d, J = 8.0 Hz, 1H), 11.35 ppm (s, 1H). ¹³C NMR ([D₆]DMSO, 25 °C): δ = 53.1, 56.6 (CH₂), 58.5 (CH₂), 72.1, 72.8, 77.9, 90.1, 102.4, 141.8, 151.0 (C), 163.5 (C), 168.9 ppm (C). HRMS (ES⁺), m/z calculated for (M+H)⁺ C₁₂H₁₇N₂O₉S: 365.0655, found: 365.0639.

5’-Deoxy-5’-SO₂-(carboxymethylsulfonyl)uridine 10: A suspension of compound 9 (0.1 g, 0.27 mmol) and TMTOH (0.24 g, 1.35 mmol) in DCE (15 mL) was heated at 70°C for 6 h. After completion of reaction, volatile matters were evaporated under reduced pressure and the crude mass thus obtained, was purified over silica gel column [Eluent: 20-50% of MeOH in CHCl₃] to afford acid 10 (0.07 g, 70%). Hygroscopic solid; ¹H NMR ([D₆]DMSO, 25 °C): δ = 3.53-3.56 (m, 1H), 3.68-3.77 (m, 2H), 3.91-3.99 (m, 3H), 4.09-4.11 (m, 1H), 4.18-4.22 (m, 1H), 5.59 (d, J = 5.6 Hz, 1H), 5.62 (d, J = 8.0 Hz, 1H), 5.71-5.74 (m, 1H), 7.64 (d, J = 8.0 Hz, 1H), 11.35 ppm (s, 1H). ¹³C NMR ([D₆]DMSO, 25 °C): δ = 53.1, 56.6 (CH₂), 58.5 (CH₂), 72.1, 72.8, 77.9, 90.1, 102.4, 141.8, 151.0 (C), 163.5 (C), 168.9 ppm (C). HRMS (ES⁺), m/z calculated for (M+H)⁺ C₁₂H₁₇N₂O₉S: 365.0655, found: 365.0639.
= 8.0 Hz, 1H), 5.75 (d, J = 4.8 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 11.36 ppm (s, 1H). $^{13}$C NMR, 50 MHz ([D6]DMSO, 25 °C): δ = 55.0 (CH$_2$), 60.6 (CH$_2$), 72.1, 72.5, 77.7, 89.2, 101.9, 141.1, 150.6 (C), 163.0 (C), 164.8 ppm (C). HRMS (ES$^+$), m/z calculated for (M+H)$^+$ C$_{11}$H$_{15}$N$_2$O$_9$S: 351.0498, found: 351.0497.

4-(1,2,3-Triazol-1-yl)-1-[β-D-5-S-(carboxymethylthio)-2,3-isopropylideneribofuranosyl]pyrimidin-2(1H)-one 11: Compound 5 (0.8 g, 2.15 mmol) was converted to compound 11 (0.74 g, 81%) following the method described in Ref. 7. [Eluent: 60-80% of EtOAc in pet ether]. White solid. M.p. 136-140°C; $^1$H NMR (CDCl$_3$, 25°C, TMS): δ = 1.29 (s, 3H), 1.51 (s, 3H), 2.99-3.01 (m, 2H), 3.21 (d, J = 14.8 Hz, 1H), 3.28 (d, J = 14.8 Hz, 1H), 3.66 (s, 3H), 4.33-4.37 (m, 1H), 4.80-4.82 (m, 1H), 5.01-5.03 (m, 1H), 5.72 (d, J = 1.6 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 8.06 (s, 1H), 8.07 (d, J = 7.2 Hz, 1H), 9.18 ppm (s, 1H). $^{13}$C NMR (CDCl$_3$, 25°C, TMS): δ = 25.1, 26.9, 33.5 (CH$_2$), 34.6 (CH$_2$), 52.3, 83.3, 84.8, 87.8, 94.8, 96.7, 114.2 (C), 143.2, 149.2, 153.8 (C), 154.0, 159.6 (C), 170.3 ppm (C). HRMS (ES$^+$), m/z calculated for (M+H)$^+$ C$_{17}$H$_{22}$N$_5$O$_6$S: 424.1291, found: 424.1291.
4-(1,2,3-Triazol-1-yl)-1-[β-D-5-SO₂-(carboxymethylsulfonyl)-2,3-isopropylideneribofuranosyl]pyrimidin-2(1H)-one 12: A solution of compound 11 (0.5 g, 1.18 mmol) dissolved in DCM (11 mL) was added dropwise into MMPP (1.16 g, 2.36 mmol) moistened with water (0.24 mL). The reaction mixture was stirred for 3 h and then filtered though celite bed. Filtrate was dried over anhydrous CaCl₂, concentrated under reduced pressure and the crude mass thus obtained was purified by flash column chromatography [Eluent: 2-8% MeOH in CHCl₃] to afford compound 12 (0.43 g, 80%). Hygroscopic solid. ¹H NMR ([D₆]DMSO, 25 °C): δ = 1.30 (s, 3H), 1.50 (s, 3H), 3.59 (s, 3H), 3.81-3.86 (m, 1H), 3.91-3.97 (m, 1H), 4.34 (s, 2H), 4.53-4.57 (m, 1H), 4.95-4.97 (m, 1H), 5.21-5.23 (m, 1H), 5.96 (s, 1H), 7.01 (d, J = 7.2 Hz, 1H), 8.41 (s, 1H), 8.54 (d, J = 7.2 Hz, 1H), 9.44 ppm (s, 1H). ¹³C NMR ([D₆]DMSO, 25 °C): δ = 25.7, 27.5, 53.4, 56.9 (CH₂), 58.7 (CH₂), 84.1, 84.5, 84.7, 95.1, 97.7, 113.9 (C), 144.6, 152.8, 154.3, 155.0 (C), 160.1 (C), 164.2 ppm (C). HRMS (ES⁺), m/z calculated for (M+H)⁺ C₁₇H₂₂N₅O₈S: 456.1189, found: 456.1189.

5′-Deoxy-5′-SO₂-[(methoxycarbonyl)methylsulfonyl]-2′,3′-O-isopropylidene-5-iodocytidine 13: To a solution of compound 12 (0.1 g, 0.22 mmol) in THF (5 mL) NH₄OH (0.6 mL) was added and
stirred for 2.5 h. The volatile matters were removed under reduced pressure and the semi-solid mass thus obtained, was purified by column chromatography [Eluent: 2-7% MeOH in CHCl₃] to afford compound 13 (0.06 g, 72%). White solid; M.p. 184-188°C (decomposes); ¹H NMR, ([D6]DMSO, 25 ℃): δ = 1.27 (s, 3H), 1.46 (s, 3H), 3.61 (s, 3H), 3.72-3.77 (m, 1H), 3.90-3.95 (m, 1H), 4.24-4.33 (m, 2H), 4.40-4.44 (m, 1H), 4.89-4.92 (m, 1H), 5.06-5.08 (m, 1H), 5.63 (s, 1H), 5.68 (d, J = 7.2 Hz, 1H), 7.28 (bs, 2H), 7.66 ppm (d, J = 7.6 Hz, 1H). ¹³C NMR ([D6]DMSO, 25 ℃): δ = 25.7, 27.6, 53.3, 57.3 (CH₂), 58.6 (CH₂), 83.4, 84.8, 85.0, 95.0, 97.1, 113.5 (C), 145.8, 155.6 (C), 164.1 (C), 167.0 ppm (C). HRMS (ES⁺), m/z calculated for (M+H)⁺ C₁₅H₂₂N₃O₈S: 404.1128, found: 404.1121.

5′-Deoxy-5′-SO₂-(carboxymethylsulfonyl)cytidine 14: A suspension of compound 13 (0.05 g, 0.12 mmol) and TMTOH (0.11 g, 0.60 mmol) was heated at 70°C for 4 h in DCE. All the volatile matters were then removed under reduced pressure. The obtained crude mass was stirred with 10% TFA in DCM (5 mL) at room temperature. After 3 h, the volatile matters were evaporated to dryness under reduced pressure and residual liquid was co-evaporated with a mixture of toluene and carbon tetrachloride. The residue was washed with CHCl₃ first and then triturated well with chilled Et₂O to obtain compound 14 (0.022 g, 50%). White hygroscopic solid. ¹H NMR, ([D6]DMSO, 25 ℃): δ = 3.64-3.76 (m, 4H), 4.38 (bs, 1H), 4.87 (bs, 1H), 4.97-4.98 (m, 1H), 5.65-5.69 (m, 2H), 7.24 (bs, 1H), 7.32 (bs, 1H), 7.63 ppm (d, J = 7.2 Hz, 1H). ¹³C NMR ([D6]DMSO, 25 ℃): δ = 55.8 (CH₂), 61.3 (CH₂), 81.9, 84.3, 84.5, 94.8, 95.1, 144.7, 145.8.
155.3 (C), 164.9 (C), 166.6 ppm (C). HRMS (ES^+), m/z calculated for (M+H)^+ C_{11}H_{16}N_{3}O_{8}S: 350.0658, found: 350.0671.

\[
\begin{align*}
N^6,N^6\text{-Bis(tert-butoxycarbonyl)-2',3'-isopropylidene-5'-O-(4-}
\text{methylbenzenesulfonyl)adenosine 16: To a solution of compound 15^8 (1.13 g, 2.24 mmol) in}
\text{dry DCM (30 mL), TEA (0.93 mL, 6.72 mmol) and p-toluenesulfonyl chloride (0.64 g, 3.36}
\text{mmol) were added at 0 °C. The reaction mixture was allowed to warm at room temperature and}
\text{stirred for 8 h. Satd. NaHCO}_3\text{ solution was added slowly into the reaction mixture. The organic}
\text{layer was separated with additional DCM (20 mL). Resulting organic layer was washed with}
\text{water and brine, separated, dried over anhyd. CaCl}_2\text{ and finally concentrated under reduced}
\text{pressure. The crude residue thus obtained was purified by column chromatography [Eluent: 30-}
\text{40% of EtOAc in pet ether] to afford compound 16 (1.2 g, 80%) as white hygroscopic solid.}^1\text{H}
\text{NMR, 200 MHz (CDCl}_3\text{, 25°C, TMS): }\delta = 1.30 (s, 3H), 1.42 (s, 18H), 1.53 (s, 3H), 2.34 (s, 2H),
\text{4.16-4.19 (m, 2H), 4.41-4.43 (m, 1H), 4.96-5.00 (m, 1H), 5.25-5.29 (m, 1H), 6.10 (d, } J = 1.6 \text{ Hz},
\text{1H), 7.18 (d, } J = 8.2 \text{ Hz, 1H), 7.57 (d, } J = 8.0 \text{ Hz, 1H), 8.10 (s, 1H), 8.69 ppm (s, 1H); }^{13}\text{C NMR,}
\text{50 MHz (CDCl}_3\text{, 25°C, TMS): }\delta = 21.5, 25.2, 27.1, 27.8, 68.9 (\text{CH}_2), 81.3, 83.9 (\text{C}), 84.0, 84.3,
\text{90.9, 114.8 (C), 127.8, 129.2 (C), 129.9, 132.1 (C), 143.8, 145.3 (C), 150.5 (C), 150.6 (C), 152.0,}
\text{152.2 ppm (C). HRMS (ES^+), m/z calculated for (M+H)^+ C}_{30}\text{H}_{40}\text{N}_{5}\text{O}_{10}\text{S: 662.2496, found:}
\text{662.2480.}
\end{align*}
\]
\[ N^6-(\text{tert-Butoxycarbonyl})-2',3'-\text{isopropylidene}-5'-\text{deoxy}-5'-S-\]
\[(\text{methoxycarbonyl})\text{methylthio}]\text{adenosine 17}: \] To a suspension of NaH (60% in dispersed in mineral oil, 0.58 g, 14.5 mmol) in DMF (10 mL), methyl-2-mercaptoacetate (3.08 mL, 24.6 mmol) was added slowly at 0 °C under argon. The suspension was allowed to warm at room temperature while the solution turned yellow. The reaction mixture was cooled to 0 °C and compound 16 (2.61 g, 3.9 mmol) in DMF (5 mL) was added to it. After 6 h, aq satd NH₄Cl solution was added to the reaction mixture and was partitioned and washed with EtOAc (2x50 mL). Combined organic layers were washed with brine, separated, dried over anhyd. Na₂SO₄ and filtered. The filtrate was removed under reduced pressure and the residue was purified over a silica gel column to afford compound 17 as transparent gum (1.33 g, 70%).[Eluent: 40-50% of EtOAc in pet ether]. \(^1\)H NMR, 200 MHz (CDCl₃, 25°C, TMS): \(\delta = 1.40 \text{ (s, 3H)}, 1.56 \text{ (s, 9H)}, 1.62 \text{ (s, 3H)}, 2.95-2.99 \text{ (m, 2H)}, 3.23 \text{ (s, 2H)}, 3.67 \text{ (s, 3H)}, 4.41-4.49 \text{ (m, 1H)}, 5.07-5.12 \text{ (m, 1H)}, 5.48-5.52 \text{ (m, 1H)}, 6.14 \text{ (d, } J = 2.2 \text{ Hz, 1H)}, 8.20 \text{ (s, 1H)}, 8.78 \text{ (s, 1H)}, 9.14 \text{ ppm (s, 1H)}; \(^{13}\)C NMR, 50 MHz (CDCl₃, 25°C, TMS): \(\delta = 25.3, 27.1, 28.1, 33.5 \text{ (CH₂)}, 34.5 \text{ (CH₂)}, 52.4, 82.2 \text{ (C)}, 83.6, 84.0, 86.4, 90.7, 114.7 \text{ (C)}, 122.4 \text{ (C)}, 142.0, 149.9 \text{ (C)}, 150.3 \text{ (C)}, 153.0, 170.3 \text{ ppm (C)}. \) HRMS (ES\(^+\)), m/z calculated for (M+H\(^+\)) \(\text{C}_{21}\text{H}_{30}\text{N}_{5}\text{O}_{7}\text{S}: 496.1866, \) found: 496.1887.
$N^6$-\((\text{tert-Butoxycarbonyl})\)-2',3'-isopropylidene-5'-deoxy-5'-SO$_2$-

\[(\text{methoxycarbonyl})\text{methylsulfonyl}]\text{adenosine 18:}\] MMPP (4.3 g, 8.7 mmol) was added to a solution of thio compound 17 (1.3 g, 2.6 mmol) in anhyd. MeOH (20 mL) and the mixture was stirred at room temperature and N$_2$ atmosphere. After 8 h, this reaction mixture was concentrated, treated with satd. aq NaHCO$_3$ and the solution was washed with EtOAc (2x25 mL). Organic layers were separated, dried over anhyd. Na$_2$SO$_4$, filtered and the filtrate was concentrated under reduced pressure. The residue thus obtained was purified over silica gel column to afford corresponding sulfone compound 18 (1.2 g, 84%) [Eluent: 60-70% of EtOAc in pet ether]. White solid. M.p. 96-100°C; $^1$H NMR, 200 MHz (CDCl$_3$, 25°C, TMS): $\delta$ = 1.39 (s, 3H), 1.57 (s, 9H), 1.62 (s, 3H), 3.49-3.61 (m, 4H), 3.79-4.10 (m, 3H), 4.76-4.84 (m, 1H), 5.27-5.32 (m, 1H), 5.40-5.44 (m, 1H), 6.19 (d, $J$ = 1.2 Hz, 1H), 8.09 (s, 1H), 8.54 (s, 1H), 8.78 ppm (s, 1H); $^{13}$C NMR, 50 MHz (CDCl$_3$, 25°C, TMS): $\delta$ = 25.4, 27.1, 28.2, 53.1, 56.0 (CH$_2$), 58.3 (CH$_2$), 82.5 (C), 82.7, 83.9, 84.1, 90.7, 115.2 (C), 122.5 (C), 142.2, 149.9 (C), 150.2 (C), 150.4 (C), 153.2, 163.1 ppm (C). HRMS (ES$^+$), m/z calculated for (M+H)$^+$ C$_{21}$H$_{30}$N$_5$O$_9$S: 528.1764, found: 528.1779.
5'-Deoxy-5'-SO₂-[(methoxycarbonyl)methylsulfonyl]adenosine 19: Compound 18 (0.1 g, 0.19 mmol) was dissolved in aq 70% acetic acid (5 mL) and heated under reflux for 12 h. The reaction mixture was cooled, volatile matters were removed under reduced pressure. The crude mass thus obtained was purified by column chromatography [Eluent: 15-20% of MeOH in CHCl₃] to obtain compound 19 (0.06 g, 83%). White solid. Mp. 135-140°C; ¹H NMR ([D₆]DMSO, 25°C): δ = 3.56 (s, 3H), 3.66-3.70 (m, 1H), 3.95-4.01 (m, 1H), 4.28-4.35 (m, 4H), 4.66-4.68 (m, 1H), 5.63 (bs, 2H), 5.93 (d, J = 4.8 Hz, 1H), 7.56 (bs, 2H), 8.19 (s, 1H), 8.38 ppm (s, 1H); ¹³C NMR ([D₆]DMSO, 25°C): δ = 53.2, 57.1 (CH₂), 58.7 (CH₂), 73.1, 73.6, 78.7, 89.0, 119.9 (C), 141.0, 149.7 (C), 152.5, 156.1 (C), 164.0 ppm (C). HRMS (ES⁺), m/z calculated for (M+H)⁺ C₁₃H₁₈N₅O₇S: 388.0927, found: 388.0919.

5'-Deoxy-5'-SO₂-(carboxymethylsulfonyl)adenosine 20: A suspension of compound 19 (0.1 g, 0.26 mmol) and trimethyltinhydroxide (TMTOH) (0.2 g, 1.10 mmol) in DCE (10 mL) was heated at 70°C for 8 h. After completion of reaction, volatile matters were evaporated under reduced pressure and the crude mass thus obtained, was purified over silica gel column to obtain the acid 20 [Eluent: 20-50% of MeOH in CHCl₃] (0.05 g, 50%). White hygroscopic solid. ¹H NMR ([D₆]DMSO, 25°C): δ = 3.73-3.82 (m, 3H), 3.86-3.91 (m, 1H), 4.58 (bs, 1H), 5.14-5.15
(bs, 1H), 5.41 (bs, 1H), 6.19 (s, 1H), 7.31 (bs, 2H), 8.16 (s, 1H), 8.31 ppm (s, 1H); \(^{13}\)C NMR ([D6]DMSO, 25°C): \(\delta = 55.1\) (CH\(_2\)), 60.9 (CH\(_2\)), 80.9, 83.7, 84.0, 89.5, 119.5 (C), 140.4, 149.0 (C), 153.2, 156.5 (C), 164.6 ppm (C). HRMS (ES\(^{+}\)), m/z calculated for (M+H)\(^{+}\) C\(_{12}\)H\(_{16}\)N\(_{5}\)O\(_{7}\)S: 374.0770, found: 374.0778.
Proton NMR of compound 2S

$^{13}$C NMR of compound 2S
DEPT 135 NMR of compound 2S
Proton NMR of compound 3

$^{13}$C NMR of compound 3
DEPT 135 NMR of compound 3

HPLC report of compound 3
DEPT 135 NMR of compound 5
DEPT 135 NMR of compound 6
DEPT 135 NMR of compound 7
Proton NMR of compound 8

$^{13}$C NMR of compound 8
DEPT 135 NMR of compound 8
Proton NMR of compound 9

$^{13}$C NMR of compound 9
DEPT 135 NMR of compound 9
Proton NMR of compound 10

$^{13}$C NMR of compound 10
DEPT 135 NMR of compound 10
Proton NMR of compound 11

$^{13}$C NMR of compound 11
DEPT 135 NMR of compound 11
DEPT 135 NMR of compound 12
Proton NMR of compound 13

$^{13}$C NMR of compound 13
DEPT 135 NMR of compound 13
Proton NMR of compound 14

$^{13}$C NMR of compound 14
DEPT 135 NMR of compound 14

HPLC report of compound 14
Proton NMR of compound 16

$^{13}$C NMR of compound 16

S-41
DEPT 135 NMR of compound 16
Proton NMR of compound 17

$^1^3$C NMR of compound 17
DEPT 135 NMR of compound 17
Proton NMR of compound 18

$^{13}$C NMR of compound 18
DEPT 135 NMR of compound 18
Proton NMR of compound 19

$^{13}$C NMR of compound 19
Proton NMR of compound 20

$^1$C NMR of compound 20
DEPT 135 NMR of compound 20
Proton NMR (200 MHz) of UV active fragment

$^{13}$C NMR (50 MHz) of UV active fragment
A comparative proton NMR (in [D6]DMSO, 200 MHz) of (A) UV active fragment and (B) commercially available uracil.
$^1$H NMR (50 MHz) of commercially available uracil

DEPT 135 NMR (50 MHz) of commercially available uracil

S-53
HPLC profiles (Applied gradient: Acetonitrile; flow rate of 1.0 mL/min, λ = 254 nm)

HPLC profiles of UV active fragment

HPLC profiles of uracil

S-54
**HPLC profile of co-injected uracil and UV active fragment**

An overlaid HPLC profile coalescing at the same RT (2.9 min.)
ESI(+) MS of UV active fragment

(M+H)^+ matches with uracil

Proton NMR (in D_2O + HPLC grade acetonitrile as internal standard, 200 MHz) of UV inactive fragment

S-56
From the comparative NMR, MS and overlaid HPLC profile it was confirmed that isolated UV active fragment was uracil which resulted from compound 9 under mentioned hydrolytic conditions other than TMTOH.

**Biophysical experiments:**

**Agarose Gel electrophoresis assay:**

Inhibition of RNase A was assayed qualitatively by the degradation of tRNA in an agarose gel. In this method, 20 μL of RNase A (2.0 μM) was mixed with 20 μL (0.20 mM) of all acidic compounds 3, 7, 10, 14 and 20 to a final volume of 100 μL and the resulting solutions incubated for 3 h. 20 μL aliquots of the incubated mixtures were then mixed with 20 μL of tRNA solution (5.0 mg/mL tRNA, freshly dissolved in RNase free water) and incubated for another 30 min. Then 10 μL of sample buffer (containing 10% glycerol and 0.025% bromophenol blue) was
added to this mixture and 15 µL from each solution was taken and loaded into a 1.1% agarose gel. The gel was run using 0.04 M Tris-Acetic acid-EDTA (TAE) buffer (pH 8.0). The residual tRNA was visualized by ethidium bromide staining under UV light.

![Figure I](image)

**Figure I**: Comparative agarose gel electrophoresis image for the inhibition of RNase A (2.0 µM): (lane1) tRNA; (lane2) tRNA and RNase A; (lanes 3-7) tRNA, RNase A and compounds 7, 3, 20, 10 and 14 respectively (in 0.20 mM concentration).

The relative intensities of residual tRNA appeared under UV light with respect to lane 2 has been detected by KODAK MI software and depicted by corresponding histogram (see Figure 3 in original manuscript).

**Inhibition Kinetics:**

The inhibition of RNase A by compounds 3, 7, 10, 14 and 20 were assessed individually by a spectrophotometric method as described by Anderson and co-workers. The assay was performed in 0.1 M Mes-NaOH buffer, pH 6.0 containing 0.1 M NaCl using 2',3'-cCMP as the substrate. The inhibition constants were calculated from initial velocity data using Lineweaver-Burk plot. For the Lineweaver-Burk plot the reciprocal of initial velocity was plotted against the reciprocal of substrate concentration at a constant inhibitor concentration according to the following equation:

\[
\frac{1}{v} = \frac{K_m}{V_{max}} \left(1 + \frac{[I]}{K_i}\right) \frac{1}{[S]} + \frac{1}{V_{max}} \left(1 + \frac{[I]}{K_i}\right)
\]

Here \(v\) is the initial velocity, \([S]\) the substrate concentration, \([I]\) the inhibitor concentration, \(K_m\) the Michaelis constant, \(K_i\) the inhibition constant, and \(V_{max}\) the maximum velocity. The kinetics
experiments were performed with two fixed inhibitor concentrations and another in absence of inhibitor with varying substrate (2',3'-cCMP) concentrations. The slopes from the double reciprocal plot were again plotted against the corresponding inhibitor concentrations to get inhibition constants ($K_i$).

**Lineweaver-Burk plots:**

**Figure II:** Lineweaver-Burk plots for inhibition of RNase A by 3 of 25.0 (▲), 12.5 (■), 0 (●) µM, 2',3'-cCMP concentrations (0.85-0.52 mM) and RNase A concentration of 10.0 µM.

**Figure III:** Lineweaver-Burk plots for inhibition of RNase A by 7 of 194.0 (▲), 97.0 (■), 0 (●) µM, 2',3'-cCMP concentrations (0.88-0.61 mM) and RNase A concentration 8.1 µM.
Docking studies:

Probable binding conformations of the inhibitors with RNase A were predicted with the aid of molecular docking studies. During this exercise the crystal structure of the protein 1FS3 (PDB entry for RNase A) was downloaded from the Protein Data Bank. Water molecules and other ions present in the crystal structures were subtracted to prepare the protein PDB file for docking. The 3D structures of compounds 3, 7, 10, 14 and 20 were generated in Sybyl6.92 (Tripos Inc., St. Louis, USA) and their energy-minimized conformations obtained using the MMFF94 force field with MMFF94 charges and a gradient of 0.005 kcal/mole and 1000 iterations with all other default parameters. The FlexX software as part of the Sybyl suite was used for docking of the ligands to the protein. The ranking of the generated solutions was performed using a scoring function that estimates the free binding energy ($\Delta G$) of the protein-ligand complex considering various types of molecular interactions as described in Rarey et al. The docked poses were visualized by Pymol.
From the docking pictures, it was evident that carboxymethylsulfonyl modified nucleosides interacted better than the carboxymethylthio analog 7. Compound 3 showed comparable available interactions with 10, 14 and 20. Still, it emerged as weaker inhibitor than 10 and 14 presumably due to lower acidity.

The average distance of 14 from the active site residues was found to be less compared to other carboxymethylthio and carboxymethylsulfonyl derivatives such as 7, 10 and 20. Moreover, a comparative docking study between inhibitor 10 and 14 (See Table VI) indicates notable increment in H-bonding interactions of later with enzyme active site. Much better and more effective interactions with nucleobase as well as with the carboxy group of 14 than 10 is observed here. Hence, significant lowering in $K_i$ value is achieved when the nucleobase of pyrimidine nucleoside is altered from uracil to cytosine.

On the other hand, the purine base of a nucleoside should be ideally recognized by the B$_2$ subsite of the active site of RNase A. Here, the docking study revealed that purine nucleobase of 20 was inclined exclusively towards subsite B$_1$ instead of B$_2$. As a result, the nucleobase recognition is poor for 20 (see Table V). The reason behind the higher $K_i$ value of 20 thus can be explained. If the purine nucleobase were in close proximity of the B$_2$ subsite, $K_i$ value for compound 20 might be low.

Docked poses and the distances between inhibitor to the enzyme active site after docking studies have been depicted and tabulated below.
**Figure V:** Stereoview of the docked pose of 3 with RNase A (1FS3).

**Table I:** Hydrogen bonding distance (Å) of compound 3 with amino acid residues of RNase A (1FS3)

<table>
<thead>
<tr>
<th>Residue</th>
<th>Distance</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val43 (C=O of amide)</td>
<td>3.30 [N3]</td>
<td></td>
</tr>
<tr>
<td>Lys 41 Nζ</td>
<td>3.10</td>
<td>[5′-Amide NH], 2.90 [O sugar ring]</td>
</tr>
<tr>
<td>His119 Nδ1</td>
<td>1.80</td>
<td>[3′-OH]</td>
</tr>
<tr>
<td>Gln11 Nε2</td>
<td>2.80</td>
<td>[5′-Amide NH], 3.40 [NH₂ of aspartic acid]</td>
</tr>
<tr>
<td>Arg39 NH1</td>
<td>2.6</td>
<td>[C=O of aspartyl β-COOH group]</td>
</tr>
<tr>
<td>Arg39 NH2</td>
<td>2.6</td>
<td>[C=O of aspartyl β-COOH group]</td>
</tr>
<tr>
<td>Lys7 Nζ</td>
<td>2.98</td>
<td>[amide C=O of aspartic acid]</td>
</tr>
</tbody>
</table>
Figure VI: Stereoview of the docked pose of 7 with RNase A (1FS3).

Table II: Hydrogen bonding distance (Å) of compound 7 with amino acid residues of RNase A (1FS3)

<table>
<thead>
<tr>
<th>1FS3</th>
<th>Compound 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lys1  Nζ</td>
<td>2.86 [O Acid]</td>
</tr>
<tr>
<td>Lys7  Nζ</td>
<td>2.68 [O Acid], 3.16 [Sugar ring]</td>
</tr>
<tr>
<td>His12 Ne2</td>
<td>3.30 [O2], 3.09 [N2]</td>
</tr>
<tr>
<td>Lys41 Nζ</td>
<td>2.52 [O4]</td>
</tr>
</tbody>
</table>
**Figure VII:** Stereoview of the docked pose of 10 with RNase A (1FS3).

**Table III:** Hydrogen bonding distance (Å) of compound 10 with amino acid residues of RNase A (1FS3)

<table>
<thead>
<tr>
<th></th>
<th>1FS3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lys7 Nζ</td>
<td>2.70 [OH of acid]</td>
</tr>
<tr>
<td>Lys 41 Nζ</td>
<td>3.21 [O2], 3.13 [O sugar ring]</td>
</tr>
<tr>
<td>His12 Ne2</td>
<td>2.67 [O2 of 5′-SO₂ group]</td>
</tr>
<tr>
<td>Gln11 Ne2</td>
<td>2.85 [O1 of 5′-SO₂ group], 3.23 [OH of acid]</td>
</tr>
<tr>
<td>Phe120 amide NH</td>
<td>3.32 [O2 of 5′-SO₂ group]</td>
</tr>
<tr>
<td>Val43 amide C=O</td>
<td>2.75 [2′-OH], 2.23 [O2]</td>
</tr>
<tr>
<td>Arg39 Nη1</td>
<td>3.09 [N3]</td>
</tr>
</tbody>
</table>
Figure VIII: Stereoview of the docked pose of 14 with RNase A (1FS3).

Table IV: Hydrogen bonding distances (Å) of compound 14 with amino acid residues of RNase A (1FS3)

<table>
<thead>
<tr>
<th></th>
<th>1FS3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lys7 Nζ</td>
<td>2.85 [OH of acid ]</td>
</tr>
<tr>
<td>His12 Nε2</td>
<td>2.73 [O1 of 5′-SO₂ group]</td>
</tr>
<tr>
<td>Arg39 Nη1</td>
<td>3.7 [N3 ]</td>
</tr>
<tr>
<td>Arg39 Nη2</td>
<td>3.19 [N3]</td>
</tr>
<tr>
<td></td>
<td>3.18 [NH₂ of nucleobase]</td>
</tr>
<tr>
<td>Lys41 Nζ</td>
<td>3.34 [N1]</td>
</tr>
<tr>
<td></td>
<td>3.84 [O2]</td>
</tr>
<tr>
<td>Gln11 Nε2</td>
<td>2.52 [O2 of 5′-SO₂ group]</td>
</tr>
<tr>
<td></td>
<td>3.8 [C=O of acid ]</td>
</tr>
<tr>
<td>Phe120 amide NH</td>
<td>3.24 [O1 of 5′-SO₂ group]</td>
</tr>
<tr>
<td>Val43 amide C=O</td>
<td>2.55 [C=O of acid ]</td>
</tr>
<tr>
<td>Val118 amide C=O</td>
<td>2.50 [OH of acid ]</td>
</tr>
</tbody>
</table>
Figure IX: Stereoview of the docked pose of 20 with RNase A (1FS3)

Table V: Hydrogen bonding distance (Å) of compound 20 with amino acid residues of RNase A (1FS3)

<table>
<thead>
<tr>
<th>IFS3</th>
<th>Bonding Distance</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lys7 Nζ</td>
<td>3.30</td>
<td>[O1 of 5'-SO₂ group]</td>
</tr>
<tr>
<td>His12 Nε2</td>
<td>3.70</td>
<td>[O2 of 5'-SO₂ group]</td>
</tr>
<tr>
<td>His119 Nδ1</td>
<td>2.60</td>
<td>[CO of acid group]</td>
</tr>
<tr>
<td>His119 Nδ1</td>
<td>3.80</td>
<td>[OH of acid group]</td>
</tr>
<tr>
<td>Phe120 amide NH</td>
<td>3.00</td>
<td>[OH of acid group]</td>
</tr>
<tr>
<td>Lys41 Nζ</td>
<td>3.30</td>
<td>[2'-OH]</td>
</tr>
<tr>
<td>Thr 45 Oγ1</td>
<td>2.30</td>
<td>[N6-adenine]</td>
</tr>
<tr>
<td>Gln11 Nε2</td>
<td>3.00</td>
<td>[O1 of 5'-SO₂ group]</td>
</tr>
<tr>
<td>Gln11 Oε1</td>
<td>3.20</td>
<td>[O1 of 5'-SO₂ group]</td>
</tr>
</tbody>
</table>
**Table VI:** Comparative hydrogen bonding distances (Å) between compound 14 and 10 with amino acid residues of RNase A (1FS3)

<table>
<thead>
<tr>
<th>1FS3</th>
<th><img src="image" alt="Compounds" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lys7 Nζ</td>
<td>2.85 [OH of acid]</td>
</tr>
<tr>
<td>His12 Nε2</td>
<td>2.73 [O1 of 5′-SO₂ group]</td>
</tr>
<tr>
<td>Arg39 Nη1</td>
<td>3.7 [N3]</td>
</tr>
<tr>
<td>Arg39 Nη2</td>
<td>3.19 [N3] 3.18 [NH₂ of nucleobase]</td>
</tr>
<tr>
<td>Gln11 Nε2</td>
<td>2.52 [O2 of 5′-SO₂ group] 3.8 [C=O of acid]</td>
</tr>
<tr>
<td>Phe120 amide NH</td>
<td>3.24 [O1 of 5′-SO₂ group]</td>
</tr>
<tr>
<td>Val43 amide C=O</td>
<td>2.55 [C=O of acid]</td>
</tr>
<tr>
<td>Val118 amide C=O</td>
<td>2.50 [OH of acid]</td>
</tr>
</tbody>
</table>
References and notes:


