



Synthesis and Impurity Research of 2-Thioadenosine Monohydrate

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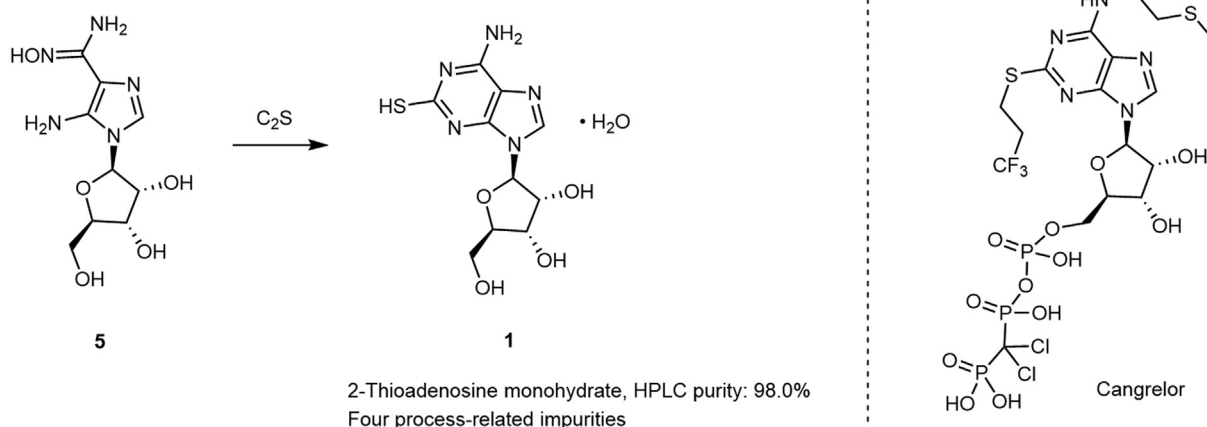
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Abstract

2-Thioadenosine monohydrate (1) is a vital intermediate in the synthesis of cangrelor. However, its industrial-scale preparation process and the analysis of the impurities formed during this process remained largely unknown. Herein, cangrelor was synthesized from oxidate adenosine, and the key step involved in the synthesis of compound 1 from intermediate 5. The effects of key synthesis parameters that influenced the reaction, including reaction temperature and time, were discussed. Moreover, four process-related impurities were purified, synthesized, and identified via nuclear magnetic resonance spectroscopy and high-resolution mass spectrometry. The process can be utilized to produce 1 on a kilogram scale, with a high-performance liquid chromatography purity of 98.0%. The study sheds light on and helps drug manufacturers further understand the formation process of impurities in the preparation of cangrelor.

Keywords

- ▶ cangrelor
- ▶ 2-thioadenosine monohydrate
- ▶ a kilogram scale
- ▶ impurities

[#] These authors contributed equally to this work.

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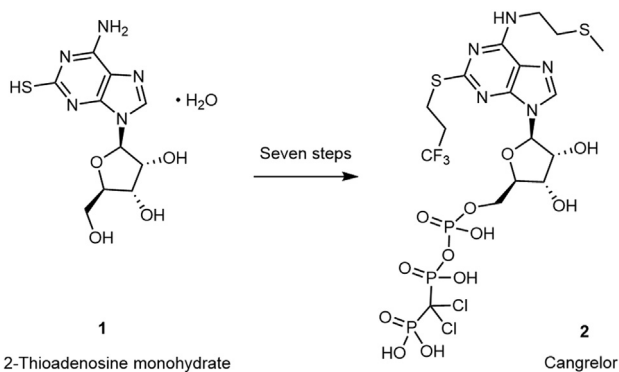
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Introduction

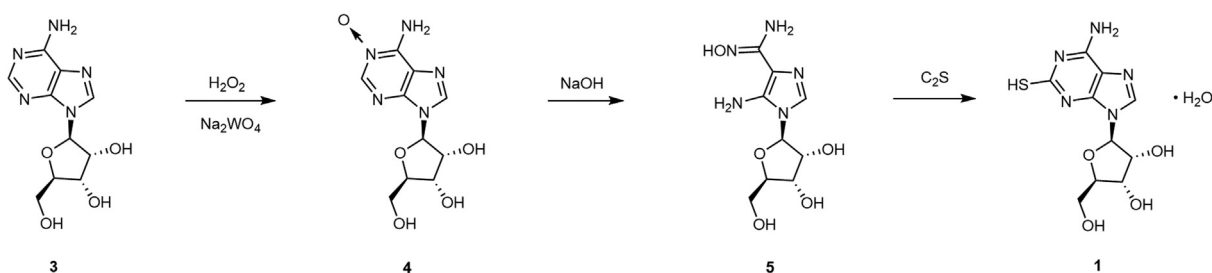
Platelets play a critical role in hemostasis and its pathophysiology. However, numerous common pathologies or interventions result in undesired platelet activation, which may lead to excessive platelet aggregation and the generation of occlusive thrombi. Therapeutics that control platelet reactivity are widely used in clinical practice, and the development of new drugs with similar effects is of high research interest in the pharmaceutical industry. Currently approved drugs such as clopidogrel, prasugrel, ticagrelor, and cangrelor are platelet adenosine diphosphate (ADP) receptor antagonists that target the platelet P2Y12 receptor.

Cangrelor is the primary ingredient of an antiplatelet drug produced by The Medicines Company, and it was approved by the Food and Drug Administration in June 2016. It is an inhibitor of ADP receptor P2Y12 and can reduce platelet aggregation by restricting adenylyl cyclase activity.¹ It is designated for percutaneous arterial intervention and arterial syndrome to prevent thrombosis. During its synthesis, 2-thioadenosine monohydrate (**1**) is an important intermediate,^{2,3} which can be used to obtain cangrelor in seven steps (**→Scheme 1**).⁴ Thus, investigating a practical and scalable process for manufacturing **1** and understanding the formation of its impurities are essential for the industrial production and quality control of the drug cangrelor.

After a preliminary study, compound **1** was obtained from oxidate adenosine (**3**), a commercially available material. The synthetic route is described in **→Scheme 2**. First, the reaction of **3** with hydrogen peroxide produced **4**,^{5,6} which was hydrolyzed and ring-opened using a sodium hydroxide solution to acquire **5**. Compound **5** was further reacted with carbon disulfide to



Scheme 1 Structure of 2-thioadenosine monohydrate (**1**) and cangrelor (**2**).



Scheme 2 Synthesis route of compound **1**.

achieve ring closure and obtain the target product (**1**). The route endowed product **1** with a purity of 98.0% and a final yield of 46.4%. Each impurity was less than 0.30%. **1** was presented as a monohydrate, which was confirmed via thermogravimetric analysis (TGA).

During this process, we detected four process-related impurities, which considerably impact the separation and purification processes as well as the quality of the product. Additionally, according to the guidelines on impurities in drug substances published by the International Conference on Harmonization, it is essential to isolate these impurities in their pure form for analytical method development. In the study, they were prepared, separated, purified, and identified. The study provided valuable insights into impurity formation during the preparation of compound **1** and cangrelor.

Results and Discussion

During the laboratory optimization of **1**, we identified several process-related impurities. None of these impurities are commercially available; thus, no preparation methods have been reported.⁷⁻⁹ In this study, four process-related impurities, **6**, **7**, **8**, and **9**, were identified, synthesized, and characterized. Moreover, the key parameters that influenced their formation were also investigated. In addition, the causes of impurity formation were also discussed.

Impurities Structure

The molecular weights of **6**, **7**, **8**, and **9** were identified via high-resolution mass spectrometry (HRMS) and characterized via high-performance liquid chromatography (HPLC; **→Fig. 1**). Based on the spectral data, these impurities were identified as the compounds shown in **→Scheme 3**. The impurities can be effectively removed via recrystallization in the postprocessing step of **1**.

Impurities Source and Reaction Conditions Optimization

Compound **5** reacted with excess carbon disulfide in water and methanol at 100°C to produce **1**. The impurities formed in the process were illustrated in **→Scheme 4**. Under high pressure, the hydroxylamine of compound **5** reduces to amidine to give **6**. Moreover, due to excess carbon disulfide, the amino group of compound **1** was substituted with the sulfhydryl group to generate the bis-mercapto impurity **7**.

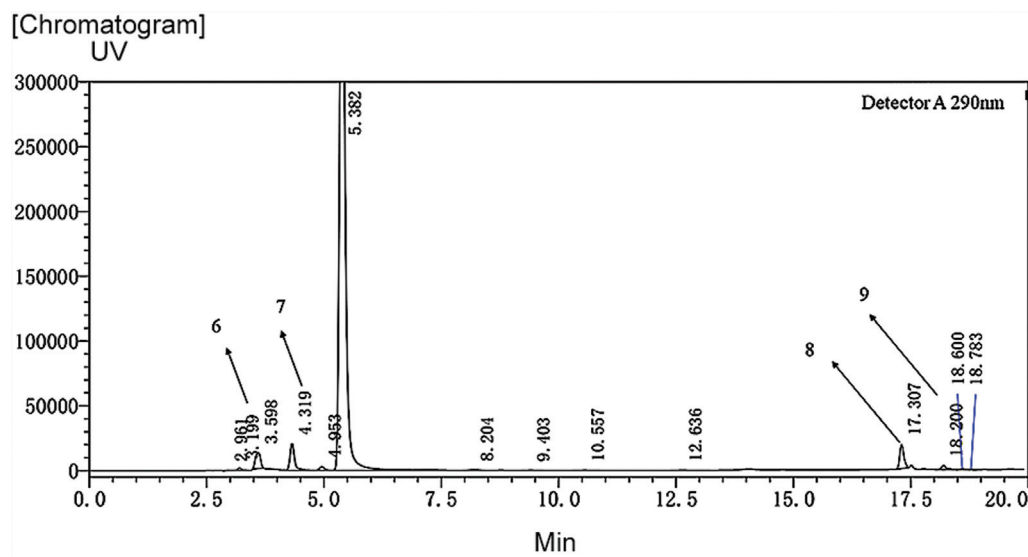
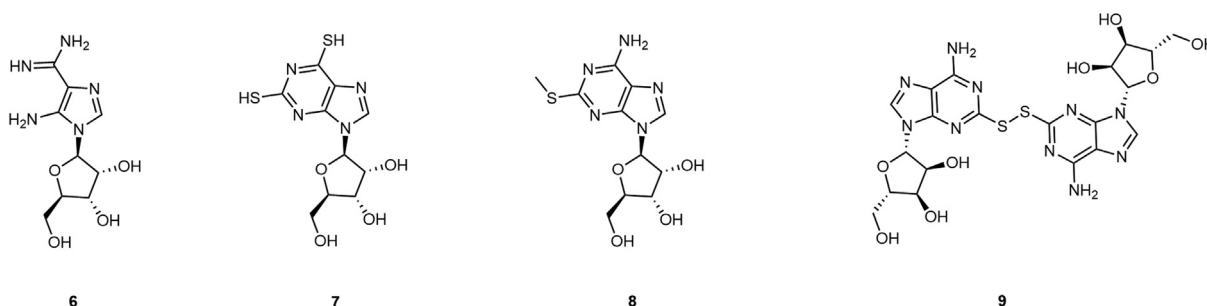


Fig. 1 High-performance liquid chromatography chromatogram of process-related impurities and 2-thioadenosine monohydrate (1).



Scheme 3 Structures of process-related impurities of 6, 7, 8, and 9.

Under high pressure, the sulfhydryl group of compound **1** reacted with methanol to form **8**.^{10,11} Both the structures of **1** and cangrelor contain the sulfur element. Sulfur, as an oxygen group element, exhibits both oxidizability and reducibility owing to its unique outer six electrons. Compounds that contain sulfur often exhibit various biological activities.^{12–16} Bimolecular of compound **1** underwent oxidative coupling under high pressure to produce impurity **9**, which was consistent with the reported study.^{17,18}

The reaction temperature and time had a considerable impact on the generation of **6**, **7**, **8**, and **9**. When the reaction temperature was 120°C, the contents of **6**, **7**, **8**, and **9** in the reaction solution were 2.00, 3.13, 2.52, and 0.61%, respectively (►Table 1, entry 1). However, when the temperature was reduced to 100°C, the contents of **6**, **7**, **8**, and **9** decreased to 0.63, 0.53, 0.20, and 0.13%, respectively (►Table 1, entry 3). Additionally, extending the reaction time reduced the purity of **1** in the reaction mixture (►Table 1, entry 4). Nevertheless, recrystallization reduces the content of each impurity to less than 0.30% in the target product.

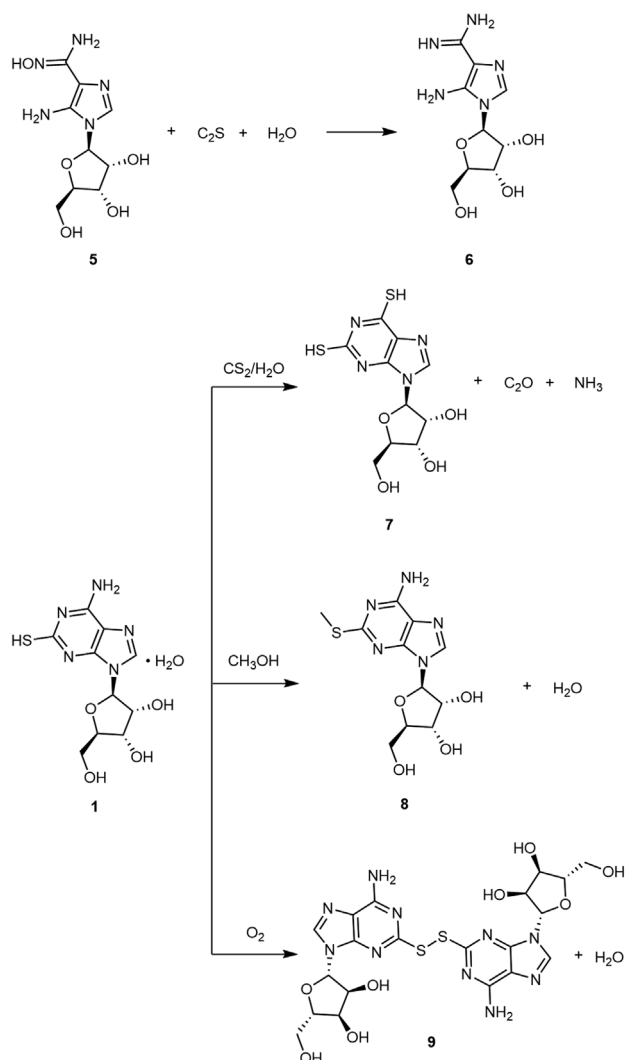
In this study, we developed a new liquid chromatography–mass spectrometry (LC–MS) method, which was used to investigate the formation of impurities (►Fig. 2).

Preparation and Characterization of Impurities

Impurity 6: The mother liquor was obtained via a degradation experiment; consequently, **6** was prepared via the preparative liquid phase. The HRMS of **6** exhibited a molecular ion peak at $m/z = 258.1322$ $[M + H]^+$ (calculated mass: 257.1124) in the positive-ion mode, which was the same as the predicted molecular formula of $C_9H_{15}N_5O_4$. Moreover, the HPLC purity of **6** was approximately 95%. We speculated that the impurity formation was caused by the reduction of intermediate **4**. Based on the spectral data (HRMS, ¹H nuclear magnetic resonance [NMR], and ¹³C NMR), we confirmed the structure of **6**.

Impurity 7: The preparation method was the same as that used for **6**. The HRMS of **7** showed a molecular ion peak at $m/z = 339.0188$ $[M + Na]^+$ (calculated mass: 316.0300) in the positive-ion mode, which was consistent with the predicted molecular formula of $C_{10}H_{12}N_4O_4S_2$. The purity of **7** reached only 86%.

Impurity 8: 2-Thioadenosine reacted with dimethyl sulfate and sodium hydroxide solution, and **8** was obtained after postprocessing and purification. HRMS revealed a molecular ion peak at $m/z = 314.1049$ $[M + H]^+$ (calculated mass: 313.0485) in the positive-ion mode, corresponding to the predicted molecular formula of $C_{11}H_{15}N_5O_4S$. **8** was prepared with a purity of 96%.



Scheme 4 Source of impurities 6, 7, 8, and 9.

Impurity 9: Compound **9** was synthesized by reacting 2-thioadenosine with iodine using methanol as the solvent. The compound had an HRMS molecular ion peak at $m/z = 597.1351$ [$M + Na$]⁺ (calculated mass: 596.1220) in the positive-ion mode, which matched the predicted molecular formula of C₂₀H₂₄N₁₀O₈S₂. A sample of **9** with a purity of approximately 96% was prepared, and its structure was confirmed via NMR spectroscopy.

The detailed identification of the impurities can be verified by HRMS, ¹H NMR, ¹³C NMR, and infrared (IR) spectroscopy (in Experimental Section). This study complies with regulatory norms and is therefore valuable in the quality assessment of **1**.

Conclusion

In this study, we developed a synthetic production process for **1** with remarkable industrialization potential and identified the effects of several key synthesis parameters. Four process-related impurities generated during the preparation of **1** were purified and synthesized and then identified and characterized via HRMS, ¹H NMR, ¹³C NMR, and IR spectroscopy.

The optimized process for synthesizing **1** achieved its kilogram-scale production with an HPLC purity of 98.0%. As this work conforms to regulatory protocols, it provides an effective quality assessment of **1**.

Experimental Section

General Methods

All solvents and reagents were obtained from commercial sources and used without further purification. Moreover, NMR spectra were recorded on an Avance III 600 MHz spectrometer (Bruker, Karlsruhe, Germany). The solvent used for NMR spectroscopy was dimethyl sulfoxide-*d*₆ (DMSO-*d*₆) with tetramethylsilane as the internal reference. HRMS spectra were recorded on a Bruker Maxis 4G. TGA was performed on a TA Instruments TGA Q500 analyzer at a heating rate of 10°C/min in a nitrogen atmosphere. Additionally, the chemical purity was determined using HPLC on a Shimadzu chromatography system with a ultraviolet detector. The diluents for **1**, **6**, **7**, **8**, and **9** were as follows: (A) 0.01 mol/L Na₂HPO₄ in water, adjusted to pH 6.0 with phosphoric acid and (B) methanol; column: ODS-SP (Super C18, 4.6 mm × 250 mm, 5.0 μm); temperature: 40°C; flow rate: 1.0 mL/min and 290 nm. Procedure: The reference solution was injected into the chromatographic system consecutively three times. Then, the sample was inserted into the chromatographic system twice. Finally, the chromatograms were recorded, and the response for the major peak was measured. The relative standard deviation of the peak area for replicate injections of the reference solution must not be more than 2.0%. The assay of 2-thioadenosine was calculated compared with that of the reference solution. LC-MS was conducted using an Agilent LC-MS system consisting of Agilent 1260 LC equipped with a single quadrupole mass detector and electrospray ionization interface (Agilent Technologies, Santa Clara, California, United States). Melting points (mp) were determined on a WRS-1B (Shanghai YiCe Apparatus & Equipment Co., Ltd) device and used without correction. IR spectra were recorded using IR Tracer-100 (Shimadzu).

Preparation of (E)-5-Amino-1-((2S,3R,4S,5R)-3,4-Dihydroxy-5-(Hydroxymethyl)Tetrahydrofuran-2-yl)-N'-Hydroxy-1H-Imidazole-4-Carboximidamide (Compound 5)

A mixture of adenosine (**3**; 64.3 kg and 240.6 mol), water (144.0 kg), and sodium tungstate (5.28 kg and 23.4 mol) was stirred at 40 to 50°C. Hydrogen peroxide solution (30%, 227.1 kg, and 2,003.2 mol) was dripped into the continuously stirred mixture at a temperature below 60°C; then, the reaction temperature was maintained at 55 to 60°C for 6 to 7 hours. The reaction was monitored using HPLC and deemed to be completed when the composition of **3** was less than 1.5%. The reaction mixture was slowly cooled to 20 to 25°C and stirred for another 2 hours. The resulting mixture was filtered and washed with water (50 kg) to yield a wet solid (intermediate **4**). Next, another mixture of water (110.4 kg) and sodium hydroxide (34.8 kg and 870.0 mol) was stirred at 40 to 50°C; consequently, intermediate **4** was added in several batches. The reaction mixture was stirred at

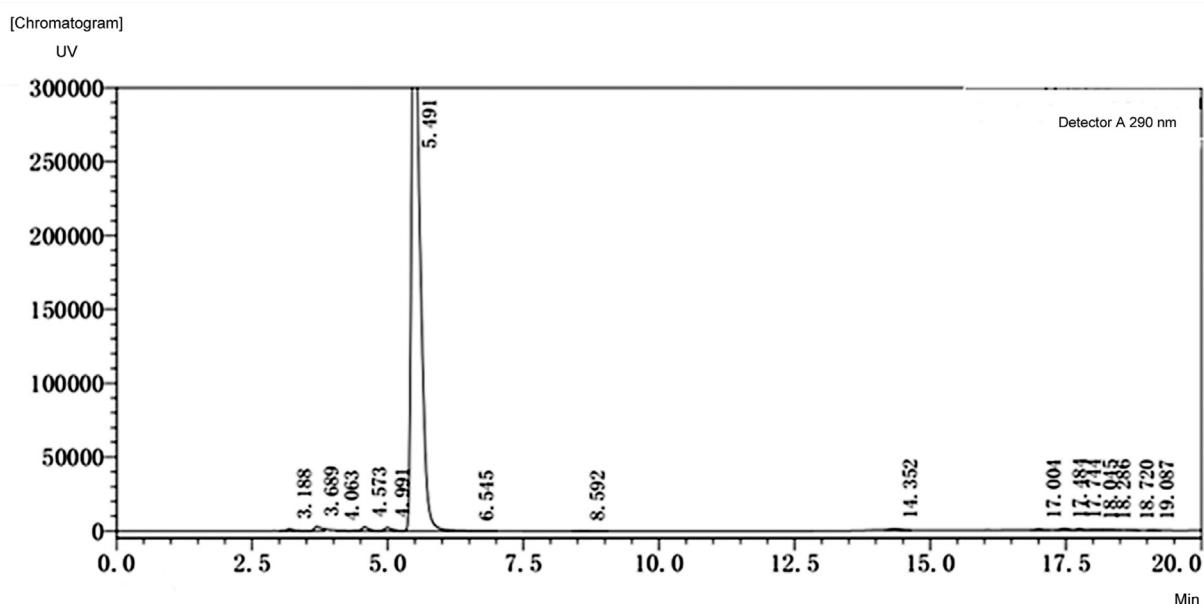
Table 1 Reaction conditions optimization of generating compound 1 from 5

Entry ^a	Temperature (°C)	Time (h)	HPLC (%) ^b				
			1	6	7	8	9
1	120	3	90.60	2.00	3.13	2.52	0.61
2	110	3	95.90	1.04	1.83	0.59	0.11
3	100	3	97.12	0.63	0.53	0.20	0.13
4	100	5	95.60	1.04	1.83	0.57	0.12

Abbreviation: HPLC, high-performance liquid chromatography.

^aRaw ratio of compound 5: water: CH₃OH: CS₂ = 1: 4.3: 13.3: 8.6; 1.2–1.9 MPa.

^bArea percentage according to HPLC of the reaction mixture.



Iteration Results
Detector A 290 nm

Peak name	Retention time (min)	Area (mAu * min)	Relative area (%)
1	3.188	10124	0.230
2	3.689	27612	0.626
3	4.063	3092	0.070
4	4.573	23331	0.529
5	4.991	21142	0.479
6	5.491	4284148	97.123
7	6.545	1602	0.036
8	8.592	2685	0.061
9	14.352	8878	0.201
10	17.004	4300	0.097
11	17.484	8811	0.200
12	17.744	5593	0.127
13	18.045	3342	0.076
14	18.286	3321	0.075
15	18.720	1144	0.026
16	19.087	1939	0.044
Total		4411065	100.000

→ 6

→ 7

→ 8

→ 9

Fig. 2 Typical spectrum of the crude product of compound 1 using liquid chromatography–mass spectrometry. The retention time of 1 was 5.41 minutes.

75 to 80°C for 3 to 4 hours. Again, we monitored the reaction with HPLC until it indicated that the content of 4 was less than 1.0%. After the reaction was complete, the reaction mixture was cooled to 20 to 25°C. Subsequently, 15% hydrochloric acid was added to

adjust the pH of the reaction mixture to pH 8 to 10. The resulting mixture was filtered and washed with methanol (25 kg); then, the filtrate was then concentrated to dryness and used directly in the following step.

Preparation of 2-Thioadenosine Monohydrate (Compound 1)

A 1,000 L autoclave was charged with water (120 kg), methanol (370 kg), intermediate **5** (27.87 kg, 102.0 mol, converted), and carbon disulfide (240 kg) under a nitrogen atmosphere. The reaction mixture was heated in the autoclave at 100 to 105°C for 3 hours at a pressure of approximately 1.2 to 1.9 MPa. HPLC was used to monitor the reaction, which proceeded to the next phase when the content of intermediate **5** fell below 1.0%. After the reaction mixture was cooled to 20 to 25°C, the layers were separated. Approximately 120 to 150 kg of carbon disulfide was extracted from the lower layer and concentrated to remove the remaining feed liquid. Next, the reaction mixture was cooled to 0 to 5°C and stirred for 1 hour, and a crude yellow solid was isolated via filtration. The crude product was recrystallized with ammonia/*n*-butanol/hydrochloric acid to obtain **1** as a yellow solid (24.73 kg; 81% yield; 98.0% HPLC purity; mp: 197.4°C, decomposition, lit. mp: 196–199°C). ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.64 (s, 1H), 8.55 (s, 1H), 5.89 (d, *J* = 5.5 Hz, 1H), 5.61 (d, *J* = 6.0 Hz, 1H), 5.27 (d, *J* = 5.1 Hz, 1H), 5.09 (t, *J* = 5.5 Hz, 1H), 4.54 (q, *J* = 5.3 Hz, 1H), 4.16 (q, *J* = 4.5 Hz, 1H), 3.96 (q, *J* = 4.0 Hz, 1H), 3.67 (dt, *J* = 12.0, 4.6 Hz, 1H), 3.56 (ddd, *J* = 12.0, 5.6, 4.0 Hz, 1H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 174.2, 152.5, 150.1, 140.2, 113.1, 87.5, 86.2, 74.1, 70.9, 61.9. HRMS (*m/z*): calcd. for C₁₀H₁₄N₅O₄S⁺ [M + H]⁺ 300.0688; found: 300.0786. *Anal.* calcd. for C₁₀H₁₅N₅O₅S: C, 37.85; H, 4.76; N, 22.07; S, 10.10; found: C, 36.94; H, 4.74; N, 21.86; S, 9.86. The loss upon drying was 1.26% (water).

Preparation of 5-Amino-1-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(Hydroxymethyl)Tetrahydrofuran-2-yl)-1*H*-Imidazole-4-Carboximidamide (Compound 6)

The synthesis of compound **6** was performed according to Fujii et al's method.⁷ The reaction mixture was obtained via the degradation experiment of **1**. We used HPLC to monitor the reaction; then, the mixture was filtered after the completion of the reaction. The solvent was removed from the organic layer and then extracted using dichloromethane (DCM). Preparative chromatography was then used to concentrate and purify the solvent. Finally, we obtained an analytical sample of impurity **6**, which appeared as a yellow solid (100 mg; 95.0% HPLC purity; amorph, no mp, lit. mp: 174–175°C). ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.25–7.91 (m, 3H), 7.47 (s, 1H), 6.76 (s, 1H), 5.48 (d, *J* = 6.4 Hz, 1H), 4.13 (t, *J* = 5.9 Hz, 1H), 3.91 (t, *J* = 4.0 Hz, 1H), 3.79 (d, *J* = 3.2 Hz, 1H), 3.52 (s, 2H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 157.9, 143.6, 132.0, 106.9, 87.7, 85.8, 72.9, 70.2, 61.0. HRMS (*m/z*): calcd. for C₉H₁₆N₅O₄⁺ [M + H]⁺ 258.1124; found: 258.1322. *Anal.* calcd. for C₉H₁₆N₅O₄: C, 42.04; H, 5.88; N, 27.22; found: C, 41.91; H, 5.89; N, 27.12. IR (cm⁻¹): 2945, 1716, 1240.

Preparation of (2*R*,3*R*,4*S*,5*R*)-2-(2,6-Dimercapto-9*H*-Purin-9-yl)-5-(Hydroxymethyl)Tetrahydrofuran-3,4-Diol (Compound 7)

The synthesis of compound **7** was performed according to Marumoto et al's method.⁸ The reaction mixture was

obtained via the degradation of compound **1**. HPLC was used to monitor the reaction, and the reaction mixture was filtered when the reaction was finished. Next, the solvent was removed from the organic layer and then extracted using DCM. The solvent was concentrated and purified via preparative chromatography to produce an analytical yellow solid sample of impurity **7** (100 mg; 86.0% HPLC purity; amorph, no mp, lit. mp: 240°C). ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.74 (s, 1H), 8.34 (s, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.34 (s, 1H), 5.87 (d, *J* = 6.3 Hz, 1H), 5.69 (d, *J* = 6.1 Hz, 1H), 4.61 (t, *J* = 5.6 Hz, 1H), 4.14 (dd, *J* = 5.0, 3.0 Hz, 1H), 3.96 (q, *J* = 3.5 Hz, 1H), 3.67 (dd, *J* = 12.2, 3.7 Hz, 1H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 156.1, 152.3, 148.9, 139.8, 129.4, 87.8, 85.8, 73.3, 70.5, 61.6. HRMS (*m/z*): calcd. for C₁₀H₁₂N₄O₄S₂Na⁺ [M + Na]⁺ 339.0300; found: 339.0188.

Preparation of (2*R*,3*R*,4*S*,5*R*)-2-(6-Amino-2-(Methylthio)-9*H*-Purin-9-yl)-5-(Hydroxymethyl)Tetrahydrofuran-3,4-Diol Monohydrate (Compound 8)

First, NaOH (1.14 g and 28.50 mmol) was added to a solution of **1** (5.00 g and 15.77 mmol) in 35 mL *N,N*-dimethylformamide (DMF) and stirred at room temperature for 0.5 hours. Next, dimethyl sulfate (2.33 g and 18.47 mmol) was added dropwise, and the mixture was stirred for 5.5 hours. Consequently, additional dimethyl sulfate (1.60 g and 12.68 mmol) was added, followed by stirring for 20 hours. Subsequently, NaOH (1.14 g and 28.50 mmol) was added, and the mixture was stirred for 1.5 hours. In the reaction mixture, the purity of **8** was 47%. The mixture was cooled to below 10°C, then 45 mL of water was added dropwise, and it was stirred for 10 minutes. After the precipitates were filtered and the filter cake was dissolved in 20 mL DMF, 0.20 g triethyl phosphite and 0.20 g sodium dithionite were added. Next, 24 mL of water was added dropwise at a temperature below 10°C and the slurry was stirred for 0.5 hours. The precipitates were isolated via filtration to obtain a solid (2.25 g; 98.1% HPLC purity; mp: 174.0–77.6°C, lit. mp: 225.0–228.5°C, anhydrous).⁸ ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.23 (s, 1H), 7.36 (s, 2H), 5.83 (d, *J* = 6.0 Hz, 1H), 5.42 (d, *J* = 6.2 Hz, 1H), 5.18 (d, *J* = 4.8 Hz, 1H), 5.01 (t, *J* = 5.6 Hz, 1H), 4.62 (q, *J* = 5.9 Hz, 1H), 4.15 (q, *J* = 4.8 Hz, 1H), 3.92 (q, *J* = 4.1 Hz, 1H), 3.64 (dt, *J* = 11.7, 4.8 Hz, 1H), 3.59 to 3.48 (m, 1H), 2.47 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 164.3, 155.6, 150.3, 138.9, 117.0, 87.4, 85.5, 73.4, 70.7, 61.7, 13.8. HRMS (*m/z*): calcd. for C₁₁H₁₆N₅O₄S⁺ [M + H]⁺: 314.0485; found: 314.1049. *Anal.* calcd. for C₁₁H₁₅N₅O₄S: C, 39.87; H, 5.17; N, 21.14; S, 9.68; found: C, 40.03; H, 4.84; N, 21.46; S, 9.62. IR (cm⁻¹): 3342, 1643, 1049. According to the TGA analysis, the weight loss of **8** was 3.41% at approximately 180°C.

Preparation of (2*S*,2'*S*,3*R*,3'*R*,4*S*,4'*S*,5*S*,5'*S*)-5,5'-(Disulfanediy)bis(6-Amino-9*H*-Purine-2,9-Diyl)Bis(2-(Hydroxymethyl)Tetrahydrofuran-3,4-Diol) (Compound 9)

Iodine particles (0.96 g and 3.78 mmol) were added to a solution of **1** (2.50 g and 7.88 mmol) in 10 mL of methanol, and the mixture was stirred at 15 to 20°C for 7 hours. The precipitates were filtered and washed with 3 mL of

methanol to obtain a filter cake with a purity of 88.69%. The product was recrystallized with DMF and water and then washed with methanol to obtain a solid (1.48 g, 93.6% HPLC purity; mp: 237.2°C, decomposition, lit. mp: 235°C, decomposition, anhydrous).⁸ ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.27 (s, 2H), 7.53 (s, 4H), 5.81 (d, *J* = 6.0 Hz, 2H), 5.41 (d, *J* = 6.2 Hz, 2H), 5.14 (d, *J* = 4.8 Hz, 2H), 4.93 (t, *J* = 5.5 Hz, 2H), 4.55 (q, *J* = 5.8 Hz, 2H), 4.11 (q, *J* = 4.5 Hz, 2H), 3.89 (q, *J* = 4.1 Hz, 2H), 3.60 (dt, *J* = 11.4, 4.5 Hz, 2H), 3.48 (dt, *J* = 11.4, 4.8 Hz, 2H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 161.4, 155.8, 150.3, 139.2, 117.7, 87.0, 85.6, 73.4, 70.5, 61.6. HRMS (*m/z*): calcd. for C₂₀H₂₅N₁₀O₈S₂⁺ [M + H]⁺ 597.1220; found: 597.1351. *Anal.* calcd. for C₂₀H₂₄N₁₀O₈S₂: C, 37.97; H, 4.46; N, 22.14; S, 10.14; found: C, 38.18; H, 4.38; N, 22.00; S, 9.97. IR (cm⁻¹): 3385, 1654, 1321. The TGA test revealed that the weight loss of compound **9** was 4.87% at approximately 100°C.

Supplementary Material

The HPLC, HRMS, NMR, TGA, or IR spectroscopy results of **6**, **7**, **8**, **9**, and **4**, as well as spectroscopy results of compound **1**, including HPLC, HRMS, ¹H NMR, ¹³C RMS, DEPT, H-H COSY, HSQC, HMBC, IR, TGA, and COA are presented in the **►Supplementary Figs. S1–S37** (available in online version).

Conflicts of Interest

None declared.

Acknowledgments

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