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EFFICIENT SYNTHESIS OF PURINE DERIVATIVES BY ONE-POT THREE-COMPONENT MANNICH TYPE REACTION

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Abstract - An efficient and facile three-component Mannich-type reaction on purine rings was described. This reaction proceeded smoothly under the catalysis of ethylenediamine at ambient temperature in high regioselectivities with exclusive N9-alkylated products. A wide range of purine derivatives were obtained in high yields.

Mannich-type reaction is one of the most useful reactions in organic synthesis due to the products including β -amino carbonyl motifs which are useful reaction intermediates.¹ Many scientists devoted themselves to these researchs and compounds of kinds of different structures were obtained.² Among them, one-pot three-component Mannich-type reactions which can give a wide range of structural variations have attracted wide attentions, and this structural diversity made the Mannich-type reaction more valuable.³

The discovery and wide application of acyclovir⁴ greatly stimulated the research interest in the synthesis of purine derivatives and searching new antiviral drugs.⁵ Penciclovir, famciclovir, and ganciclovir *et al.* were developed in succession and applied in clinic. There were many routes to obtain purine derivatives. Alkylation,⁶ Michael addition⁷ and Mitsunobu reaction⁸ were commonly used ones. These methods often gave purine derivatives in high yields. However, Mannich-type reaction was less used in the preparation of purine derivatives.⁹

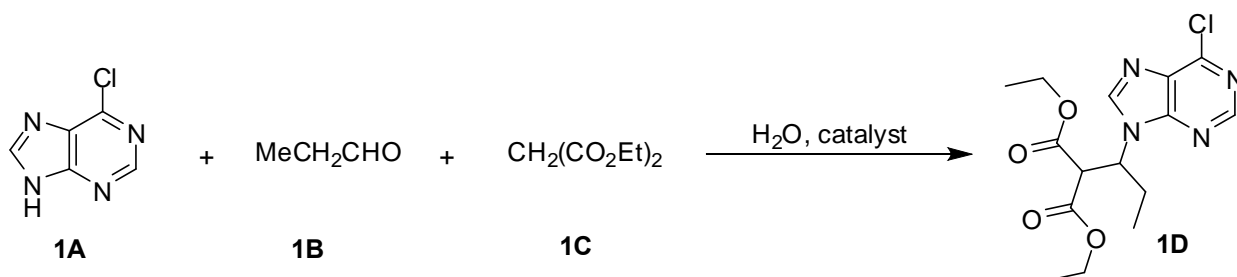
Herein we described the efficient synthesis of purine derivatives through one-pot three-component Mannich-type reactions with ethylenediamine as catalyst. The reaction finished at ambient temperature

(15–20 °C) within 8 h, giving good to excellent isolated yields. The analogues of the products brought about by other kinds of reactions were obtained by two steps or four steps, which made yield low and work tedious.¹⁰

The optimization of reaction conditions was begun with studying the influence of catalysts on the three-component Mannich-type reaction with 6-chloro-9*H*-purine (**1A**), propionaldehyde (**1B**) and diethyl malonate (**1C**) in water at 15 °C. As shown in Table 1, the reaction does not occur without addition of a catalyst (entry 1). Many catalysts, including K₂CO₃, Cs₂CO₃, Na₂HPO₄·12H₂O, AcONa, AcOH and triethylamine (Table 1, entries 2–7) can hardly promote reactions at 15 °C. Further research showed that 50 mol% of ethylenediamine could catalyze reaction smoothly and gave desired product alone in 90% isolated yield (entries 8–15).

Continuously increasing or reducing the amount of ethylenediamine both led to decreased yields (entries 8–15). Temperature also had some effect on the yield of the product. The reaction proceeded successfully at 15–20 °C and gave single product with high isolated yields (entries 13, 16 and 17). Increasing temperature to 50 °C, the isolated yield gradually decreased because of the emergence of by-products (entries 18–20). Further screening of reaction time showed that the reaction can be completed within 8 h (entries 21–24). Therefore, we chose 50 mol% ethylenediamine as catalyst and the reactions were conducted at ambient temperature (15–20 °C) within 8 h.

Table 1. Optimizing conditions for three-component Mannich-type reaction of 6-chloro-9*H*-purine (**1A**), propionaldehyde (**1B**) and diethyl malonate (**1C**).^a



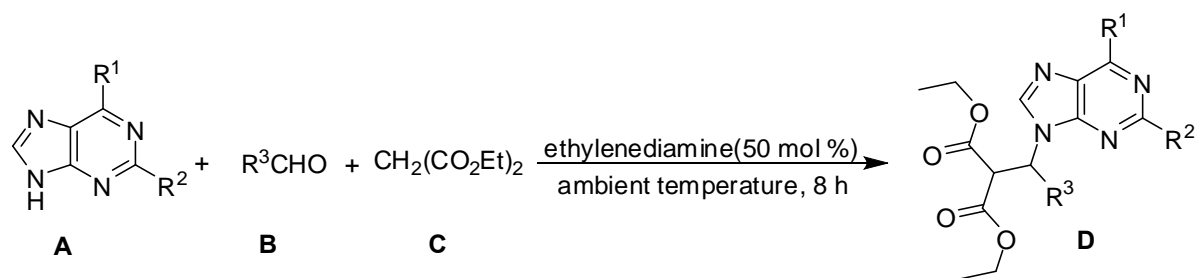
Entry	Solvent	Cat.	T (°C)	T (h)	Yield (%) ^b
1	H ₂ O	--	15	6	NR
2	H ₂ O	K ₂ CO ₃ (1 eq)	15	6	NR
3	H ₂ O	Cs ₂ CO ₃ (1 eq)	15	6	Trace
4	H ₂ O	Na ₂ HPO ₄ ·12H ₂ O (1 eq)	15	6	NR
5	H ₂ O	AcONa (1 eq)	15	6	NR

6	H ₂ O	AcOH (1 eq)	15	6	NR
7	H ₂ O	triethylamine (1 eq)	15	6	20%
8	H ₂ O	ethylenediamine (1 eq)	15	6	72%
9	H ₂ O	ethylenediamine (1.2 eq)	15	6	40%
10	H ₂ O	ethylenediamine (1.5 eq)	15	6	Trace
11	H ₂ O	ethylenediamine (2 eq)	15	6	NR
12	H ₂ O	ethylenediamine (0.6 eq)	15	6	87%
13	H ₂ O	ethylenediamine (0.5 eq)	15	6	90%
14	H ₂ O	ethylenediamine (0.4 eq)	15	6	83%
15	H ₂ O	ethylenediamine (0.2 eq)	15	6	51%
16	H ₂ O	ethylenediamine (0.5 eq)	10	6	87%
17	H ₂ O	ethylenediamine (0.5 eq)	20	6	90%
18	H ₂ O	ethylenediamine (0.5 eq)	30	6	78%
19	H ₂ O	ethylenediamine (0.5 eq)	40	6	60%
20	H ₂ O	ethylenediamine (0.5 eq)	50	6	45%
21	H ₂ O	ethylenediamine (0.5 eq)	15	8	91%
22	H ₂ O	ethylenediamine (0.5 eq)	15	12	89%
23	H ₂ O	ethylenediamine (0.5 eq)	15	16	87%
24	H ₂ O	ethylenediamine (0.5 eq)	15	30	82%

^a The reaction was performed with **1A** (0.3 mmol), **1B** (0.36 mmol) and **1C** (0.36 mmol) in 1.5 mL H₂O.

^b Isolated yield of **1D** based on **1A**.

To evaluate the general applicability and versatility of the method, a group of different purine derivatives and aliphatic aldehydes were subjected to the optimized reaction conditions and the results were shown in Table 2. As can be seen in Table 2, some of the purine substrates reacted ideally and gave high yields in water. Others can dissolve in water only partly or minimally, which resulted in poor reaction. When the solvents were changed into mixed solvent (H₂O: DMF= 1:1) or DMSO, all the substrates gave desired products in high yields. We also investigated the influence of aliphatic aldehydes (entries 1, 15-18) and most of the aliphatic aldehydes reacted smoothly giving single products. Confusingly, when formaldehyde was used in the reaction, the conversion was very low.

Table 2. Reactions of various substrates.^a

Entry	R ¹	R ²	R ³	Product	Solvent	T (°C)	Yield (%) ^b
1	Cl	H	Et	1D	H ₂ O	15	91
2	Cl	NH ₂	Et	2D	H ₂ O:DMF (1:1)	15	89
3	Cl	Cl	Et	3D	H ₂ O	15	80
4	NH ₂	H	Et	4D	H ₂ O:DMF (1:1)	15	86
5	N(CH ₂ CH ₂ OH) ₂	H	Et	5D	H ₂ O:DMF (1:1)	15	73
6	NEt ₂	H	Et	6D	DMSO	20	80
7	I	H	Et	7D	H ₂ O	15	75
8	NEt ₂	Cl	Et	8D	DMSO	20	65
9		H	Et	9D	H ₂ O:DMF (1:1)	15	92
10		H	Et	10D	H ₂ O	15	78
11		H	Et	11D	H ₂ O	15	70
12		H	Et	12D	DMSO	20	55
13		Cl	Et	13D	DMSO	20	86
14		NH ₂	Et	14D	DMSO	20	90
15	Cl	H	Me	15D	H ₂ O	15	87
16	Cl	H	<i>n</i> -Pr	16D	H ₂ O	15	75

17	Cl	H	<i>i</i> -Pr	17D	H ₂ O	15	88
18	Cl	H	H	18D	H ₂ O	15	20

^aReaction conditions: **A** (0.3 mmol), **B** (0.36 mmol), **C** (0.36 mmol), ethylenediamine (0.15 mmol), solvent (1.5 mL).

^bIsolated yield of **D** based on **A**.

The reaction gave high regioselectivities. As we know, the products of Mannich reaction of aliphatic aldehyde are prone to mixtures. Ethylenediamine can also be potentially involved in Mannich reaction. In our experiments, the single products were generated and ethylenediamine-related products were not found. The probable reason was that the reaction did not proceed by the classical Mannich path. That is, propionaldehyde and diethyl malonate interacted firstly to produce unsaturated ester in the presence of ethylenediamine, then Michael addition of purine with the unsaturated ester proceeded. Ethylenediamine took positive charge, which prevented ethylenediamine from reacting. In order to locate the side chain, the Heteronuclear Multiple-Bond Correlation (HMBC) spectroscopy of **1D** was performed. As shown in Figure 1, C₄ exhibited the ³J correlation with H_{1'} (peak A) while C₅ showed no correlation with protons in side chain, indicating that the side chain is located at N9 of purine.

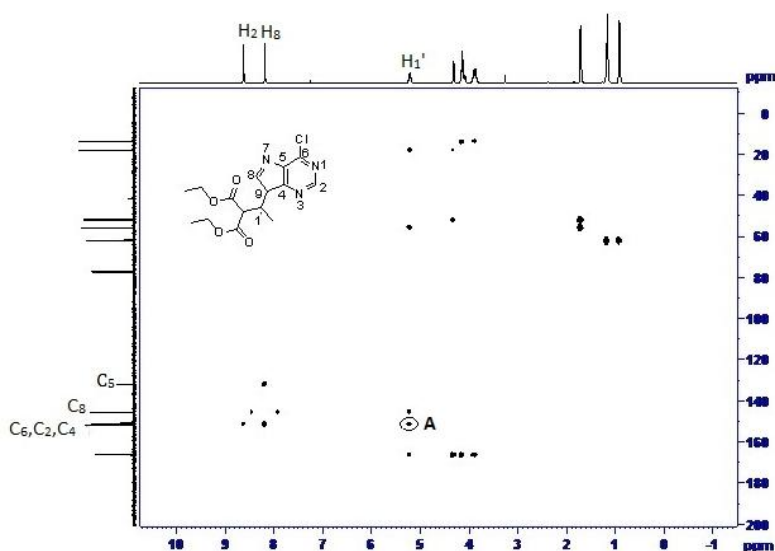


Figure 1. HMBC spectroscopy of **1D** in CDCl₃ solution.

In conclusion, we have developed a simple and efficient methodology for the preparation of purine derivatives by one-pot three-component Mannich-type reaction on purine rings. Compared with previously known approaches which contained more steps and not mild reaction conditions, this method catalyzed by ethylenediamine had only one step with which the reaction can proceed at ambient temperature. A number of functional groups can be tolerated.

EXPERIMENTAL

All reagents were purchased and used without further purification. Thin layer chromatography (TLC) was used to detect all reactions and 200-300 mesh silica gel was used as the stationary phase for column chromatography. Melting points were detected with a micro melting point apparatus and uncorrected. ^1H NMR spectra were recorded on a Bruker Avance 400 MHz instrument. ^{13}C NMR spectra were recorded on a Bruker Avance 100 MHz instrument. HMBC Spectroscopy was recorded on a Bruker Avance 400 MHz instrument. Chemical shifts (δ) were given in parts per million after calibration to residual isotopic solvent (CHCl_3 : $\delta\text{H} = 7.26$ ppm, $\delta\text{C} = 77.0$ ppm). Coupling constants (J) were given in hertz. electrospray ionization time-of-flight mass spectrometry (ESI-TOFMS) produced on a Bruker micrOTOF mass spectrometer. Infrared spectra were recorded in KBr with an Avatar360E. S. P. FTIR spectrophotometer.

General procedure for the reaction of 6-chloro-9H-purine (1A), propionaldehyde (1B) and diethyl malonate (1C)

6-Chloro-9H-purine (0.3 mmol), ethylenediamine (0.15 mmol), malonate (0.36 mmol), and propionaldehyde (0.36 mmol) were successively added to 1.5 mL water. This mixture was stirred at 15 °C for 8 h and extracted with EtOAc for three times. The organic layer was combined, dried with anhydrous Na_2SO_4 and evaporated to dryness. The crude mixture was purified by silica gel chromatography to give target product.

Diethyl 2-(1-(6-chloro-9H-purin-9-yl)propyl)malonate (1D): a white solid; mp 78–80 °C; IR (KBr disc) ν 3109, 3069, 2979, 2938, 2906, 2879, 1729, 1706, 1590, 1562, 1492, 1439, 1369, 1336, 1209, 1144, 1095 cm^{-1} ; ^1H NMR (400MHz, CDCl_3): δ 8.75 (s, 1H), 8.23 (s, 1H), 5.03 (t, $J = 10.4$ Hz, 1H), 4.45 (d, $J = 9.8$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 4.09–3.87 (m, 2H), 2.54–2.34 (m, 1H), 2.23–1.77 (m, 1H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.01 (t, $J = 7.1$ Hz, 3H), 0.78 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 166.5, 166.4, 151.7, 151.6, 151.2, 146.1, 131.9, 62.3, 62.1, 58.3, 55.3, 24.4, 13.9, 13.7, 10.6. HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{19}\text{ClN}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 355.1168. Found: 355.1165.

Diethyl 2-(1-(2-amino-6-chloro-9H-purin-9-yl)propyl)malonate (2D): a white solid; mp 69–71 °C; IR (KBr disc) ν 3456, 3306, 3197, 2980, 2938, 1747, 1732, 1622, 1610, 1559, 1409, 1372, 1304, 1208, 1143, 1030 cm^{-1} ; ^1H NMR (400MHz, CDCl_3): δ 7.87 (s, 1H), 5.80 (s, 1H), 4.85 (td, $J = 11.3, 3.4$ Hz, 1H), 4.38 (d, $J = 10.1$ Hz, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 4.02 (t, $J = 7.2$ Hz, 2H), 2.30–2.38 (m, 1H), 1.89–1.94 (m, 1H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.06 (t, $J = 7.1$ Hz, 3H), 0.79 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100MHz, CDCl_3) δ 166.6, 166.4, 159.0, 153.6, 151.2, 142.9, 125.2, 62.2, 62.0, 57.4, 55.3, 24.2, 13.9, 13.7, 10.6. HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{20}\text{ClN}_5\text{O}_4$ $[\text{M}+\text{H}]^+$ 370.1277. Found 370.1287.

Diethyl 2-(1-(2,6-dichloro-9H-purin-9-yl)propyl)malonate (3D): a white solid; mp 88–90 °C; IR (KBr disc) ν 3130, 2982, 2939, 1744, 1721, 1594, 1550, 1359, 1315, 1218, 1178, 1141 cm^{-1} ; ^1H NMR (400

MHz, CDCl₃): δ 8.26 (s, 1H), 5.04–4.98 (m, 1H), 4.34 (d, J = 9.6 Hz, 1H), 4.29–4.24 (m, 2H), 4.08–3.99 (m, 2H), 2.39–2.30 (m, 1H), 2.06–2.00 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H), 0.81 (t, J = 7.3 Hz, 3H); ¹³C NMR (100MHz, CDCl₃) δ 166.3, 166.3, 152.9, 152.6, 151.7, 146.8, 130.9, 62.4, 62.1, 58.2, 55.1, 24.4, 13.9, 13.7, 10.6. HRMS (ESI) calcd. for C₁₅H₁₉Cl₂N₄O₄ [M+H]⁺ 389.0778. Found 389.0777.

Diethyl 2-(1-(6-amino-9H-purin-9-yl)propyl)malonate (4D): a white solid; mp 144–146 °C; IR (KBr disc) ν 3433, 3330, 3212, 3119, 2972, 2937, 1739, 1712, 1652, 1600, 1474, 1365, 1333, 1293, 1214, 1181, 1089, 1023, 1000 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.33 (s, 1H), 7.82 (s, 1H), 5.95 (s, 2H), 4.89 (td, J = 11.3, 3.5 Hz, 1H), 4.47 (d, J = 10.1 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.99–3.92 (m, 2H), 2.44–2.36 (m, 1H), 1.95–1.89 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H), 0.75 (t, J = 7.3 Hz, 3H); ¹³C NMR (100MHz, CDCl₃) δ 166.8, 166.7, 155.6, 152.7, 149.9, 141.4, 120.0, 62.1, 61.9, 57.8, 55.5, 24.5, 14.0, 13.7, 10.6. HRMS (ESI) calcd. for C₁₅H₂₁N₅O₄ [M+H]⁺ 336.1666. Found 336.1666.

Diethyl 2-(1-(6-(bis(2-hydroxyethyl)amino)-9H-purin-9-yl)propyl)malonate (5D): a white solid; mp 210–212 °C; IR (KBr disc) ν 3352, 2976, 2877, 1747, 1731, 1585, 1480, 1369, 1336, 1217, 1037 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.29 (s, 1H), 7.83 (s, 1H), 4.90 (td, J = 11.3, 3.4 Hz, 1H), 4.49 (d, J = 9.9 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.24–3.83 (m, 10H), 2.53–2.30 (m, 1H), 1.97–1.81 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H), 0.75 (t, J = 7.3 Hz, 3H); ¹³C NMR (100MHz, CDCl₃) δ 166.8, 166.6, 156.9, 151.7, 150.6, 140.0, 120.1, 62.2, 61.9, 57.8, 55.3, 52.0, 24.2, 14.0, 13.7, 10.6. HRMS (ESI) calcd. for C₁₉H₂₉N₅O₆ [M+H]⁺ 424.2191. Found 424.2200.

Diethyl 2-(1-(6-(diethylamino)-9H-purin-9-yl)propyl)malonate (6D): a white solid; mp 219–221 °C; IR (KBr disc) ν 3114, 2976, 2934, 2877, 1751, 1736, 1586, 1563, 1520, 1479, 1370, 1284, 1030 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 1H), 7.75 (s, 1H), 4.89 (td, J = 11.3, 3.2 Hz, 1H), 4.52 (d, J = 10.1 Hz, 1H), 4.28–4.23 (q, J = 9.8 Hz, 2H), 4.16–3.93 (m, 6H), 2.46–2.38 (m, 1H), 2.12–1.66 (m, 1H), 1.29 (t, J = 7.1 Hz, 9H), 1.00 (t, J = 7.1 Hz, 3H), 0.77 (t, J = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.0, 166.7, 153.7, 152.2, 150.4, 139.0, 119.9, 62.0, 61.7, 57.5, 55.5, 43.0, 42.8, 24.3, 14.0, 13.6, 10.6. HRMS (ESI) calcd. for C₁₉H₂₉N₅O₄ [M+H]⁺ 392.2292. Found 392.2303.

Diethyl 2-(1-(6-iodo-9H-purin-9-yl)propyl)malonate (7D): a white solid. mp 102–104 °C; IR (KBr disc) ν 3110, 2975, 2937, 2791, 2695, 1731, 1737, 1643, 1584, 1004 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.62 (s, 1H), 8.19 (s, 1H), 5.01–4.94 (m, 1H), 4.43 (d, J = 9.8 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.04–3.90 (m, 2H), 2.47–2.39 (m, 1H), 2.02–1.96 (m, 1H), 1.29 (t, J = 7.1 Hz, 4H), 1.01 (t, J = 7.1 Hz, 3H), 0.76 (t, J = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.5, 166.4, 151.7, 147.8, 145.4, 138.9, 122.3, 62.3, 62.1, 58.4, 55.3, 24.4, 14.0, 13.7, 10.6. HRMS (ESI) calcd. for C₁₅H₁₉I_N₄O₄ [M+H]⁺ 447.0524. Found 447.0523.

Diethyl 2-(1-(2-chloro-6-(diethylamino)-9H-purin-9-yl)propyl)malonate (8D): a white solid. mp 63–65 °C; IR (KBr disc) ν 3115, 2977, 2936, 2877, 1750, 1733, 1584, 1462, 1321, 1097, 1030 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.73 (s, 1H), 4.86 (td, $J = 11.2, 3.4$ Hz, 1H), 4.40 (d, $J = 9.8$ Hz, 1H), 4.27–4.22 (q, $J = 7.2$, 2H), 4.18 (s, 1H), 4.01 (q, $J = 7.1$ Hz, 2H), 3.73 (s, 2H), 2.52–2.25 (m, 1H), 1.95–1.89 (m, 1H), 1.30 (t, $J = 7.1$ Hz, 9H), 1.05 (t, $J = 7.1$ Hz, 3H), 0.77 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 166.6, 153.9, 153.5, 151.6, 139.3, 118.8, 62.1, 61.8, 57.4, 55.3, 43.6, 42.6, 24.3, 14.0, 13.7, 10.6. HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{28}\text{N}_5\text{O}_4$ $[\text{M}+\text{H}]^+$ 426.1902. Found 426.1913.

Diethyl 2-(1-(2-chloro-6-bis-(*t*-Butyloxycarbonyl)-9H-purin-9-yl)propyl)malonate (9D): a white solid; mp 102–104 °C; IR (KBr disc) ν 3126, 2980, 2937, 1789, 1749, 1729, 1602, 1371, 1299, 1254, 1213, 1143, 1115 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.84 (s, 1H), 8.12 (s, 1H), 5.00 (td, $J = 11.3, 3.6$ Hz, 1H), 4.47 (d, $J = 9.9$ Hz, 1H), 4.25 (q, $J = 7.1$ Hz, 2H), 4.03–3.88 (m, 2H), 2.49–2.41 (m, 1H), 2.01–1.95 (m, 1H), 1.43 (s, 18H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.00 (t, $J = 7.1$ Hz, 3H), 0.74 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 166.4, 153.1, 151.7, 150.3, 145.5, 129.2, 83.6, 62.2, 61.9, 58.0, 55.4, 27.7, 24.3, 14.0, 13.7, 10.5. HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{37}\text{N}_5\text{O}_8$ $[\text{M}+\text{H}]^+$ 536.2715. Found 536.2754.

Diethyl 2-(1-(6-(4-ethylpiperazin-1-yl)-9H-purin-9-yl)propyl)malonate (10D): a white solid; mp 78–80 °C; IR (KBr disc) ν 3109, 2973, 2936, 2887, 2809, 1737, 1732, 1585, 1566, 1476, 1332, 1003 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.28 (s, 1H), 7.72 (s, 1H), 4.85 (td, $J = 11.2, 3.4$ Hz, 1H), 4.45 (d, $J = 10.0$ Hz, 1H), 4.39–4.04 (m, 6H), 4.01–3.85 (m, 2H), 2.60–2.51 (m, 4H), 2.43 (q, $J = 7.2$ Hz, 2H), 2.40–2.27 (m, 1H), 1.92–1.83 (m, 1H), 1.24 (t, $J = 7.1$ Hz, 4H), 1.09 (t, $J = 7.2$ Hz, 3H), 0.97 (t, $J = 7.1$ Hz, 3H), 0.71 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 166.6, 153.8, 152.0, 150.8, 139.1, 120.3, 62.0, 61.8, 57.5, 55.4, 52.9, 52.4, 24.3, 14.0, 13.7, 11.9, 10.6. HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{32}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^+$ 433.2558. Found 433.2562.

Diethyl 2-(1-(6-(4-methylpiperazin-1-yl)-9H-purin-9-yl)propyl)malonate (11D): a white solid; mp 206–208 °C; IR (KBr disc) ν 3110, 2975, 2937, 2791, 2695, 1731, 1737, 1643, 1584, 1004 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.32 (s, 1H), 7.77 (s, 1H), 4.90 (td, $J = 11.1, 3.2$ Hz, 1H), 4.50 (d, $J = 10.0$ Hz, 1H), 4.41–4.15 (m, 6H), 4.04–3.92 (m, 2H), 2.55 (t, $J = 4.9$ Hz, 4H), 2.50–2.39 (m, 1H), 2.36 (s, 3H), 1.94–1.88 (m, 1H), 1.30 (d, $J = 7.1$ Hz, 3H), 1.02 (t, $J = 7.1$ Hz, 3H), 0.75 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 166.6, 153.8, 152.0, 150.8, 139.2, 120.3, 62.1, 61.8, 57.5, 55.4, 55.1, 46.2, 24.3, 14.0, 13.7, 10.6. HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{30}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^+$ 419.2401. Found 419.2396.

Diethyl 2-(1-(6-(piperidin-1-yl)-9H-purin-9-yl)propyl)malonate (12D): a white solid; mp 70–72 °C; IR (KBr disc) ν 3111, 2977, 2935, 2854, 1733, 1750, 1583, 1563, 1465, 1336, 1294, 1247, 1214, 1180, 1026 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 8.31 (s, 1H), 7.75 (s, 1H), 4.89 (td, $J = 11.3, 3.3$ Hz, 1H), 4.51 (d, $J = 10.0$ Hz, 1H), 4.27–4.22 (m, 6H), 4.03–3.91 (m, 2H), 2.47–2.33 (m, 1H), 1.94–1.86 (m, 1H),

1.75–1.64 (m, 6H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.01 (t, $J = 7.1$ Hz, 3H), 0.76 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 166.7, 153.8, 152.1, 150.6, 138.8, 120.2, 62.0, 61.8, 57.5, 55.5, 26.1, 24.8, 24.4, 14.0, 13.7, 10.6. HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{29}\text{N}_5\text{O}_4$ $[\text{M}+\text{H}]^+$ 404.2292. Found 404.2296.

Diethyl 2-(1-(2-chloro-6-(piperidin-1-yl)-9H-purin-9-yl)propyl)malonate (13D): a white solid; mp 124–126 °C; IR (KBr disc) ν 3121, 3022, 2977, 2938, 2867, 1742, 1720, 1586, 1468, 1309, 1270, 1211, 1112, 1026 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.74 (s, 1H), 4.86 (td, $J = 11.2, 3.5$ Hz, 1H), 4.71–3.74 (m, 9H), 2.47–2.29 (m, 1H), 1.95–1.83 (m, 1H), 1.71 (s, 6H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.06 (t, $J = 7.1$ Hz, 3H), 0.77 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 166.6, 153.8, 153.6, 151.9, 139.0, 118.9, 62.1, 61.8, 57.4, 55.3, 26.1, 24.6, 24.3, 14.0, 13.7, 10.6. HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{28}\text{ClN}_5\text{O}_4$ $[\text{M}+\text{H}]^+$ 438.1903. Found 438.1920.

Diethyl 2-(1-(2-amino-6-(pyrrolidin-1-yl)-9H-purin-9-yl)propyl)malonate (14D): a white solid; mp 118–120 °C; IR (KBr disc) ν 3479, 3345, 3223, 2970, 2936, 2876, 1753, 1729, 1633, 1584, 1490, 1453, 1405, 1209, 1030 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.46 (s, 1H), 4.85 (s, 2H), 4.73 (td, $J = 11.3, 3.3$ Hz, 1H), 4.46 (d, $J = 10.0$ Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 4.16–3.87 (m, 4H), 3.65 (s, 2H), 2.4–2.30 (m, 1H), 1.96 (s, 4H), 1.84–1.75 (m, 1H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.06 (t, $J = 7.1$ Hz, 3H), 0.75 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.1, 166.8, 159.3, 153.5, 152.2, 137.1, 115.6, 61.9, 61.7, 56.9, 55.4, 24.0, 14.0, 13.7, 10.6. HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{28}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^+$ 405.2245. Found 405.2256.

Diethyl 2-(1-(6-chloro-9H-purin-9-yl)ethyl)malonate (15D): a white solid; mp 196–198 °C. IR (KBr disc) ν 3113, 3069, 2984, 2940, 2906, 1738, 1723, 1591, 1562, 1492, 1445, 1370, 1336, 1093 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.76 (s, 1H), 8.28 (s, 1H), 5.33 (dq, $J = 9.4, 7.0$ Hz, 1H), 4.44 (d, $J = 9.5$ Hz, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 4.10–3.94 (m, 2H), 1.84 (d, $J = 7.0$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.05 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.4, 166.4, 151.6, 151.4, 151.0, 145.4, 132.0, 62.3, 62.1, 55.7, 52.0, 17.9, 14.0, 13.7. HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{17}\text{ClN}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 341.1011. Found 341.1027.

Diethyl 2-(1-(6-chloro-9H-purin-9-yl)butyl)malonate (16D): a white solid, mp 69–71 °C; IR (KBr disc) ν 3110, 3069, 2964, 2936, 2875, 1732, 1737, 1591, 1561, 1471, 1442, 1370, 1337, 1339, 1200, 1097, 936 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.69 (s, 1H), 8.16 (s, 1H), 5.08 (td, $J = 11.5, 3.3$ Hz, 1H), 4.38 (d, $J = 9.9$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 3.98–3.85 (m, 2H), 2.47–2.35 (m, 1H), 1.86–1.73 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.16–1.05 (m, 1H), 0.95 (t, 7.1 Hz, 3H), 0.91–0.88 (m, 1H), 0.82 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.5, 166.4, 151.7, 151.6, 151.1, 146.0, 131.9, 62.4, 62.1, 56.4, 55.4, 33.0, 19.2, 14.0, 13.7, 13.2. HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{21}\text{ClN}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 369.1324. Found 369.1335.

Diethyl 2-(1-(6-chloro-9H-purin-9-yl)-2-methylpropyl)malonate (17D): a white solid; mp 190–192 °C; IR (KBr disc) ν 3115, 3067, 2976, 2938, 2877, 1749, 1733, 1589, 1558, 1437, 1395, 1372, 1336,

1203, 1028, 940 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.75 (s, 1H), 8.43 (s, 1H), 5.13 (t, $J = 8.1$ Hz, 1H), 4.44 (d, $J = 8.5$ Hz, 1H), 4.11 (q, $J = 7.1$ Hz, 2H), 4.07–4.01 (m, 2H), 2.56 (dq, $J = 13.7, 6.8$ Hz, 1H), 1.17 (t, $J = 7.1$ Hz, 3H), 1.08–0.96 (m, 6H), 0.84 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.5, 166.5, 152.5, 151.7, 151.0, 146.0, 131.1, 62.3, 62.1, 60.5, 53.6, 31.0, 20.1, 18.6, 13.8, 13.7. HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{21}\text{ClN}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 369.1324. Found 369.1342.

Diethyl 2-((6-chloro-9H-purin-9-yl)methyl)malonate (18D): an oil; IR (KBr disc) ν 3112, 3068, 2968, 2875, 1746, 1730, 1590, 1437, 1390, 1372, 1337, 1201, 946 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.75 (s, 1H), 8.20 (s, 1H), 4.79 (d, $J = 7.2$ Hz, 2H), 4.27–4.11 (m, 5H), 1.23 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.62, 152.10, 146.06, 62.48, 51.19, 42.47, 13.91. HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{15}\text{ClN}_4\text{O}_4$ $[\text{M}+\text{Na}]^+$ 349.0674. Found 349.0669.

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