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Design, Synthesis, and Activity Evaluation of Novel Acyclic Nucleosides as Potential Anticancer Agents *In Vitro* and *In Vivo*

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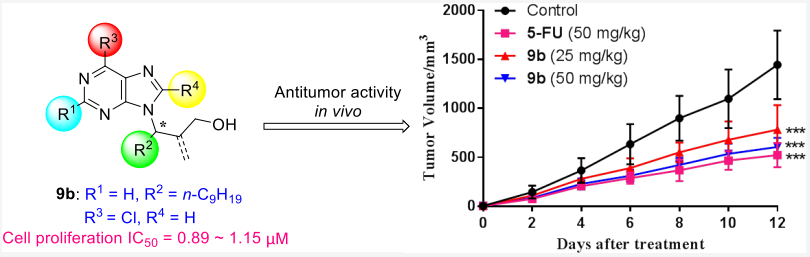

ABSTRACT: In the present work, 103 novel acyclic nucleosides were designed, synthesized, and evaluated for their anticancer activities *in vitro* and *in vivo*. The structure−activity relationship (SAR) studies revealed that most target compounds inhibited the growth of colon cancer cells *in vitro*, of which 3-(6-chloro-9*H*-purin-9-yl)dodecan-1-ol (**9b**) exhibited the most potent effect against the HCT-116 and SW480 cells with IC_{50} values of 0.89 and 1.15 μM, respectively. Furthermore, all of the (*R*)-configured acyclic nucleoside derivatives displayed more potent anticancer activity compared to their (*S*)-counterparts. Mechanistic studies revealed that compound **9b** triggered apoptosis in the cancer cell lines *via* depolarization of the mitochondrial membrane and effectively inhibited colony formation. Importantly, compound **9b** inhibited the growth of the SW480 xenograft in a mouse model with low systemic toxicity. These results indicated that acyclic nucleoside compounds are viable as potent and effective anticancer agents, and compound **9b** may serve as a promising lead compound that merits further attention in future anticancer drug discovery.

1. INTRODUCTION

Acyclic nucleoside compounds (ANCs) are one of the most versatile scaffolds in medicinal chemistry owing to their unique physicochemical and biological properties. The absence of a glycosidic bond increases the resistance of ANCs to chemical and biological degradation,[1−6] and the flexible acyclic chain allows structural adaptability for interacting with the active site of multiple enzymes.[7−15] Over the last few decades, R&D in ANCs has resulted in the successful launch of several approved antiviral drugs (e.g., Ganciclovir, Famciclovir, Penciclovir, Figure 1) and is still providing a number of novel bioactive compounds.

The mature acyclic nucleoside preparation methods have provided a convenient synthesis of ANCs,[16,17] which have been proved to possess excellent bioactivities. Since the pioneer work of De Clercq and Holý in 1976 at the symposium on synthetic nucleosides, nucleotides, and polynucleotides, acyclic nucleoside phosphonates have been recognized as a key class of antiviral agents.[18] In 1977, Acyclovir with an acyclic side chain, 2-hydroxyethoxymethyl at the N9 position, was first discovered as an antiherpetic agent.[19,20] In 1978, De Clercq and Holý reported an acyclic nucleoside, (*S*)-9-(2,3-dihydroxypropyl)adenine, with broad-spectrum antiviral activity.[21] In 1999, Raić-Malić et al. developed the synthesis of acyclic nucleosides containing 2,3-epoxypropyl, 3-amino-2-hydroxypropyl, or 2,3-epoxypropyl ether moieties and their antitumor and antiviral activities.[22] Later, Raić-Malić et al. reported the synthesis and biological evaluation of fluorinated and iodinated acyclic purine nucleoside analogues bearing 9-(2-hydroxypropyl) and 9-(2-hydroxyethoxymethyl) side chains.[23] In 2006, Mintas et al. reported the synthesis of unsaturated acyclic and epoxide nucleoside analogues and evaluation of their antiviral and cytostatic activities.[24,25] In 2015, Raić-Malić et al. reported the discovery of new acid ceramidase-targeted acyclic 5-alkynyl and 5-heteroaryl uracil nucleosides.[26] Although some studies on the antitumor activities of acyclic nucleosides have been reported,[27−33] in view of the frequent occurrence of chemoresistance against the current anticancer drugs, there is an urgent demand for developing novel chemotherapeutic agents with high potency and low toxicity. Based on our extensive research work on the

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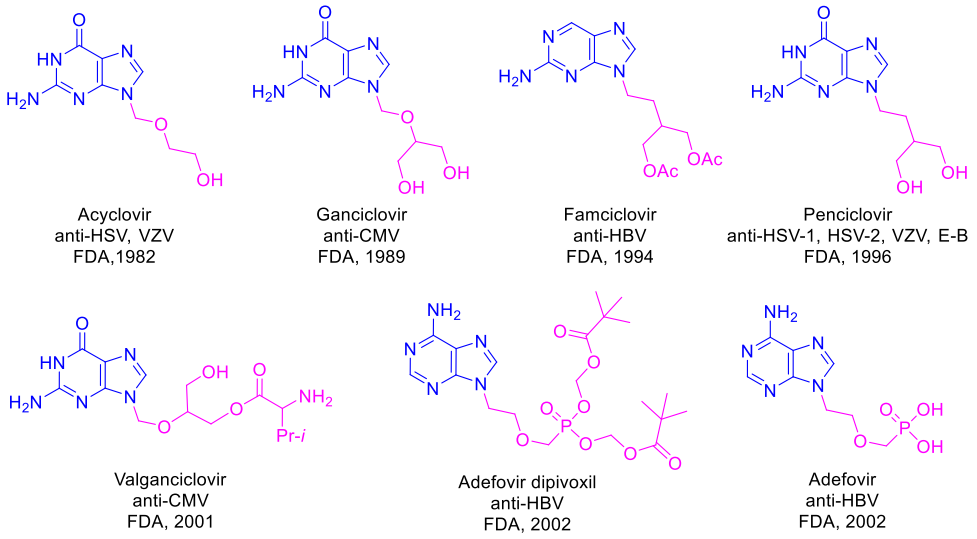

Figure 1. Acyclic nucleoside and nucleotide drugs.

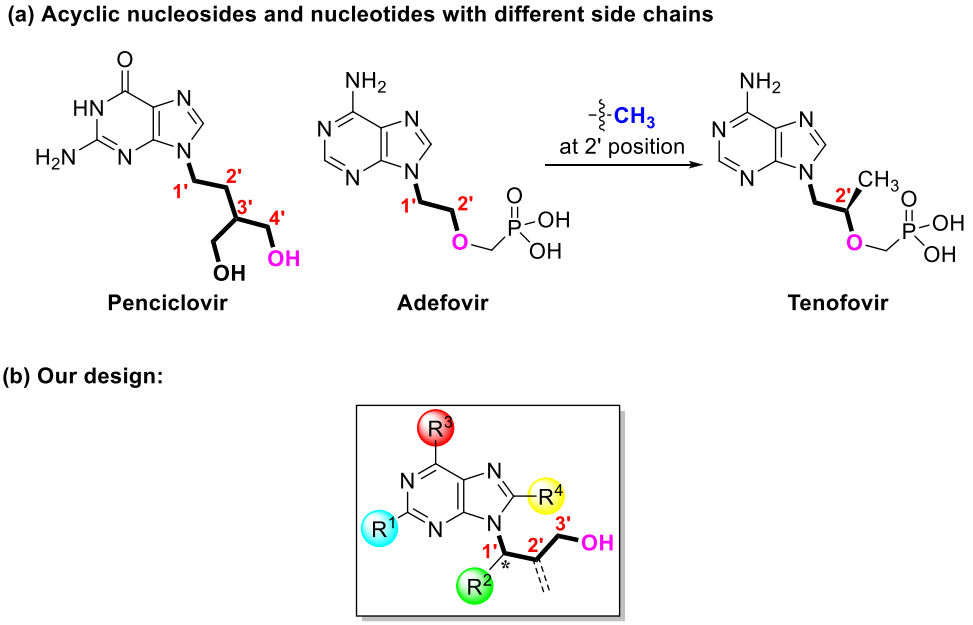

Figure 2. Design of acyclic nucleosides.

synthetic methodology of acyclic nucleosides,[34−36] we will study the antitumor activities of the synthesized acyclic nucleosides. To this end, we constructed a library of 103 novel acyclic nucleoside derivatives and evaluated their anticancer activities through established *in vitro* and *in vivo* assays.

2. DESIGN

First, the side chains of Penciclovir and Adefovir are structurally analyzed. In addition to a hydroxyl group, the length of the side chain is four and two carbon atoms, respectively (Figure 2a). Therefore, we design the acyclic nucleosides containing a side chain with a length of three carbon atoms and a hydroxyl group (Figure 2b). Second, when a methyl group is introduced into the C2′-position of Adefovir, a chiral carbon emerges and a new acyclic nucleotide drug Tenofovir is formed (Figure 2a). Thus, we design the acyclic nucleosides bearing a side chain with different alkyl groups at the C1′-position, which form a chiral center, or a C═C double bond at the C2′-position (Figure 2b). Finally, the C2, C6, and C8 positions of the purine ring could also be altered. It should be noted that the above studies on the structure−activity relationship (SAR) of ANCs are all aimed at antiviral activities, and the SAR of antitumor activities of ANCs is less reported. In particular, the SAR of our designed ANCs containing a side chain with a length of three carbon atoms has not been systematically reported. To probe into the SAR of our designed acyclic purine nucleoside analogues, a molecular library of 103 acyclic nucleosides was synthesized and the anticancer activities were evaluated.

3. CHEMISTRY

At first, all compounds were synthesized and isolated as racemic mixtures. Except for **1b**, **3b**, **16b**, **4c**, **5c**, **6c**, **5k**, and **10k**, all ANCs generated in the compound library were novel. Acyclic nucleoside compounds **1a**−**12a**, **1b**−**15b**, **4c**−**9c**, **4d**−

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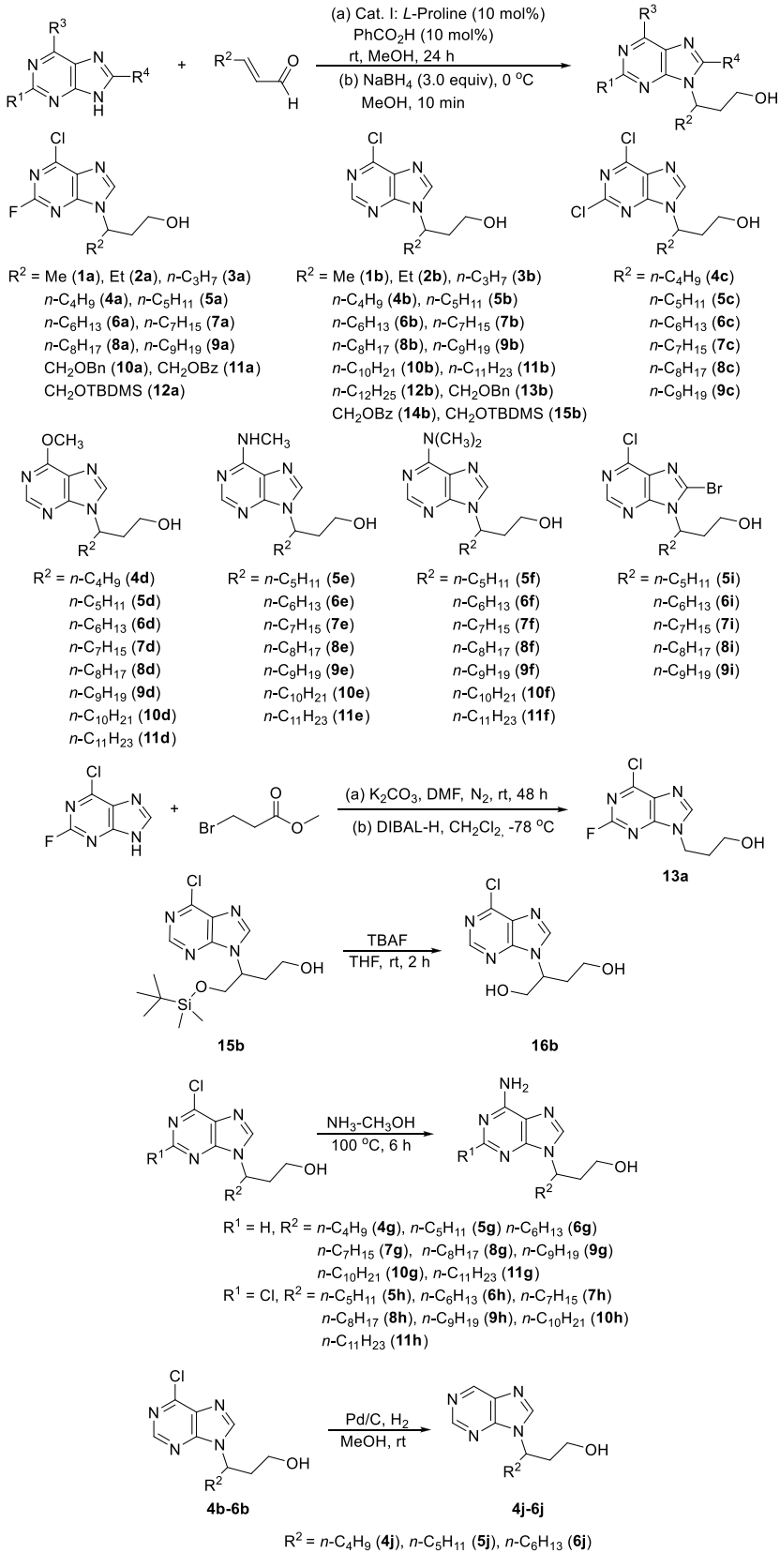
Scheme 1. Syntheses of 1a−13a, 1b−16b, 4c−9c, 4d−11d, 5e−11e, 5f−11f, 4g−11g, 5h−11h, 5i−9i, 4j−6j, and 5k−10k



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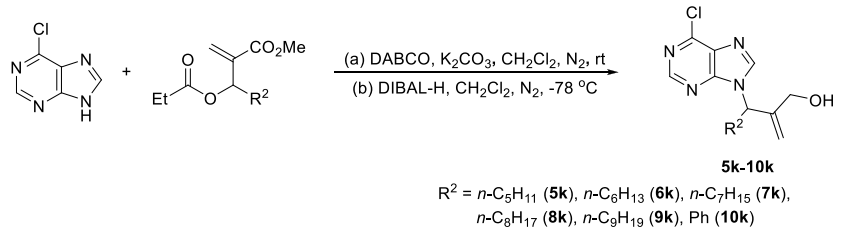
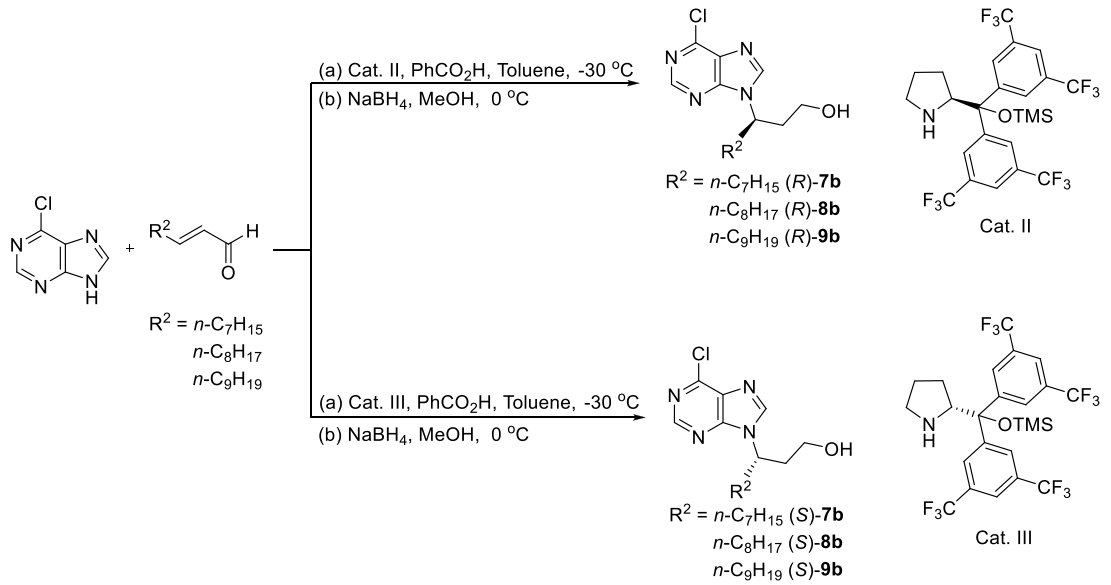
Scheme 1. continued



Scheme 2. Asymmetric Syntheses of (*R*)- and (*S*)-configurations of the compounds 7b, 8b, and 9b



11d, **5e**−**11e**, **5f**−**11f**, and **5i**−**9i** were synthesized in 26.7−89.5% overall yields *via* L-proline (Cat. I)-catalyzed aza-Michael addition of purine bases to *α*,*β*-unsaturated aldehydes, followed by treatment of the resulting Michael adducts with $NaBH_4$ in MeOH at 0 °C (Scheme 1). In addition, the structure of the compounds **6a** and **8b** was determined *via* single-crystal X-ray diffraction analysis (Supporting Information (SI), Figures S4 and S5). Compound **13a** was then obtained by the nucleophilic substitution reaction of 6-chloro-2-fluoropurine with methyl 3-bromopropionate and DIBAL-H (diisobutyl aluminum hydride)-mediated reduction of the nucleophilic product giving the yield of 65.3%. Compound **16b** was obtained in 83.5% yield through the deprotection of the silyl ether group in compound **15b** by tetrabutylammonium fluoride (TBAF). Compounds **g** (**4g**−**11g**) or **h** (**5h**−**11h**) series were obtained by the nucleophilic substitution reaction of **b** or **c** series with ammonia in MeOH in the yields of 67.5−75.9% (Scheme 1). Finally, compounds **4b**−**6b** were dechlorinated by Pd/C-mediated hydrogenolysis in methanol to generate **4j**−**6j** in 63.1−66.5% yield. Compounds **5k**−**10k** were then obtained by introducing an olefin double bond in the side chain of 6-chloropurine from MBH adducts through allyl amination in 36.8−43.2% yield (Scheme 1).

The stereochemistry of a chiral compound could usually affect its bioactivities obviously. To further elucidate the impact of stereochemistry on the anticancer activity of these novel ANCs, several chiral acyclonucleosides with (*R*)-configuration were generated in 51.3−56.2% overall yield and 91−95% ee from 6-chloro-9*H*-purine and several acroleins using (*R*)-prolinol-derived chiral secondary amine II as the organocatalyst (Cat. II) and subsequent reduction with sodium borohydride (Scheme 2). The *S* enantiomers were obtained using catalyst III with opposite configuration at 50.5−54.8% overall yield and 91−95% ee (Scheme 2). In addition, the absolute configuration of the compound (*R*)-**9b** was determined *via* single-crystal X-ray diffraction analysis (SI, Figure S6).

4. RESULTS AND DISCUSSION

4.1. *In Vitro* Anticancer Activities. At first, all compounds were tested using their racemic mixtures against the HCT-116 and SW480 human colon cancer cell lines, using 5-fluorocrail (5-FU) as the positive control. As shown in Table 1, compounds **1a**−**13a**, **6b**−**11b**, **4c**−**9c**, **7d**−**11d**, **7e**−**11e**, **8f**−**11f**, **8g**−**11g**, **8h**−**11h**, and **5i**−**9i** exhibited moderate to potent antitumor activities against both cell lines.

In compound **a** series (R^1 = F, R^3 = Cl, R^4 = H), all of the acyclonucleosides with R^2 as H (**13a**) or C1−C9 linear alkyl (**1a**−**9a**) showed anticancer activities (IC_{50} = 7.44−39.81 *μ*M) and the R^2 on the 1′ position has a mild but regular impact on their anticancer activities, which first increased and then decreased gradually with the increase of the 1′ position alkyl chain length, with *n*-amyl (**5a**) being found to be optimal against cell lines HCT-116 and SW480 (IC_{50} = 8.66, 7.44 *μ*M). With the introduction of heteroatoms and a phenyl ring to the 1′-position of the purine side chain, i.e., R^2 = CH_2OBn (**10a**), CH_2OBz (**11a**), and $CH_2OTBDMS$ (**12a**), their anticancer activities (IC_{50} = 5.17−8.02 *μ*M) were comparable to those of **5a**.

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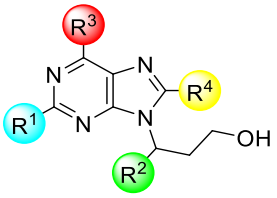
Table 1. Anticancer Activities of Acyclic Nucleoside Compounds



					IC_{50} (μM)[a]	
compound	R^1	R^2	R^3	R^4	HCT-116[b]	SW480[b]
1a	F	Me	Cl	H	19.76 ± 1.46	16.83 ± 1.09
2a	F	Et	Cl	H	18.85 ± 1.22	19.84 ± 1.11
3a	F	*n*-C_3H_7	Cl	H	16.47 ± 3.03	17.19 ± 1.69
4a	F	*n*-C_4H_9	Cl	H	13.46 ± 2.33	13.18 ± 2.01
5a	F	*n*-C_5H_{11}	Cl	H	8.66 ± 1.48	7.44 ± 1.25
6a	F	*n*-C_6H_{13}	Cl	H	9.96 ± 0.72	12.94 ± 1.39
7a	F	*n*-C_7H_{15}	Cl	H	17.57 ± 3.96	26.12 ± 2.26
8a	F	*n*-C_8H_{17}	Cl	H	24.22 ± 4.17	14.98 ± 0.80
9a	F	*n*-C_9H_{19}	Cl	H	32.05 ± 2.42	12.46 ± 2.06
10a	F	CH_2OBn	Cl	H	5.24 ± 0.65	7.17 ± 1.25
11a	F	CH_2OBz	Cl	H	5.17 ± 0.75	7.24 ± 0.92
12a	F	$CH_2OTBDMS$	Cl	H	7.78 ± 1.21	8.02 ± 0.75
13a	F	H	Cl	H	39.81 ± 3.72	29.70 ± 2.95
1b	H	Me	Cl	H	>50	>50
2b	H	Et	Cl	H	>50	>50
3b	H	*n*-C_3H_7	Cl	H	>50	>50
4b	H	*n*-C_4H_9	Cl	H	>50	>50
5b	H	*n*-C_5H_{11}	Cl	H	>50	>50
6b	H	*n*-C_6H_{13}	Cl	H	11.94 ± 1.17	16.74 ± 2.12
7b	H	*n*-C_7H_{15}	Cl	H	4.16 ± 2.39	3.63 ± 2.37
8b	H	*n*-C_8H_{17}	Cl	H	1.65 ± 0.43	1.37 ± 0.36
9b	H	*n*-C_9H_{19}	Cl	H	0.89 ± 0.21	1.15 ± 0.31
10b	H	*n*-$C_{10}H_{21}$	Cl	H	4.93 ± 0.69	3.16 ± 0.36
11b	H	*n*-$C_{11}H_{23}$	Cl	H	7.59 ± 0.62	5.29 ± 0.90
12b	H	*n*-$C_{12}H_{25}$	Cl	H	>50	>50
13b	H	CH_2OBn	Cl	H	>50	>50
14b	H	CH_2OBz	Cl	H	>50	>50
15b	H	$CH_2OTBDMS$	Cl	H	>50	31.70 ± 4.14
16b	H	CH_2OH	Cl	H	>50	>50
4c	Cl	*n*-C_4H_9	Cl	H	15.49 ± 2.01	30.90 ± 1.39
5c	Cl	*n*-C_5H_{11}	Cl	H	6.17 ± 0.89	6.01 ± 0.85
6c	Cl	*n*-C_6H_{13}	Cl	H	12.10 ± 1.68	12.42 ± 1.80
7c	Cl	*n*-C_7H_{15}	Cl	H	12.79 ± 1.75	13.56 ± 3.25
8c	Cl	*n*-C_8H_{17}	Cl	H	22.15 ± 3.15	24.04 ± 2.49
9c	Cl	*n*-C_9H_{19}	Cl	H	32.56 ± 3.12	36.30 ± 1.75
4d	H	*n*-C_4H_9	OCH_3	H	>50	>50
5d	H	*n*-C_5H_{11}	OCH_3	H	>50	>50
6d	H	*n*-C_6H_{13}	OCH_3	H	>50	>50
7d	H	*n*-C_7H_{15}	OCH_3	H	15.28 ± 2.53	23.92 ± 2.16
8d	H	*n*-C_8H_{17}	OCH_3	H	12.77 ± 4.15	24.55 ± 4.37
9d	H	*n*-C_9H_{19}	OCH_3	H	2.53 ± 0.25	3.25 ± 0.30
10d	H	*n*-$C_{10}H_{21}$	OCH_3	H	7.53 ± 0.83	8.26 ± 0.86
11d	H	*n*-$C_{11}H_{23}$	OCH_3	H	8.23 ± 2.18	9.70 ± 1.41
5e	H	*n*-C_5H_{11}	$NHCH_3$	H	>50	>50
6e	H	*n*-C_6H_{13}	$NHCH_3$	H	>50	>50
7e	H	*n*-C_7H_{15}	$NHCH_3$	H	12.53 ± 3.01	15.26 ± 4.28

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Table 1. continued

compound	R^1	R^2	R^3	R^4	IC_{50} (μM)[a] HCT-116[b]	SW480[b]
8e	H	*n*-C_8H_{17}	$NHCH_3$	H	3.73 ± 0.47	3.77 ± 0.71
9e	H	*n*-C_9H_{19}	$NHCH_3$	H	5.41 ± 1.03	4.45 ± 0.91
10e	H	*n*-$C_{10}H_{21}$	$NHCH_3$	H	12.70 ± 1.43	11.99 ± 1.97
11e	H	*n*-$C_{11}H_{23}$	$NHCH_3$	H	15.38 ± 2.29	12.79 ± 2.39
5f	H	*n*-C_5H_{11}	$N(CH_3)_2$	H	>50	>50
6f	H	*n*-C_6H_{13}	$N(CH_3)_2$	H	>50	>50
7f	H	*n*-C_7H_{15}	$N(CH_3)_2$	H	>50	>50
8f	H	*n*-C_8H_{17}	$N(CH_3)_2$	H	19.84 ± 2.67	21.61 ± 1.71
9f	H	*n*-C_9H_{19}	$N(CH_3)_2$	H	9.81 ± 0.66	12.24 ± 1.33
10f	H	*n*-$C_{10}H_{21}$	$N(CH_3)_2$	H	5.49 ± 1.69	3.32 ± 0.69
11f	H	*n*-$C_{11}H_{23}$	$N(CH_3)_2$	H	12.03 ± 0.99	11.75 ± 1.00
4g	H	*n*-C_4H_9	NH_2	H	>50	>50
5g	H	*n*-C_5H_{11}	NH_2	H	>50	>50
6g	H	*n*-C_6H_{13}	NH_2	H	>50	>50
7g	H	*n*-C_7H_{15}	NH_2	H	>50	>50
8g	H	*n*-C_8H_{17}	NH_2	H	11.55 ± 1.81	20.68 ± 1.47
9g	H	*n*-C_9H_{19}	NH_2	H	10.54 ± 2.66	6.03 ± 1.62
10g	H	*n*-$C_{10}H_{21}$	NH_2	H	2.59 ± 0.41	1.20 ± 0.17
11g	H	*n*-$C_{11}H_{23}$	NH_2	H	13.35 ± 2.66	11.61 ± 0.95
5h	Cl	*n*-C_5H_{11}	NH_2	H	>50	>50
6h	Cl	*n*-C_6H_{13}	NH_2	H	>50	>50
7h	Cl	*n*-C_7H_{15}	NH_2	H	>50	>50
8h	Cl	*n*-C_8H_{17}	NH_2	H	20.99 ± 2.76	13.14 ± 2.02
9h	Cl	*n*-C_9H_{19}	NH_2	H	14.84 ± 3.19	12.22 ± 2.30
10h	Cl	*n*-$C_{10}H_{21}$	NH_2	H	11.83 ± 2.00	13.13 ± 1.24
11h	Cl	*n*-$C_{11}H_{23}$	NH_2	H	19.95 ± 2.05	17.78 ± 1.08
5i	H	*n*-C_5H_{11}	Cl	Br	18.29 ± 1.33	23.81 ± 1.34
6i	H	*n*-C_6H_{13}	Cl	Br	16.12 ± 1.15	14.13 ± 1.01
7i	H	*n*-C_7H_{15}	Cl	Br	16.22 ± 1.69	14.44 ± 1.52
8i	H	*n*-C_8H_{17}	Cl	Br	22.39 ± 2.07	17.78 ± 1.13
9i	H	*n*-C_9H_{19}	Cl	Br	26.91 ± 3.79	24.98 ± 1.76
4j	H	*n*-C_4H_9	H	H	>50	>50
5j	H	*n*-C_5H_{11}	H	H	>50	>50
6j	H	*n*-C_6H_{13}	H	H	>50	>50
5-FU					10.81 ± 0.69	9.70 ± 1.22

[a]The antiproliferation activities of individual compounds against tumor cells were determined by the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay. Data are mean ± standard error of the mean (SEM) values from three independent experiments. [b]Both HCT-116 and SW480 are human colon carcinoma cell lines.

Similarly, in compound **b** series (R^1 = R^4 = H, R^3 = Cl), acyclonucleosides **1b**−**12b** also showed a similar trend in anticancer activities, which first increased and then decreased gradually as the 1′-position alkyl chain length increases. Compound **9b**, with the 1′-position of the purine side chain substituted by *n*-nonyl, exhibited the highest anticancer activities against cell lines HCT-116 and SW480 (IC_{50} = 0.89, 1.15 μM), which were about 10-fold more potent than those of the positive control 5-FU (IC_{50} = 10.81, 9.70 μM). The anticancer activities were lost when R^2 was replaced with CH_2OBn (**13b**), CH_2OBz (**14b**), $CH_2OTBDMS$ (**15b**), and CH_2OH (**16b**).

In compound **c** series (R^1 = R^3 = Cl, R^4 = H), R^1 of **a** series was changed from F to Cl, the resulting acyclonucleosides **4c**−**9c** showed similar anticancer activities (IC_{50} = 6.01−36.30 μM) to those of **4a**−**9a** (IC_{50} = 7.44−32.05 μM), and also the length of alkyl chains on the 1′-position of **4c**−**9c** has a similar impact on their anticancer activities, which first increased and then decreased gradually with the increase of 1′-position alkyl chains.

In compound **d**, **e**, **f**, and **g** series (R^1 = R^4 = H, R^3 = OMe (**d**), $NHCH_3$ (**e**), $N(CH_3)_2$ (**f**), and NH_2 (**g**), respectively), the data pointed toward the same trend that all **4d**−**11d**, **5e**−**11e**, **5f**−**11f**, and **4g**−**11g** displayed anticancer activities that first increased and then decreased gradually as the 1′-position alkyl chain length increases. Compound **10g**, with the 1′-position of the purine side chain substituted by *n*-decyl, exhibited the highest anticancer activities against cell lines

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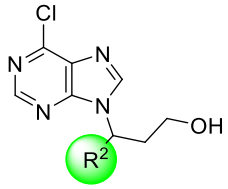
HCT-116 and SW480 (IC_{50} = 2.59, 1.20 μM), which were about 4−10-fold more potent than those of the positive control 5-FU (IC_{50} = 10.81, 9.70 μM). In compound **h** series (R^1 = Cl, R^3 = NH_2, R^4 = H), acyclonucleosides **5h−11h** also continued the same tendency as those of **d**, **e**, **f**, and **g** series.

With the introduction of bromine to the 8-position of the purine skeleton (compound **i** series, R^1 = H, R^3 = Cl, R^4 = Br), all of the resulting acyclonucleosides **5i−9i** showed moderate and not much different anticancer activities with IC_{50} values in the range of 14.13−26.91 μM. The length of alkyl chains on the 1′-position of **5i−9i** also has a slight impact on their anticancer activities, which first increased and then decreased gradually with the increase of 1′-position alkyl chains, with *n*-hexyl (**6i**) and *n*-heptyl (**7i**) being found optimal against cell lines HCT-116 and SW480 (IC_{50} = 14.13−16.22 μM). When 2-, 6-, and 8-positions of the purine skeleton were non-substituted (compound **j** series, R^1 = R^3 = R^4 = H), acyclonucleosides **4j−6j** exhibited no antitumor activity, which implied that the 1−2 substituents like halogens on the purine skeleton contributed greatly to their bioactivities.

Next, some selected compounds (**5c**, **10g**, **11a**, **9b**, **10b**, and **9e**) were further tested against other cancer cells including HeLa, A549, and U87MG, and all of them showed good antitumor activities, whereas 5-FU was inactive with the IC_{50} > 50 μM (Table S1). To clarify the impact of stereochemistry on anticancer activity, both (*R*)- and (*S*)-configured chiral acyclic nucleosides (**7b−9b**) were synthesized asymmetrically and assessed by an MTT assay in this regard (Table 2). All of the

Table 2. Inhibitory Effects of Compounds 7b−9b (*rac*-, *R*-, and *S*-) on Cancer Cell Proliferation



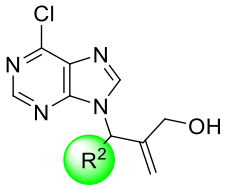
compound	R^2	configuration	IC_{50} (μM)[a] HCT-116[b]	SW480[b]
7b	*n*-C_7H_{15}	*rac*	4.16 ± 1.39	3.63 ± 1.37
		R	2.67 ± 0.37	2.93 ± 0.38
		S	10.72 ± 0.91	3.82 ± 0.97
8b	*n*-C_8H_{17}	*rac*	1.65 ± 0.43	1.37 ± 0.36
		R	1.12 ± 0.28	0.32 ± 0.25
		S	3.40 ± 0.64	2.33 ± 0.40
9b	*n*-C_9H_{19}	*rac*	0.89 ± 0.21	1.15 ± 0.31
		R	0.45 ± 0.10	1.63 ± 0.35
		S	1.05 ± 0.16	3.62 ± 0.66
5-FU			10.81 ± 0.69	9.70 ± 1.22

[a]The antiproliferation activities of individual compounds against tumor cells were determined by the MTT assay. Data are mean ± SEM values from three independent experiments. [b]Both HCT-116 and SW480 are human colon carcinoma cell lines.

(*R*)-configured acyclonucleoside derivatives showed several fold better anticancer activity than their corresponding antipodes, indicating that the (*R*)-configuration of the chiral center benefited the antiproliferative activity.

As shown in Table 3, the introduction of an olefin double bond to the side chain of purines resulted in acyclonucleosides

Table 3. Inhibitory Effect of Compounds 5k−10k on Cancer Cell Proliferation



compound	R^2	IC_{50} (μM)[a] HCT-116[b]	SW480[b]
5k	*n*-C_5H_{11}	>50	>50
6k	*n*-C_6H_{13}	30.21 ± 2.35	32.03 ± 2.08
7k	*n*-C_7H_{15}	22.39 ± 2.18	29.42 ± 2.01
8k	*n*-C_8H_{17}	19.43 ± 2.06	16.22 ± 1.29
9k	*n*-C_9H_{19}	>50	27.61 ± 1.90
10k	Ph	33.33 ± 3.13	12.91 ± 3.97
5-FU		10.81 ± 0.69	9.70 ± 1.22

[a]The antiproliferation activities of individual compounds against tumor cells were determined by the MTT assay. Data are mean ± SEM values from three independent experiments. [b]Both HCT-116 and SW480 are human colon carcinoma cell lines.

5k−10k with somewhat decreased anticancer activities compared with those of corresponding compound **b** series.

Using the hydroxyl group as a handle, simple synthetic manipulation of the promising compound **9b** readily converted it into its OMs, N_3, triazole, Cl, and phosphonoethyl derivatives (**9ba−9be**) in 63.8−75.6% yields and 90−94% *ee*. Furthermore, the diethylphosphonate function of compound **9b** could also be deprotected to generate the corresponding phosphonic acid **9bf** in 44.9% yield (Scheme 3).

As shown in Table 4, when the hydroxyl group on the side chain of **9b** was substituted by several other types of functional groups, all of the derivatives (**9ba−9be**) exerted moderate to potent anticancer activities (IC_{50} = 1.04−13.49 μM) and the azide-substituted **9bb** was found optimal to exhibit the same level of activities as those of **9b**. However, the phosphonic acid **9bf** had almost no antitumor activity. By comparing the antitumor activities of acyclic nucleoside **9b** and phosphonic acid **9bf**, it could be seen that the hydroxyl group in the side chain of **9b** does not form the corresponding nucleoside triphosphate.

Based on the step-by-step investigation of structure−activity relationships, compound **9b** was identified as the most active compound possessing potent *in vitro* anticancer activity against colon cancer cell lines HCT-116 and SW480 with the IC_{50} values of 0.89 and 1.15 μM, respectively, and therefore was selected for further bioactivity evaluation.

4.2. Toxicity against Human Colon Epithelial Cell. The toxicity of compound **9b** against normal cell lines was evaluated using the normal colon epithelial cell line NCM460 with 5-FU as the positive control. As shown in Figure 3, there was no significance between compound **9b** and 5-FU on toxicity against the human colon epithelial cell line NCM460 at 2, 10, and 50 μM.

4.3. Apoptosis Induced by Compound 9b. A slight G0/G1 phase arrest was caused by representative compound **9b** at 16 μM (SI, Figure S1),[37] prompting us to explore further the cell apoptosis induced by this compound. In this analysis, colon cancer cells were treated with vehicle or a solution of

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Scheme 3. Syntheses of Compounds 9ba−9bf

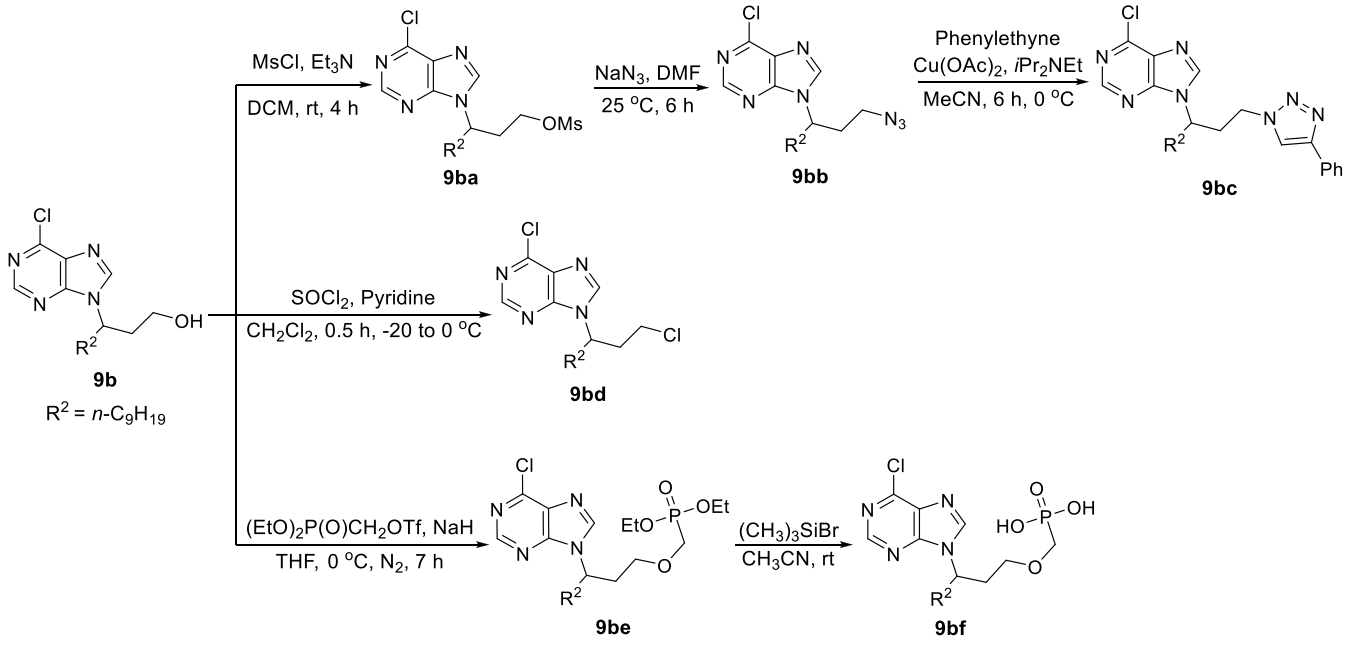
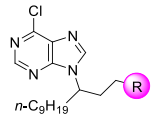


Table 4. Inhibitory Effect of Compounds 9ba−9be on Cancer Cell Proliferation[b]



Compound	R	Configuration	IC_{50} (μM)[a]	
			HCT-116[b]	SW480[b]
9ba	OMs	*rac*	5.44 ± 0.47	5.39 ± 1.28
		R	9.48 ± 1.58	9.72 ± 1.06
9bb	N_3	*rac*	1.04 ± 0.28	1.20 ± 0.58
		R	1.19 ± 0.27	1.22 ± 0.58
9bc		*rac*	13.49 ± 3.77	9.92 ± 2.17
		R	8.13 ± 1.02	8.57 ± 0.89
9bd	Cl	*rac*	10.18 ± 2.55	7.18 ± 2.26
		R	9.58 ± 2.46	3.18 ± 0.97
9be	$OCH_2P(O)(OCH_2CH_3)_2$	*rac*	9.11 ± 1.04	4.79 ± 1.63
		R	10.91 ± 1.26	5.57 ± 1.43
9bf	$OCH_2P(O)(OH)_2$	*rac*	>50	>50
5-FU			10.81 ± 0.69	9.70 ± 1.22

[a]The antiproliferation activities of individual compounds against tumor cells were determined by the MTT assay. Data are mean ± SEM values from three independent experiments. [b]Both HCT-116 and SW480 are human colon carcinoma cell lines.

compound **9b** at different concentrations (2, 4, 8, 16, or 32 μM) for 48 h sequentially and then stained with Annexin V-fluorescein isothiocyanate (FITC) and propidium iodide (PI) in a dark environment. The percentages of apoptotic cells were determined by flow cytometry.[38,39] As shown in Figure 4, compound **9b** induced apoptosis in a concentration-dependent manner, and the percentage of apoptotic cells increased from 6 to 69% in SW480.

The apoptosis induced by compound **9b** in HCT-116 cells is shown in Figure S2 (SI). As the concentration of **9b** increased, the proportion of apoptotic cells also increased steadily from 12 to 66%. The results suggest that compound **9b** could

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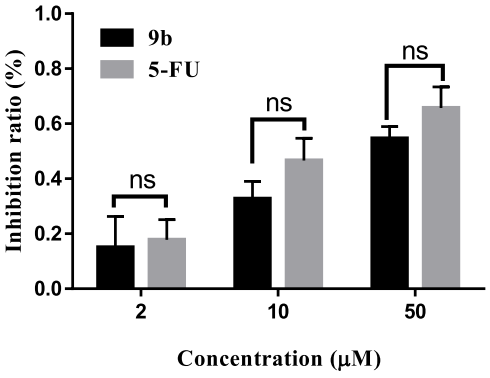

Figure 3. Toxicity of compound **9b** on NCM460.

effectively induce apoptosis in cancer cells in a dose-dependent manner.

4.4. Analysis of the Expression of Apoptosis-Related Proteins (Bax, P53, Bcl-xl, and Cleaved-PARP) Induced by Compound 9b. To probe further into the apoptosis induced by compound **9b**, Bax, P53, Bcl-xl, and Cleaved-PARP were determined with western blotting as the markers of apoptosis.[40−44] As shown in Figure 5, along with the increasing concentrations of compound **9b**, the expressions of Bax, P53, and Cleaved-PARP were also found to increase gradually, whereas the expression of Bcl-xl decreased gradually, suggesting that compound **9b** could induce apoptosis.

4.5. Mitochondrial Membrane Potential (MMP) Assay. The loss of mitochondrial membrane potential (MMP) is considered to be a limiting factor in the apoptotic pathway, which has been regarded as a target for antitumor agents and hence is of high value in controlling cell apoptosis.[45] To investigate the role of mitochondria in the apoptosis induced by compound **9b**, SW480 cells were stained with JC-1, and the effect of compound **9b** on MMP was measured. JC-1 is capable of selectively entering mitochondria, either to form monomers that emit green fluorescence at low MMP or to form aggregates that emit red fluorescence at high MMP. Images acquired using fluorescence microscopy showed that the green area (low MMP) was significantly enlarged with the increasing concentrations of compound **9b** (Figure 6A). Furthermore, flow cytometry results showed that the number of treated cells emitting red fluorescence decreased significantly, while the number of treated cells emitting green fluorescence obviously increased, indicating considerable dissipation of MMP (Figure 6B). The results suggest that the dissipation of MMP may participate in the apoptosis induced by compound **9b**. However, treatment of SW480 cells for 48 h with compound **9b** and Q-VD-OPh,[46] a pan-caspase inhibitor, led only to a negligible change in the proportion of apoptotic cells, suggesting that cell apoptosis induced by compound **9b** did not occur through the caspase signaling pathway (SI, Figure S3).

4.6. Inhibition of Colony Formation by Compound 9b. The effect of compound **9b** on the colony formation of HCT-116 and SW480 was also evaluated. Cells were treated with a solution of compound **9b** at various concentrations for 48 h and allowed to grow for another 14 days in a regular culture medium, and digital images were taken. As shown in Figure 7, the exposure of HCT-116 and SW480 cells to the solutions of compound **9b** at low concentrations resulted in a significant inhibition of colony formation. Cancer cell growth was completely abolished at concentrations of 16 μM and above.

4.7. Metabolic Stability *In Vitro*. Metabolic stability of compound **9b** in human and mouse liver microsome was tested. As shown in Table 5, the $t_{1/2}$ of compound **9b** in human liver microsome was 10 min, which is similar to that of 5-FU in the literature.[47]

4.8. Acute Toxicity of Compound 9b. An acute toxicity assay was performed to assess the safety of compound **9b** *in vivo*. As summarized in Table 6, the LD_{50} value of compound **9b** was 220 mg/kg, which is similar to that of 5-FU in the literature.[47]

4.9. Inhibition Activities of 9b on Tumor Growth in a Xenograft Mice Model. The *in vivo* antitumor activities of compound **9b** were evaluated on the SW480 xenograft mice model.[48] As shown in Figure 8, eight BALB/C mice per group were administered *via* intraperitoneal injection with vehicle, compound **9b** (at dosages of 25 and 50 mg/kg), or 5-FU at a

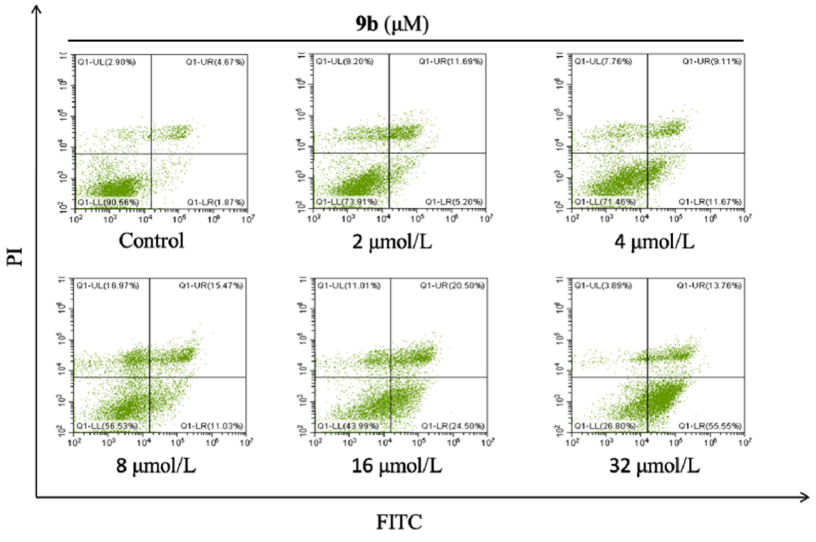

Figure 4. Induction of apoptosis on SW480 cells by compound **9b**. Flow cytometry analysis of apoptotic SW480 cells induced by compound **9b** at different concentrations. Cells were treated with vehicle or compound **9b** at 2, 4, 8, 16, and 32 μM for 48 h.

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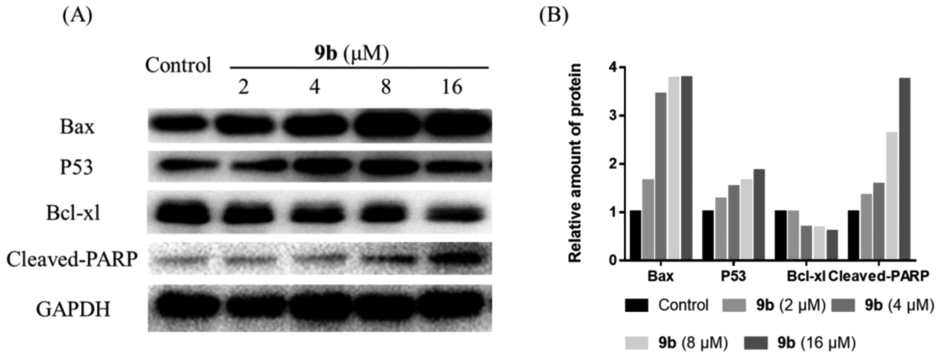

Figure 5. (A) Western blotting analysis of cell-apoptosis-related proteins after treatment with compound **9b** at different concentrations. (B) Relative amount of protein after treatment with compound **9b** at different concentrations.

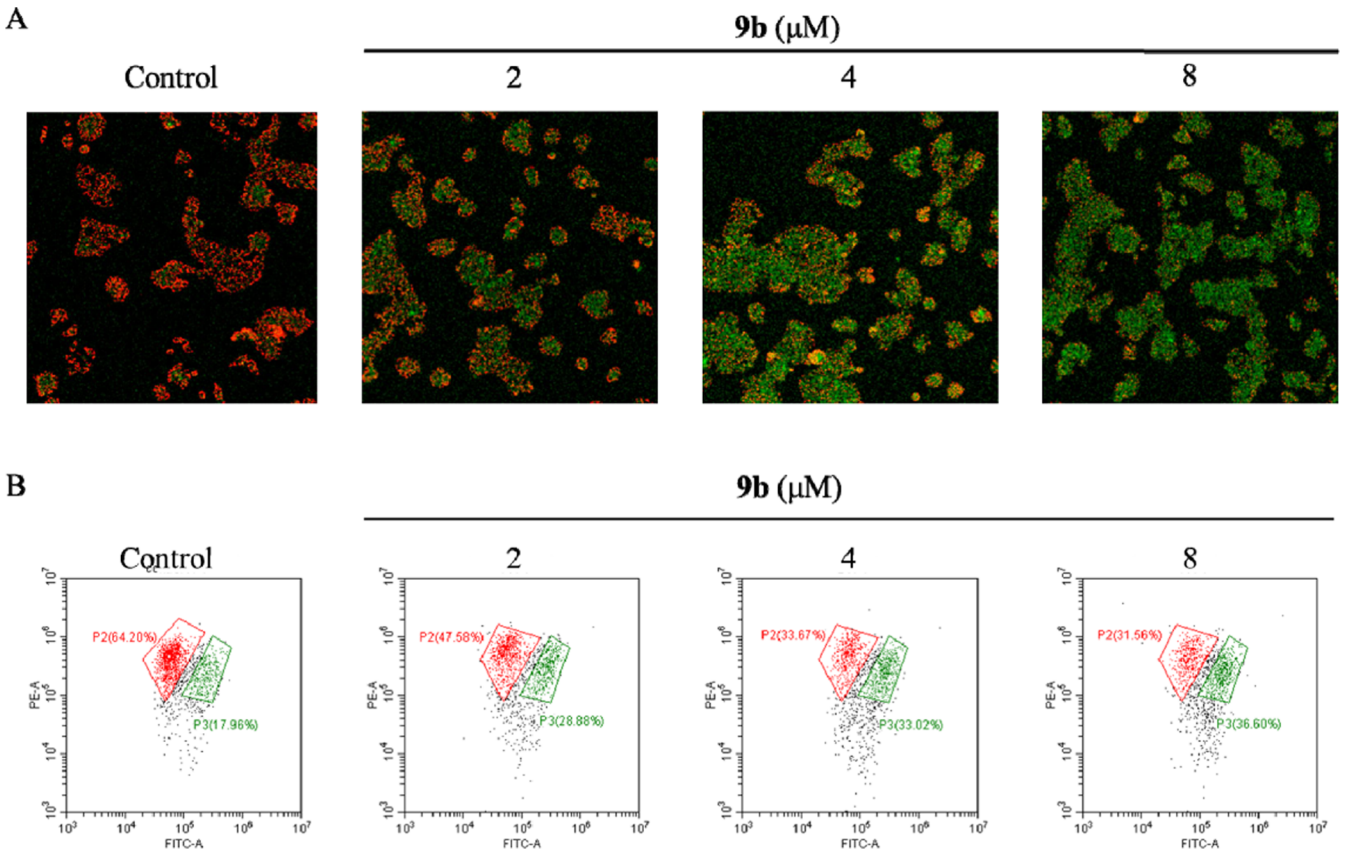

Figure 6. Collapse of the mitochondrial membrane potential on SW480 cells treated by compound **9b**. (A) Changes in the mitochondrial membrane potential were observed using the JC-1 kit under fluorescence microscopy. (B) Flow cytometry was used to detect the mitochondrial membrane potential on SW480 cells.

dosage of 50 mg/kg, once every 2 days over a period of 12 days. As shown in Figure 8A–D, compound **9b** significantly inhibited tumor growth in a dose-dependent manner as measured by tumor weight and volume. At the same time, the body weight of the treated mice did not show any significant decrease, suggesting that this compound may have favorable toxicity properties. As shown in Figure 8E, H & E staining of the tumors showed that the tumors were significantly necrotic after the administration of compound **9b**.

4.10. Fishing for Targets. To identify the targets of these compounds, the biotin-annexed probe **21** and the diazirine-based probe **23** were synthesized and their antitumor activities were tested *in vitro* (Schemes 4, 5, and Table 7).[49,50] Both compounds **21** and **23** showed an inhibitory effect on cancer cell proliferation to some extent.

The biotin-annexed compounds **21** and the diazirine-based probe **23** were tested as noncovalent and covalent binding probes, respectively, to explore the interaction between the acyclic nucleoside moiety and the target proteins. Probes were incubated with SW480 cell lysate, and the linkers were used as negative controls. After incubating overnight, the proteins bounded to probes were pulled down by streptavidin-conjugated beads. The **23**- and **22**-treated samples were separated with sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), transferred to a poly(vinylidene fluoride) (PVDF) member, and incubated with avidin-HRP antibody, which can bind to biotin. As shown in Figure 9A, the

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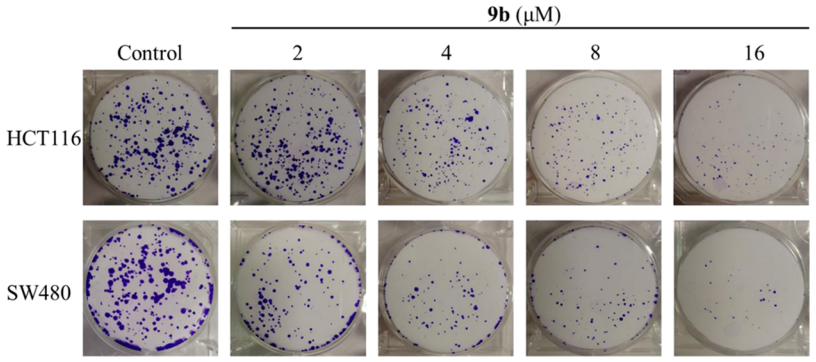

Figure 7. Inhibitory effects of compound **9b** on colony formation of HCT-116 cells and SW480 cells.

Table 5. Metabolic Stability of Compound 9b *In Vitro*

species	$T_{1/2}$[a] (min)	clint *in vitro*[b] (mL/min/g protein)
human	10.8	195
mouse	1.00	2106

[a]$T_{1/2}$: Half-life time. [b]Clint *in vitro*: Intrinsic clearance *in vitro*.

compound-**23**-treated group exhibited a distinct band at 75 Kd, while the linker-**22**-treated and input groups did not show any obvious band. Then, both biotin-annexed compound **21** and the diazirine-based probe **23** were separated with SDS-PAGE and stained by silver staining. The results are shown in Figure 9B,C, which are in agreement with the western blotting results, where obvious bands were discovered at 75 Kd. The silver-stained bands were separated for protein mass spectrometry. Protein mass spectrometry for the **22**-treated band and the **23**-treated band revealed that nucleolin, ezrin, ATP-dependent RNA helicase, or ATP-binding cassette protein might be the targets of these molecules. The target validation is underway in this lab.

5. CONCLUSIONS

In summary, a series of novel acyclic nucleoside compounds were designed, synthesized, and evaluated for their anticancer activities *in vitro* and *in vivo*. Structure−activity relationship studies revealed that many of the target compounds demonstrated *in vitro* anticancer activities, among which **9b** was discovered as the most active compound against colon cancer cells HCT-116 and SW480 with IC_{50} values of 0.89 and 1.15 μM, respectively. All chiral acyclic nucleoside derivatives with an (*R*)-configuration showed anticancer activities several folds better than those of their (*S*)-enantiomers, and the (*R*)-**9b** showed remarkable anticancer activity against colon cancer cells HCT-116 with an IC_{50} value of 0.45 μM.

Compound **9b** was found to arrest the cell cycle slightly at the G0/G1 phase. Cell apoptosis was induced in the presence of compound **9b**, as evidenced by the significant increment on the expression of proapoptosis proteins Bax and P53, as well as the cleavage fragment of PARP. On the other hand, the antiapoptosis protein Bcl-xl was found to attenuate substantially upon treatment with compound **9b**. Further mechanistic studies suggested that the dissipation of MMP may participate in the apoptosis induced by compound **9b**, while the caspase signaling pathway inhibitor Q-VD-OPh may have little effect on cell apoptosis. Compound **9b** was also shown to have a long-term toxicity, in the sense that it can effectively inhibit the colony formation. Moreover, *in vivo* studies showed that compound **9b** could inhibit tumor growth and induce tumor necrosis without affecting the body weight of mice, indicating a potent anticancer activity and low toxicity. The LD_{50} value and metabolic stability *in vitro* of compound **9b** is similar to that of 5-FU.

As an ongoing effort to develop promising drug candidates, we are currently working to decipher the cellular targets of the anticancer ANCs reported herein. The biotin-annexed probe and the diazirine-based probe were synthesized to identify the targets of these compounds, and an obvious band was discovered at 75 Kd. The bands were separated, and the protein mass spectrometry revealed that nucleolin, ezrin, ATP-dependent RNA helicase, or ATP-binding cassette protein

Table 6. Acute Toxicity of Compound 9b on Balb/C Mice

group		number of dead mice				total death	survival (%)
		day 1	day 2	day 3	days 4−15		
300 mg/kg	female	5	0	0	0	10	0
	male	5	0	0	0		
250 mg/kg	female	3	1	0	0	8	20
	male	2	2	0	0		
200 mg/kg	female	3	0	0	0	3	70
	male	0	0	0	0		
150 mg/kg	female	0	0	0	0	0	100
	male	0	0	0	0		
100 mg/kg	female	0	0	0	0	0	100
	male	0	0	0	0		
vehicle	female	0	0	0	0	0	100
	male	0	0	0	0		

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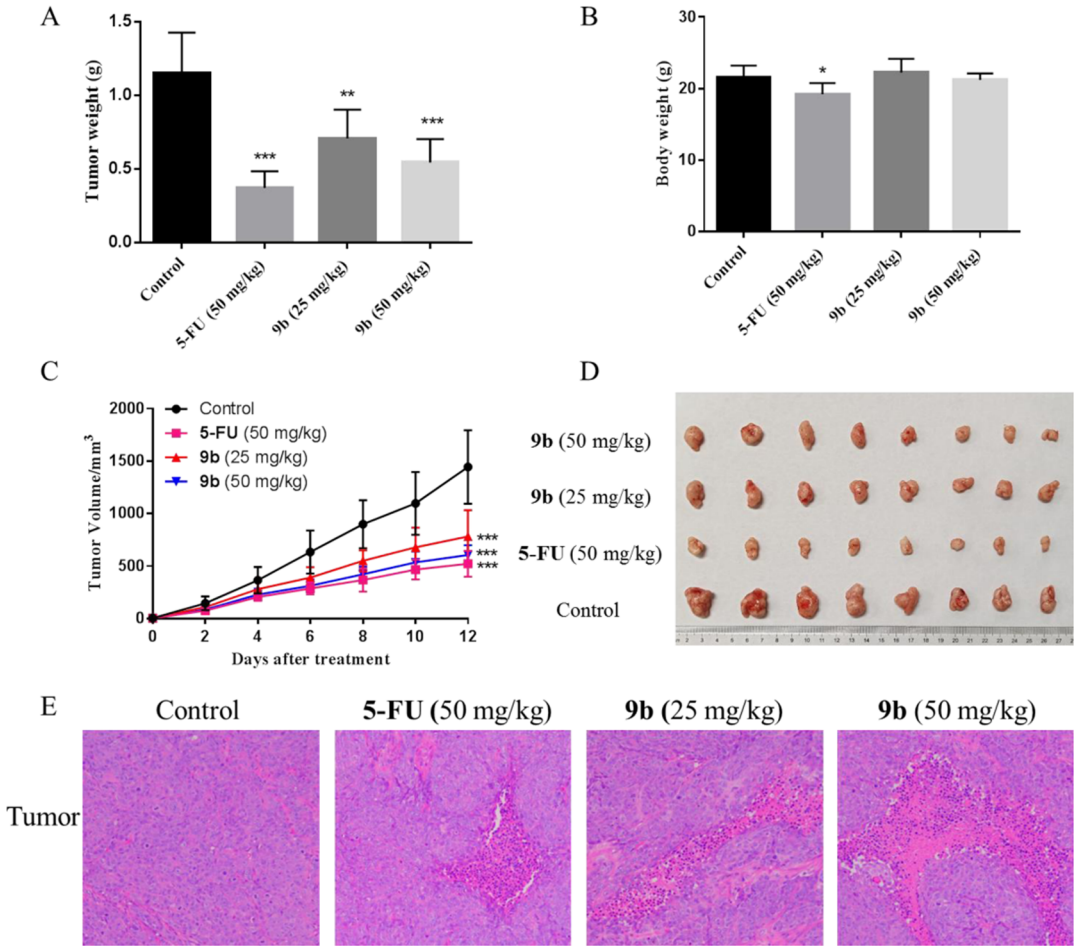
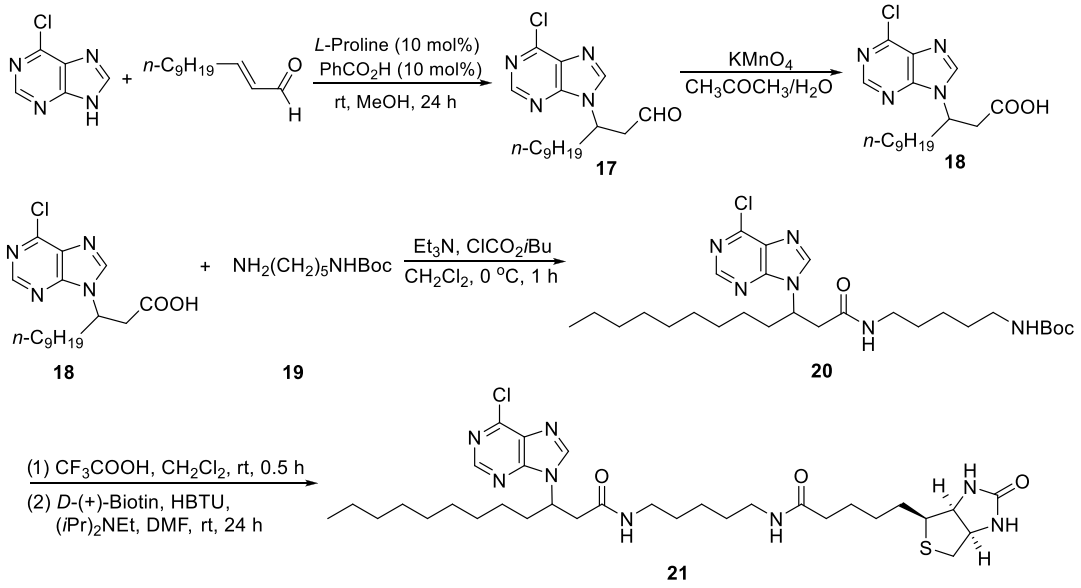


Figure 8. *In vivo* anticancer activity of compound **9b** on the SW480 xenograft mice model. Female BALB/C nude mice were administered by intraperitoneal injection with the vehicle, compound **9b**, at dosages of 25 and 50 mg/kg, or 5-FU at a dosage of 50 mg/kg (n = 8 each group), once every 2 days for 12 days. Average tumor weight (A), average body weight (B), average tumor volume (C), and the isolated tumors (D) were measured. Data are expressed as the mean ± standard error (n = 8). * indicates $P < 0.05$, ** indicates $P < 0.01$, and *** indicates $P < 0.001$ vs control. H & E staining analysis of tumors in nude mice on the SW480 xenograft mice model (E).

Scheme 4. Synthesis of the Biotin-Annexed Probe 21



might be the targets of these molecules. The target validation is underway in this lab.

From a groundbreaking point of view, acyclic nucleoside compound **9b** has demonstrated remarkable potential to be

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Scheme 5. Synthesis of the Diazirine-Based Probe 23

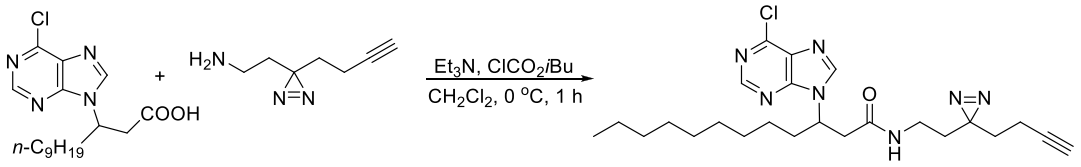

Table 7. Inhibitory Effect of Biotin-Annexed Probe 21 and Diazirine Photoaffinity Probe 23 on Cancer Cell Proliferation

	IC_{50} (μM)[a] ± SEM	
compound	HCT-116[b]	SW480[b]
21	44.74 ± 4.22	45.23 ± 3.26
23	21.49 ± 2.34	13.00 ± 1.65
5-FU	10.81 ± 0.69	9.70 ± 1.22

[a]The antiproliferation activities of individual compounds against tumor cells were determined by the MTT assay. Data are mean ± SEM values from three independent experiments. [b]Both HCT-116 and SW480 are human colon carcinoma cell lines.

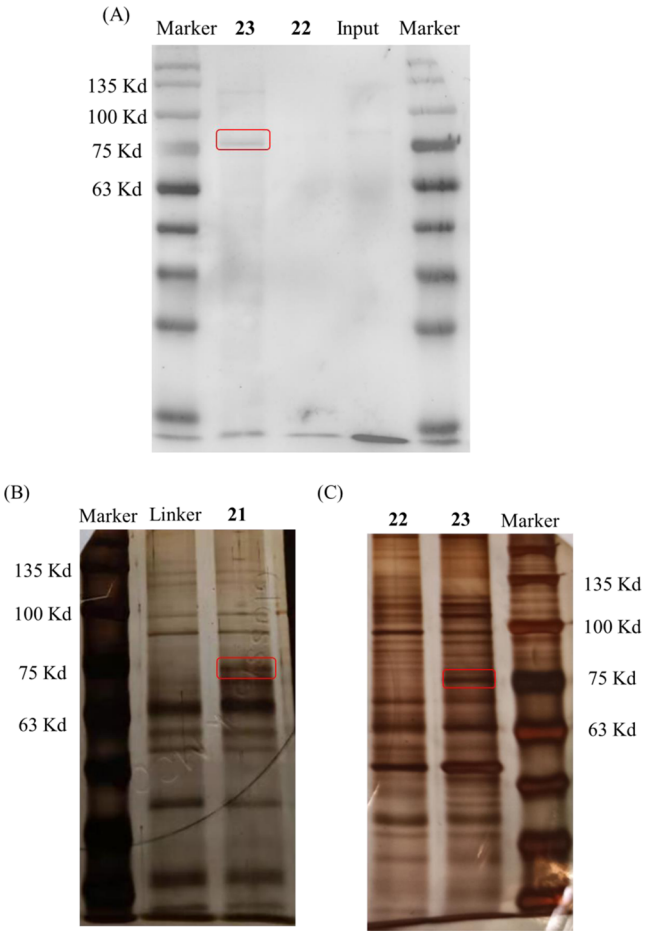

Figure 9. Western blotting and silver staining results of the pull-down samples. (A) Merger of bright field and chemiluminescence of the PVDF member. (B) and (C) Silver staining results of the SDS-PAGE gel.

used as a lead for further development of a brand-new class of anticancer agents. Therefore, this work may open an avenue to further explore the use of ANCs as new and efficacious anticancer agents and is of great significance in the development of more efficient agents for cancer therapy in the future.

6. EXPERIMENTAL SECTION

6.1. General Methods for Chemistry. The purities of all targeted compounds were confirmed to be >95% by high-performance liquid chromatography (HPLC) (SI). All commercial reagents and solvents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectral data were recorded with a Bruker 400 or 600 MHz spectrometer in $CDCl_3$, CD_3OD, D_2O, or DMSO-d_6 using tetramethylsilane (TMS) as the internal standard. Optical rotation was recorded on the Autopol polarimeter. All products were further characterized by high-resolution mass spectrometry (HRMS). HRMS was recorded on an ABI/Sciex QStar mass spectrometer (ESI). Chiral HPLC analysis was recorded on Thermo Scientific Dionex Ultimate 3000 and Agilent Technologies 1260 Infinity. Optical rotations were reported as follows: $[\alpha]_D^T$ (c: = g/100 mL, in solvent). Optical rotations were recorded on an Autopol automatic polarimeter. Targeted compounds were analyzed by a Thermo Scientific UltiMate 3000 HPLC instrument with a UV–visible detector (5 μm, 4.6 mm × 150 mm Agilent C_{18} column).

*6.1.1. 3-(6-Chloro-2-fluoro-9H-purin-9-yl)butan-1-ol (**1a**).* 6-Chloro-2-fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, crotonaldehyde (24.9 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by thin-layer chromatography (TLC). Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **1a** as a white solid in 35.6 mg (72.9% yield). White solid. mp: 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 4.98–4.87 (m, 1H), 3.72–3.63 (m, 1H), 3.44–3.35 (m, 1H), 2.30–2.25 (m, 1H), 2.25–2.11 (m, 2H), 1.71 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 155.9, 153.6, 153.5, 152.9, 152.7, 145.1, 145.0, 130.7, 130.6, 58.6, 50.1, 38.3, 20.5; ESI-HRMS (m/z) calcd $C_9H_{11}ClFN_4O$ ($M + H^+$), 245.0600; found, 245.0601.

*6.1.2. 3-(6-Chloro-2-fluoro-9H-purin-9-yl)pentan-1-ol (**2a**).* 6-Chloro-2-fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-pent-2-enal (29.3 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **2a** as a white solid in 38.2 mg (74.0% yield). White solid. mp: 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 4.69–

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4.59 (m, 1H), 3.69−3.61 (m, 1H), 3.37−3.28 (m, 1H), 2.45 (s, 1H), 2.28−2.17 (m, 2H), 2.17−2.09 (m, 1H), 2.08−1.96 (m, 1H), 0.83 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 155.9, 153.8, 153.7, 152.8, 152.6, 145.73, 145.7, 130.6, 130.5, 58.5, 56.6, 36.5, 27.4, 10.9; ESI-HRMS (m/z) calcd $C_{10}H_{13}ClFN_4O$ (M + H$^+$), 259.0756; found, 259.0762.

*6.1.3. 3-(6-Chloro-2-fluoro-9H-purin-9-yl)hexan-1-ol (**3a**).* 6-Chloro-2-fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-hex-2-enal (34.8 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **3a** as a white solid in 38.1 mg (70.0% yield). White solid. mp: 113−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 4.80−4.71 (m, 1H), 3.70−3.61 (m, 1H), 3.36−3.27 (m, 1H), 2.27−2.16 (m, 3H), 2.16−2.07 (m, 1H), 1.97−1.87 (m, 1H), 1.30−1.20 (m, 1H), 1.19−1.08 (m, 1H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 155.9, 153.8, 153.7, 152.9, 152.7, 145.62, 145.59, 130.61, 130.57, 58.5, 54.6, 36.8, 36.2, 19.6, 13.6; ESI-HRMS (m/z) calcd $C_{11}H_{15}ClFN_4O$ (M + H$^+$), 273.0913; found, 273.0920.

*6.1.4. 3-(6-Chloro-2-fluoro-9H-purin-9-yl)heptan-1-ol (**4a**).* 6-Chloro-2-fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-hept-2-enal (39.3 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **4a** as a white solid in 41.2 mg (72.0% yield). White solid. mp: 118−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 4.76−4.67 (m, 1H), 3.67−3.60 (m, 1H), 3.35−3.27 (m, 1H), 2.82 (s, 1H), 2.27−2.14 (m, 2H), 2.14−2.06 (m, 1H), 1.99−1.89 (m, 1H), 1.32−1.19 (m, 3H), 1.09−0.96 (m, 1H), 0.80 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 156.0, 153.8, 153.7, 152.9, 152.7, 145.61, 145.58, 130.64, 130.59, 58.6, 54.9, 36.9, 33.9, 28.4, 22.2, 13.9; ESI-HRMS (m/z) calcd $C_{12}H_{17}ClFN_4O$ (M + H$^+$), 287.1069; found, 287.1078.

*6.1.5. 3-(6-Chloro-2-fluoro-9H-purin-9-yl)octan-1-ol (**5a**).* 6-Chloro-2-fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-oct-2-enal (44.8 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **5a** as a white solid in 45.6 mg (76.0% yield). White solid. mp: 115−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 4.77−4.66 (m, 1H), 3.70−3.59 (m, 1H), 3.35−3.27 (m, 1H), 2.77 (s, 1H), 2.27−2.15 (m, 2H), 2.15−2.06 (m, 1H), 1.99−1.87 (m, 1H), 1.26−1.17 (m, 5H), 1.11−1.01 (m, 1H), 0.79 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 155.8, 153.8, 153.6, 152.7, 152.5, 145.78, 145.75, 130.50, 130.45, 58.4, 55.0, 36.7, 34.1, 31.2, 25.9, 22.4, 13.9; ESI-HRMS (m/z) calcd $C_{13}H_{19}ClFN_4O$ (M + H$^+$), 301.1226; found, 301.1235.

*6.1.6. 3-(6-Chloro-2-fluoro-9H-purin-9-yl)nonan-1-ol (**6a**).* 6-Chloro-2-fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-non-2-enal (49.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **6a** as a white solid in 49.6 mg (78.9% yield). White solid. mp: 114−116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 4.76−4.66 (m, 1H), 3.67−3.59 (m, 1H), 3.35−3.26 (m, 1H), 2.61 (s, 1H), 2.26−2.15 (m, 2H), 2.15−2.05 (m, 1H), 1.98−1.88 (m, 1H), 1.29−1.10 (m, 7H), 1.10−0.96 (m, 1H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 155.9, 153.8, 153.6, 152.7, 152.5, 145.74, 145.71, 130.53, 130.48, 58.4, 55.0, 36.8, 34.2, 31.5, 28.7, 26.2, 22.5, 14.0; ESI-HRMS (m/z) calcd $C_{14}H_{21}ClFN_4O$ (M + H$^+$), 315.1382; found, 315.1383.

*6.1.7. 3-(6-Chloro-2-fluoro-9H-purin-9-yl)decan-1-ol (**7a**).* 6-Chloro-2-fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dec-2-enal (54.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **7a** as a white solid in 48.2 mg (73.2% yield). White solid. mp: 104−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 4.77−4.67 (m, 1H), 3.67−3.59 (m, 1H), 3.35−3.26 (m, 1H), 2.91 (s, 1H), 2.26−2.15 (m, 2H), 2.15−2.05 (m, 1H), 1.99−1.87 (m, 1H), 1.25−1.13 (m, 9H), 1.10−0.98 (m, 1H), 0.80 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 155.9, 153.8, 153.7, 152.9, 152.7, 145.64, 145.61, 130.61, 130.56, 58.5, 54.9, 36.9, 34.2, 31.7, 29.1, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{15}H_{23}ClFN_4O$ (M + H$^+$), 329.1539; found, 329.1540.

*6.1.8. 3-(6-Chloro-2-fluoro-9H-purin-9-yl)undecan-1-ol (**8a**).* 6-Chloro-2-fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-undec-2-enal (59.5 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **8a** as a white solid in 55.2 mg (80.7% yield). White solid. mp: 116−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 4.76−4.67 (m, 1H), 3.68−3.60 (m, 1H), 3.36−3.26 (m, 1H), 2.32 (s, 1H), 2.25−2.15 (m, 2H), 2.15−2.06 (m, 1H), 1.99−1.88 (m, 1H), 1.28−1.21 (m, 4H), 1.21−1.15 (m, 7H), 1.11−1.00 (m, 1H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 155.9, 153.8,

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153.7, 152.8, 152.7, 145.7, 145.6, 130.6, 130.5, 58.5, 54.9, 36.8, 34.2, 31.8, 29.3, 29.2, 29.1, 26.3, 22.7, 14.1; ESI-HRMS (m/z) calcd $C_{16}H_{25}ClFN_4O$ (M + H^+), 343.1695; found, 343.1697.

*6.1.9. 3-(6-Chloro-2-fluoro-9H-purin-9-yl)dodecan-1-ol (**9a**).* 6-Chloro-2-fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dodec-2-enal (64.4 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **9a** as a white solid in 58.7 mg (82.4% yield). White solid. mp: 113−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 4.76−4.67 (m,1H), 3.68−3.60 (m, 1H), 3.35−3.26 (m, 1H), 2.50 (s, 1H), 2.26−2.15 (m, 2H), 2.14−2.06 (m, 1H), 1.98−1.88 (m, 1H), 1.27−1.21 (m, 4H), 1.21−1.14 (m, 9H), 1.10−1.00 (m, 1H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 155.9, 153.8, 153.6, 152.8, 152.6, 145.72, 145.68, 130.6, 130.5, 58.5, 55.0, 36.8, 34.2, 31.9, 29.5, 29.4, 29.3, 29.1, 26.3, 22.7, 14.1; ESI-HRMS (m/z) calcd $C_{17}H_{27}ClFN_4O$ (M + H^+), 357.1852; found, 357.1850.

*6.1.10. 4-(Benzyloxy)-3-(6-chloro-2-fluoro-9H-purin-9-yl)butan-1-ol (**10a**).* 6-Chloro-2- fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-4-(benzyloxy)but-2-enal (52.8 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **10a** as a white solid in 54.7 mg (78.2% yield). White solid. mp: 96−97 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.25−7.22 (m, 3H), 7.13−7.10 (m, 2H), 4.98−4.93 (m, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 3.96 (dd, J = 10.2, 6.6 Hz, 1H), 3.76 (dd, J = 10.2, 3.6 Hz, 1H), 3.70−3.64 (m, 1H), 3.42−3.36 (m, 1H), 2.47 (s, 1H), 2.32−2.26 (m, 1H), 2.20−2.14 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.6, 156.2, 153.6, 153.5, 152.5, 152.4, 146.6, 146.5, 137.0, 130.32, 130.29, 128.5, 128.2, 127.9, 73.4, 69.8, 58.3, 54.0, 33.1; ESI-HRMS (m/z) calcd $C_{16}H_{17}ClFN_4O_2$ (M + H^+), 351.1019; found, 351.1020.

*6.1.11. 2-(6-Chloro-2-fluoro-9H-purin-9-yl)-4-hydroxybutyl Benzoate (**11a**).* 6-Chloro- 2-fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-4-oxobut-2-en-1-yl benzoate (57.0 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **11a** as a white solid in 58.7 mg (80.6% yield). White solid. mp: 138−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.85 (d, J = 7.6 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 5.25−5.16 (m, 1H), 4.89 (dd, J = 12.0, 8.0 Hz, 1H), 4.73 (dd, J = 12.0, 4.0 Hz, 1H), 3.85−3.77 (m, 1H), 3.53−3.44 (m, 1H), 2.52−2.42 (m, 1H), 2.39−2.29 (m, 1H), 2.18 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 157.8, 156.3, 153.7, 153.6, 153.0, 152.9, 145.94, 145.92, 133.8, 130.7, 130.6, 129.6, 128.9, 128.7, 64.9, 58.1, 53.8, 32.4; ESI-HRMS (m/z) calcd $C_{16}H_{15}ClFN_4O_3$ (M + H^+), 365.0811; found, 365.0809.

*6.1.12. 4-(tert-Butyldimethylsilyl)-3-(6-chloro-2-fluoro-9H-purin-9-yl)butan-1-ol (**12a**).* 6-Chloro-2-fluoro-9*H*-purine (34.5 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-4-((tert-butyldimethylsilyl)oxy)but-2-enal (60.0 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 2:1) to give the target compound **12a** as a white solid in 58.9 mg (78.8% yield). White solid. mp: 83−85 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (s, 1H), 4.92−4.87 (m, 1H), 4.05 (dd, J = 10.8, 5.4 Hz, 1H), 3.91 (dd, J = 10.8, 3.6 Hz, 1H), 3.73−3.69 (m, 1H), 3.47−3.42 (m, 1H), 2.41 (s, 1H), 2.33−2.27 (m, 1H), 2.21−2.14 (m, 1H), 0.80 (s, 9H), −0.06 (d, J = 11.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 156.0, 153.8, 153.6, 152.7, 152.5, 146.4, 146.4, 130.24, 130.19, 64.1, 58.5, 55.3, 33.0, 25.8, 18.1, −5.5, −5.7; ESI-HRMS (m/z) calcd $C_{15}H_{25}ClFN_4O_2Si$ (M + H^+), 375.1414; found, 375.1424.

*6.1.13. 3-(6-Chloro-2-fluoro-9H-purin-9-yl)propan-1-ol (**13a**).* 6-Chloro-2-fluoro-9*H*-purine (1.55 g, 10 mmol), potassium carbonate (1.66 g, 12 mmol), and dry *N*,*N*-dimethylformamide (DMF) (25.0 mL) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 0 °C for 1 h under a N_2 atmosphere. Then, methyl 3-bromopropionate (1.3 mL, 12 mmol) was slowly added to the reaction mixture. The reaction was stirred at room temperature for 48 h and detected by TLC. Then, water was added to the reaction and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 3:1) to give the compound methyl 3-(6-chloro-2-fluoro- 9*H*-purin-9-yl)propanoate as a pale-yellow solid in 2.08 g (80.6% yield). The solution of methyl 3-(6-chloro-2-fluoro-9*H*-purin-9-yl)propanoate (25.8 mg, 0.1 mmol) in dry CH_2Cl_2 (1.0 mL) was cooled to −78 °C under N_2. DIBAL-H (0.3 mL, 1.0 M in toluene, 0.3 mmol) was added dropwise at −78 °C. The reaction was stirred at −78 °C for 20 min and then stirred at room temperature until methyl 3-(6-chloro-2-fluoro-9*H*-purin-9-yl)propanoate was completely consumed. After that, the reaction was quenched with 10% NaOH solution. Then, water was added to the residue and the mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **13a** as a white solid in 18.6 mg (80.9% yield). White solid. mp: 111−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 4.43 (t, J = 6.8 Hz, 2H), 3.65 (t, J = 5.4 Hz, 2H), 2.24 (s, 1H), 2.18−2.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 156.3, 154.0, 153.8, 153.0, 152.8, 146.6, 146.5, 130.5, 130.4, 58.5, 41.4, 31.8; ESI-HRMS (m/z) calcd $C_8H_9ClFN_4O$ (M + H^+), 231.0443; found, 231.0442.

*6.1.14. 3-(6-Chloro-9H-purin-9-yl)butan-1-ol (**1b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, crotonaldehyde (24.9 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added

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to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **1b** as a white solid in 38.0 mg (84.1% yield). White solid. mp: 104−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.19 (s, 1H), 5.08−4.98 (m, 1H), 3.71−3.59 (m, 1H), 3.33−3.21 (m, 1H), 2.80 (s, 1H), 2.26−2.04 (m, 2H), 1.75 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.9, 151.7, 151.4, 144.0, 131.9, 58.4, 49.3, 39.2, 20.7; ESI-HRMS (m/z) calcd $C_9H_{12}ClN_4O$ (M + H^+), 227.0694; found, 227.0694.

*6.1.15. 3-(6-Chloro-9H-purin-9-yl)pentan-1-ol (**2b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-pent-2-enal (29.3 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **2b** as a white solid in 39.4 mg (82.1% yield). White solid. mp: 100−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.14 (s, 1H), 4.79−4.70 (m, 1H), 3.67−3.60 (m, 1H), 3.28−3.19 (m, 1H), 2.69 (s, 1H), 2.28−2.12 (m, 3H), 2.12−1.99 (m, 1H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.2, 151.8, 151.3, 144.6, 131.9, 58.4, 55.8, 37.2, 27.6, 11.0; ESI-HRMS (m/z) calcd $C_{10}H_{14}ClN_4O$ (M + H^+), 241.0851; found, 241.0855.

*6.1.16. 3-(6-Chloro-9H-purin-9-yl)hexan-1-ol (**3b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-hex-2-enal (34.8 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **3b** as a white solid in 40.1 mg (78.9% yield). White solid. mp: 105−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.14 (s, 1H), 4.91−4.81 (m, 1H), 3.69−3.58 (m, 1H), 3.20 (t, J = 9.2 Hz, 1H), 2.47 (s, 1H), 2.27−2.08 (m, 3H), 2.03−1.91 (m, 1H), 1.34−1.12 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 151.8, 151.3, 144.5, 131.9, 58.4, 53.8, 37.6, 36.4, 19.6, 13.6; ESI-HRMS (m/z) calcd $C_{11}H_{16}ClN_4O$ (M + H^+), 255.1007; found, 255.1014.

*6.1.17. 3-(6-Chloro-9H-purin-9-yl)heptan-1-ol (**4b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-hept-2-enal (39.3 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **4b** as a white solid in 44.0 mg (82.3% yield). White solid. mp: 87−89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.14 (s, 1H), 4.88−4.78 (m, 1H), 3.68−3.58 (m, 1H), 3.25−3.15 (m, 1H), 2.49 (s, 1H), 2.28−2.07 (m, 3H), 2.05−1.94 (m, 1H), 1.39−1.19 (m, 3H), 1.15−1.02 (m, 1H), 0.83 (t, J = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.2, 151.8, 151.4, 144.5, 131.9, 58.4, 54.1, 37.7, 34.1, 28.5, 22.3, 13.9; ESI-HRMS (m/z) calcd $C_{12}H_{18}ClN_4O$ (M + H^+), 269.1164; found, 269.1166.

*6.1.18. 3-(6-Chloro-9H-purin-9-yl)octan-1-ol (**5b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-oct-2-enal (44.8 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **5b** as a white solid in 45.7 mg (81.1% yield). White solid. mp: 113−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.13 (s, 1H), 4.86−4.76 (m, 1H), 3.65−3.57 (m, 1H), 3.26−3.17 (m, 1H), 2.87 (s, 1H), 2.22−2.10 (m, 3H), 2.01−1.91 (m, 1H), 1.28−1.16 (m, 5H), 1.12−1.03 (m, 1H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.7, 151.2, 144.7, 131.8, 58.3, 54.2, 37.5, 34.3, 31.2, 26.0, 22.4, 14.0; ESI-HRMS (m/z) calcd $C_{13}H_{20}ClN_4O$ (M + H^+), 283.1320; found, 283.1330.

*6.1.19. 3-(6-Chloro-9H-purin-9-yl)nonan-1-ol (**6b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-non-2-enal (49.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **6b** as a white solid in 49.1 mg (83.2% yield). White solid. mp: 99−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.13 (s, 1H), 4.88−4.77 (m, 1H), 3.66−3.58 (m, 1H), 3.26−3.16 (m, 1H), 2.59 (s, 1H), 2.27−2.08 (m, 3H), 2.03−1.93 (m, 1H), 1.29−1.15 (m, 7H), 1.14−1.05 (m, 1H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 151.8, 151.4, 144.5, 131.9, 58.4, 54.1, 37.6, 34.4, 31.6, 28.8, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{14}H_{22}ClN_4O$ (M + H^+), 297.1477; found, 297.1479.

*6.1.20. 3-(6-Chloro-9H-purin-9-yl)decan-1-ol (**7b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dec-2-enal (54.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **7b** as a white solid in 52.8 mg (85.2% yield). White solid. mp: 101−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.13 (s, 1H), 4.86−4.76 (m, 1H), 3.65−3.57 (m, 1H), 3.26−3.16 (m, 1H), 2.84 (s, 1H), 2.25−2.09 (m, 3H), 2.02−1.91 (m, 1H), 1.27−1.12 (m, 9H), 1.10−1.01 (m, 1H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.7, 151.2, 144.6, 131.8, 58.3, 54.2, 37.5, 34.3, 31.7, 29.04,

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29.03, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{15}H_{24}ClN_4O$ ($M + H^+$), 311.1633; found, 311.1633.

*6.1.21. (R)-3-(6-Chloro-9H-purin-9-yl)decan-1-ol ((R)-**7b**).* Toluene (2.0 mL), benzoic acid (2.4 mg, 0.02 mmol), (*E*)-dec-2-enal (54.7 μL, 0.3 mmol), and (*S*)-2-[(bis(3,5-bis(trifluoromethyl)-phenyl)trimethylsilanyloxy)methyl]pyrrolidine (Cat. II) (11.9 mg, 0.02 mmol) were added to a reaction tube with a magnetic stirring bar. The mixture was stirred for 30 min at room temperature, and then, 6-chloro-9*H*-purine (30.9 mg, 0.2 mmol) was added at −30 °C. The reaction was stirred at −30 °C for 24 h and detected by TLC. The resulting mixture was diluted with precooled MeOH (1.0 mL). $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added, and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound (*R*)-**7b** as a white solid in 34.0 mg (54.8% yield). White solid. mp: 101−102 °C. $[\alpha]_D^{20}$ = −8.4 (*c* = 0.14, $CHCl_3$), 91% ee [CHIRALCEL ID, *n*-hexane/2-propanol = 95/5, flow rate = 0.8 mL/min, temperature = 25 °C, λ = 250 nm, retention time: 30.142 min (minor), 32.460 min (major)]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.13 (s, 1H), 4.86−4.76 (m, 1H), 3.65−3.57 (m, 1H), 3.26−3.16 (m, 1H), 2.84 (s, 1H), 2.25−2.09 (m, 3H), 2.02−1.91 (m, 1H), 1.27−1.12 (m, 9H), 1.10−1.01 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.7, 151.2, 144.6, 131.8, 58.3, 54.2, 37.5, 34.3, 31.7, 29.04, 29.03, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{15}H_{24}ClN_4O$ ($M + H^+$), 311.1633; found, 311.1633.

*6.1.22. (S)-3-(6-Chloro-9H-purin-9-yl)decan-1-ol ((S)-**7b**).* Toluene (2.0 mL), benzoic acid (2.4 mg, 0.02 mmol), (*E*)-dec-2-enal (54.7 μL, 0.3 mmol), and (*R*)-2-[(bis(3,5-bis(trifluoromethyl)-phenyl)trimethylsilanyloxy)methyl]pyrrolidine (Cat. III) (11.9 mg, 0.02 mmol) were added to a reaction tube with a magnetic stirring bar. The mixture was stirred for 30 min at room temperature and then 6-chloro-9*H*-purine (30.9 mg, 0.2 mmol) was added at −30 °C. The reaction was stirred at −30 °C for 24 h and detected by TLC. The resulting mixture was diluted with precooled MeOH (1.0 mL). $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added, and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound (*S*)-**7b** as a white solid in 33.2 mg (53.5% yield). White solid. mp: 101−102 °C. $[\alpha]_D^{20}$ = 8.4 (*c* = 0.14, $CHCl_3$), 91% ee [CHIRALCEL ID, *n*-hexane/2-propanol = 95/5, flow rate = 0.8 mL/min, temperature = 25 °C, λ = 250 nm, retention time: 29.500 min (major), 34.580 min (minor)]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.13 (s, 1H), 4.86−4.76 (m, 1H), 3.65−3.57 (m, 1H), 3.26−3.16 (m, 1H), 2.84 (s, 1H), 2.25−2.09 (m, 3H), 2.02−1.91 (m, 1H), 1.27−1.12 (m, 9H), 1.10−1.01 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.7, 151.2, 144.6, 131.8, 58.3, 54.2, 37.5, 34.3, 31.7, 29.04, 29.03, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{15}H_{24}ClN_4O$ ($M + H^+$), 311.1633; found, 311.1633.

*6.1.23. 3-(6-Chloro-9H-purin-9-yl)undecan-1-ol (**8b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-undec-2-enal (59.5 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **8b** as a white solid in 51.1 mg (78.8% yield). White solid. mp: 106−108 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.13 (s, 1H), 4.86−4.76 (m, 1H), 3.66−3.57 (m, 1H), 3.27−3.15 (m, 1H), 2.80 (s, 1H), 2.25−2.10 (m, 3H), 2.02−1.91 (m, 1H), 1.25−1.20 (m, 4H), 1.20−1.14 (m, 7H), 1.12−1.02 (m, 1H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.8, 151.3, 144.6, 131.8, 58.3, 54.2, 37.5, 34.4, 31.8, 29.3, 29.2, 29.1, 26.3, 22.7, 14.1; ESI-HRMS (m/z) calcd $C_{16}H_{26}ClN_4O$ ($M + H^+$), 325.1790; found, 325.1795.

*6.1.24. (R)-3-(6-Chloro-9H-purin-9-yl)decan-1-ol ((R)-**8b**).* Toluene (2.0 mL), benzoic acid (2.4 mg, 0.02 mmol), (*E*)-undec-2-enal (59.5 μL, 0.3 mmol), and (*S*)-2-[(bis(3,5-bis(trifluoromethyl)-phenyl)trimethylsilanyloxy)methyl]pyrrolidine (Cat. II) (11.9 mg, 0.02 mmol) were added to a reaction tube with a magnetic stirring bar. The mixture was stirred for 30 min at room temperature, and then, 6-chloro-9*H*-purine (30.9 mg, 0.2 mmol) was added at −30 °C. The reaction was stirred at −30 °C for 24 h and detected by TLC. The resulting mixture was diluted with precooled MeOH (1.0 mL). $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added, and the reaction was stirred for 10 min. Then, the reaction was quenched with saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound (*R*)-**8b** as a white solid in 34.1 mg (52.6% yield). White solid. mp: 101−102 °C. $[\alpha]_D^{20}$ = −2.9 (*c* = 0.14, $CHCl_3$), 91% ee [CHIRALCEL ID, *n*-hexane/2-propanol = 95/5, flow rate = 0.8 mL/min, temperature = 25 °C, λ = 250 nm, retention time: 28.368 min (minor), 30.165 min (major)]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.13 (s, 1H), 4.86−4.76 (m, 1H), 3.65−3.57 (m, 1H), 3.26−3.16 (m, 1H), 2.84 (s, 1H), 2.25−2.09 (m, 3H), 2.02−1.91 (m, 1H), 1.27−1.12 (m, 9H), 1.10−1.01 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.7, 151.2, 144.6, 131.8, 58.3, 54.2, 37.5, 34.3, 31.7, 29.04, 29.03, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{16}H_{26}ClN_4O$ ($M + H^+$), 325.1790; found, 325.1795.

*6.1.25. (S)-3-(6-Chloro-9H-purin-9-yl)decan-1-ol ((S)-**8b**).* Toluene (2.0 mL), benzoic acid (2.4 mg, 0.02 mmol), (*E*)-undec-2-enal (59.5 μL, 0.3 mmol), and (*R*)-2-[(bis(3,5-bis(trifluoromethyl)-phenyl)trimethylsilanyloxy)methyl]pyrrolidine (Cat. III) (11.9 mg, 0.02 mmol) were added to a reaction tube with a magnetic stirring bar. The mixture was stirred for 30 min at room temperature, and then, 6-chloro-9*H*-purine (30.9 mg, 0.2 mmol) was added at −30 °C. The reaction was stirred at −30 °C for 24 h and detected by TLC. The resulting mixture was diluted with precooled MeOH (1.0 mL). $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added, and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound (*S*)-**8b** as a white solid in 32.7 mg (50.5% yield). White solid. mp: 101−102 °C. $[\alpha]_D^{20}$ = 3.0 (*c* = 0.20, $CHCl_3$), 92% ee [CHIRALCEL ID, *n*-hexane/2-propanol = 95/5, flow rate = 0.8 mL/min, temperature = 25 °C, λ = 250 nm, retention time: 28.079 min (major), 32.026 min (minor)]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.13 (s, 1H), 4.86−4.76 (m, 1H), 3.65−3.57 (m, 1H), 3.26−3.16 (m, 1H), 2.84 (s, 1H), 2.25−2.09 (m, 3H), 2.02−1.91 (m, 1H), 1.27−1.12 (m, 9H), 1.10−1.01 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.7, 151.2, 144.6, 131.8, 58.3, 54.2, 37.5, 34.3, 31.7, 29.04, 29.03, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{16}H_{26}ClN_4O$ ($M + H^+$), 325.1790; found, 325.1795

*6.1.26. 3-(6-Chloro-9H-purin-9-yl)dodecan-1-ol (**9b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dodec-2-enal (64.4 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$

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(22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 3:1) to give the target compound **9b** as a white solid in 52.4 mg (77.5% yield). White solid. mp: 101−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.17 (s, 1H), 4.86−4.77 (m, 1H), 3.65−3.57 (m, 1H), 3.26−3.17 (m, 1H), 2.93 (s, 1H), 2.23−2.10 (m, 3H), 2.01−1.90 (m, 1H), 1.25−1.20 (m, 4H), 1.20−1.14 (m, 9H), 1.11−1.02 (m, 1H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.7, 151.2, 144.7, 131.8, 58.3, 54.2, 37.5, 34.3, 31.9, 29.44, 29.36, 29.2, 29.1, 26.3, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{17}H_{28}ClN_4O$ (M + H$^+$), 339.1946; found, 339.1945.

*6.1.27. (R)-3-(6-Chloro-9H-purin-9-yl)decan-1-ol ((R)-**9b**).* Toluene (2.0 mL), benzoic acid (2.4 mg, 0.02 mmol), (*E*)-dodec-2-enal (64.4 μL, 0.3 mmol), and (*S*)-2-[(bis(3,5-bis(trifluoromethyl)-phenyl)trimethylsilanyloxy)methyl]pyrrolidine (Cat. II) (11.9 mg, 0.02 mmol) were added to a reaction tube with a magnetic stirring bar. The mixture was stirred for 30 min at room temperature and then 6-chloro-9*H*-purine (30.9 mg, 0.2 mmol) was added at −30 °C. The reaction was stirred at −30 °C for 24 h and detected by TLC. The resulting mixture was diluted with precooled MeOH (1.0 mL). $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added, and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound (*R*)-**9b** as a white solid in 34.8 mg (51.5% yield). White solid. mp: 101−102 °C. $[\alpha]_D^{20}$ = −5.0 (c = 0.12, $CHCl_3$), 95% ee [CHIRALCEL ID, *n*-hexane/2-propanol = 95/5, flow rate = 0.8 mL/min, temperature = 25 °C, λ = 250 nm, retention time: 26.768 min (minor), 28.771 min (major)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.13 (s, 1H), 4.86−4.76 (m, 1H), 3.65−3.57 (m, 1H), 3.26−3.16 (m, 1H), 2.84 (s, 1H), 2.25−2.09 (m, 3H), 2.02−1.91 (m, 1H), 1.27−1.12 (m, 9H), 1.10−1.01 (m, 1H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.7, 151.2, 144.6, 131.8, 58.3, 54.2, 37.5, 34.3, 31.7, 29.04, 29.03, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{17}H_{28}ClN_4O$ (M + H$^+$), 339.1946; found, 339.1945.

*6.1.28. (S)-3-(6-Chloro-9H-purin-9-yl)decan-1-ol ((S)-**9b**).* Toluene (2.0 mL), benzoic acid (2.4 mg, 0.02 mmol), (*E*)-dodec-2-enal (64.4 μL, 0.3 mmol), and (*R*)-2-[(bis(3,5-bis(trifluoromethyl)-phenyl)trimethylsilanyloxy)methyl]pyrrolidine (Cat. III) (11.9 mg, 0.02 mmol) were added to a reaction tube with a magnetic stirring bar. The mixture was stirred for 30 min at room temperature, and then, 6-chloro-9*H*-purine (30.9 mg, 0.2 mmol) was added at −30 °C. The reaction was stirred at −30 °C for 24 h and detected by TLC. The resulting mixture was diluted with precooled MeOH (1.0 mL). $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added, and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound (*S*)-**9b** as a white solid in 33.4 mg (50.9% yield). White solid. mp: 101−102 °C. $[\alpha]_D^{20}$ = 5.0 (c = 0.12, $CHCl_3$), 95% ee [CHIRALCEL ID, *n*-hexane/2-propanol = 95/5, flow rate = 0.8 mL/min, temperature = 25 °C, λ = 250 nm, retention time: 25.799 min (major), 29.523 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.13 (s, 1H), 4.86−4.76 (m, 1H), 3.65−3.57 (m, 1H), 3.26−3.16 (m, 1H), 2.84 (s, 1H), 2.25−2.09 (m, 3H), 2.02−1.91 (m, 1H), 1.27−1.12 (m, 9H), 1.10−1.01 (m, 1H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.7, 151.2, 144.6, 131.8, 58.3, 54.2, 37.5, 34.3, 31.7, 29.04, 29.03, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{17}H_{28}ClN_4O$ (M + H$^+$), 339.1946; found, 339.1945.

*6.1.29. 3-(6-Chloro-9H-purin-9-yl)tridecan-1-ol (**10b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-tridec-2-enal (58.9 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **10b** as a white solid in 55.5 mg (78.8% yield). White solid. mp: 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.13 (s, 1H), 4.86−4.77 (m, 1H), 3.66−3.58 (m, 1H), 3.25−3.17 (m, 1H), 2.65 (s, 1H), 2.26−2.08 (m, 3H), 2.04−1.90 (m, 1H), 1.27−1.22 (m, 4H), 1.22−1.14 (m, 11H), 1.13−1.04 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 151.8, 151.4, 144.5, 131.9, 58.4, 54.1, 37.7, 34.4, 32.0, 29.6, 29.5, 29.4, 29.36, 29.1, 26.4, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{18}H_{30}ClN_4O$ (M + H$^+$), 353.2103; found, 353.2102.

*6.1.30. 3-(6-Chloro-9H-purin-9-yl)tetradecan-1-ol (**11b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-tetradec-2-enal (63.1 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **11b** as a white solid in 56.7 mg (77.4% yield). White solid. mp: 91−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.13 (s, 1H), 4.87−4.78 (m, 1H), 3.66−3.59 (m, 1H), 3.25−3.17 (m, 1H), 2.65 (s, 1H), 2.26−2.08 (m, 3H), 2.02−1.92 (m, 1H), 1.28−1.16 (m, 17H), 1.12−1.02 (m, 1H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 151.8, 151.4, 144.5, 131.9, 58.4, 54.1, 37.7, 34.4, 32.0, 29.7, 29.6, 29.5, 29.4, 29.1, 26.4, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{19}H_{32}ClN_4O$ (M + H$^+$), 367.2259; found, 367.2261.

*6.1.31. 3-(6-Chloro-9H-purin-9-yl)pentadecan-1-ol (**12b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-pentadec-2-enal (67.3 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **12b** as a white solid in 61.6 mg (81.1% yield). White solid. mp: 112−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.12 (s, 1H), 4.86−4.77 (m, 1H), 3.65−3.58 (m, 1H), 3.25−3.17 (m, 1H), 2.77 (s, 1H), 2.26−2.07 (m, 3H), 2.02−1.91 (m, 1H), 1.27−1.15 (m, 19H), 1.12−1.02 (m, 1H), 0.84 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.8, 151.3, 144.6, 131.9, 58.4, 54.1, 37.6, 34.4, 32.0, 29.7, 29.6, 29.5, 29.42, 29.4, 29.1, 26.4, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{20}H_{34}ClN_4O$ (M + H$^+$), 381.2416; found, 381.2424.

*6.1.32. 4-(Benzyloxy)-3-(6-chloro-9H-purin-9-yl)butan-1-ol (**13b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg,

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0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-4-(benzyloxy)but-2-enal (52.8 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **13b** as a colorless oil in 48.0 mg (72.3% yield). Colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (s, 1H), 8.57 (s, 1H), 7.18−7.14 (m, 3H), 7.06−7.02 (m, 2H), 5.11−5.03 (m, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.39 (d, J = 12.0 Hz, 1H), 4.03 (dd, J = 10.4, 8.0 Hz, 1H), 3.83 (dd, J = 10.4, 4.0 Hz, 1H), 3.61−3.54 (m, 1H), 3.44−3.36 (m, 1H), 2.46−2.35 (m, 1H), 2.25−2.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 151.6, 151.0, 145.7, 137.0, 131.5, 128.6, 128.2, 127.8, 73.5, 70.3, 58.1, 53.3, 33.7; ESI-HRMS (m/z) calcd $C_{16}H_{18}ClN_4O_2$ (M + H$^+$), 333.1113; found, 333.1117.

*6.1.33. 2-(6-Chloro-9H-purin-9-yl)-4-hydroxybutyl benzoate (**14b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-4-oxobut-2-en-1-yl benzoate (57.0 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **14b** as a white solid in 56.5 mg (81.7% yield). White solid. mp: 137−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.28 (s, 1H), 7.84−7.79 (m, 2H), 7.55−7.49 (m, 1H), 7.36 (t, J = 8.0 Hz, 2H), 5.33−5.24 (m, 1H), 4.93 (dd, J = 12.0, 8.0 Hz, 1H), 4.75 (dd, J = 12.0, 4.0 Hz, 1H), 3.82−3.73 (m, 1H), 3.47−3.37 (m, 1H), 2.92 (s, 1H), 2.51−2.41 (m, 1H), 2.39−2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 151.9, 151.3, 145.2, 133.7, 131.9, 129.6, 129.0, 128.7, 65.0, 57.9, 53.4, 32.8; ESI-HRMS (m/z) calcd $C_{16}H_{16}ClN_4O_3$ (M + H$^+$), 347.0905; found, 347.0914.

*6.1.34. 4-(tert-Butyldimethylsilyl)-3-(6-chloro-9H-purin-9-yl)-butan-1-ol (**15b**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-4-((tert-butyldimethylsilyl)oxy)but-2-enal (60.0 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 2:1) to give the target compound **15b** as a white solid in 51.4 mg (72.2% yield). White solid. mp: 105−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.32 (s, 1H), 5.01−4.93 (m, 1H), 4.08 (dd, J = 10.8, 5.6 Hz, 1H), 3.95 (dd, J = 10.8, 3.2 Hz, 1H), 3.72−3.63 (m, 1H), 3.40−3.30 (m, 1H), 3.02 (s, 1H), 2.33−2.23 (m, 1H), 2.21−2.12 (m, 1H), 0.79 (s, 9H), −0.07 (d, J = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 151.6, 151.1, 145.6, 131.5, 64.4, 58.2, 54.8, 33.5, 25.7, 18.1, −5.6, −5.7; ESI-HRMS (m/z) calcd $C_{15}H_{26}ClN_4O_2Si$ (M + H$^+$), 357.1508; found, 357.1511.

*6.1.35. 2-(6-Chloro-9H-purin-9-yl)butane-1,4-diol (**16b**).* Compound **15b** (35.6 mg, 0.1 mmol), tetrabutylammonium fluoride (52.4 mg, 0.2 mmol), and tetrahydrofuran (1.0 mL) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at room temperature for 2 h and detected by TLC. Then, the solution was concentrated in vacuo. Finally, the residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **16b** as a white solid in 40.4 mg (83.5% yield). White solid. mp: 143−144 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.71 (s, 1H), 8.62 (s, 1H), 4.98−4.92 (m, 1H), 4.12 (dd, J = 12.0, 7.8 Hz, 1H), 3.92 (dd, J = 12.0, 4.2 Hz, 1H), 3.62−3.56 (m, 1H), 3.44−3.38 (m, 1H), 2.42−2.35 (m, 1H), 2.24−2.16 (m, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 153.5, 152.6, 151.1, 148.3, 132.5, 63.8, 59.0, 58.0, 33.6; ESI-HRMS (m/z) calcd $C_9H_{12}ClN_4O_2$ (M + H$^+$), 243.0643; found, 243.0644.

*6.1.36. 3-(2,6-Dichloro-9H-purin-9-yl)heptan-1-ol (**4c**).* 2,6-Dichloro-9*H*-purine (37.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-hept-2-enal (39.3 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **4c** as a white solid in 45.8 mg (75.8% yield). White solid. mp: 143−144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 4.80−4.71 (m, 1H), 3.69−3.61 (m, 1H), 3.35−3.26 (m, 1H), 2.29−2.16 (m, 3H), 2.16−2.07 (m, 1H), 2.02−1.91 (m, 1H), 1.33−1.23 (m, 3H), 1.12−0.99 (m, 1H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 152.8, 151.9, 145.5, 131.1, 58.6, 54.8, 37.1, 34.0, 28.4, 22.2, 13.9; ESI-HRMS (m/z) calcd $C_{12}H_{17}Cl_2N_4O$ (M + H$^+$), 303.0774; found, 303.0775.

*6.1.37. 3-(2,6-Dichloro-9H-purin-9-yl)octan-1-ol (**5c**).* 2,6-Dichloro-9*H*-purine (37.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-oct-2-enal (44.8 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **5c** as a white solid in 52.6 mg (83.2% yield). White solid. mp: 113−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 4.80−4.71 (m, 1H), 3.69−3.59 (m, 1H), 3.36−3.25 (m, 1H), 2.33 (s, 1H), 2.22−2.16 (m, 2H), 2.15−2.06 (m, 1H), 1.99−1.88 (m, 1H), 1.26−1.18 (m, 5H), 1.12−1.02 (m, 1H), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 152.7, 151.8, 145.5, 131.0, 58.5, 54.9, 37.0, 34.2, 31.2, 26.0, 22.4, 14.0; ESI-HRMS (m/z) calcd $C_{13}H_{19}Cl_2N_4O$ (M + H$^+$), 317.0930; found, 317.0939.

*6.1.38. 3-(2,6-Dichloro-9H-purin-9-yl)nonan-1-ol (**6c**).* 2,6-Dichloro-9*H*-purine (37.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-non-2-enal (49.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash

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column chromatography on silica gel (PE/EA = 1:1) to give the target compound **6c** as a white solid in 51.5 mg (78.1% yield). White solid. mp: 118−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 4.80−4.71 (m, 1H), 3.68−3.60 (m, 1H), 3.35−3.26 (m, 1H), 2.42 (s, 1H), 2.23−2.16 (m, 2H), 2.16−2.06 (m, 1H), 2.00−1.89 (m, 1H), 1.27−1.12 (m, 7H), 1.10−1.00 (m, 1H), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 152.7, 151.8, 145.5, 131.0, 58.5, 54.9, 37.0, 34.3, 31.5, 28.7, 26.2, 22.5, 14.0; ESI-HRMS (m/z) calcd $C_{14}H_{21}Cl_2N_4O$ (M + H$^+$), 331.1087; found, 331.1083.

*6.1.39. 3-(2,6-Dichloro-9H-purin-9-yl)decan-1-ol (**7c**).* 2,6-Dichloro-9*H*-purine (37.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dec-2-enal (54.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **7c** as a white solid in 52.7 mg (76.6% yield). White solid. mp: 111−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 4.80−4.70 (m, 1H), 3.69−3.59 (m, 1H), 3.36−3.26 (m, 1H), 2.40 (s, 1H), 2.23−2.15 (m, 2H), 2.15−2.06 (m, 1H), 2.00−1.89 (m, 1H), 1.26−1.12 (m, 9H), 1.11−0.99 (m, 1H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 152.7, 151.8, 145.5, 131.0, 58.5, 54.9, 37.0, 34.3, 31.7, 29.0, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{15}H_{23}Cl_2N_4O$ (M + H$^+$), 345.1243; found, 345.1249.

*6.1.40. 3-(2,6-Dichloro-9H-purin-9-yl)undecan-1-ol (**8c**).* 2,6-Dichloro-9*H*-purine (37.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-undec-2-enal (59.5 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **8c** as a white solid in 56.4 mg (78.8% yield). White solid. mp: 112−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 4.81−4.70 (m, 1H), 3.68−3.59 (m, 1H), 3.36−3.26 (m, 1H), 2.42 (s, 1H), 2.24−2.16 (m, 2H), 2.15−2.06 (m, 1H), 2.00−1.88 (m, 1H), 1.29−1.14 (m, 11H), 1.11−1.01 (m, 1H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 152.7, 151.8, 145.5, 131.0, 58.5, 54.9, 37.0, 34.3, 31.8, 29.3, 29.2, 29.1, 26.3, 22.7, 14.1; ESI-HRMS (m/z) calcd $C_{16}H_{25}Cl_2N_4O$ (M + H$^+$), 359.1400; found, 359.1399.

*6.1.41. 3-(2,6-Dichloro-9H-purin-9-yl)dodecan-1-ol (**9c**).* 2,6-Dichloro-9*H*-purine (37.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dodec-2-enal (64.4 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **9c** as a white solid in 62.6 mg (84.1% yield). White solid. mp: 94−96 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 4.78−4.71 (m, 1H), 3.66−3.60 (m, 1H), 3.34−3.28 (m, 1H), 2.74 (s, 1H), 2.25−2.15 (m, 2H), 2.15−2.06 (m, 1H), 1.98−1.89 (m, 1H), 1.25−1.19 (m, 5H), 1.19−1.11 (m, 8H), 1.08−1.00 (m, 1H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 152.8, 151.9, 145.5, 131.0, 58.6, 54.8, 37.0, 34.3, 31.9, 29.5, 29.4, 29.3, 29.1, 26.3, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{17}H_{27}Cl_2N_4O$ (M + H$^+$), 373.1556; found, 373.1561.

*6.1.42. 3-(6-Methoxy-9H-purin-9-yl)heptan-1-ol (**4d**).* 6-Methoxy-9*H*-purine (30.0 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-hept-2-enal (39.3 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **4d** as a white solid in 43.6 mg (82.2% yield). White solid. mp: 68−71 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.94 (s, 1H), 4.83−4.76 (m, 1H), 4.19 (s, 3H), 3.61−3.55 (m, 1H), 3.27 (s, 1H), 3.12 (td, J = 10.8, 3.6 Hz, 1H), 2.23−2.16 (m, 1H), 2.16−2.09 (m,1H), 2.01−1.91 (m, 2H), 1.35−1.25 (m, 3H), 1.18−1.10 (m, 1H), 0.84 (t, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.4, 152.5, 152.1, 140.8, 121.5, 58.2, 54.5, 52.7, 38.7, 34.2, 28.6, 22.3, 14.0; ESI-HRMS (m/z) calcd $C_{13}H_{21}N_4O_2$ (M + H$^+$), 265.1659; found, 265.1660.

*6.1.43. 3-(6-Methoxy-9H-purin-9-yl)octan-1-ol (**5d**).* 6-Methoxy-9*H*-purine (30.0 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-oct-2-enal (44.8 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **5d** as a white solid in 47.3 mg (85.1% yield). White solid. mp: 73−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.92 (s, 1H), 4.81−4.72 (m, 1H), 4.16 (s, 3H), 3.61−3.49 (m, 2H), 3.18−3.08 (m, 1H), 2.21−2.08 (m, 2H), 2.02−1.88 (m, 2H), 1.29−1.18 (m, 5H), 1.15−1.07 (m, 1H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 152.4, 152.0, 140.9, 121.5, 58.1, 54.4, 52.9, 38.4, 34.5, 31.3, 26.0, 22.4, 14.0; ESI-HRMS (m/z) calcd $C_{14}H_{23}N_4O_2$ (M + H$^+$), 279.1816; found, 279.1812.

*6.1.44. 3-(6-Methoxy-9H-purin-9-yl)nonan-1-ol (**6d**).* 6-Methoxy-9*H*-purine (30.0 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-non-2-enal (49.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **6d** as a white solid in 48.8 mg (83.6% yield). White solid. mp: 73−74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.93 (s, 1H), 4.82−4.73 (m, 1H), 4.18 (s, 3H), 3.62−3.52 (m, 1H), 3.40 (s, 1H), 3.18−3.07 (m, 1H), 2.24−2.06 (m, 2H), 2.00−1.92 (m, 2H), 1.30−1.14 (m, 8H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz,

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$CDCl_3$) δ 161.3, 152.5, 152.0, 140.8, 121.5, 58.1, 54.4, 52.8, 38.6, 34.5, 31.6, 28.8, 26.3, 22.5, 14.1; ESI-HRMS (m/z) calcd $C_{15}H_{25}N_4O_2$ (M + H^+), 293.1972; found, 293.1973.

*6.1.45. 3-(6-Methoxy-9H-purin-9-yl)decan-1-ol (**7d**).* 6-Methoxy-9*H*-purine (30.0 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dec-2-enal (54.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **7d** as a white solid in 53.0 mg (86.7% yield). White solid. mp: 69−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.93 (s, 1H), 4.83−4.73 (m, 1H), 4.18 (s, 3H), 3.64−3.50 (m, 1H), 3.40 (s, 1H), 3.18−3.06 (m, 1H), 2.23−2.06 (m, 2H), 2.00−1.93 (m, 2H), 1.29−1.13 (m, 10H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 152.5, 152.0, 140.8, 121.5, 58.1, 54.4, 52.8, 38.6, 34.5, 31.7, 29.12, 29.08, 26.4, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{16}H_{27}N_4O_2$ (M + H^+), 307.2129; found, 307.2130.

*6.1.46. 3-(6-Methoxy-9H-purin-9-yl)undecan-1-ol (**8d**).* 6-Methoxy-9*H*-purine (30.0 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-undec-2-enal (59.5 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **8d** as a white solid in 57.3 mg (89.5% yield). White solid. mp: 68−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.92 (s, 1H), 4.82−4.72 (m, 1H), 4.16 (s, 3H), 3.69−3.29 (m, 2H), 3.13 (td, J = 10.8, 3.6 Hz, 1H), 2.22−2.06 (m, 2H), 2.02−1.88 (m, 2H), 1.26−1.20 (m, 4H), 1.20−1.10 (m, 8H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 152.4, 152.0, 140.9, 121.5, 58.1, 54.4, 52.9, 38.5, 34.5, 31.8, 29.4, 29.2, 29.1, 26.4, 22.7, 14.1; ESI-HRMS (m/z) calcd $C_{17}H_{29}N_4O_2$ (M + H^+), 321.2285; found, 321.2289.

*6.1.47. 3-(6-Methoxy-9H-purin-9-yl)dodecan-1-ol (**9d**).* 6-Methoxy-9*H*-purine (30.0 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dodec-2-enal (64.4 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **9d** as a white solid in 58.9 mg (88.1% yield). White solid. mp: 66−68 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.93 (s, 1H), 4.83−4.72 (m, 1H), 4.18 (s, 3H), 3.61−3.53 (m, 1H), 3.41 (s, 1H), 3.13 (td, J = 10.8, 3.6 Hz, 1H), 2.23−2.06 (m, 2H), 2.00−1.92 (m, 2H), 1.28−1.21 (m, 5H), 1.21−1.13 (m, 9H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 152.5, 152.0, 140.9, 121.5, 58.1, 54.4, 52.8, 38.6, 34.5, 31.9, 29.5, 29.4, 29.3, 29.2, 26.4, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{18}H_{31}N_4O_2$ (M + H^+), 335.2442; found, 335.2448.

*6.1.48. 3-(6-Methoxy-9H-purin-9-yl)tridecan-1-ol (**10d**).* 6-Methoxy-9*H*-purine (30.0 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-tridec-2-enal (58.9 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **10d** as a white solid in 57.1 mg (82.1% yield). White solid. mp: 49−51 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.93 (s, 1H), 4.83−4.73 (m, 1H), 4.18 (s, 3H), 3.62−3.53 (m, 1H), 3.39 (s, 1H), 3.13 (td, J = 11.2, 3.6 Hz, 1H), 2.24−2.07 (m, 2H), 2.01−1.90 (m, 2H), 1.28−1.22 (m, 5H), 1.22−1.16 (m, 11H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.3, 152.5, 152.0, 140.8, 121.5, 58.1, 54.4, 52.8, 38.6, 34.5, 32.0, 29.6, 29.5, 29.42, 29.36, 29.2, 26.4, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{19}H_{33}N_4O_2$ (M + H^+), 349.2598; found, 349.2606.

*6.1.49. 3-(6-Methoxy-9H-purin-9-yl)tetradecan-1-ol (**11d**).* 6-Methoxy-9*H*-purine (30.0 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-tetradec-2-enal (63.1 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **11d** as a white solid in 61.9 mg (85.5% yield). White solid. mp: 57−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.93 (s, 1H), 4.83−4.73 (m, 1H), 4.18 (s, 3H), 3.62−3.53 (m, 1H), 3.37 (s, 1H), 3.12 (td, J = 11.2, 3.6 Hz, 1H), 2.24−2.06 (m, 2H), 2.01−1.90 (m, 2H), 1.29−1.23 (m, 5H), 1.23−1.16 (m, 13H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 152.5, 152.0, 140.8, 121.5, 58.1, 54.4, 52.8, 38.6, 34.5, 32.0, 29.66, 29.65, 29.5, 29.43, 29.41, 29.2, 26.4, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{20}H_{35}N_4O_2$ (M + H^+), 363.2755; found, 363.2759.

*6.1.50. 3-(6-(Methylamino)-9H-purin-9-yl)octan-1-ol (**5e**).* *N*-Methyl-9*H*-purin-6-amine (29.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-oct-2-enal (44.8 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 25:1) to give the target compound **5e** as a white solid in 16.1 mg (29.1% yield). White solid. mp: 109−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.72 (s, 1H), 6.48−6.41 (m, 1H), 4.75−4.65 (m, 1H), 4.34 (s, 1H), 3.57−3.50 (m, 1H), 3.23−3.08 (m, 4H), 2.19−2.09 (m, 1H), 2.09−2.00 (m, 1H), 1.95−1.83 (m, 2H), 1.25−1.10 (m, 6H), 0.79 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 153.1, 149.2, 138.0, 119.6, 57.9, 52.3, 38.8, 34.5, 31.3, 27.7, 26.1, 22.5, 14.0; ESI-HRMS (m/z) calcd $C_{14}H_{24}N_5O$ (M + H^+), 278.1975; found, 278.1985.

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*6.1.51. 3-(6-(Methylamino)-9H-purin-9-yl)nonan-1-ol (**6e**).* *N*-Methyl-9*H*-purin-6-amine (29.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-non-2-enal (49.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 25:1) to give the target compound **6e** as a white solid in 15.5 mg (26.7% yield). White solid. mp: 94−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.74 (s, 1H), 6.41 (s, 1H), 4.75−4.66 (m, 1H), 4.31 (s, 1H), 3.59−3.51 (m, 1H), 3.26−3.06 (m, 4H), 2.20−2.10 (m, 1H), 2.10−2.00 (m, 1H), 1.97−1.83 (m, 2H), 1.27−1.12 (m, 8H), 0.80 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7, 153.1, 149.3, 137.9, 119.7, 57.9, 52.2, 39.0, 34.5, 31.6, 28.9, 27.6, 26.4, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{15}H_{26}N_5O$ (M + H^+), 292.2132; found, 292.2137.

*6.1.52. 3-(6-(Methylamino)-9H-purin-9-yl)decan-1-ol (**7e**).* *N*-Methyl-9*H*-purin-6-amine (29.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dec-2-enal (54.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 25:1) to give the target compound **7e** as a white solid in 19.0 mg (31.1% yield). White solid. mp: 68−69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.73 (s, 1H), 6.39−6.30 (m, 1H), 4.76−4.65 (m, 1H), 4.32 (s, 1H), 3.58−3.50 (m, 1H), 3.23−3.06 (m, 4H), 2.20−2.10 (m, 1H), 2.10−2.01 (m, 1H), 1.97−1.82 (m, 2H), 1.27−1.13 (m, 10H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 153.1, 149.2, 138.0, 119.6, 57.9, 52.3, 38.8, 34.5, 31.7, 29.12, 29.06, 27.6, 26.4, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{16}H_{28}N_5O$ (M + H^+), 306.2288; found, 306.2288.

*6.1.53. 3-(6-(Methylamino)-9H-purin-9-yl)undecan-1-ol (**8e**).* *N*-Methyl-9*H*-purin-6-amine (29.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-undec-2-enal (59.5 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 25:1) to give the target compound **8e** as a white solid in 20.9 mg (32.8% yield). White solid. mp: 88−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.77 (s, 1H), 6.24 (s, 1H), 4.78−4.67 (m, 1H), 3.96 (s, 1H), 3.61−3.52 (m, 1H), 3.32−3.05 (m, 4H), 2.23−2.11 (m, 1H), 2.10−2.02 (m, 1H), 1.99−1.82 (m, 2H), 1.30−1.22 (m, 5H), 1.22−1.17 (m, 5H), 0.84 (t, J = 6.8 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7, 153.1, 149.2, 138.0, 119.7, 57.9, 52.3, 38.9, 34.5, 31.8, 29.4, 29.2, 27.6, 26.4, 22.7, 14.1; ESI-HRMS (m/z) calcd $C_{17}H_{30}N_5O$ (M + H^+), 320.2445; found, 320.2440.

*6.1.54. 3-(6-(Methylamino)-9H-purin-9-yl)dodecan-1-ol (**9e**).* *N*-Methyl-9*H*-purin-6-amine (29.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dodec-2-enal (64.4 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 25:1) to give the target compound **9e** as a white solid in 18.5 mg (27.8% yield). White solid. mp: 92−94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.75 (s, 1H), 5.93 (s, 1H), 4.81−4.66 (m, 1H), 4.01 (s, 1H), 3.61−3.51 (m, 1H), 3.22 (s, 3H), 3.09 (t, J = 11.6 Hz, 1H), 2.25−2.13 (m, 1H), 2.13−2.04 (m, 1H), 2.00−1.89 (m, 1H), 1.81 (t, J = 12.8 Hz, 1H), 1.29−1.18 (m, 14H), 0.86 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 153.1, 149.4, 137.9, 119.6, 57.9, 52.3, 38.9, 34.5, 31.9, 29.5, 29.4, 29.3, 29.2, 27.7, 26.4, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{18}H_{32}N_5O$ (M + H^+), 334.2601; found, 334.2600.

*6.1.55. 3-(6-(Methylamino)-9H-purin-9-yl)tridecan-1-ol (**10e**).* *N*-Methyl-9*H*-purin-6-amine (29.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-tridec-2-enal (58.9 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 25:1) to give the target compound **10e** as a white solid in 19.3 mg (27.8% yield). White solid. mp: 76−77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.74 (s, 1H), 6.09 (s, 1H), 4.78−4.65 (m, 1H), 4.08 (s, 1H), 3.60−3.51 (m, 1H), 3.21 (s, 3H), 3.14−3.04 (m, 1H), 2.22−2.13 (m, 1H), 2.13−2.04 (m, 1H), 2.00−1.89 (m, 1H), 1.87−1.76 (m, 1H), 1.29−1.24 (m, 6H), 1.23−1.19 (m, 10H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7, 153.2, 149.4, 137.8, 119.7, 58.0, 52.0, 39.2, 34.5, 32.0, 29.6, 29.6, 29.5, 29.4, 29.2, 27.7, 26.5, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{19}H_{34}N_5O$ (M + H^+), 348.2758; found, 348.2753.

*6.1.56. 3-(6-(Methylamino)-9H-purin-9-yl)tetradecan-1-ol (**11e**).* *N*-Methyl-9*H*-purin-6-amine (29.8 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-tetradec-2-enal (63.1 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 25:1) to give the target compound **11e** as a white solid in 21.5 mg (29.8% yield). White solid. mp: 90−91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.75 (s, 1H), 6.03 (s, 1H), 4.79−4.68 (m, 1H), 4.04 (s, 1H), 3.60−3.52 (m, 1H), 3.21 (s, 3H), 3.13−3.05 (m, 1H), 2.23−2.12 (m, 1H), 2.12−2.04 (m, 1H), 1.99−1.90 (m, 1H), 1.85−1.77 (m, 1H), 1.30−1.23 (m, 8H), 1.23−1.18 (m, 10H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7, 153.2, 149.3, 137.8, 119.7, 58.0, 52.0, 39.3, 34.5, 32.0, 29.8, 29.6, 29.6, 29.5, 29.4, 29.3,

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27.7, 26.5, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{20}H_{36}N_5O$ (M + H^+), 362.2914; found, 362.2919.

*6.1.57. 3-(6-(Dimethylamino)-9H-purin-9-yl)octan-1-ol (**5f**).* *N*,*N*-Dimethyl-9*H*-purin-6-amine (32.6 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-oct-2-enal (44.8 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **5f** as a colorless oil in 45.6 mg (78.3% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.71 (s, 1H), 4.74−4.64 (m, 1H), 3.96 (s, 1H), 3.72−3.30 (m, 7H), 3.05 (td, J = 11.2, 3.2 Hz, 1H), 2.18−1.96 (m, 2H), 1.94−1.83 (m, 1H), 1.82−1.70 (m, 1H), 1.30−1.13 (m, 6H), 0.78 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 152.3, 151.0, 136.2, 119.8, 57.8, 51.5, 39.3, 38.7, 34.4, 31.4, 26.1, 22.5, 14.0; ESI-HRMS (m/z) calcd $C_{15}H_{26}N_5O$ (M + H^+), 292.2132; found, 292.2131.

*6.1.58. 3-(6-(Dimethylamino)-9H-purin-9-yl)nonan-1-ol (**6f**).* *N*,*N*-Dimethyl-9*H*-purin-6-amine (32.6 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-non-2-enal (49.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **6f** as a colorless oil in 47.0 mg (77.1% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.70 (s, 1H), 4.73−4.64 (m, 1H), 3.94 (s, 1H), 3.68−3.27 (m, 7H), 3.05 (td, J = 10.8, 3.2 Hz, 1H), 2.17−2.06 (m, 1H), 2.05−1.96 (m, 1H), 1.94−1.83 (m, 1H), 1.82−1.72 (m, 1H), 1.28−1.08 (m, 8H), 0.78 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 152.3, 151.0, 136.3, 119.8, 57.8, 51.6, 39.3, 38.7, 34.5, 31.6, 28.9, 26.3, 22.5, 14.0; ESI-HRMS (m/z) calcd $C_{16}H_{28}N_5O$ (M + H^+), 306.2288; found, 306.2295.

*6.1.59. 3-(6-(Dimethylamino)-9H-purin-9-yl)decan-1-ol (**7f**).* *N*,*N*-Dimethyl-9*H*-purin-6-amine (32.6 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dec-2-enal (54.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **7f** as a colorless oil in 51.1 mg (80.1% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.70 (s, 1H), 4.74−4.64 (m, 1H), 4.09 (s, 1H), 3.75−3.23 (m, 7H), 3.05 (td, J = 11.2, 3.2 Hz, 1H), 2.16−1.96 (m, 2H), 1.94−1.82 (m, 1H), 1.82−1.71 (m, 1H), 1.26−1.08 (m, 10H), 0.78 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 152.3, 151.0, 136.3, 119.8, 57.8, 51.6, 39.3, 38.7, 34.5, 31.7, 29.14, 29.06, 26.4, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{17}H_{30}N_5O$ (M + H^+), 320.2445; found, 320.2447.

*6.1.60. 3-(6-(Dimethylamino)-9H-purin-9-yl)undecan-1-ol (**8f**).* *N*,*N*-Dimethyl-9*H*-purin-6-amine (32.6 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-undec-2-enal (59.5 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **8f** as a colorless oil in 52.7 mg (79.2% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.70 (s, 1H), 4.74−4.63 (m, 1H), 4.03 (s, 1H), 3.73−3.18 (m, 7H), 3.05 (td, J = 10.8, 3.2 Hz, 1H), 2.16−1.96 (m, 2H), 1.93−1.82 (m, 1H), 1.82−1.71 (m, 1H), 1.25−1.09 (m, 12H), 0.79 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 152.3, 151.0, 136.2, 119.8, 57.8, 51.5, 39.3, 38.6, 34.5, 31.8, 29.4, 29.18, 29.17, 26.4, 22.7, 14.1; ESI-HRMS (m/z) calcd $C_{18}H_{32}N_5O$ (M + H^+), 334.2601; found, 334.2603.

*6.1.61. 3-(6-(Dimethylamino)-9H-purin-9-yl)dodecan-1-ol (**9f**).* *N*,*N*-Dimethyl-9*H*-purin-6-amine (32.6 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dodec-2-enal (64.4 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **9f** as a colorless oil in 51.6 mg (74.3% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.68 (s, 1H), 4.72−4.60 (m, 1H), 4.19 (s, 1H), 3.71−3.19 (m, 7H), 3.05 (td, J = 11.2, 3.6 Hz, 1H), 2.14−1.92 (m, 2H), 1.92−1.69 (m, 2H), 1.25−1.03 (m, 14H), 0.77 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 152.2, 150.9, 136.3, 119.8, 57.8, 51.6, 39.2, 38.6, 34.5, 31.9, 29.42, 29.37, 29.2, 29.1, 26.3, 22.7, 14.1; ESI-HRMS (m/z) calcd $C_{19}H_{34}N_5O$ (M + H^+), 348.2758; found, 348.2764.

*6.1.62. 3-(6-(Dimethylamino)-9H-purin-9-yl)tridecan-1-ol (**10f**).* *N*,*N*-Dimethyl-9*H*-purin-6-amine (32.6 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-tridec-2-enal (58.9 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **10f** as a colorless oil in 55.3 mg (76.6% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.73 (s, 1H), 4.78−4.68 (m, 1H), 4.27 (s, 1H), 3.75−3.33 (m, 7H), 3.09−2.99 (m, 1H), 2.22−2.10 (m, 1H), 2.10−2.01 (m, 1H), 1.99−1.87 (m, 2H), 1.79−1.67 (m, 1H), 1.28−1.23 (m, 6H), 1.22−1.18 (m, 10H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 152.4, 151.1, 136.1, 119.9, 57.9, 51.4, 39.5, 38.7, 34.5, 32.0, 29.63, 29.57, 29.5, 29.4, 29.3, 26.5, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{20}H_{36}N_5O$ (M + H^+), 362.2914; found, 362.2917.

*6.1.63. 3-(6-(Dimethylamino)-9H-purin-9-yl)tetradecan-1-ol (**11f**).* *N*,*N*-Dimethyl-9*H*-purin-6-amine (32.6 mg, 0.2 mmol), L-

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proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-tetradec-2-enal (63.1 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **11f** as a colorless oil in 55.0 mg (73.3% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.73 (s, 1H), 4.78−4.67 (m, 1H), 4.29 (s, 1H), 3.88−3.26 (m, 7H), 3.11−2.99 (m, 1H), 2.22−2.10 (m, 1H), 2.09−2.00 (m, 1H), 2.00−1.87 (m, 1H), 1.29−1.17 (m, 18H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 152.3, 151.1, 136.2, 119.8, 57.8, 51.5, 39.4, 38.7, 34.5, 32.0, 29.67, 29.66, 29.6, 29.5, 29.4, 29.2, 26.4, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{21}H_{38}N_5O$ (M + H^+), 376.3071; found, 376.3076.

*6.1.64. 3-(6-Amino-9H-purin-9-yl)heptan-1-ol (**4g**).* Compound **4b** (26.9 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to give the target compound **4g** as a white solid in 17.2 mg (69.1% yield). White solid. mp: 118−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.81 (s, 1H), 6.27 (s, 2H), 4.79−4.67 (m, 1H), 4.19 (s, 1H), 3.61−3.53 (m, 1H), 3.20−3.09 (m, 1H), 2.23−2.03 (m, 2H), 2.00−1.86 (m, 2H), 1.34−1.22 (m, 3H), 1.21−1.09 (m, 1H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.9, 152.9, 150.5, 138.9, 119.5, 58.0, 52.4, 38.8, 34.2, 28.6, 22.3, 14.0; ESI-HRMS (m/z) calcd $C_{12}H_{20}N_5O$ (M + H^+), 250.1662; found, 250.1664.

*6.1.65. 3-(6-Amino-9H-purin-9-yl)octan-1-ol (**5g**).* Compound **5b** (28.3 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to give the target compound **5g** as a white solid in 19.6 mg (74.1% yield). White solid. mp: 109−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.83 (s, 1H), 6.55 (s, 2H), 4.79−4.67 (m, 1H), 4.50 (s, 1H), 3.61−3.54 (m, 1H), 3.23−3.13 (m, 1H), 2.22−2.12 (m, 1H), 2.11−2.03 (m, 1H), 2.00−1.88 (m, 2H), 1.28−1.14 (m, 6H), 0.80 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 153.0, 150.6, 138.8, 119.5, 58.0, 52.3, 39.0, 34.5, 31.4, 26.1, 22.5, 14.0; ESI-HRMS (m/z) calcd $C_{13}H_{22}N_5O$ (M + H^+), 264.1819; found, 264.1818.

*6.1.66. 3-(6-Amino-9H-purin-9-yl)nonan-1-ol (**6g**).* Compound **6b** (29.7 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to give the target compound **6g** as a white solid in 21.0 mg (75.9% yield). White solid. mp: 119−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.82 (s, 1H), 6.62 (s, 2H), 4.77−4.68 (m, 1H), 4.63 (s, 1H), 3.61−3.53 (m, 1H), 3.23−3.14 (m, 1H), 2.22−2.11 (m, 1H), 2.11−2.02 (m, 1H), 2.02−1.86 (m, 2H), 1.28−1.13 (m, 8H), 0.80 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 153.0, 150.5, 138.9, 119.5, 58.0, 52.4, 38.9, 34.5, 31.6, 28.9, 26.4, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{14}H_{24}N_5O$ (M + H^+), 278.1975; found, 278.1981.

*6.1.67. 3-(6-Amino-9H-purin-9-yl)decan-1-ol (**7g**).* Compound **7b** (31.1 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to give the target compound **7g** as a white solid in 21.0 mg (72.3% yield). White solid. mp: 124−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.83 (s, 1H), 6.57 (s, 2H), 4.80−4.67 (m, 1H), 4.52 (s, 1H), 3.61−3.54 (m, 1H), 3.22−3.14 (m, 1H), 2.22−2.12 (m, 1H), 2.11−2.03 (m, 1H), 2.01−1.86 (m, 2H), 1.27−1.12 (m, 10H), 0.81 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 152.9, 150.5, 138.9, 119.4, 58.0, 52.5, 38.8, 34.6, 31.8, 29.2, 29.1, 26.4, 22.7, 14.1; ESI-HRMS (m/z) calcd $C_{15}H_{26}N_5O$ (M + H^+), 292.2132; found, 292.2132.

*6.1.68. 3-(6-Amino-9H-purin-9-yl)undecan-1-ol (**8g**).* Compound **8b** (32.5 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to give the target compound **8g** as a white solid in 21.1 mg (69.1% yield). White solid. mp: 136−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.81 (s, 1H), 6.69 (s, 2H), 4.76−4.66 (m, 1H), 4.60 (s, 1H), 3.60−3.53 (m, 1H), 3.23−3.14 (m, 1H), 2.20−2.10 (m, 1H), 2.10−2.02 (m, 1H), 2.01−1.85 (m, 2H), 1.27−1.20 (m, 4H), 1.20−1.10 (m, 8H), 0.81 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 152.9, 150.4, 138.9, 119.4, 58.0, 52.5, 38.7, 34.6, 31.8, 29.4, 29.2, 26.4, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{16}H_{28}N_5O$ (M + H^+), 306.2288; found, 306.2287.

*6.1.69. 3-(6-Amino-9H-purin-9-yl)dodecan-1-ol (**9g**).* Compound **9b** (33.9 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to give the target compound **9g** as a white solid in 22.2 mg (69.5% yield). White solid. mp: 120−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.82 (s, 1H), 6.61 (s, 2H), 4.79−4.66 (m, 1H), 4.51 (s, 1H), 3.62−3.52 (m, 1H), 3.23−3.13 (m, 1H), 2.22−2.11 (m, 1H), 2.11−2.02 (m, 1H), 2.01−1.85 (m, 2H), 1.31−1.21 (m, 5H), 1.20−1.14 (m, 9H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 152.9, 150.3, 138.9, 119.4, 58.0, 52.6, 38.6, 34.6, 31.9, 29.5, 29.4, 29.3, 29.2, 26.4, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{17}H_{30}N_5O$ (M + H^+), 320.2445; found, 320.2455.

*6.1.70. 3-(6-Amino-9H-purin-9-yl)tridecan-1-ol (**10g**).* Compound **10b** (35.3 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to give the target compound **10g** as a white solid in 22.6 mg (67.9% yield). White solid. mp: 105−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.81 (s, 1H), 6.11 (s, 2H), 4.79−4.69 (m, 1H), 4.06 (s, 1H), 3.61−3.54 (m, 1H), 3.19−3.09 (m, 1H), 2.23−2.13 (m, 1H), 2.13−2.04 (m, 1H), 2.00−1.83 (m, 2H), 1.28−1.23 (m, 5H), 1.23−1.18 (m, 11H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 153,0, 150.5, 138.9, 119.4, 58.0, 52.4, 38.9, 34.5, 32.0, 29.63, 29.58, 29.5, 29.4, 29.2, 26.5, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{18}H_{32}N_5O$ (M + H^+), 334.2601; found, 334.2605.

*6.1.71. 3-(6-Amino-9H-purin-9-yl)tetradecan-1-ol (**11g**).* Compound **11b** (36.7 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to give the target compound **11g** as a white solid in 24.7 mg (71.1% yield). White solid. mp: 93−94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.81 (s, 1H), 6.12 (s, 2H), 4.78−4.69 (m, 1H), 4.05 (s, 1H), 3.61−3.54 (m, 1H), 3.18−3.09 (m, 1H), 2.24−2.12 (m, 1H), 2.12−2.04 (m, 1H), 2.01−1.83 (m, 2H), 1.28−1.24 (m, 5H), 1.24−1.18 (m, 13H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 153.0, 150.5, 138.9, 119.4, 58.0, 52.4, 38.9, 34.5, 32.0, 29.7, 29.6, 29.5, 29.4, 29.2, 26.5, 22.8, 14.2; ESI-

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HRMS (m/z) calcd $C_{19}H_{34}N_5O$ (M + H^+), 348.2758; found, 348.2768.

*6.1.72. 3-(6-Amino-2-chloro-9H-purin-9-yl)octan-1-ol (**5h**).* Compound **5c** (31.7 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 30:1) to give the target compound **5h** as a white solid in 20.3 mg (68.3% yield). White solid. mp: 154−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 6.09 (s, 2H), 4.73−4.61 (m, 1H), 3.65−3.55 (m, 1H), 3.29−3.18 (m, 1H), 2.98−2.86 (m, 1H), 2.24−2.12 (m, 1H), 2.12−2.04 (m, 1H), 2.03−1.88 (m, 2H), 1.28−1.25 (m, 5H), 1.20−1.14 (m, 1H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.3, 154.1, 151.6, 139.5, 118.3, 58.4, 53.1, 38.4, 34.5, 31.4, 26.1, 22.5, 14.0; ESI-HRMS (m/z) calcd $C_{13}H_{21}ClN_5O$ (M + H^+), 298.1429; found, 298.1433.

*6.1.73. 3-(6-Amino-2-chloro-9H-purin-9-yl)nonan-1-ol (**6h**).* Compound **6c** (33.1 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 30:1) to give the target compound **6h** as a white solid in 21.0 mg (67.5% yield). White solid. mp: 120−123 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.79 (s, 2H), 4.69−4.62 (m, 1H), 3.66−3.56 (m, 2H), 3.31−3.25 (m, 1H), 2.20−2.11 (m, 1H), 2.08−1.99 (m, 2H), 1.95−1.86 (m, 1H), 1.28−1.15 (m, 7H), 1.14−1.07 (m, 1H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.5, 154.0, 151.4, 139.5, 118.3, 58.3, 53.2, 38.2, 34.6, 31.6, 28.9, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{14}H_{23}ClN_5O$ (M + H^+), 312.1586; found, 312.1594.

*6.1.74. 3-(6-Amino-2-chloro-9H-purin-9-yl)decan-1-ol (**7h**).* Compound **7c** (34.5 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 30:1) to give the target compound **7h** as a white solid in 23.3 mg (71.8% yield). White solid. mp: 134−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 6.88 (s, 2H), 4.72−4.62 (m, 1H), 3.92 (s, 1H), 3.65−3.56 (m, 1H), 3.35−3.25 (m, 1H), 2.22−2.11 (m, 1H), 2.11−2.00 (m, 2H), 1.96−1.84 (m, 1H), 1.28−1.13 (m, 10H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.5, 154.0, 151.4, 139.5, 118.3, 58.3, 53.2, 38.2, 34.6, 31.8, 29.2, 29.1, 26.3, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{15}H_{25}ClN_5O$ (M + H^+), 326.1742; found, 326.1746.

*6.1.75. 3-(6-Amino-2-chloro-9H-purin-9-yl)undecan-1-ol (**8h**).* Compound **8c** (35.9 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 30:1) to give the target compound **8h** as a white solid in 25.2 mg (72.2% yield). White solid. mp: 138−140 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (s, 1H), 6.40 (s, 2H), 4.73−4.60 (m, 1H), 3.67−3.56 (m, 1H), 3.37−3.01 (m, 2H), 2.25−2.11 (m, 1H), 2.11−1.98 (m, 2H), 1.98−1.86 (m, 1H), 1.27−1.24 (m, 5H), 1.23−1.19 (m, 6H), 1.17−1.10 (m, 1H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4, 154.1, 151.5, 139.5, 118.3, 58.4, 53.1, 38.3, 34.6, 31.9, 29.4, 29.23, 29.21, 26.4, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{16}H_{27}ClN_5O$ (M + H^+), 340.1899; found, 340.1905.

*6.1.76. 3-(6-Amino-2-chloro-9H-purin-9-yl)dodecan-1-ol (**9h**).* Compound **9c** (37.3 mg, 0.1 mmol) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 30:1) to give the target compound **9h** as a white solid in 26.2 mg (74.2% yield). White solid. mp: 46−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 6.82 (s, 2H), 4.73−4.62 (m, 1H), 3.80 (s, 1H), 3.67−3.55 (m, 1H), 3.35−3.24 (m, 1H), 2.22−2.11 (m, 1H), 2.10−2.00 (m, 2H), 1.96−1.85 (m, 1H), 1.29−1.23 (m, 4H), 1.22−1.17 (m, 9H), 1.14−1.08 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4, 154.1, 151.5, 139.5, 118.3, 58.4, 53.1, 38.3, 34.6, 32.0, 29.53, 29.47, 29.3, 29.2, 26.4, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{17}H_{29}ClN_5O$ (M + H^+), 354.2055; found, 354.2054.

*6.1.77. 3-(6-Amino-2-chloro-9H-purin-9-yl)tridecan-1-ol (**10h**).* 3-(2,6-Dichloro-9*H*- purin-9-yl)tridecan-1-ol (38.7 mg, 0.1 mmol) (for 3-(2,6-dichloro-9*H*-purin-9-yl)tridecan-1-ol: prepared according to the procedure for the synthesis of **9c**, using 2,6-dichloro-9*H*-purine to react with (*E*)-tridec-2-enal) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 30:1) to give the target compound **10h** as a white solid in 25.5 mg (69.5% yield). White solid. mp: 131−132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 6.81 (s, 2H), 4.71−4.62 (m, 1H), 3.66−3.56 (m, 2H), 3.33−3.23 (m, 1H), 2.21−2.11 (m, 1H), 2.11−1.99 (m, 2H), 1.95−1.85 (m, 1H), 1.27−1.17 (m, 15H), 1.15−1.07 (m, 1H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 154.1, 151.6, 139.5, 118.4, 58.4, 53.1, 38.4, 34.6, 29.64, 29.58, 29.5, 29.4, 29.2, 26.4, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{18}H_{31}ClN_5O$ (M + H^+), 368.2212; found, 368.2214.

*6.1.78. 3-(6-Amino-2-chloro-9H-purin-9-yl)tetradecan-1-ol (**11h**).* 3-(2,6-Dichloro-9*H*- purin-9-yl)tetradecan-1-ol (40.1 mg, 0.1 mmol) (for 3-(2,6-dichloro-9*H*-purin-9-yl)tridecan-1-ol: prepared according to the procedure for the synthesis of **9c**, using 2,6-dichloro-9*H*-purine to react with (*E*)-tetradec-2-enal) and ammonia (2.0 mL, 7.0 M in MeOH) were added to a reaction tube with a magnetic stirring bar. The reaction was stirred at 100 °C for 6 h and detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 30:1) to give the target compound **11h** as a white solid in 27.8 mg (73.0% yield). White solid. mp: 127−128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 6.80 (s, 2H), 4.71−4.61 (m, 1H), 3.61 (s, 2H), 3.34−3.22 (m, 1H), 2.22−2.10 (m, 1H), 2.10−1.98 (m, 2H), 1.96−1.84 (m, 1H), 1.27−1.16 (m, 17H), 1.16−1.07 (m, 1H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 154. 0, 151.4, 139.6, 118.3, 58.3, 53.3, 38.2, 34.6, 32.0, 29.7, 29.6, 29.5, 29.4, 29.2, 26.4, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{19}H_{33}ClN_5O$ (M + H^+), 382.2368; found, 382.2365.

*6.1.79. 3-(8-Bromo-6-chloro-9H-purin-9-yl)octan-1-ol (**5i**).* 8-Bromo-6-chloro-9*H*-purine (46.6 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-oct-2-enal (44.8 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 3:1) to give the target compound **5i** as a white solid in 27.8 mg (77.1% yield). White solid. mp: 74−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 4.88 (s, 1H), 3.69−3.61 (m, 1H), 3.39−3.29 (m, 1H), 2.66 (s, 1H), 2.50−2.37 (m, 1H), 2.22−2.11 (m, 1H), 1.95−1.85 (m, 1H), 1.84−1.74 (m, 1H), 1.28−1.17 (m, 5H), 1.04−0.93 (m, 1H), 0.80 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.6, 151.4, 149.6, 136.3, 132.2, 59.0, 58.2, 35.3, 33.0, 31.3, 26.0, 22.5, 14.0; ESI-HRMS (m/z) calcd $C_{13}H_{19}BrClN_4O$ (M + H^+), 361.0425; found, 361.0430.

*6.1.80. 3-(8-Bromo-6-chloro-9H-purin-9-yl)nonan-1-ol (**6i**).* 8-Bromo-6-chloro-9*H*-purine (46.6 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-non-2-enal (49.7 μL, 0.3 mmol) was added to the reaction

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mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 3:1) to give the target compound **6i** as a white solid in 29.7 mg (79.5% yield). White solid. mp: 61−63 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 4.87 (s, 1H), 3.68−3.60 (m, 1H), 3.39−3.29 (m, 1H), 2.66 (s, 1H), 2.50−2.37 (m, 1H), 2.21−2.10 (m, 1H), 1.96−1.85 (m, 2H), 1.27−1.12 (m, 7H), 1.03−0.93 (m, 1H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 151.4, 149.6, 136.2, 132.2, 58.9, 58.2, 35.3, 33.0, 31.6, 28.8, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{14}H_{21}BrClN_4O$ (M + H$^+$), 375.0582; found, 375.0582.

*6.1.81. 3-(8-Bromo-6-chloro-9H-purin-9-yl)decan-1-ol (**7i**).* 8-Bromo-6-chloro-9*H*-purine (46.6 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dec-2-enal (54.7 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 3:1) to give the target compound **7i** as a white solid in 32.2 mg (83.2% yield). White solid. mp: 60−62 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (s, 1H), 4.85 (s, 1H), 3.67−3.61 (m, 1H), 3.37−3.30 (m, 1H), 2.67 (s, 1H), 2.49−2.38 (m, 1H), 2.20−2.12 (m, 1H), 1.96−1.84 (m, 2H), 1.31−1.25 (m, 1H), 1.24−1.19 (m, 4H), 1.19−1.13 (m, 4H), 1.02−0.94 (m, 1H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.6, 151.4, 149.6, 136.1, 132.2, 59.0, 58.2, 35.3, 33.0, 31.7, 29.11, 29.05, 26.3, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{15}H_{23}BrClN_4O$ (M + H$^+$), 389.0738; found, 389.0740.

*6.1.82. 3-(8-Bromo-6-chloro-9H-purin-9-yl)undecan-1-ol (**8i**).* 8-Bromo-6-chloro-9*H*-purine (46.6 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-undec-2-enal (59.5 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 3:1) to give the target compound **8i** as a white solid in 33.6 mg (83.5% yield). White solid. mp: 63−65 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 4.86 (s, 1H), 3.68−3.62 (m, 1H), 3.38−3.31 (m, 1H), 2.68 (s, 1H), 2.50−2.40 (m, 1H), 2.20−2.13 (m, 1H), 1.95−1.87 (m, 1H), 1.63 (s, 1H), 1.26−1.21 (m, 4H), 1.20−1.15 (m, 7H), 1.04−0.95 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.6, 151.4, 149.7, 136.2, 132.3, 59.0, 58.2, 35.3, 33.0, 31.9, 29.4, 29.21, 29.17, 26.3, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{16}H_{25}BrClN_4O$ (M + H$^+$), 403.0895; found, 403.0895.

*6.1.83. 3-(8-Bromo-6-chloro-9H-purin-9-yl)dodecan-1-ol (**9i**).* 8-Bromo-6-chloro-9*H*-purine (46.6 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dodec-2-enal (64.4 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the solution was cooled to 0 °C. After that, $NaBH_4$ (22.7 mg, 0.6 mmol) was slowly added and the reaction was stirred for 10 min. Then, the reaction was quenched with a saturated ammonium chloride solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 3:1) to give the target compound **9i** as a white solid in 33.5 mg (80.6% yield). White solid. mp: 70−71 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (s, 1H), 4.85 (s, 1H), 3.67−3.61 (m, 1H), 3.38−3.30 (m, 1H), 2.67 (s, 1H), 2.48−2.39 (m, 1H), 2.20−2.11 (m, 1H), 1.95−1.80 (m, 2H), 1.26−1.20 (m, 4H), 1.20−1.14 (m, 9H), 1.02−0.93 (m, 1H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 151.4, 149.6, 136.2, 132.2, 58.9, 58.2, 35.3, 33.0, 31.9, 29.5, 29.4, 29.3, 29.1, 26.3, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{17}H_{27}BrClN_4O$ (M + H$^+$), 417.1051; found, 417.1058.

*6.1.84. 3-(9H-Purin-9-yl)heptan-1-ol (**4j**).* Compound **4b** (26.9 mg, 0.1 mmol), Pd/C (10 wt %), and methanol (1.0 mL) were added to a reaction tube with a magnetic stirring bar under H_2 (1 atm). The reaction was stirred at room temperature until compound **4b** was completely consumed, which was detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 30:1) to give the target compound **4j** as a colorless oil in 15.3 mg (65.8% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.93 (s, 1H), 8.12 (s, 1H), 4.89−4.79 (m, 1H), 3.64−3.57 (m, 1H), 3.24−3.08 (m, 2H), 2.26−2.07 (m, 3H), 2.05−1.92 (m, 1H), 1.33−1.20 (m, 3H), 1.15−1.02 (m, 1H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 151.8, 149.0, 144.4, 134.2, 58.4, 53.1, 38.0, 34.2, 28.6, 22.3, 13.9; ESI-HRMS (m/z), calcd $C_{12}H_{19}N_4O$ (M + H$^+$), 235.1553; found, 235.1561.

*6.1.85. 3-(9H-Purin-9-yl)octan-1-ol (**5j**).* Compound **5b** (28.3 mg, 0.1 mmol), Pd/C (10 wt %), and methanol (1.0 mL) were added to a reaction tube with a magnetic stirring bar under H_2 (1 atm). The reaction was stirred at room temperature until compound **5b** was completely consumed, which was detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 30:1) to give the target compound **5j** as a colorless oil in 15.6 mg (63.1% yield). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.96 (s, 1H), 8.13 (s, 1H), 4.94−4.75 (m, 1H), 3.67−3.54 (m, 1H), 3.27−3.08 (m, 1H), 2.92 (s, 1H), 2.30−2.11 (m, 2H), 2.11−1.93 (m, 2H), 1.30−1.21 (m, 5H), 1.19−1.10 (m, 1H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 151.9, 149.1, 144.2, 134.3, 58.4, 52.9, 38.2, 34.4, 31.4, 26.1, 22.5, 14.0; ESI-HRMS (m/z) calcd $C_{13}H_{21}N_4O$ (M + H$^+$), 249.1710; found, 249.1713.

*6.1.86. 3-(9H-Purin-9-yl)nonan-1-ol (**6j**).* Compound **6b** (29.7 mg, 0.1 mmol), Pd/C (10 wt %), and methanol (1.0 mL) were added to a reaction tube with a magnetic stirring bar under an atmosphere of H_2 (1 atm). The reaction was stirred at room temperature until compound **6b** was completely consumed, which was detected by TLC. Then, the residue was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 30:1) to give the target compound **6j** as a colorless oil in 17.4 mg (66.5% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.97 (s, 1H), 8.13 (s, 1H), 4.92−4.81 (m, 1H), 3.66−3.57 (m, 1H), 3.22−3.13 (m, 1H), 2.60 (s, 1H), 2.28−2.13 (m, 2H), 2.10−1.96 (m, 2H), 1.28−1.24 (m, 6H), 1.22−1.20 (m, 2H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 151.9, 149.1, 144.2, 134.3, 58.4, 52.9, 38.2, 34.5, 31.6, 28.9, 26.4, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{14}H_{23}N_4O$ (M + H$^+$), 263.1866; found, 263.1865.

*6.1.87. 3-(6-Chloro-9H-purin-9-yl)-2-methyleneoctan-1-ol (**5k**).* 6-Chloro-9*H*-purine (0.93 g, 6 mmol), K_2CO_3 (0.83 g, 6 mmol), DABCO (0.022 g, 0.2 mmol), and methyl 2-methylene-3-(propionyloxy) octanoate (0.48 g, 2 mmol) in CH_2Cl_2 (15.0 mL) were added to a reaction tube with a magnetic stirring bar under N_2. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, to the mixture was added a saturated brine solution and it was extracted with CH_2Cl_2 three times. The combined organic

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extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 2:1) to give the compound methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methyleneoctanoate as a colorless oil. Then, the solution of methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methyleneoctanoate (32.2 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL) was cooled to −78 °C under N_2. DIBAL-H (0.3 mL, 0.3 mmol, 1.0 M in toluene) was added dropwise and stirred at −78 °C for 20 min. The reaction was stirred at room temperature until methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methyleneoctanoate was completely consumed, which was detected by TLC. The reaction was quenched with 10% NaOH solution. Then, the mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **5k** as a colorless oil in 11.0 mg (37.7% yield). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.18 (s, 1H), 5.36 (s, 1H), 5.36 (t, J = 7.2 Hz, 1H), 5.25 (s, 1H), 4.13−4.01 (m, 2H), 2.28−2.18 (m, 3H), 1.27−1.23 (m, 5H), 1.21−1.16 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.0, 151.4, 148.8, 146.3, 144.1, 136.1, 115.0, 64.5, 56.4, 32.5, 31.3, 26.1, 22.5, 14.0; ESI-HRMS (m/z) calcd $C_{14}H_{20}ClN_4O$ (M + H^+), 295.1320; found, 295.1326.

*6.1.88. 3-(6-Chloro-9H-purin-9-yl)-2-methylenenonan-1-ol (**6k**).* 6-Chloro-9*H*-purine (0.93 g, 6 mmol), K_2CO_3 (0.83 g, 6 mmol), DABCO (0.022 g, 0.2 mmol), and methyl 2-methylene-3-(propionyloxy)nonanoate (0.51 g, 2 mmol) in CH_2Cl_2 (15.0 mL) were added to a reaction tube with a magnetic stirring bar under N_2. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, to the mixture was added a saturated brine solution and it was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 2:1) to give the compound methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methylenenonanoate as a colorless oil. Then, the solution of methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methylenenonanoate (33.6 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL) was cooled to −78 °C under N_2. DIBAL-H (0.3 mL, 0.3 mmol, 1.0 M in toluene) was added dropwise and stirred at −78 °C for 20 min. The reaction was stirred at room temperature until methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methylenenonanoate was completely consumed, which was detected by TLC. The reaction was quenched with 10% NaOH solution. Then, the mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **6k** as a colorless oil in 12.7 mg (41.1% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.18 (s, 1H), 5.36 (s, 1H), 5.20 (t, J = 8.0 Hz, 1H), 5.25 (s, 1H), 4.13−4.01 (m, 2H), 2.58 (s, 1H), 2.27−2.18 (m, 2H), 1.34−1.26 (m, 3H), 1.26−1.17 (m, 5H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.01, 151.97, 151.3, 146.2, 144.2, 131.7, 114.9, 64.4, 56.5, 32.6, 31.6, 28.8, 26.4, 22.6, 14.1; ESI-HRMS (m/z) calcd $C_{15}H_{22}ClN_4O$ (M + H^+), 309.1477; found, 309.1473.

*6.1.89. 3-(6-Chloro-9H-purin-9-yl)-2-methylenedecan-1-ol (**7k**).* 6-Chloro-9*H*-purine (0.93 g, 6 mmol), K_2CO_3 (0.83 g, 6 mmol), DABCO (0.022 g, 0.2 mmol), and methyl 2-methylene-3-(propionyloxy)decanoate (0.54 g, 2 mmol) in CH_2Cl_2 (15.0 mL) were added to a reaction tube with a magnetic stirring bar under N_2. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, to the mixture was added a saturated brine solution and it was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 2:1) to give the compound methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methylenedecanoate as a colorless oil. Then, the solution of methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methylenedecanoate (35.0 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL) was cooled to −78 °C under N_2. DIBAL-H (0.3 mL, 0.3 mmol, 1.0 M in toluene) was added dropwise and stirred at −78 °C for 20 min. The reaction was stirred at room temperature until methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methylenedecanoate was completely consumed, which was detected by TLC. The reaction was quenched with 10% NaOH solution. Then, the mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **7k** as a colorless oil in 13.9 mg (43.2% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.18 (s, 1H), 5.36 (s, 1H), 5.32 (t, J = 8.0 Hz, 1H), 5.25 (s, 1H), 4.14−4.01 (m, 2H), 2.38 (s, 1H), 2.27−2.18 (m, 2H), 1.33−1.27 (m, 3H), 1.26−1.19 (m, 7H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.02, 151.99, 151.3, 146.3, 144.2, 131.8, 114.9, 64.5, 56.4, 32.6, 31.8, 29.13, 29.08, 26.4, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{16}H_{24}ClN_4O$ (M + H^+), 323.1633; found, 323.1642.

*6.1.90. 3-(6-Chloro-9H-purin-9-yl)-2-methyleneundecan-1-ol (**8k**).* 6-Chloro-9*H*-purine (0.93 g, 6 mmol), K_2CO_3 (0.83 g, 6 mmol), DABCO (0.022 g, 0.2 mmol), and methyl 2-methylene-3-(propionyloxy)undecanoate (0.57 g, 2 mmol) in CH_2Cl_2 (15.0 mL) were added to a reaction tube with a magnetic stirring bar under N_2. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, to the mixture was added a saturated brine solution and it was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 2:1) to give the compound methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methyleneundecanoate as a colorless oil. Then, the solution of methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methyleneundecanoate (36.4 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL) was cooled to −78 °C under N_2. DIBAL-H (0.3 mL, 0.3 mmol, 1.0 M in toluene) was added dropwise and stirred at −78 °C for 20 min. The reaction was stirred at room temperature until methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methyleneundecanoate was completely consumed, which was detected by TLC. The reaction was quenched with 10% NaOH solution. Then, the mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **8k** as a colorless oil in 12.4 mg (36.8% yield). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.18 (s, 1H), 5.36 (s, 1H), 5.32 (t, J = 7.2 Hz, 1H), 5.24 (s, 1H), 4.12−4.02 (m, 2H), 2.47 (s, 1H), 2.26−2.18 (m, 2H), 1.32−1.27 (m, 2H), 1.27−1.23 (m, 3H), 1.23−1.15 (m, 7H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.03, 152.01, 151.4, 146.3, 144.1, 131.8, 114.9, 64.5, 56.4, 32.6, 31.9, 29.4, 29.23, 29.17, 26.4, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{17}H_{26}ClN_4O$ (M + H^+), 337.1790; found, 337.1795.

*6.1.91. 3-(6-Chloro-9H-purin-9-yl)-2-methylenedodecan-1-ol (**9k**).* 6-Chloro-9*H*-purine (0.93 g, 6 mmol), K_2CO_3 (0.83 g, 6 mmol), DABCO (0.022 g, 0.2 mmol), and methyl 2-methylene-3-(propionyloxy)dodecanoate (0.60 g, 2 mmol) in CH_2Cl_2 (15.0 mL) were added to a reaction tube with a magnetic stirring bar under N_2. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, to the mixture was added a saturated brine solution and it was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 2:1) to give the compound methyl 3-(6-chloro-9*H*-purin-9-yl)-2-methylenedodecanoate as a colorless oil. Then, the solution of methyl 3-(6-chloro-9*H*-purin- 9-yl)-2-methylenedodecanoate (37.8 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL) was cooled to −78 °C under N_2. DIBAL-H (0.3 mL, 0.3 mmol, 1.0 M in toluene) was added dropwise and stirred at −78 °C for 20 min. The reaction was stirred at room temperature until methyl 3-(6-chloro- 9*H*-purin-9-yl)-2-methylenedodecanoate was completely consumed, which was detected by TLC. The reaction was quenched with 10% NaOH solution. Then, the mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **9k** as a colorless oil in 14.1 mg (40.1% yield). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.18 (s, 1H), 5.36 (s, 1H), 5.32 (t, J = 8.0 Hz, 1H), 5.23 (s, 1H), 4.14−4.00 (m, 2H), 2.72 (s, 1H), 2.26−2.15 (m, 2H), 1.29−1.09 (m, 14H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz,

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$CDCl_3$) δ 152.01, 151.97, 151.3, 146.2, 144.2, 131.7, 114.9, 64.4, 56.5, 32.5, 31.9, 29.5, 29.4, 29.3, 29.2, 26.4, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{18}H_{28}ClN_4O$ (M + H^+), 351.1946; found, 351.1945.

*6.1.92. 2-((6-Chloro-9H-purin-9-yl)(phenyl)methyl)prop-2-en-1-ol (**10k**).* 6-Chloro-9*H*-purine (0.93 g, 6 mmol), K_2CO_3 (0.83 g, 6 mmol), DABCO (0.022 g, 0.2 mmol), and methyl 2-(phenyl-(propionyloxy)methyl)acrylate (0.50 g, 2 mmol) in CH_2Cl_2 (15.0 mL) were added to a reaction tube with a magnetic stirring bar under N_2. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, to the mixture was added a saturated brine solution and it was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 4:1) to give the compound methyl 2-((6-chloro-9*H*-purin-9-yl)(phenyl)methyl)acrylate as a white solid. Then, the solution of methyl 2-((6-chloro-9*H*-purin-9-yl)(phenyl) methyl)acrylate (32.8 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL) was cooled to −78 °C under N_2. DIBAL-H (0.3 mL, 0.3 mmol, 1.0 M in toluene) was added dropwise and stirred at −78 °C for 20 min. The reaction was stirred at room temperature until methyl 2-((6-chloro-9*H*-purin-9-yl)(phenyl)-methyl)acrylate was completely consumed, which was detected by TLC. The reaction was quenched with 10% NaOH solution. Then, the mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 2:1) to give the target compound **10k** as a white solid in 12.8 mg (42.8% yield). White solid. mp: 113−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.95 (s, 1H), 7.48−7.38 (m, 3H), 7.38−7.28 (m, 2H), 6.62 (s, 1H), 5.51 (s, 1H), 4.70 (s, 1H), 4.21 (s, 2H), 2.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 151.6, 151.4, 145.9, 144.8, 134.8, 131.9, 129.6, 129.57, 128.6, 115.8, 64.4, 60.0; ESI-HRMS (m/z) calcd $C_{15}H_{14}ClN_4O$ (M + H^+), 301.0851; found, 301.0855.

*6.1.93. 3-(6-Chloro-9H-purin-9-yl)dodecyl methanesulfonate (**9ba**).* Compound **9b** (169.1 mg, 0.5 mmol) and Et_3N (173.0 μL, 1.25 mmol) were added to CH_2Cl_2 (10.0 mL) at 0 °C. Methanesulfonyl chloride (58.0 μL, 0.75 mmol) was slowly added to the solution. The mixture was stirred for 4 h at room temperature. Then, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic phase was dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue was further purified by flash column chromatography on silica gel (PE/EA = 2:1) to give the target compound **9ba** as a white solid in 157.6 mg (75.6% yield). White solid. mp: 73−74 °C. For (*R*)-**9ba**: prepared according to the procedure for the synthesis of the above racemic **9ba** using (*R*)-**9b** (169.1 mg, 0.5 mmol) to replace racemic **9b** (169.1 mg, 0.5 mmol). $[\alpha]_D^{20}$ = −2.7 (*c* = 0.30, $CHCl_3$), 94% ee [CHIRALCEL IA, *n*-hexane/2-propanol = 95/5, flow rate = 0.8 mL/min, temperature = 25 °C, λ = 250 nm, retention time: 47.048 min (minor), 51.301 min (major)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.12 (s, 1H), 4.75−4.65 (m, 1H), 4.25−4.18 (m, 1H), 3.98−3.90 (m, 1H), 2.91 (s, 3H), 2.71−2.60 (m, 1H), 2.47−2.35 (m, 1H), 2.24−2.14 (m, 1H), 2.00−1.88 (m, 1H), 1.26−1.13 (m, 13H), 1.07−0.95 (m, 1H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 151.8, 151.5, 145.0, 132.3, 65.8, 54.8, 37.6, 34.2, 33.9, 31.9, 29.5, 29.4, 29.3, 29.0, 26.2, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{18}H_{30}ClN_4O_3S$ (M + H^+), 417.1722; found, 417.1719.

*6.1.94. 9-(1-Azidododecan-3-yl)-6-chloro-9H-purine (**9bb**).* NaN_3 (97.5 mg, 1.5 mmol) was added to a solution of racemic **9ba** (124.8 mg, 0.3 mmol) in DMF (5.0 mL) at 0 °C. Then, the reaction was stirred at 25 °C for 6 h and detected by TLC. After that, water (10.0 mL) was added to quench the reaction. The resulting mixture was extracted with ethyl acetate three times. The organic phases were combined and washed with saturated brine solution. The organic phase was dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue was further purified by flash column chromatography on silica gel (PE/EA = 3:1) to give the target racemic **9bb** as a colorless oil in 81.1 mg (74.5% yield). Colorless oil. For (*R*)-**9bb**: prepared according to the procedure for the synthesis of the above racemic **9bb** using (*R*)-**9ba** (124.8 mg, 0.3 mmol) to replace racemic **9ba** (124.8 mg, 0.3 mmol). $[\alpha]_D^{20}$ = −22.5 (*c* = 0.08, $CHCl_3$), 94% ee [CHIRALCEL IA, *n*-hexane/2-propanol = 98/2, flow rate = 0.6 mL/min, temperature = 25 °C, λ = 250 nm, retention time: 34.051 min (minor), 39.148 min (major)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.09 (s, 1H), 4.71−4.61 (m, 1H), 3.38−3.29 (m, 1H), 3.07−2.99 (m, 1H), 2.44−2.34 (m, 1H), 2.23−2.09 (m, 2H), 1.99−1.88 (m, 1H), 1.27−1.15 (m, 13H), 1.09−0.98 (m, 1H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 151.9, 151.4, 144.6, 132.2, 55.3, 48.1, 34.3, 33.7, 31.9, 29.5, 29.4, 29.3, 29.0, 26.2, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{17}H_{27}ClN_7$ (M + H^+), 364.2011; found, 364.2014.

*6.1.95. 6-Chloro-9-(1-(4-phenyl-1H-1,2,3-triazol-1-yl)dodecan-3-yl)-9H-purine (**9bc**).* Compound **9bb** (36.3 mg, 0.1 mmol), phenylacetylene (16.5 μL, 0.15 mmol), and $Cu(OAc)_2$ (0.9 mg, 0.005 mmol) were added sequentially to acetonitrile (1.0 mL). The mixture was stirred until $Cu(OAc)_2$ was completely dissolved. Subsequently, iPr_2NEt (1.7 μL, 0.01 mmol) was added and the reaction mixture was stirred at 0 °C for 6 h. Then, water (2.0 mL) was added to quench the reaction. The resulting mixture was extracted with ethyl acetate three times. The organic phases were combined and washed with saturated brine solution. The organic phase was dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue was further purified by flash column chromatography on silica gel (PE/EA = 3:1) to give the target racemic **9bc** as a white solid in 32.8 mg (70.5% yield). White solid. mp: 98−100 °C. For (*R*)-**9bc**: prepared according to the procedure for the synthesis of the above racemic **9bc** using (*R*)-**9bb** (36.3 mg, 0.1 mmol) to replace racemic **9bb** (36.3 mg, 0.1 mmol). $[\alpha]_D^{20}$ = −48.4 (*c* = 0.22, $CHCl_3$), 94% ee [CHIRALCEL IA, *n*-hexane/2-propanol = 70/30, flow rate = 0.8 mL/min, temperature = 25 °C, λ = 250 nm, retention time: 21.317 min (major), 25.346 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.16 (s, 1H), 7.80−7.74 (m, 2H), 7.67 (s, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.37−7.31 (m, 1H), 4.61−4.50 (m, 1H), 4.37−4.28 (m, 1H), 4.20−4.09 (m, 1H), 2.99−2.86 (m, 1H), 2.66−2.55 (m, 1H), 2.26−2.13 (m, 1H), 1.96−1.85 (m, 1H), 1.25−1.12 (m, 13H), 1.01−0.90 (m, 1H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 151.8, 151.6, 148.1, 145.2, 132.3, 130.3, 129.1, 128.5, 125.8, 120.0, 55.6, 47.0, 34.7, 34.3, 31.9, 29.4, 29.31, 29.25, 29.0, 26.2, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{25}H_{33}ClN_7$ (M + H^+), 466.2480; found, 466.2484.

*6.1.96. 6-Chloro-9-(1-chlorododecan-3-yl)-9H-purine (**9bd**).* Compound **9b** (169.1 mg, 0.5 mmol) and pyridine (44.5 μL, 0.55 mmol) were added to CH_2Cl_2 (0.5 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 5 min. A solution of SO_2Cl_2 (39.9 μL, 0.55 mmol) in CH_2Cl_2 (0.5 mL) was slowly added dropwise. The reaction mixture was stirred at −20 °C for 15 min and then at 0 °C for another 15 min. After that, the CH_2Cl_2 was evaporated and the residue was suspended in diethyl ether. After filtration to remove the precipitate, the organic phase was evaporated in vacuo. The residue was further purified by flash column chromatography on silica gel (PE/EA = 2:1) to give the target racemic **9bd** as a colorless oil in 133.5 mg (75.0% yield). Colorless oil. For (*R*)-**9bd**: prepared according to the procedure for the synthesis of the above racemic **9bd** using (*R*)-**9b** (169.1 mg, 0.5 mmol) to replace racemic **9b** (169.1 mg, 0.5 mmol). $[\alpha]_D^{20}$ = −21.8 (*c* = 0.15, $CHCl_3$), 93% ee [CHIRALCEL IA, *n*-hexane/2-propanol = 95/5, flow rate = 0.8 mL/min, temperature = 25 °C, λ = 250 nm, retention time: 9.979 min (minor), 11.190 min (major)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.09 (s, 1H), 4.81−4.70 (m, 1H), 3.55−3.46 (m, 1H), 3.18−3.08 (m, 1H), 2.75−2.64 (m, 1H), 2.39−2.28 (m, 1H), 2.26−2.14 (m, 1H), 1.98−1.86 (m, 1H), 1.26−1.11 (m, 13H), 1.06−0.94 (m, 1H), 0.82 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 151.7, 151.4, 145.1, 132.3, 55.6, 41.0, 36.4, 33.8, 31.9, 29.4, 29.3, 29.2, 29.0, 26.2, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{17}H_{27}Cl_2N_4$ (M + H^+), 357.1607; found, 357.1608.

*6.1.97. Diethyl (((3-(6-Chloro-9H-purin-9-yl)dodecyl)oxy)-methyl)phosphonate (**9be**).* A solution of **9b** (33.8 mg, 0.1 mmol) in dry THF (0.5 mL) was slowly added to a stirred suspension of NaH (12.0 mg, 0.5 mmol) in dry THF (0.5 mL) at −15 °C under N_2. Then, the reaction mixture was stirred at −15 °C for 5 min. After that,

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a solution of ((diethoxyphosphoryl)oxy) methyl trifluoromethanesulfonate (90.0 mg, 0.3 mmol) in THF (1.0 mL) was slowly added to the above reaction mixture and the reaction mixture was stirred at 0 °C for 7 h. Then, water (10.0 mL) was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 three times. The organic phases were combined and washed with a saturated brine solution. The organic phase was dried over anhydrous sodium sulfate and then concentrated in vacuo. The residue was further purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 90:1) to give the target racemic **9be** as a colorless oil in 31.1 mg (63.8% yield). Colorless oil. For (*R*)-**9be**: prepared according to the procedure for the synthesis of the above racemic **9be** using (*R*)-**9b** (33.8 mg, 0.1 mmol) to replace racemic **9b** (33.8 mg, 0.1 mmol). $[\alpha]_D^{20} = -1.7$ (c = 0.23, $CHCl_3$), 92% ee [CHIRALCEL ID, *n*-hexane/2-propanol = 80/20, flow rate = 0.8 mL/min, temperature = 25 °C, λ = 250 nm, retention time: 19.747 min (minor), 21.282 min (major)]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.14 (s, 1H), 4.76−4.67 (m, 1H), 4.20−4.06 (m, 4H), 3.69−3.58 (m, 2H), 3.58−3.52 (m, 1H), 3.24−3.12 (m, 1H), 2.44−2.34 (m, 1H), 2.28−2.16 (m, 2H), 1.99−1.87 (m, 1H), 1.37−1.29 (m, 6H), 1.26−1.23 (m, 3H), 1.23−1.16 (m, 10H), 1.06-0.97 (m, 1H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.9, 151.7, 151.2, 145.6, 132.3, 69.6, 69.6, 65.9, 64.8, 62.54, 62.50, 55.3, 34.2, 34.1, 31.9, 29.5, 29.4, 29.3, 29.1, 26.4, 22.8, 16.7, 16.6, 14.2; ESI-HRMS (m/z) calcd $C_{22}H_{39}ClN_4O_4P$-(M + H^+), 489.2392; found, 489.2396.

*6.1.98. Diethyl (((3-(6-Chloro-9H-purin-9-yl)dodecyl)oxy)-methyl)phosphonic acid (**9bf**).* To a solution of **9be** (48.8 mg, 0.1 mmol) in anhydrous acetonitrile was added bromotrimethylsilane (132.0 μL, 1 mmol) at 0 °C. The reaction was stirred at room temperature overnight and detected by TLC. Then, the reaction mixture was concentrated in vacuo. After that, water and CH_2Cl_2 were added. Then, the pH value of the mixture was adjusted to 7−8 by adding 10% sodium hydroxide solution. Finally, the water phase was concentrated in vacuo. The residue was purified by reversed phase column chromatography (H_2O/MeOH = 3:1) to give the target compound **9bf** as a white solid in 19.4 mg (44.9% yield). White solid. mp: >320 °C (Note: the melting point of **9bf** exceeds the measuring range of the thermometer). ^{1}H NMR (400 MHz, D_2O) δ 8.85 (s, 1H), 8.70 (s, 1H), 3.64−3.52 (m, 1H), 3.51−3.32 (m, 3H), 2.60−2.36 (m, 2H), 2.26−2.11 (m, 1H), 2.10−1.95 (m, 1H), 1.25−1.07 (m, 2H), 1.06−0.96 (m, 1H), 0.93−0.84 (m, 5H), 0.83−0.70 (m, 7H), 0.51 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, D_2O) δ 151.63, 149.13, 145.76, 141.24, 123.45, 69.43, 68.94, 68.84, 67.93, 53.98, 34.53, 33.95, 31.09, 28.09, 28.01, 27.49, 24.81, 21.95, 13.40; ^{31}P NMR (162 MHz, D_2O) δ 13.62; ESI-HRMS (m/z) calcd $C_{18}H_{31}ClN_4O_4P$ (M + H^+), 433.1766; found, 433.1773.

*6.1.99. 3-(6-Chloro-9H-purin-9-yl)dodecanal (**17**).* 6-Chloro-9*H*-purine (30.9 mg, 0.2 mmol), L-proline (2.3 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and methanol (1.5 mL) were added to a reaction tube with a magnetic stirring bar. Then, (*E*)-dodec-2-enal (64.4 μL, 0.3 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 24 h and detected by TLC. Then, the reaction was quenched with a saturated brine solution and concentrated in vacuo. Then, water was added to the residue and the mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 3:1) to give the target compound **17** as a white solid in 53.8 mg (80.1% yield). White solid. mp: 83−85 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.70 (s, 1H), 8.15 (s, 1H), 5.03−4.96 (m, 1H), 3.55 (dd, J = 18.6, 8.4 Hz, 1H), 3.12 (dd, J = 18.6, 4.8 Hz, 1H), 2.29−2.21 (m, 1H), 1.96−1.88 (m, 1H), 1.28−1.21 (m, 4H), 1.21−1.15 (m, 9H), 1.05−0.98 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.3, 151.6, 151.5, 151.3, 145.6, 132.3, 52.4, 47.5, 33.5, 31.9, 29.5, 29.3, 29.3, 28.9, 26.2, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{17}H_{26}ClN_4O$ (M + H^+), 337.1790; found, 337.1785.

*6.1.100. 3-(6-Chloro-9H-purin-9-yl)dodecanoic Acid (**18**).* To a solution of compound **17** (674.4 mg, 2.0 mmol) in acetone (5 mL)/water (2 mL) was added $KMnO_4$ (632.1 mg, 4.0 mmol) in one portion. The reaction was stirred at room temperature until compound **17** was completely consumed, which was detected by TLC. Then, the reaction mixture was quenched by adding solid $NaHSO_3$ to give a thick brown sludge. After filtering through a pad of Celite using acetone/water as the eluent, a pale-yellow solution was obtained, which was concentrated in vacuo to afford a white solid. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to give the target compound **18** as a white solid in 561.4 mg (83.5% yield). White solid. mp: 167−169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.19 (s, 1H), 4.93−4.83 (m, 1H), 3.64 (s, 1H), 3.34 (dd, J = 17.2, 9.6 Hz, 1H), 2.97 (dd, J = 17.2, 4.0 Hz, 1H), 2.38−2.26 (m, 1H), 2.05−1.94 (m, 1H), 1.28−1.24 (m, 4H), 1.23−1.17 (m, 9H), 1.11−1.00 (m, 1H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 151.9, 151.5, 151.2, 145.9, 131.9, 55.1, 38.1, 33.3, 31.9, 29.5, 29.4, 29.3, 29.0, 26.3, 22.8, 14.2; ESI-HRMS (m/z) calcd $C_{17}H_{26}ClN_4O_2$ (M + H^+), 353.1739; found, 353.1731.

*6.1.101. tert-Butyl (5-(3-(6-Chloro-9H-purin-9-yl)-dodecanamido)pentyl)carbamate (**20**).* To a stirred solution of compound **18** (70.4 mg, 0.2 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added dropwise triethylamine (41.6 μL, 0.3 mmol). After 20 min, isobutyl chloroformate (38.9 μL, 0.3 mmol) was added dropwise to the above reaction mixture at 0 °C and the reaction was stirred for another 30 min. Then, 5-(*tert*-butoxycarbonylamino)-pentyl amine (60.7 mg, 0.3 mmol) was added dropwise at 0 °C and the reaction mixture was stirred for 20 min. The reaction was reacted at room temperature until compound **18** was completely consumed, which was detected by TLC. After that, water (2.0 mL) was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **20** as a colorless oil in 81.6 mg (76.1% yield). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.13 (s, 1H), 5.76 (s, 1H), 4.99−4.91 (m, 1H), 4.61 (s, 1H), 3.15−2.98 (m, 5H), 2.82 (dd, J = 15.0, 4.8 Hz, 1H), 2.32−2.23 (m, 1H), 1.97−1.89 (m, 1H), 1.42 (s, 9H), 1.39−1.32 (m, 2H), 1.28−1.21 (m, 6H), 1.21−1.15 (m, 9H), 1.10−1.03 (m, 2H), 1.03−0.96 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.0, 156.3, 151.6, 151.5, 151.2, 146.4, 132.4, 79.3, 56.1, 40.5, 40.1, 39.3, 33.3, 31.9, 29.7, 29.5, 29.4, 29.3, 29.0, 28.8, 28.6, 26.4, 23.7, 22.7, 14.2; ESI-HRMS (m/z) calcd $C_{27}H_{46}ClN_6O_3$ (M + H^+), 537.3314; found, 537.3314.

*6.1.102. Biotin-Annexed Probe **21**.* A solution of **20** (80.4 mg, 0.15 mmol) and CF_3COOH (2 mL) in CH_2Cl_2 (2 mL) was stirred at room temperature for 10 min. Then, the reaction mixture was concentrated in vacuo to afford the corresponding deprotected amine. To a solution of the above deprotected amine in anhydrous DMF (7 mL), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU, 56.9 mg, 0.15 mmol), iPr$_2$NEt (24.8 μL, 0.3 mmol), and a solution of *D*-(+)-biotin (24.4 mg, 0.1 mmol) in anhydrous DMF (3 mL) were added subsequently. The reaction mixture was stirred at room temperature for 24 h under N_2 and detected by TLC. After that, water was added to the solution and the reaction mixture was extracted with ethyl acetate three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 12:1) to give the target compound **21** as a white solid in 23.8 mg (36.0% yield). White solid. mp: 54−56 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.72 (s, 1H), 7.86 (t, J = 5.6 Hz, 1H), 7.66 (t, J = 5.6 Hz, 1H), 6.38 (s, 1H), 6.33 (s, 1H), 5.02−4.92 (m, 1H), 4.33−4.27 (m, 1H), 4.15−4.10 (m, 1H), 3.12−3.06 (m, 1H), 2.98−2.77 (m, 8H), 2.57 (d, J = 12.4 Hz, 1H), 2.18−2.07 (m, 1H), 2.03 (t, J = 7.2 Hz, 2H), 1.92−1.81 (m, 1H), 1.66−1.56 (m, 1H), 1.54−1.40 (m, 4H), 1.26−1.23 (m, 4H), 1.18−1.11 (m, 13H), 1.06−0.99 (m, 2H), 0.98−0.90 (m, 1H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.7, 168.5, 162.6, 151.8, 151.1, 149.0, 147.0, 131.0, 61.0, 59.2, 55.4, 54.1, 38.2, 35.2, 33.1, 31.2, 28.7, 28.6, 28.5, 28.5, 28.1, 28.0, 25.3, 23.5, 22.0, 13.9; ESI-HRMS (m/z) calcd $C_{32}H_{52}ClN_8O_3S$ (M + H^+), 663.3566; found, 663.3571.

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*6.1.103. Diazirine Photoaffinity Probe **23**.* To a stirred solution of compound **18** (70.4 mg, 0.2 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added dropwise triethylamine (41.6 μL, 0.3 mmol). After 20 min, isobutyl chloroformate (38.9 μL, 0.3 mmol) was added dropwise to the above reaction mixture at 0 °C and the reaction was stirred for another 30 min. Then, 2-(3-(but-3-yn-1-yl)-3*H*-diazirin-3-yl)ethan-1-amine (38.4 μL, 0.3 mmol) was added dropwise at 0 °C and the reaction mixture was stirred for 20 min. The reaction was reacted at room temperature until compound **18** was completely consumed, which was detected by TLC. After that, water (2.0 mL) was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to give the target compound **23** as a colorless oil in 83.8 mg (88.9% yield). Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.11 (s, 1H), 5.84−5.78 (m, 1H), 4.96−4.89 (m, 1H), 3.15 (dd, J = 15.6, 9.6 Hz, 1H), 2.99−2.92 (m, 1H), 2.90−2.84 (m, 1H), 2.81 (dd, J = 15.0, 4.8 Hz, 1H), 2.32−2.23 (m, 1H), 1.95 (t, J = 2.5 Hz, 1H), 1.95−1.90 (m, 1H), 1.90−1.83 (m, 2H), 1.53−1.38 (m, 4H), 1.25−1.17 (m, 5H), 1.17−1.12 (m, 8H), 1.02−0.94 (m, 1H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.07, 151.58, 151.44, 151.09, 146.28, 132.41, 82.70, 69.52, 55.90, 40.33, 34.40, 33.19, 32.13, 31.90, 31.82, 29.40, 29.31, 29.21, 28.93, 26.64, 26.30, 22.65, 14.12, 13.14; ESI-HRMS (m/z) calcd $C_{24}H_{35}ClN_7O$ ($M + H^+$), 472.2586; found, 472.2585.

6.2. Reagents and Antibodies. These compounds were dissolved in dimethyl sulfoxide (DMSO, Kermel) at a concentration of 100 mM and stored at 4 °C. Dulbecco's modified Eagle's medium (DMEM), RPMI-1640 medium, McCoy's 5A medium, phosphate buffer (PBS), and fetal bovine serum (FBS) were purchased from ThermoFisher Scientific. Poly(vinylidene fluoride) (PVDF) membrane was purchased from Millipore. Bax, Bcl-xl, and cleaved-PARP primary antibodies were purchased from Proteintech; antirabbit or antimouse IgG horseradish peroxidase (HRP) -linked secondary antibodies were purchased from Arigo (China); the cell apoptosis detection kit was purchased from BD Biosciences; P53 and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) primary antibodies, crystal violet staining solution, BCA protein assay kit, IP lysis buffer, mitochondrial membrane potential assay kit, and cell-cycle analysis kit were purchased from Beyotime (China); and Q-VD-OPh was purchased from MedChemExpress.

6.3. MTT Cell Viability Assay. The antiproliferation activities of synthesized compounds were assessed by an MTT assay. Cells were cultured in DMEM, RPMI-1640, or McCoy's 5A medium supplemented with 10% FBS and 1% penicillin-streptomycin solution (10 000 U/mL penicillin and 10 000 μg/mL streptomycin) at 37 °C under 5% CO_2. Then, 5×10^3 cells per well were seeded into 96-well plates for 24 h and then treated with compounds at various concentrations or DMSO (diluent) for 48 h. Then, 20 μL of MTT solution (5 mg/mL in PBS) was added to each well and incubated at 37 °C for 4 h. Next, the MTT solution was replaced with DMSO (150 μL). Absorbance of each well was tested by a microplate reader (Multiskan FC, Thermo) at a 570 nm wavelength. Assays were performed in triplicates. Data were analyzed by GraphPad Prism 6. Data are mean ± SEM values from three independent experiments.

6.4. Annexin V-FITC/PI Apoptosis Assay. Around 5×10^5 SW480 cells per well were seeded into six-well plates, incubated overnight, and treated with compound **9b** at specified concentrations for 48 h. Then, the cells were collected, washed twice with PBS, and costained with Annexin V-FITC and PI in a dark place for 15 min at room temperature according to the kit manual. Apoptotic cells were detected with flow cytometry, and 10 000 cells were counted each time.

6.5. Western Blotting Assay. SW480 cells were seeded into six-well plates, incubated overnight, and treated with compound **9b** at specified concentrations for 48 h. The cells were collected, and the cell samples were lysed by IP lysis buffer. Protein concentrations were quantified by the BCA protein assay kit. Cell extracts were separated by electrophoresis on sodium dodecyl sulfate polyacrylamide gels and transferred onto a poly(vinylidene fluoride) (PVDF) membrane. After blocking with 5% BSA in TBST, the membrane was interacted with GAPDH, Bax, P53, Bcl-xl, and cleaved-PARP primary antibody overnight at 1:2000 dilutions. Then, the membrane was interacted with appropriate secondary antibodies conjugated with horseradish peroxidase (HRP) at room temperature for 2 h. Protein bands are visualized by chemiluminescence reagents.

6.6. MMP Determination. Around 5×10^5 SW480 cells per well were seeded into a six-well plate for 24 h at 37 °C. Then, cells were treated with diluent (DMSO) or specified concentrations of compound **9b** for 24 h. For flow cytometer detection, cells were collected with a trypsin solution, washed twice with PBS, followed by adding JC-1 binding solution, and then incubated in the incubator at 37 °C for 20 min in a dark place, centrifuged, and washed 3 times with JC-1 staining buffer. After resuspending with JC-1 staining buffer, the samples were analyzed with a flow cytometer. For fluorescence detection, cells were washed twice with PBS, stained with the JC-1 binding solution at 37 °C for 20 min in a dark place, and washed twice with JC-1 staining buffer. Images were taken under a fluorescence microscope.

6.7. Colony Formation Assay. HCT-116 cells and SW480 cells were seeded in six-well plates with a density of 1500 cells per well and maintained in a regular culture medium. After 24 h, the cells were treated with compound **9b** at indicated concentrations for 48 h. The culture medium was changed every 72 h. At the end of 14 days, the wells were washed twice with PBS, fixed with methanol for 20 min, and stained with 2 mL of crystal violet staining solution for 30 min at room temperature. The wells were then washed with PBS three times and allowed to dry. Photographs were then taken.

6.8. Metabolic Stability Assay. Microsomes were dissolved in 0.1 M Tris buffer (pH 7.40) containing 5 mM $MgCl_2$, 0.1 μM compound **9b**, or 0.01% DMSO (negative control) and 0.005% bovine serum albumin (BSA) at the concentration of 0.33 mg/mL and incubated at 37 °C for 10 min. The reaction was started by the addition of NADPH (final concentration 1 mM). Aliquots were sampled at 0, 7, 17, 30, and 60 min, and methanol (cold in 4 °C) was added to terminate the reaction. After centrifugation (4000 rpm, 5 min), samples were then analyzed by LC-MS/MS.

6.9. Acute Toxicity Assay. Balb/C mice were divided into six groups randomly (n = 10, five male and five female) and injected intraperitoneally with various dosages of compound **9b** (75, 62.5, 50, 37.5, or 25 mg/kg) or a diluent (DMSO/castor oil/PBS = 1:1:8) per 4 h; after 4 times of injection, mice were fed for 14 days and the number of dead mice were recorded every day. The LD_{50} value was evaluated in GraphPad Prism 6.0.

6.10. Xenograft Tumor Growth Assay in Nude Mice. All animal studies and procedures were approved by the Animal Ethics Committee of School of Pharmacy, Fudan University. BALB/C nude mice at 5 weeks of age were purchased from Shanghai Slac Laboratory Animal Co. Ltd. (Shanghai, China) and housed under a specific pathogen-free environment in an animal holding unit (AHU) of Fudan University (Shanghai, China). Mice were injected with SW480 cells (4×10^6 per mouse) subcutaneously. Seven days after injection, mice were randomly divided into four groups (n = 8) and administered intraperitoneally with 25 or 50 mg/kg compound **9b** (dissolved in PBS containing 5% ethanol and 5% cremophor EL, 0.2 mL per mouse), 5-FU at 50 mg/kg, or vehicle control (0.2 mL of the diluent) once every 2 days for 12 days. At the end of the experiment, the mice were weighed and sacrificed and tumors were collected and fixed with 4% paraformaldehyde and embedded in paraffin. H & E staining was used to further analyze the solid tumors of mice.

6.11. Pull-Down Assay. The biotin-annexed probe **21** or the diazirine-based probe **23** was incubated with SW480 cell lysate at 4 °C overnight. The streptavidin conjugate beads (30 μL) were added and incubated for 8 h at 4 °C. Then, the beads were washed 10 times with Western and IP cell lysis buffer. After that, the Western and IP cell lysis buffer (20 μL) and the loading buffer (5 μL) were added and boiled for 10 min. For the diazirine-based probe **23**, after 20 min of irradiation at 360 nm, the probe **23** was incubated with the azide−PEG3−biotin conjugate for 3 h at 4 °C. After that, it was incubated

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with streptavidin conjugate beads. Then, the biotin-annexed probe **21** or the diazirine-based probe **23** was separated with 8−10% SDS-PAGE gel and stained with a silver staining kit according to the instruction. The gel was fixed with 50% ethyl alcohol containing 10% acetic acid for 40 min at room temperature. Then, the gel was washed with 15% ethyl alcohol and double-distilled water for 15 min, sequentially. The gel was then sensitized and colored. Specific bands were separated, and protein mass spectrometry analyses were conducted.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.0c01717.

Experimental procedures, spectral data and purity table of target compounds, biological evaluation assay, and crystallographic data (PDF)

Molecular formula strings and some data (CSV)

Recommended compound characterization checklist (XLS)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

ANCs, acyclic nucleoside compounds; TBAF, tetrabutylammonium fluoride; DMF, *N*,*N*-dimethylformamide; SEM, standard error of the mean; TLC, thin-layer chromatography; TMS, tetramethylsilane; NMR, nuclear magnetic resonance; ESI, electrospray ionization; FBS, fetal bovine serum; PBS, phosphate-buffered saline; IBCF, isobutyl chloroformate; DIBAL-H, diisobutyl aluminum hydride; DIPEA, *N*,*N*-diisopropylethylamine; HBTU, *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate; R&D, research and development; H&E, staining, hematoxylin−eosin staining; THF, tetrahydrofuran; MTT, 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide; PARP, poly ADP-ribose polymerase; MMP, mitochondrial membrane potential; PE, petroleum ether; EA, ethyl acetate

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