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Copper-Catalyzed Intramolecular Cyclization of *N*-Propargyl-Adenine: Synthesis of Purine-Fused Tricyclics

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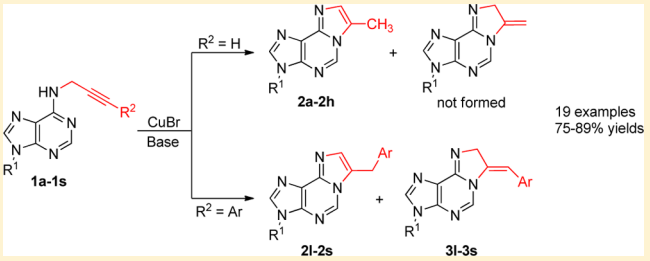
Supporting Information

ABSTRACT: A novel protocol to construct fluorescent purine-fused tricyclic products via intramolecular cyclization of *N*-propargyl-adenine has been developed. With CuBr as the catalyst, a series of purine-fused tricyclic products were obtained in good to excellent yields (19 examples, 75−89% yields). When R_2 was a hydrogen atom in *N*-propargyl-adenines, the reactions only afforded the endocyclic double bond products. When R_2 was an aryl group, the electron-donating groups favored the endocyclic double bond products, while the electron-withdrawing groups favored the exocyclic double bond products.



Purine-fused tricyclic and polycyclic derivatives are an important class of nitrogen-containing heterocycles that have attracted considerable attention in biochemistry, molecular biology, and toxicology.[1] For example, purine-fused tricyclic 1,N^6-ethenoadenine (Figure 1) has been widely studied

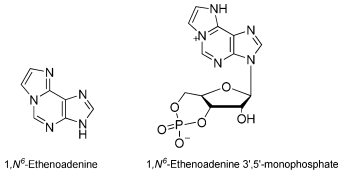
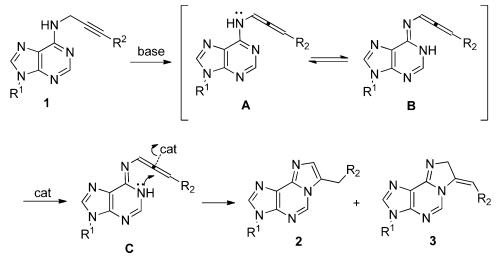


Figure 1. Selected examples of purine-fused tricyclics exhibited high fluorescence properties.

because of their excellent fluorescence properties.[2] And 1,N^6-ethenoadenine 3′,5′-monophosphate is a highly fluorescent probe.[2f,g] Thus, chemists have tried to synthesize different purine-fused polycyclics and studied their fluorescence properties and biological activities.[3] The classical approach for the synthesis of purine-fused polycyclics is via the reaction of haloacetaldehyde with adenine or adenosine.[4] Although great endeavor has been devoted to the synthesis of purine-fused polycyclics, the structure diversity of purine-fused polycyclic derivatives is still very limited. Therefore, searching for a new approach for the synthesis of purine-fused polycyclic with structure diversity is highly desirable.

We proposed the purine-fused tricyclics could be constructed as follows (Scheme 1): allenamine intermediate **A** might be generated from substrate **1** and a base,[5,6] and then intermediate **B**, the tautomer of **A**, could be activated by a catalyst, and the

Scheme 1. Synthesis of Purine-Fused Tricyclic Derivatives Starting from *N*-Propargyl-adenine



nucleophilic attack of N1 to allenamine through **C** would lead to the formation of two purine-fused tricyclic products **2** and **3**. In the context of ongoing projects on the modification of purine analogues,[7,8] herein we report a useful and facile alternative process for the synthesis of fluorescent purine-fused tricyclic derivatives by using substituted propargyl-adenine compounds as starting material.[9]

Initially, we conducted our study by treating *N*-propargyl-9-benzyl-adenine **1a** with CuBr in the presence of $CsCO_3$ in dioxane (Table 1). To our delight, the cyclization reaction occurred, and purine-fused tricyclic product **2a** was formed, though the yield was not satisfied (entry 1). Next, some quaternary ammonium salts such as *n*-Bu_4NBr, Me_4NBr, or Me_4NCl were added into the reaction (entries 2−5).[10] The results showed that *n*-Bu_4NBr was the best one affording product **2a** with 86% yield (entry 4). When the catalyst loading

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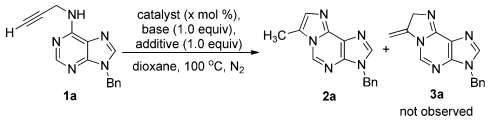
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (x)	base	additive	yield (%)[b]
1	CuBr (20)	Cs_2CO_3	–	55
2	CuBr (20)	Cs_2CO_3	n-Bu_4NI	48
3	CuBr (20)	Cs_2CO_3	Me_4NBr	25
4	CuBr (20)	Cs_2CO_3	Me_4NCl	32
5	CuBr (20)	Cs_2CO_3	n-Bu_4NBr	86
6	CuBr (10)	Cs_2CO_3	n-Bu_4NBr	87
7[c]	CuBr (10)	Cs_2CO_3	n-Bu_4NBr	52
8[d]	CuBr (10)	Cs_2CO_3	n-Bu_4NBr	60
9[e]	CuBr (10)	Cs_2CO_3	n-Bu_4NBr	72
10	CuBr (10)	Na_2CO_3	n-Bu_4NBr	60
11	CuBr (10)	K_2CO_3	n-Bu_4NBr	72
12	CuBr (10)	t-BuOK	n-Bu_4NBr	trace
13	CuCl (10)	Cs_2CO_3	n-Bu_4NBr	68
14	CuI (10)	Cs_2CO_3	n-Bu_4NBr	79
15	$CuBr_2$ (10)	Cs_2CO_3	n-Bu_4NBr	trace

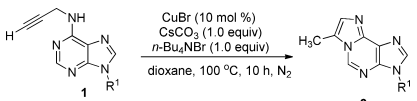
[a]The reactions were carried out with **1a** (0.3 mmol), catalyst, base (0.3 mmol), solvent (2.0 mL), additive (1.0 equiv) in a Schlenk tube at 100 °C for 10 h under N_2 atmosphere. [b]Isolated yield. [c]Toluene was used as the solvent. [d]MeCN was used as the solvent. [e]DMF was used as the solvent.

was lowered to 10 mol %, the reaction also proceeded well, giving the product **2a** with 87% yield (entry 6). The screening of solvents showed that dioxane was the suitable one (entries 6–9). Next, a range of bases were examined, and Cs_2CO_3 emerged as the best choice (entries 10–12). Subsequently, several copper salts were probed (entries 13–15), and for $CuCl_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, $CuSO_4$, trace amounts of products were obtained. It was found that Cu(I) exhibited better catalytic activity than Cu(II), and CuBr was the most suitable copper source. Finally, the optimal conditions were determined to be 10 mol % of CuBr, 1.0 equiv of $CsCO_3$, and 1 equiv of n-Bu_4NBr in dioxane (entry 6).

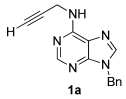
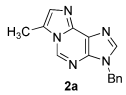
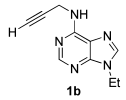
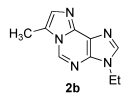
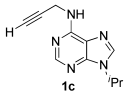
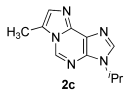
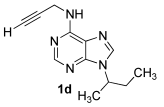
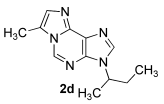
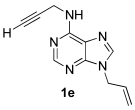
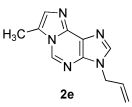
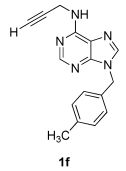
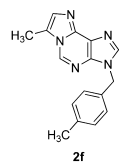
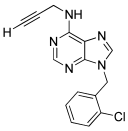
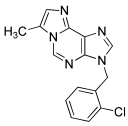
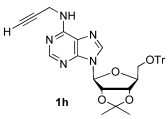
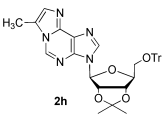
With the optimized conditions (Table 1, entry 6) in hand, the scope of this cyclization reaction was investigated. As shown in Table 2, a series of N9-substituted substrates, including alkyl, benzyl, allyl, and sugar groups, were subjected to the optimized reaction conditions. The results showed that all the substrates could be transformed into the purine-fused tricyclics in good yields (**2a**–**2h**, 76–88% yields). Notably, the allyl substituted **1e** and glycosidic substituted **1h** are suitable substrates for the reactions (78% yield for **2e**, 87% yield for **2h**), which offers an ideal opportunity for further synthetic manipulation.

Subsequently, various N-propargyl-adenines **1i**–**1s** with different aryl groups at the terminal position of alkynyl part were synthesized via Sonogashira coupling reactions. As shown in Table 3, when Ar was phenyl group, the corresponding purine-fused tricyclic products **2i** and **3i** were obtained in 88% total yield, in which the endocyclic double bond product **2i** was the major form (entry 1). Next, a series of electron-donating groups at the benzene ring in the alkenyl part of 9-benzyl-adenines were evaluated (entries 2–7). When *ortho*- or *meta*-methyl substituted substrates were explored, the reactions proceeded well, affording purine-fused tricyclic products in excellent yields, in which the endocyclic double bond products **2j** and **2k** were the major form (entries 2–3). Meanwhile, the

Table 2. Effect of N9-Substitutent in the *N*-Propargyl-adenine[a]



R^1= alkyl, allyl, benzyl, sugar

entry	Substrate	Product	yield (%)[b]
1			87
2			88
3			85
4			84
5			78
6			80
7			76
8			87

[a]The reactions were carried out with **1** (0.3 mmol), CuBr (10 mol %), $CsCO_3$ (0.3 mmol), dioxane (2.0 mL), n-Bu_4NBr (0.3 mmol) in a Schlenk tube at 100 °C for 10 h under N_2 atmosphere. [b]Isolated yield.

3,5-dimethylphenyl substituted substrate **1l** could also be tolerated in the reaction, giving the endocyclic double bond product **2l** as the major form (entry 4). Furthermore, several alkoxy groups (OCH_3, OEt) substituted substrates were tested, and the cyclization reactions worked well, affording the corresponding purine-fused tricyclic products in 85–88% yields, in which the endocyclic double bond products **2m**, **2n**, **2o** were the major form, respectively (entries 5–7). Then, several electron-withdrawing groups at the benzene ring in the alkenyl part of 9-benzyl-adenines were examined (entries 8–10). To our delight, these substrates (**1p**–**1r**) could afford the cyclization products in good yields (75–88% yields). Contrarily, the exocyclic double bond products **3p**, **3q**, **3r** were the

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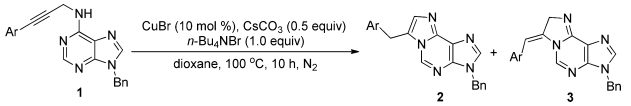
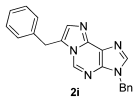
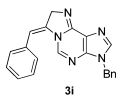
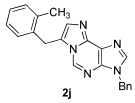
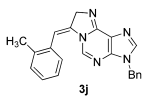
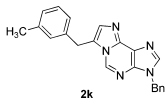
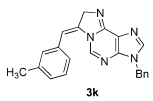
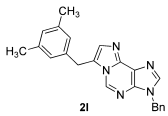
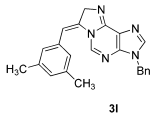
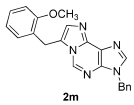
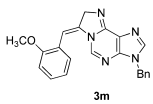
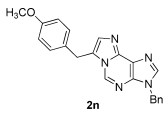
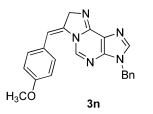
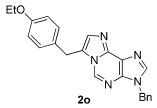
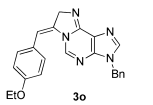
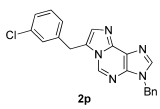
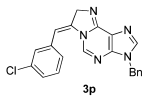
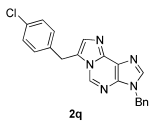
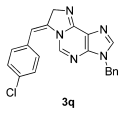
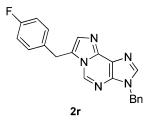
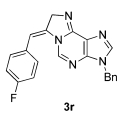
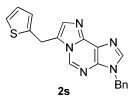
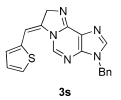
Table 3. Effect of Aryl Groups at the Terminal Position of Alkynyl Part in *N*-Propargyl-adenine[a]



entry	1	Product 2	Product 3	yield (%)[b]	2:3
1	1i			88	99:1
2	1j			89	92:8
3	1k			87	91:9
4	1l			79	87:13
5	1m			85	86:14
6	1n			85	88:12
7	1o			88	92:8
8[c]	1p			81	47:53
9	1q			88	45:55
10	1r			75	43:57
11	1s			77	45:55

[a]The reactions were carried out with **1** (0.3 mmol), CuBr (10 mol %), $CsCO_3$ (0.15 mmol), dioxane (2.0 mL), *n*-Bu_4NBr (0.3 mmol) in a Schlenk tube at 100 °C for 10 h under N_2 atmosphere. [b]Isolated yield. [c]The *Z*-configuration of product **3p** was confirmed by NOESY spectrum.

major form (entries 8−10). Particularly noteworthy is that the terminal alkynes with heterocyclic connections could also survive this reaction well (entry 11). Take product **3p** as the representative product; the structure of **3p** with exocyclic *Z*-form double bond was confirmed by the ^1H, ^{13}C, and NOESY spectra (see Supporting Information for details). It should be noted that the isomerization of products **2** and **3** could not occur under the optimized reaction conditions. Meanwhile, the endocyclic double product **2** and the exocyclic double product **3** could be separated through column chromatography. In addition, the fluorescence properties of selected products (**2i**, **2j**, **2m**) were studied, and the results indicated that these products showed moderate fluorescence intensity (see Supporting Information for details).

In conclusion, we have developed a new approach to construct purine-fused tricyclic products via copper-catalyzed intramolecular cyclization of *N*-propargyl-adenine. With CuBr as the catalyst, a series of purine-fused tricyclic products were obtained in good to excellent yields (19 examples, 75−89% yields). Meanwhile, the cyclization reactions only afforded the endocyclic double bond products with *N*-propargyl-adenines as the starting materials. As for the electronic effects of the substituents at the benzene ring in the alkenyl part, the electron-donating groups favored the endocyclic double bond products. Contrarily, the electron-withdrawing groups favored the exocyclic double bond products.

EXPERIMENTAL SECTION

General Methods. Melting points were recorded with a melting point microapparatus and are uncorrected. NMR spectra were recorded with a 400 NMR spectrometer for ^1H NMR, 100 MHz for ^{13}C NMR. Chemical shifts δ were given in ppm relative to tetramethylsilane in $CDCl_3$ or $(CD_3)_2SO$ for ^1H and ^{13}C NMR. High resolution mass spectra are taken using Q-TOF system, with electrospray ionization (ESI) as the ionization method used for the HRMS measurement. All reactions were set up in air (with no use of a glovebox) and carried out in a sealed pressure tube.

Typical Procedures. *For the Synthesis of **2a−2h**.* In a sealed tube, **1a−1h** (0.3 mmol), CuBr (4.3 mg, 0.03 mmol), $CsCO_3$ (97.7 mg, 0.3 mmol), *n*-Bu_4NBr (96.7 mg, 0.3 mmol), and then dioxane (2.0 mL) were added, and the reaction mixture was heated at 100 °C for 10 h. After cooling down to room temperature, the mixture was diluted with brine (3.0 mL) and extracted with EtOAc (3 × 3.0 mL). Then, the organic layer was collected and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with Pet/EtOAc mixtures) to give the desired products.

*For the Synthesis of **2i−2s** and **3i−3s**.* In a sealed tube, **1i−1s** (0.3 mmol), CuBr (4.3 mg, 0.03 mmol), $CsCO_3$ (48.4 mg, 0.15 mmol), *n*-Bu_4NBr (96.7 mg, 0.3 mmol), and then dioxane (2.0 mL) were added, and the reaction mixture was heated at 100 °C for 10 h. After cooling down to room temperature, the mixture was diluted with brine (3.0 mL) and extracted with EtOAc (3 × 3.0 mL). Then, the organic layer was collected and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with Pet/EtOAc mixtures) to give the desired products.

*For the Synthesis of Starting Materials **1a−1h**.*[11,12] 6-Chloro-9-substituent-purine (3.0 mmol), propargylic amide (3.6 mmol), Et_3N (3.6 mmol), and ethanol (10.0 mL) were added in a 50 mL tube. The tube was refluxed in a 90 °C bath and stirred for 6 h. After cooling down to room temperature, the mixture was diluted with water and then extracted with EtOAc. The extracts were combined, washed with brine, and then dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography on silica gel (eluting with Pet/EtOAc mixtures) to give the 6-proargylic-9-substituent-adenine.

*For the Synthesis of Starting Materials **1i−1s**.*[11,12] 6-Proargylic-9-benzyl-adenine (1.5 mmol), iodobenzene (2.25 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), and Et_3N (5.0 mL) were added in a 50

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mL tube. The tube was stirred for 12 h at 35 °C. After cooling down to room temperature, the mixture was diluted with water and then extracted with EtOAc. The extracts were combined, washed with brine, and then dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography on silica gel (eluting with Pet/EtOAc mixtures) to give the 6-proargylic-9-substituent-adenine.

*3-Benzyl-7-methyl-3H-imidazo[2,1-i]purine (**2a**).* Yellow solid (68.7 mg, 87%): mp 195−197 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.97 (s, 1H), 8.39 (s, 1H), 7.29−7.22 (m, 6H), 5.50 (s, 2H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 133.3, 131.0, 128.8, 128.1, 127.4, 47.6, 9.1; HRMS calcd for $C_{15}H_{14}N_5$ [M + H$^+$] 264.1244, found 264.1236; IR (KBr) ν_{max} 3054, 2975, 2924, 1637, 1371 cm^{-1}.

*3-Ethyl-7-methyl-3H-imidazo[2,1-i]purine (**2b**).* Brown oil (52.5 mg, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.96 (s, 1H), 7.37 (s, 1H), 7.36 (q, J = 7.2 Hz, 2H), 2.59 (s, 3H), 1.59 (q, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 138.6, 133.0, 131.0, 123.7, 118.9, 39.4, 15.7, 9.2; HRMS calcd for $C_{10}H_{11}N_5Na$ [M + Na$^+$] 224. 0907, found 224. 0899; IR (KBr) ν_{max} 2961, 2874, 1679, 1371 cm^{-1}.

*3-Isopropyl-7-methyl-3H-imidazo[2,1-i]purine (**2c**).* Brown oil (54.9 mg, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.99 (s, 1H), 7.32 (s, 1H), 4.94−4.87 (m, 1H), 2.56 (s, 3H), 1.64 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.8, 132.8, 130.8, 123.8, 118.9, 47.7, 22.8, 9.2; HRMS calcd for $C_{11}H_{14}N_5$ [M + H$^+$] 216.1244, found 216.1237; IR (KBr) ν_{max} 2969, 2933, 2877, 1638, 1370 cm^{-1}.

*3-(Sec-butyl)-7-methyl-3H-imidazo[2,1-i]purine (**2d**).* Brown oil (57.7 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.96 (s, 1H), 7.51 (s, 1H), 4.68−4.60 (m, 1H), 2.51 (s, 3H), 2.07−1.90 (m, 2H), 1.62 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 140.9, 139.4, 138.9, 134.3, 123.0, 107.4, 53.6, 29.8, 20.8, 14.1, 10.6; HRMS calcd for $C_{12}H_{16}N_5$ [M + H$^+$] 230.1400, found 230.1401; IR (KBr) ν_{max} 2969, 2933, 2877, 1638, 1370 cm^{-1}.

*3-Allyl-7-methyl-3H-imidazo[2,1-i]purine (**2e**).* White solid (49.9 mg, 78%): mp 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.21 (s, 1H), 7.54 (s, 1H), 6.12−6.03 (m, 1H), 5.35 (d, J = 10.4 Hz, 1H), 5.23 (d, J = 16.8 Hz, 1H), 5.02−4.98 (m, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 141.3, 138.6, 135.4, 133.7, 130.3, 122.7, 120.3, 117.8, 108.6, 46.0, 9.2; HRMS calcd for $C_{11}H_{12}N_5$ [M + H$^+$] 214.1087, found 214.1083; IR (KBr) ν_{max} 3077, 2920, 1639, 1369 cm^{-1}.

*7-Methyl-3-(4-methylbenzyl)-3H-imidazo[2,1-i]purine (**2f**).* Yellow solid (66.5 mg, 80%): mp 193−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.91 (s, 1H), 7.41 (s, 1H), 7.16 (dd, J = 14.4, 8.0 Hz, 4H), 5.40 (s, 2H), 2.49 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 141.0, 140.2, 139.0, 138.1, 134.5, 132.4, 129.5, 127.5, 123.0, 107.0, 47.4, 21.0, 14.2; HRMS calcd for $C_{16}H_{16}N_5$ [M + H$^+$] 278.1400, found 278.1402; IR (KBr) ν_{max} 3093, 2944, 2916, 1639, 746 cm^{-1}.

*3-(2-Chlorobenzyl)-7-methyl-3H-imidazo[2,1-i]purine (**2g**).* Brown solid (67.7 mg, 76%): mp 161−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.01 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.36 (s, 1H), 7.29−7.13 (m, 3H), 5.60 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 138.8, 134.7, 133.4, 133.3, 133.2, 131.2, 129.9, 129.8, 129.6, 127.3, 123.5, 119.1, 45.4, 9.3; HRMS calcd for $C_{15}H_{13}ClN_5$ [M + H$^+$] 298.0854, found 298.0850; IR (KBr) ν_{max} 3073, 2991, 2921, 1640, 1370, 748 cm^{-1}.

*3-((3aS,4S,6S,6aS)-2,2-Dimethyl-6-((trityloxy)methyl)-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-7-methyl-3H-imidazo[2,1-i]-purine (**2h**).* Brown oil (153.3 mg, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.01 (s, 1H), 7.38 (s, 1H), 7.34 (s, 3H), 7.32 (s, 3H), 7.17 (s, 1H), 7.15 (s, 3H), 7.13 (s, 2H), 7.11 (s, 1H), 7.09 (s, 1H), 7.07 (s, 1H), 6.20 (d, J = 2.4 Hz, 3H), 5.38 (dd, J = 6.0, 2.0 Hz, 1H), 4.98 (q, J = 3.2 Hz, 1H), 4.56−4.53 (m, 1H), 3.36−3.27 (m, 1H), 2.53 (s, 3H), 2.03 (s, 1H), 1.63 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 137.3, 133.0, 131.3, 128.5, 127.6, 126.9, 114.2, 91.3, 86.7, 86.3, 84.4, 81.9, 77.3, 76.9, 76.6, 63.9, 27.1, 25.4, 9.2; HRMS calcd for $C_{35}H_{34}N_5O_4$ [M + H$^+$] 588.2605, found 588.2603; IR (KBr) ν_{max} 3056, 3032, 2987, 2933, 1641, 1367, 1212, 1077 cm^{-1}.

*3,7-Dibenzyl-3H-imidazo[2,1-i]purine (**2i**).* Brown oil (88.6 mg, 87.1%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.93 (s, 1H), 7.46 (s, 1H), 7.31−7.23 (m, 8H), 7.21 (s, 1H), 7.19 (s, 1H), 5.40 (s, 2H), 4.31 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 138.8, 136.1, 135.4, 133.6, 132.3, 128.9, 128.3, 128.1, 127.4, 127.1, 47.6, 30.4; HRMS calcd for $C_{21}H_{18}N_5$ [M + H$^+$] 340.1557, found 340.1550; IR (KBr) ν_{max} 3100, 3029, 2923, 1640, 1374 cm^{-1}.

*3-Benzyl-7-benzylidene-7,8-dihydro-3H-imidazo[2,1-i]purine (**3i**).* Light yellow solid (0.9 mg, 0.9%): mp 141−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.91 (s, 1H), 7.34−7.23 (m, 8H), 7.25−7.20 (m, 3H), 5.44 (s, 1H), 4.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 141.3, 140.3, 139.0, 135.5, 134.8, 129.1, 129.0, 128.5, 128.3, 127.5, 126.4, 123.3, 107.6, 47.7, 35.6; HRMS calcd for $C_{21}H_{18}N_5$ [M + H$^+$] 340.1557, found 340.1561; IR (KBr) ν_{max} 3061, 3026, 2923, 1638, 1372, 694 cm^{-1}.

*3-Benzyl-7-(2-methylbenzyl)-3H-imidazo[2,1-i]purine (**2j**).* Brown oil (86.7 mg, 81.9%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.97 (s, 1H), 7.35−7.27 (m, 6H), 7.25−7.19 (m, 2H), 7.13 (d, J = 7.2 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 5.46 (s, 2H), 4.23 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 136.4, 135.4, 134.2, 133.7, 132.6, 130.7, 129.0, 128.6, 128.4, 127.6, 127.3, 126.5, 123.7, 121.5, 47.6, 28.2, 19.5; HRMS calcd for $C_{22}H_{19}N_5Na$ [M + Na$^+$] 376.1533, found 376.1529; IR (KBr) ν_{max} 3065, 2924, 1641, 1376, 741 cm^{-1}.

*3-Benzyl-7-(2-methylbenzylidene)-7,8-dihydro-3H-imidazo[2,1-i]-purine (**3j**).* Brown oil (7.5 mg, 7.1%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.86 (s, 1H), 7.26 (d, J = 7.2 Hz, 2H), 7.19 (d, J = 5.2 Hz, 4H), 7.12 (s, 3H), 6.95 (s, 1H), 5.37 (s, 2H), 4.13 (s, 1H) 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 141.3, 140.3, 139.2, 137.2, 136.6, 135.5, 134.8, 130.3, 130.0, 129.0, 128.4, 127.5, 126.7, 126.1, 123.3, 107.6, 47.7, 33.4, 19.5; HRMS calcd for $C_{22}H_{20}N_5$ [M + H$^+$] 354.1713, found 354.1706; IR (KBr) ν_{max} 3084, 3030, 2944, 1640, 1375, 695 cm^{-1}.

*3-Benzyl-7-(3-methylbenzyl)-3H-imidazo[2,1-i]purine (**2k**).* Brown oil (83.9 mg, 79.2%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.94 (s, 1H), 7.46 (s, 1H), 7.31−7.16 (m, 6H), 7.05 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 6.0 Hz, 2H), 5.41 (s, 2H), 4.27 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 140.4, 138.9, 138.7, 136.0, 135.4, 133.8, 132.1, 129.0, 128.9, 128.8, 128.4, 127.9, 127.5, 125.2, 123.4, 122.1, 47.7, 30.3, 21.3; HRMS calcd for $C_{22}H_{19}N_5Na$ [M + Na$^+$] 376.1533, found 376.1528; IR (KBr) ν_{max} 3135, 3029, 2941, 1640, 1371, 766 cm^{-1}.

*3-Benzyl-7-(3-methylbenzylidene)-7,8-dihydro-3H-imidazo[2,1-i]-purine (**3k**).* Orange solid (8.3 mg, 7.8%): mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.93 (s, 1H), 7.34−7.15 (m, 9H), 7.05 (d, J = 7.2 Hz, 1H), 5.45 (s, 2H), 4.12 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 141.2, 140.3, 138.9, 138.1, 135.5, 134.9, 129.9, 129.0, 128.3, 127.5, 127.1, 126.1, 123.2, 107.6, 47.7, 35.5, 21.4; HRMS calcd for $C_{22}H_{20}N_5$ [M + H$^+$] 354.1713, found 354.1705; IR (KBr) ν_{max} 3077, 3029, 2908, 1643, 1378, 699 cm^{-1}.

*3-Benzyl-7-(3,5-dimethylbenzyl)-3H-imidazo[2,1-i]purine (**2l**).* Brown oil (75.7 mg, 68.7%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.95 (s, 1H), 7.45 (s, 1H), 7.34−7.31 (m, 3H), 7.27−7.25 (m, 2H), 7.25 (s, 1H), 6.88 (s, 1H), 6.82 (s, 2H), 5.43 (s, 2H), 4.25 (s, 2H), 2.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 138.5, 136.0, 135.4, 133.9, 132.2, 129.0, 128.8, 128.4, 127.5, 126.0, 123.6, 122.1, 47.7, 30.3, 21.2; HRMS calcd for $C_{23}H_{22}N_5$ [M + H$^+$] 368.1870, found 368.1869; IR (KBr) ν_{max} 3125, 3101, 3021, 1641, 1372, 783 cm^{-1}.

*3-Benzyl-7-(3,5-dimethylbenzylidene)-7,8-dihydro-3H-imidazo-[2,1-i]purine (**3l**).* Yellow solid (11.3 mg, 10.3%): mp 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.92 (s, 1H), 7.34−7.30 (m, 3H), 7.27 (d, J = 2.4 Hz, 1H), 7.25 (s, 1H), 7.22 (s, 1H), 6.98 (s, 1H), 6.87 (s, 1H), 5.44 (s, 2H), 4.11 (s, 2H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 141.2, 140.3, 139.1, 138.9, 137.9, 135.5, 134.8, 129.0, 128.4, 128.0, 127.5, 126.9, 123.3, 107.5, 47.7, 35.4, 21.2; HRMS calcd for $C_{23}H_{22}N_5$ [M + H$^+$] 368.1870, found 368.1866; IR (KBr) ν_{max} 3125, 3082, 3015, 1636, 1375, 779, 723 cm^{-1}.

*3-Benzyl-7-(2-methoxybenzyl)-3H-imidazo[2,1-i]purine (**2m**).* Yellow oil (81.0 mg, 73.1%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s,

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1H), 7.92 (s, 1H), 7.43 (s, 1H), 7.30 (s, 3H), 7.25−7.19 (m, 3H), 7.00 (d, J = 7.2 Hz, 1H), 6.84 (t, J = 7.6 Hz, 1H), 5.43 (s, 2H), 4.29 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 140.3, 138.9, 135.5, 134.2, 132.0, 129.6, 129.0, 128.4, 127.5, 124.7, 123.5, 122.4, 120.9, 110.6, 55.5, 47.7, 23.8; HRMS calcd for $C_{22}H_{20}N_5O$ [M + H$^+$] 370.1662, found 370.1663; IR (KBr) ν_{max} 3083, 3030, 2931, 1637, 1374, 1247, 808 cm^{-1}.

*3-Benzyl-7-(2-methoxybenzylidene)-7,8-dihydro-3H-imidazo[2,1-i]purine (**3m**).* Green oil (13.2 mg, 11.9%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.91 (s, 1H), 7.31 (s, 4H), 7.26 (s, 3H), 7.18 (s, 1H), 6.90 (t, J = 8.2 Hz, 2H), 5.43 (s, 2H), 4.20 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 147.7, 141.0, 140.3, 139.1, 135.5, 134.8, 130.8, 129.0, 128.4, 127.8, 127.6, 127.5, 123.3, 120.6, 110.5, 107.5, 55.4, 47.7, 29.6; HRMS calcd for $C_{22}H_{20}N_5O$ [M + H$^+$] 370.1662, found 370.1660; IR (KBr) ν_{max} 3079, 3017, 2832, 1641, 1371, 1244, 723 cm^{-1}.

*3-Benzyl-7-(4-methoxybenzyl)-3H-imidazo[2,1-i]purine (**2n**).* Yellow oil (82.8 mg, 74.8%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.94 (s, 1H), 7.44 (s, 1H) 7.31−7.27 (m, 3H), 7.20−7.23 (m, 2H), 7.11 (d, J = 7.6 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.41 (s, 2H), 4.24 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 135.5, 133.8, 129.2, 128.9, 128.3, 127.5, 114.3, 55.2, 47.7, 29.6; HRMS calcd for $C_{22}H_{20}N_5O$ [M + H$^+$] 370.1662, found 370.1662; IR (KBr) ν_{max} 3079, 2977, 2927, 1639, 1246, 703, 525 cm^{-1}.

*3-Benzyl-7-(4-methoxybenzylidene)-7,8-dihydro-3H-imidazo[2,1-i]purine (**3n**).* Yellow solid (11.3 mg, 10.2%): mp 175−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.93 (s, 1H), 7.34−7.25 (m, 7H), 7.19 (s, 1H), 6.86 (d, J = 8.4 Hz, 2H), 5.45 (s, 2H), 4.13 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 135.5, 134.9, 131.1, 130.1, 129.0, 128.3, 127.5, 113.8, 55.2, 47.7, 34.7; HRMS calcd for $C_{22}H_{20}N_5O$ [M + H$^+$] 370.1662, found 370.1663; IR (KBr) ν_{max} 3082, 2984, 2918, 1645, 1238, 725 cm^{-1}.

*3-Benzyl-7-(4-ethoxybenzyl)-3H-imidazo[2,1-i]purine (**2o**).* Brown oil (93.1 mg, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.93 (s, 1H), 7.45 (s, 1H), 7.32 (s, 3H), 7.25 (s, 2H), 7.11 (d, J = 4.4 Hz, 2H), 6.82 (s, J = 8.0 Hz, 2H), 5.43 (s, 2H), 4.26 (s, 2H), 3.99 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 141.8, 140.3, 138.9, 135.5, 133.8, 132.3, 129.2, 129.0, 128.4, 127.9, 127.6, 123.7, 122.4, 114.9, 63.5, 47.8, 29.7, 14.8; HRMS calcd for $C_{23}H_{21}N_5NaO$ [M + Na$^+$] 406.1638, found 406.1647; IR (KBr) ν_{max} 3098, 3010, 2983, 1641, 1375, 1241, 705, 519 cm^{-1}.

*3-Benzyl-7-(4-ethoxybenzylidene)-7,8-dihydro-3H-imidazo[2,1-i]purine (**3o**).* Yellow solid (8.1 mg, 7%): mp 146−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.91 (s, 1H), 7.33−7.30 (m, 3H), 7.28 (s, 2H), 7.26−7.24 (m, 2H), 7.12 (s, 1H), 6.84 (d, J = 8.8 Hz, 2H), 5.44 (s, 2H), 4.12 (s, 2H), 4.01 (q, J = 7.20 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 148.6, 141.3, 140.3, 139.2, 135.5, 134.9, 131.0, 130.1, 129.0, 128.4, 127.5, 123.3, 114.5, 107.5, 63.4, 47.7, 34.7, 14.9; HRMS calcd for $C_{23}H_{21}N_5NaO$ [M + Na$^+$] 406.1638, found 406.1641; IR (KBr) ν_{max} 3095, 3013, 2981, 1647, 1371, 1238, 723 cm^{-1}.

*3-Benzyl-7-(3-chlorobenzyl)-3H-imidazo[2,1-i]purine (**2p**).* Brown oil (42.6 mg, 38.1%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.97 (s, 1H), 7.50 (s, 1H), 7.35−7.31 (m, 3H), 7.24−7.23 (m, 5H), 7.22 (s, 1H), 7.11−7.09 (m, 1H), 5.45 (s, 2H), 4.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 139.0, 138.2, 135.3, 134.9, 133.4, 132.7, 130.2, 129.0, 128.4, 128.3, 127.5, 126.3, 123.6, 121.0, 47.8, 30.1; HRMS calcd for $C_{21}H_{16}ClN_5Na$ [M + Na$^+$] 396.0986, found 396.0981; IR (KBr) ν_{max} 3128, 3063, 2922, 1642, 1371, 715 cm^{-1}.

*3-Benzyl-7-(3-chlorobenzylidene)-7,8-dihydro-3H-imidazo[2,1-i]purine (**3p**).* Light yellow solid (48.1 mg, 42.9%): mp 210−213 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.27 (s, 1H), 8.53 (s, 1H), δ 7.90 (s, 1H), 7.42 (s, 1H), 7.35−7.28 (m, 8H), 5.55 (s, 2H), 4.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ146.9, 141.1, 140.4, 139.2, 135.4, 134.9, 134.1, 129.7, 129.1, 129.0, 128.4, 127.5, 127.3, 126.6, 123.3, 107.7, 47.7, 35.1; HRMS calcd for $C_{21}H_{17}ClN_5$ [M + H$^+$] 374.1167, found 374.1164; IR (KBr) ν_{max} 3063, 2925, 2854, 1641, 1376, 698 cm^{-1}.

*3-Benzyl-7-(4-chlorobenzyl)-3H-imidazo[2,1-i]purine (**2q**).* Brown oil (44.3 mg, 39.6%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.97 (s, 1H), 7.48 (s, 1H), 7.34−7.27 (m, 7H), 7.16 (s, 1H), 7.14 (s, 1H), 5.44 (s, 2H), 4.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 134.7, 133.5, 133.1, 129.6, 129.2, 129.0, 128.4, 127.6, 47.8, 30.9; HRMS calcd for $C_{21}H_{17}ClN_5$ [M + H$^+$] 374.1167, found 374.1164; IR (KBr) ν_{max} 3136, 3066, 3030, 1638, 1371, 725 cm^{-1}.

*3-Benzyl-7-(4-chlorobenzylidene)-7,8-dihydro-3H-imidazo[2,1-i]purine (**3q**).* Light yellow solid (54.2 mg, 48.4%): mp 205−207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.85 (s, 1H), 7.26−7.17 (m, 1H), 8.19 (s, 1H), 5.37 (s, 2H), 4.06 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 141.4, 140.4, 139.3, 137.6, 135.5, 134.9, 132.2, 130.4, 129.0, 128.6, 128.4, 127.6, 123.3, 107.6, 47.8, 34.9; HRMS calcd for $C_{21}H_{17}ClN_5$ [M + H$^+$] 374.1167, found 374.1167; IR (KBr) ν_{max} 3136 3077, 2934, 1634, 1371, 692 cm^{-1}.

*3-Benzyl-7-(4-fluorobenzyl)-3H-imidazo[2,1-i]purine (**2r**).* Brown oil (34.6 mg, 32.3%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.89 (s, 1H), 7.25−7.20 (m, 7H), 7.34−7.27 (m, 7H), 7.09 (s, 1H), 7.07 (s, 1H), 5.36 (s, 2H), 4.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 134.7, 133.1, 129.6, 129.2, 129.0, 128.4, 127.6, 47.8, 29.9; HRMS calcd for $C_{21}H_{17}FN_5$ [M + H$^+$] 358.1463, found 358.1456; IR (KBr) ν_{max} 3084, 2937, 2839, 1638, 1375, 1240, 727 cm^{-1}.

*3-Benzyl-7-(4-fluorobenzylidene)-7,8-dihydro-3H-imidazo[2,1-i]purine (**3r**).* Brown solid (45.8 mg, 42.8%): mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.92 (s, 1H), 7.31−7.24 (m, 8H), 6.98 (t, J = 8.4 Hz, 2H), 5.44 (s, 2H), 4.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 160.4, 147.7, 141.4, 140.4, 139.2, 135.5, 134.9, 134.8, 134.8, 130.5, 130.5, 129.0, 128.4, 127.5, 123.3, 115.3, 115.1, 107.6, 47.7, 34.7; HRMS calcd for $C_{21}H_{16}FN_5Na$ [M + Na$^+$] 380.1282, found 380.1273; IR (KBr) ν_{max} 3074, 3014, 2917, 2865, 1638, 1375, 695 cm^{-1}.

*3-Benzyl-7-(thiophen-2-ylmethyl)-3H-imidazo[2,1-i]purine (**2s**).* Brown oil (35.9 mg, 34.7%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.93 (s, 1H), 7.37−7.33 (m, 5H), 7.26 (s, 1H), 7.18 (d, J = 4.8 Hz, 2H), 7.00 (s, 1H), 6.96 (s, 1H), 5.45 (s, 2H), 4.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 141.0, 140.4, 139.2, 135.4, 134.9, 129.0, 128.4, 127.5, 126.8, 125.9, 124.0, 107.6, 47.8, 29.7; HRMS calcd for $C_{19}H_{15}N_5NaS$ [M + Na$^+$] 368.0940, found 368.0947; IR (KBr) ν_{max} 3071, 2923, 1640, 1373, 1350, 688, 647 cm^{-1}.

*3-Benzyl-7-(thiophen-2-ylmethylene)-7,8-dihydro-3H-imidazo-[2,1-i]purine (**3s**).* Brown solid (43.8 mg, 42.4%): mp 165−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.94 (s, 1H), 7.38 (s, 1H), 7.34 (s, 3H), 7.27 (s, 2H), 7.19 (d, J = 4.0 Hz, 1H), 7.00 (s, 1H), 6.97 (s, 1H), 5.46 (s, 2H), 4.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 141.1, 140.4, 135.4, 135.0, 129.0, 128.4, 127.6, 126.9, 125.9, 124.1, 123.3, 107.6, 47.8, 29.8; HRMS calcd for $C_{19}H_{15}N_5NaS$ [M + Na$^+$] 368.0940, found 368.0944; IR (KBr) ν_{max} 3071, 2924, 1640, 1373, 1345, 725, 647 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of compounds **2a−2s** and **3i−3s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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