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Highly facile and regio-selective synthesis of pyrazolo[1,5-*a*]pyrimidines *via* reactions of 1,2-allenic ketones with aminopyrazoles†

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An efficient procedure for the syntheses of pyrazolo[1,5-*a*]pyrimidines through reactions of 1,2-allenic ketones with aminopyrazoles under extremely mild conditions without using any catalyst or promoter has been developed. The reactions showed excellent regio-selectivity with all the allenic ketone substrates except for those bearing an alkyl group at the internal position of the allene moiety. The reason behind this regio-selectivity dissimilarity has been explored with the aid of the B3LYP/6-31G* level of density functional theory. Moreover, this novel procedure has been successfully applied in the preparation of nucleoside-pyrazolo[1,5-*a*]pyrimidine chimeras with potent antiviral activities.

Introduction

Heterobiaryls have attracted significant attention from the scientific community due to their relevance to various biological activities. Among them, pyrazolo[1,5-*a*]pyrimidine forms the central core of a plethora of pharmaceuticals and pesticides, such as *Zaleplon*, a hypnotic drug; *Ocinaplon*, an anxiolytic drug; and *Pyrazophos*, a fungicide and insecticide (Fig. 1). Moreover, some pyrazolo[1,5-*a*]pyrimidine derivatives were found to possess anticancer,[1] antitumor,[2] anxiolytic,[3] antimicrobial,[4] antibacterial,[5] antitrichomonal,[6] and antischistosomal[7] activities, and have been examined as TSPO PET ligands,[8] hepatitis C virus inhibitors,[9] estrogen receptor ligands,[10] CRF antagonists,[11] COX-2 inhibitors,[12] and KDR kinase inhibitors.[13] These promising biological properties have prompted the development of efficient synthetic strategies toward pyrazolo[1,5-*a*]pyrimidine derivatives. So far, the available synthetic methods for pyrazolo[1,5-*a*]-pyrimidines have mostly involved the condensation of aminopyrazole with 1,3-dicarbonyl or α,β-unsaturated carbonyl compounds,[10–14] enaminonitriles, or enaminones.[15] While these methods are generally reliable, they are usually carried out in refluxing acetic acid and often suffer from poor regio-selectivity, tedious procedures, and/or low yield. Although microwave[16] and ultrasound irradiation[17] have recently been successfully used to shorten the reaction period and/or improve the yield, low regio-selectivity still remains an unsolved problem in the preparation of pyrazolo[1,5-*a*]pyrimidines by using classical synthetic protocols.

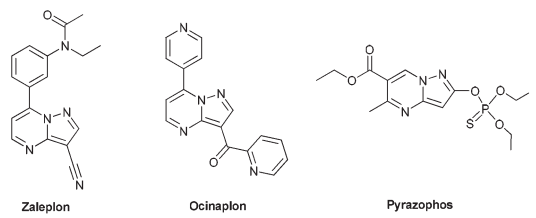

Fig. 1 Examples of the drugs with a pyrazolo[1,5-*a*]pyrimidine scaffold.

In recent years, 1,2-allenic ketones are emerging as a powerful tool in forming carbon–carbon and carbon–heteroatom bonds.[18] In particular, they are highly reactive as nucleophilic addition acceptors and usually prefer to undergo conjugate addition rather than direct addition due to their intriguing structural features.

Based on the above facts and as a continuation of our study on the synthetic applications of functionalized allene derivatives,[19] we hypothesized that an efficient and practical synthesis of pyrazolo[1,5-*a*]pyrimidines derivatives with improved regio-selectivity might be achieved by using 1,2-allenic ketones as the required 1,3-bielectrophile reagents. Herein, we would like to report our preliminary result in this regard.

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†Electronic supplementary information (ESI) available: Experimental details; characterization data; copies of the ^{1}H NMR and ^{13}C NMR spectra of **3a–ll**, **4ii–ll**, **7**, **8**, **11**, **12**; and the X-ray crystal structures of **3jj** and **4jj**. CCDC 975574 and 975575. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob42445f

Results and discussion

Our study was initiated by reacting 1-phenylbuta-2,3-dien-1-one (**1a**) with 1*H*-pyrazol-3-amine (**2a**) in ethanol. We were pleased to find that the reaction of **1a** and **2a** took place rapidly at ambient temperature in the absence of any catalyst or promoter to afford the desired pyrazolo[1,5-*a*]pyrimidine with high efficiency. More interestingly, the reaction exhibited excellent regio-selectivity in that 5-methyl-7-phenylpyrazolo-[1,5-*a*]pyrimidine (**3a**) was obtained in a yield of 85% while its regio-isomer, 7-methyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (**4a**), was formed only in a trace amount (Table 1, entry 1). To further improve the yield, the reaction was then tried in different solvents, and among the solvents screened, acetone gave the best yield of **3a** (entries 1–7). Following studies showed that increasing the amount of **2a** (entries 7–9) or elevating the reaction temperature (entries 7 and 10–11) resulted in a decrease of the yield. Thus, the optimum reaction conditions are: treating **1a** (1 equiv.) and **2a** (1 equiv.) at rt in acetone for 2 h. Under these conditions, **3a** was obtained in a yield of 91% (entry 7).

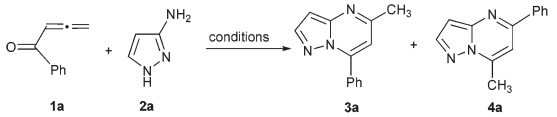
With the optimized reaction conditions in hand, we then examined the generality of the synthetic protocol toward pyrazolo[1,5-*a*]pyrimidines. Firstly, various 1-substituted and 1,4-disubstituted allenic ketones **1** were reacted with 1*H*-pyrazol-3-amine (**2a**) under standard conditions. The results listed in Table 2 showed that 1-aryl-substituted allenic ketones with various substituents on the aryl ring reacted smoothly with **2a** to afford the corresponding pyrazolo[1,5-*a*]pyrimidines in good to excellent yields (Table 2, entries 1–9). While electron-donating or electron-withdrawing substituents on the aryl ring have little effect on the reaction, *ortho*-substituted substrate gave a relatively lower yield (entry 7). Naphthyl (entry 8) and thienyl (entry 9) substituted allenic ketones afforded the corresponding products in excellent yields. Moreover, diverse functional groups, such as trifluoromethyl, halides, methoxy, and methyl group, were well tolerated under the reaction conditions. Further studies showed that 1-alkyl, such as 1-benzyl, or 1-phenethyl substituted allenic ketones could take part in this reaction efficiently (entries 10 and 11). 1-Phenylpenta-2,3-dien-1-one, an allenic ketone with a substituent at the terminal position of the allene moiety, is also a suitable substrate (entry 12). Importantly, it should be noted herein that in all the above cases, the reactions showed excellent regio-selectivity to give one of the two possible isomers dominantly.

In the next stage, the suitability of substituted aminopyrazoles (**2**) for this pyrazolo[1,5-*a*]pyrimidine synthesis was studied. The results listed in Table 3 showed that both alkyl- and aryl-substituted aminopyrazoles are suitable substrates for this reaction. It was also observed that while aryl-substituted aminopyrazoles (Table 3, entries 21 and 22) are less reactive and need a longer period to complete the reaction than alkyl-substituted ones (entries 1–20); both of them exhibited excellent regio-selectivity, thus resulting in a rapid and efficient protocol for the preparation of pyrazolo[1,5-*a*]pyrimidines with diverse substitution patterns.

To further explore the scope of the reaction, allenic ketones bearing a methyl or ethyl group on the internal position of the allene moiety were prepared, and reacted with different aminopyrozoles. To our surprise, under similar conditions, the reactions were much more sluggish and showed dramatically diminished regio-selectivity in that the two possible isomers were obtained in ratios within the range of 1 : 1 to 2 : 1 (Table 4). The structures of the two isomers were unambiguously confirmed by their spectroscopic data together with X-ray diffraction analysis (Fig. 2 and 3).[20]

Plausible pathways accounting for the formation of **3** and **4** are speculated in Scheme 1. An initial conjugate addition of the amino group of **2** on the central carbon of the allene unit

Table 1 Optimization of the conditions for the reaction of **1a** and **2a**[a]

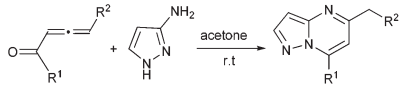


1a 2a 3a 4a

Entry	**2a** (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%) **3a**	**4a**
1	1	EtOH	rt	2	85	Trace
2	1	CH_2Cl_2	rt	2	80	Trace
3	1	CH_3CN	rt	2	83	Trace
4	1	MeOH	rt	2	85	Trace
5	1	THF	rt	2	86	Trace
6	1	DMF	rt	2	73	Trace
7	**1**	**Acetone**	**rt**	**2**	**91**	**Trace**
8	1.2	Acetone	rt	2	83	Trace
9	1.5	Acetone	rt	2	78	Trace
10	1	Acetone	40	2	82	Trace
11	1	Acetone	60	2	77	Trace

[a] Reagents and conditions: **1a** (0.5 mmol), solvent (2 mL). [b] Isolated yield.

Table 2 Preparation of pyrazolo[1,5-*a*]pyrimidine (I)[a]

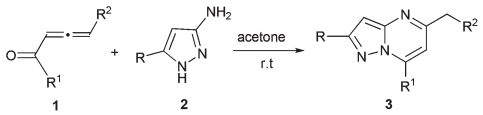


1 2a 3

Entry	R^1	R^2	Time (h)	Product	Yield[b] (%)
1	C_6H_5	H	2	**3a**	91
2	*p*-$CF_3C_6H_4$	H	2	**3b**	87
3	*p*-BrC_6H_4	H	2	**3c**	86
4	*p*-$CH_3OC_6H_4$	H	2	**3d**	82
5	*p*-$CH_3C_6H_4$	H	2	**3e**	84
6	*m*-ClC_6H_4	H	2	**3f**	90
7	*o*-FC_6H_4	H	2	**3g**	79
8	1-Naphthyl	H	2	**3h**	91
9	2-Thienyl	H	2	**3i**	88
10	Benzyl	H	2	**3j**	85
11	Phenylethyl	H	2	**3k**	89
12	C_6H_5	CH_3	2	**3l**	87

[a] Reagents and conditions: **1** (1 mmol), **2a** (1 mmol), acetone (4 mL), rt. [b] Isolated yield.

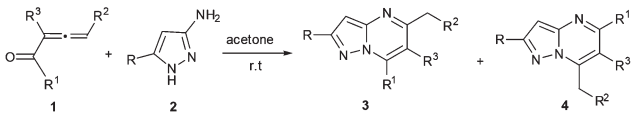
Table 3 Preparation of pyrazolo[1,5-*a*]pyrimidine (II)[a]



Entry	R^1	R^2	R	Time (h)	Product	Yield[b] (%)
1	C_6H_5	H	CH_3	1	**3m**	87
2	*o*-FC_6H_4	H	CH_3	1	**3n**	80
3	*m*-ClC_6H_4	H	CH_3	1	**3o**	89
4	*p*-BrC_6H_4	H	CH_3	1	**3p**	91
5	*p*-$CF_3C_6H_4$	H	CH_3	1	**3q**	90
6	*p*-$CH_3C_6H_4$	H	CH_3	1	**3r**	79
7	*m*,*p*-*Di*-$CH_3OC_6H_3$	H	CH_3	1	**3s**	78
8	1-Naphthyl	H	CH_3	1	**3t**	92
9	2-Thienyl	H	CH_3	1	**3u**	90
10	Benzyl	H	CH_3	1	**3v**	83
11	Phenylethyl	H	CH_3	1	**3w**	85
12	C_6H_5	CH_3	CH_3	1	**3x**	86
13	C_6H_5	H	Cyclopropyl	1	**3y**	85
14	*m*-ClC_6H_4	H	Cyclopropyl	1	**3z**	83
15	*p*-$CH_3OC_6H_4$	H	Cyclopropyl	1	**3aa**	89
16	*p*-CNC_6H_4	H	Cyclopropyl	1	**3bb**	75
17	2-Thienyl	H	Cyclopropyl	1	**3cc**	84
18	Benzyl	H	Cyclopropyl	1	**3dd**	88
19	Phenylethyl	H	Cyclopropyl	1	**3ee**	90
20	C_6H_5	CH_3	Cyclopropyl	1	**3ff**	89
21	C_6H_5	H	C_6H_5	3	**3gg**	65
22	*p*-BrC_6H_4	H	C_6H_5	3	**3hh**	60

[a] Reagents and conditions: **1** (1 mmol), **2** (1 mmol), acetone (4 mL), rt. [b] Isolated yield.

Table 4 Preparation of pyrazolo[1,5-*a*]pyrimidine (III)[a]



Entry	R^1	R^2	R^3	R	Time (h)	Product	Yield[b] (%)
1	C_6H_5	H	CH_3	H	4	**3ii** + **4ii** (**2 : 1**)	73
2	C_6H_5	H	CH_3	CH_3	4	**3jj** + **4jj** (**1.2 : 1**)	92
3	C_6H_5	H	CH_3	Cyclopropyl	4	**3kk** + **4kk** (**1 : 1**)	81
4	C_6H_5	H	CH_3CH_2	CH_3	4	**3ll** + **4ll** (**1.4 : 1**)	55

[a] Reagents and conditions: **1** (1 mmol), **2** (1 mmol), acetone (4 mL), rt. [b] Isolated yield of two products.

in **1** followed by an intramolecular cyclization would give **3**. On the other hand, a direct addition of the amino group of **2** on the carbonyl group of **1** followed by an intramolecular 6-π electrocyclization and tautomerization affords **4**.

According to the proposed mechanism, factors favouring a conjugated addition will benefit the formation of **3**. Otherwise, the selectivity toward **3** will decrease. While the competition between 1,4- and 1,2-addition can be influenced by a multiplicity of different factors, the electronic nature of the nucleophilic addition acceptor can have a predominant influence in many cases. To figure out, at least in part, the reason behind the big difference in regio-selectivity of the reactions starting from allenic ketones with or without a substituent on the internal position of the allenic moiety, the Mulliken charges of atoms in different allenic ketone substrates, 1-phenylbuta-2,3-dien-1-one (**1a**), 1-phenylpenta-2,3-dien-1-one (**1b**) and 2-methyl-1-phenylbuta-2,3-dien-1-one (**1c**), were calculated with the aid of the B3LYP/6-31G* level of density functional theory. The calculation results listed in Fig. 4 revealed that for compounds **1a** and **1b**, the positive charge of the central carbon of the allene unit (C3) is much higher than that of the carbonyl carbon (C1). Therefore, the amino group of **2** would prefer to attack on C3 rather C1 to form **3** as the dominating product. On the other hand, the difference of the positive charge between C3 and C1 in **1c**, which has a methyl group attached on the internal position of the allenic moiety, is much smaller compared with those of **1a** and **1b**, thus resulting in a dramatically diminished selectivity in the formation of **3** and **4**. As a

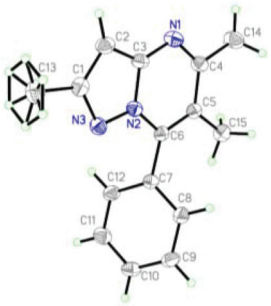


Fig. 2 The X-ray crystal structure of **3jj**.

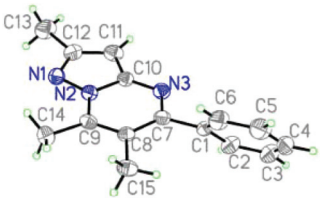
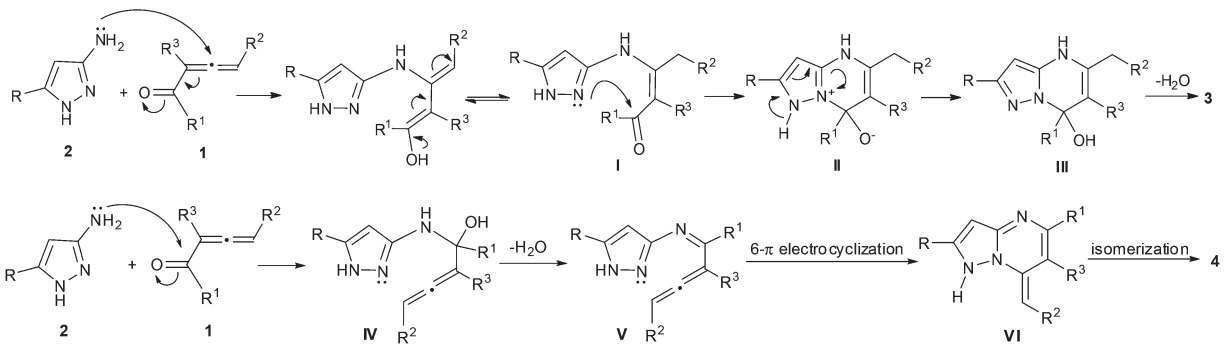


Fig. 3 The X-ray crystal structure of **4jj**.

further aspect, the reason for the difference of the positive charge of C3 in **1a**, **1b** and **1c** might be attributed to the following facts. In **1c**, due to the repulsion between the carbonyl oxygen and its neighbouring methyl group, the carbonyl group could not be as coplanar with the C2–C3 olefin as those in **1b** and **1c**, which would dramatically decrease the positive charge on its C3 position.

Next, to showcase the utility of the synthetic method developed herein, we continued our study by exploring the reaction on a larger scale. Thus, 1.01 g of 1-phenylbuta-2,3-dien-1-one (**1a**, 7 mmol) and 0.68 g of 5-methyl-1*H*-pyrazol-3-amine (**2b**, 7 mmol) were added to 20 mL of acetone. It was then stirred at rt for 3 h. From the resulting mixture, 2,5-dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (**3m**) was obtained in a yield of 78%.

Furthermore, it is well known that structural modifications of naturally occurring pyrimidine nucleosides have resulted in a large number of therapeutic agents for various diseases.[21] In this regard, we have an ongoing program on the design and synthesis of novel 5-substituted pyrimidine nucleosides as potential antiviral and antimicrobial agents.[22] With the novel method developed in this paper, we were interested in the preparation of hybrid compounds combining both pyrimidine nucleoside and pyrazolo[1,5-*a*]pyrimidine units to get new entities with potential synergetic biological activities. For this purpose, pyrimidine nucleoside derivatives bearing an allenic ketone moiety on the 5-position of the pyrimidine base (**6** and **10**) were prepared from the corresponding 5-methyl substituted nucleosides **5** and **9**, respectively.[23] Treatment of **6** with 1*H*-pyrazol-3-amine (**2a**) in acetone at rt for 2 h afforded **7** in a yield of 80%. The following aminolysis of **7** with $NH_3{\cdot}H_2O$ gave product **8** in a yield of 82%. Similarly, reacting **10** with 5-methyl-1*H*-pyrazol-3-amine (**2b**) in acetone at rt for 4 h followed by treatment with $NH_3{\cdot}H_2O$ led to a novel cytidine-pyrazolo[1,5-*a*]pyrimidine hybrid (**12**) in a total yield of 62% with excellent regio-selectivity (Scheme 2). The structures of **7**, **8**, **11** and **12** were fully characterized by their spectral data of ^{1}H NMR, ^{13}C NMR, and HRMS. Screening these novel



Scheme 1 Plausible pathway towards **3** and **4**.

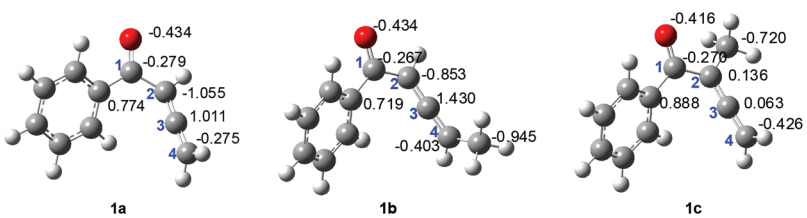
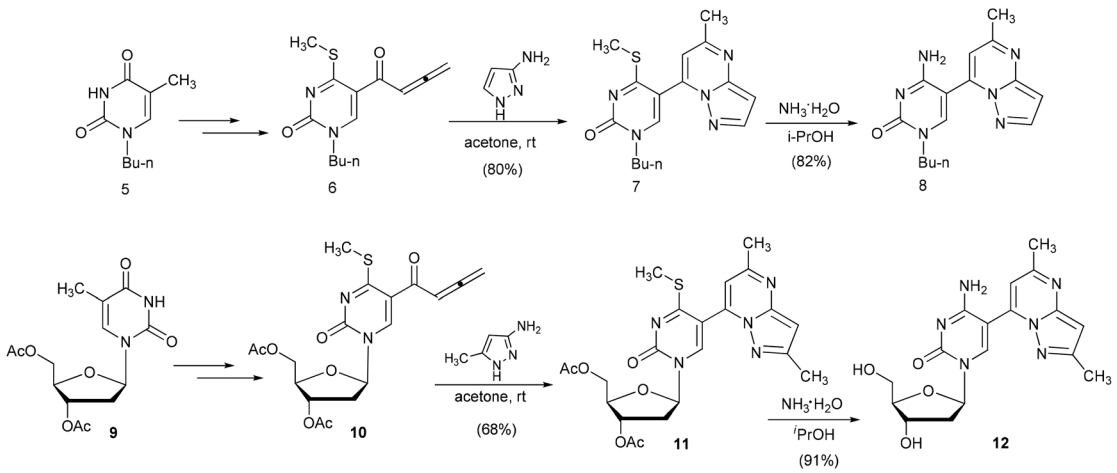


Fig. 4 Mulliken charges of some selected atoms in 1-phenylbuta-2,3-dien-1-one (**1a**), 1-phenylpenta-2,3-dien-1-one (**1b**) and 2-methyl-1-phenylbuta-2,3-dien-1-one (**1c**) with the most stable conformation computed at the B3LYP/6-31G* level of DFT.



Scheme 2 Preparation of hybrids of 5-substituted pyrimidine nucleosides and pyrazolo[1,5-*a*]pyrimidines.

5-substituted pyrimidine nucleosides as potential antiviral agents is currently underway.

Conclusions

In summary, an efficient procedure for the syntheses of pyrazolo[1,5-*a*]pyrimidines through cyclocondensation reactions of 1,2-allenic ketones with a variety of aminopyrazoles without using any catalyst or promoter has been developed. The methodology provided herein has advantages such as high yields, extremely mild conditions, a simple procedure and excellent regio-selectivity. Moreover, this novel procedure has been successfully applied in the preparation of nucleoside-pyrazolo[1,5-*a*]pyrimidine chimeras with potent antiviral activities.

Experimental

General methods

All the commercial reagents and solvents were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Splitting patterns are designated s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br. (broad). High-resolution mass spectra (HRMS) were obtained by using a MicrOTOF mass spectrometer. All reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254 0.25 mm) and components were visualized by observation under UV light.

General procedure for the preparation of pyrazolo[1,5-*a*]-pyrimidines 3, 4, 7 and 11

A mixture of 1,2-allenic ketone (1 mmol) and aminopyrazole **2** (1 mmol) in acetone (4 mL) was stirred at rt. Upon completion as indicated by TLC, the resulting mixture was concentrated under vacuum. The residue was purified by chromatography on silica gel to afford the title product.

5-Methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (3a): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.60 (s, 3H), 6.61 (d, J = 2.0 Hz, 1H), 6.71 (s, 1H), 7.51 (t, J = 3.2 Hz, 3H), 7.94–7.97 (m, 2H), 8.07 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.8, 95.9, 108.3, 128.7, 129.2, 130.9, 131.2, 144.7, 146.1, 149.5, 158.7. HRMS calcd for $C_{13}H_{12}N_3$: 210.1031 [M + H], found: 210.1037.

5-Methyl-7-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-*a*]pyrimidine (3b): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.58 (s, 3H), 6.59 (d, J = 2.4 Hz, 1H), 6.70 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 8.02–8.06 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.7, 96.2, 108.6, 119.6, 122.3, 125.0, 125.5, 125.5, 125.6, 125.6, 127.8, 129.6, 132.0, 132.3, 132.6, 132.9, 134.6, 144.4, 144.7, 149.4, 158.8. HRMS calcd for $C_{14}H_{11}F_3N_3$: 278.0905 [M + H], found: 278.0911.

7-(4-Bromophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine (3c): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.57 (s, 3H), 6.58 (d, J = 2.0 Hz, 1H), 6.66 (s, 1H), 7.59 (dd, J_1 = 6.4 Hz, J_2 = 2.0 Hz, 2H), 7.82 (dd, J_1 = 6.4 Hz, J_2 = 2.0 Hz, 2H), 8.02 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.8, 96.0, 108.1, 125.4, 129.9, 130.7, 131.9, 144.6, 144.8, 149.5, 158.6. HRMS calcd for $C_{13}H_{11}BrN_3$: 288.0136 [M + H], found: 288.0145.

7-(4-Methoxyphenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine (3d): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 (s, 3H), 3.78 (s, 3H), 6.54 (d, J = 2.0 Hz, 1H), 6.63 (s, 1H), 6.95 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.7, 55.4, 95.6, 107.4, 114.0, 123.2, 130.9, 144.4, 145.8, 149.6, 158.6, 161.6. HRMS calcd for $C_{14}H_{14}N_3O$: 240.1137 [M + H], found: 240.1131.

5-Methyl-7-*p*-tolylpyrazolo[1,5-*a*]pyrimidine (3e): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 2.60 (s, 3H), 6.61 (d, J = 2.0 Hz, 1H), 6.71 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 8.07 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 24.7, 95.7, 108.0, 128.2, 129.1, 129.3, 141.3, 144.6, 146.3, 149.5, 158.7. HRMS calcd for $C_{14}H_{14}N_3$: 224.1188 [M + H], found: 224.1181.

7-(3-Chlorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine (3f): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.56 (s, 3H), 6.58 (d, J = 2.4 Hz, 1H), 6.67 (s, 1H), 7.38–7.44 (m, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.93 (s, 1H), 8.03 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.8, 96.1, 108.4, 127.3, 129.2, 129.9, 130.9, 132.7, 134.6, 144.4, 144.7, 149.5, 158.7. HRMS calcd for $C_{13}H_{11}ClN_3$: 244.0642 [M + H], found: 244.0651.

7-(2-Fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine (3g): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.63 (s, 3H), 6.64 (d, J = 2.4 Hz, 1H), 6.76 (s, 1H), 7.26 (t, J = 9.2 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.50–7.54 (m, 1H), 7.75 (td, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 8.07 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.8, 96.1, 110.2, 110.2, 116.3, 116.6, 119.2, 124.4, 124.4, 131.1, 131.1, 132.6, 132.6, 141.3, 144.7, 149.1, 158.4, 158.7, 161.2. HRMS calcd for $C_{13}H_{11}FN_3$: 228.0937 [M + H], found: 228.0945.

5-Methyl-7-(naphthalen-1-yl)pyrazolo[1,5-*a*]pyrimidine (3h): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.63 (s, 3H), 6.69 (d, J = 2.0 Hz, 1H), 6.72 (s, 1H), 7.36–7.38 (m, 2H), 7.45–7.49 (m, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.63 (d, J = 6.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 8.01 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.8, 95.9, 110.6, 125.1, 125.2, 126.5, 127.0, 127.9, 128.7, 129.3, 130.7, 131.0, 133.6, 144.9, 146.0, 149.3, 158.6. HRMS calcd for $C_{17}H_{14}N_3$: 260.1188 [M + H], found: 260.1182.

5-Methyl-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (3i): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.61 (s, 3H), 6.61 (d, J = 2.0 Hz, 1H), 7.05 (s, 1H), 7.21 (t, J = 4.4 Hz, 1H), 7.66 (d, J = 4.8 Hz, 1H), 8.17 (d, J = 1.6 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.7, 95.8, 104.7, 127.6, 131.2, 131.5, 131.9, 139.4, 144.3, 149.5, 158.0. HRMS calcd for $C_{11}H_{10}N_3S$: 216.0595 [M + H], found: 216.0587.

7-Benzyl-5-methylpyrazolo[1,5-*a*]pyrimidine (3j): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (s, 3H), 4.42 (s, 2H), 6.19 (s, 1H), 6.56 (d, J = 2.4 Hz, 1H), 7.27–7.33 (m, 5H), 8.06 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.7, 36.2, 95.9, 107.7, 127.4, 128.9, 129.7, 134.8, 144.3, 148.1, 148.6, 158.5. HRMS calcd for $C_{14}H_{14}N_3$: 224.1188 [M + H], found: 224.1192.

5-Methyl-7-phenethylpyrazolo[1,5-*a*]pyrimidine (3k): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.46 (s, 3H), 3.10 (t, J = 7.6 Hz, 2H), 3.35 (t, J = 7.6 Hz, 2H), 6.36 (s, 1H), 6.53 (d, J = 2.4 Hz, 1H), 7.13–7.23 (m, 5H), 8.04 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.7, 31.9, 32.2, 95.7, 107.4, 126.4, 128.4, 128.6, 140.1, 144.2, 147.8, 148.6, 158.3. HRMS calcd for $C_{15}H_{16}N_3$: 238.1344 [M + H], found: 238.1341.

5-Ethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (3l): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41 (t, J = 8.0 Hz, 3H), 2.93 (q, J = 7.6 Hz, 2H), 6.68 (s, 1H), 6.79 (s, 1H), 7.56 (s, 3H), 8.01 (d, J = 3.6 Hz, 2H), 8.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.1, 31.5, 96.0, 107.4, 128.7, 129.2, 130.9, 131.4, 144.7, 144.8, 149.6, 163.6. HRMS calcd for $C_{14}H_{14}N_3$: 224.1188 [M + H], found: 224.1185.

2,5-Dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (3m): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (s, 3H), 2.60 (s, 3H), 6.41 (s, 1H), 6.66 (s, 1H), 7.53 (t, J = 2.8 Hz, 3H), 8.00–8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 24.6, 95.2, 107.5, 128.6, 129.3, 130.8, 131.4, 145.6, 150.3, 154.9, 158.2. HRMS calcd for $C_{14}H_{14}N_3$: 224.1188 [M + H], found: 224.1185.

7-(2-Fluorophenyl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (3n): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 2.57 (s, 3H), 6.40 (s, 1H), 6.64 (s, 1H), 7.20 (t, J = 9.2 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.44–7.48 (m, 1H), 7.75–7.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 24.7, 95.4, 109.3, 109.3, 116.3, 116.5, 119.4, 119.5, 124.3, 124.3, 131.2, 131.2, 132.4, 132.4, 140.6, 149.9, 154.9, 157.9, 158.7, 161.2. HRMS calcd for $C_{14}H_{13}FN_3$: 242.1094 [M + H], found: 242.1099.

7-(3-Chlorophenyl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (3o): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 2.50 (s, 3H), 2.61 (s, 3H), 6.43 (s, 1H), 6.66 (s, 1H), 7.47–7.51 (m, 2H), 7.92 (d, J = 7.2 Hz, 1H), 8.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ; 14.8, 24.7, 95.5, 107.6, 127.4, 129.3, 129.9, 130.9, 133.0, 134.7, 144.1, 150.2, 155.2, 158.3. HRMS calcd for $C_{14}H_{13}ClN_3$: 258.0798 [M + H], found: 258.0805.

7-(4-Bromophenyl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (3p): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 2.52 (s, 3H), 6.35 (s, 1H), 6.56 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 24.7, 95.4, 107.2, 125.3, 130.1, 130.8, 131.8, 144.2, 150.2, 154.9, 158.2. HRMS calcd for $C_{14}H_{13}BrN_3$: 302.0293 [M + H], found: 302.0299.

2,5-Dimethyl-7-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-*a*]-pyrimidine (3q): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.46 (s, 3H), 2.58 (s, 3H), 6.41 (s, 1H), 6.64 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7, 24.7, 95.6, 107.8, 119.7, 122.4, 125.1, 125.5, 125.6, 125.6, 125.6, 127.9, 129.7, 131.9, 132.2, 132.6, 132.9, 134.8, 143.9, 150.3, 155.1, 158.3. HRMS calcd for $C_{14}H_{13}F_3N_3$: 292.1062 [M + H], found: 292.1068.

2,5-Dimethyl-7-*p*-tolylpyrazolo[1,5-*a*]pyrimidine (3r): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 2.48 (s, 3H), 2.58 (s, 3H), 6.39 (s, 1H), 6.63 (s, 1H), 7.32 (d, J = 7.6 Hz, 2H), 7.91 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9, 21.6, 24.7, 95.1, 107.1, 128.4, 129.2, 129.3, 141.2, 145.7, 150.3, 154.8, 158.2. HRMS calcd for $C_{15}H_{16}N_3$: 238.1344 [M + H], found: 238.1341.

7-(3,4-Dimethoxyphenyl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (3s): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 2.53 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 6.34 (s, 1H), 6.60 (s, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.59 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.64 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 24.6, 55.9, 56.0, 94.9, 106.7, 110.8, 112.1, 122.6, 123.5, 145.2, 148.5, 150.4, 151.1, 154.6, 158.1. HRMS calcd for $C_{16}H_{18}N_3O_2$: 284.1399 [M + H], found: 284.1403.

2,5-Dimethyl-7-(naphthalen-1-yl)pyrazolo[1,5-*a*]pyrimidine (3t): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 2.59 (s, 3H), 6.48 (s, 1H), 6.60 (s, 1H), 7.33–7.37 (m, 1H), 7.42–7.47 (m, 2H), 7.53 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 6.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9, 24.7, 95.4, 109.9, 125.3, 125.3, 126.4, 126.9, 127.9, 128.6, 129.4, 130.7, 130.8, 133.6, 145.3, 150.0, 155.1, 158.1. HRMS calcd for $C_{18}H_{16}N_3$: 274.1344 [M + H], found: 274.1341.

2,5-Dimethyl-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (3u): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55 (s, 3H), 2.60 (s, 3H), 6.40 (s, 1H), 6.98 (s, 1H), 7.21–7.23 (m, 1H), 7.65 (d, J = 4.4 Hz, 1H), 8.31 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9, 24.7, 95.1, 103.9, 127.6, 131.3, 131.6, 131.8, 138.8, 150.3, 154.8, 157.5. HRMS calcd for $C_{12}H_{12}N_3S$: 230.0752 [M + H], found: 230.0758.

7-Benzyl-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (3v): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 2.47 (s, 3H), 4.36 (s, 2H), 6.03 (s, 1H), 6.32 (s, 1H), 7.22–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7, 24.6, 36.1, 95.2, 106.7, 127.3, 128.8, 129.8, 134.9, 147.6, 149.3, 154.4, 158.1. HRMS calcd for $C_{15}H_{16}N_3$: 238.1344 [M + H], found: 238.1345.

2,5-Dimethyl-7-phenethylpyrazolo[1,5-*a*]pyrimidine (3w): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 2.46 (s, 3H), 3.08 (t, J = 8.0 Hz, 2H), 3.31 (t, J = 8.0 Hz, 2H), 6.26 (s, 1H), 6.31 (s, 1H), 7.13–7.24 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7, 24.6, 31.8, 32.0, 95.0, 106.3, 126.4, 128.4, 128.5, 140.2, 147.3, 149.3, 154.3, 157.9. HRMS calcd for $C_{16}H_{18}N_3$: 252.1501 [M + H], found: 252.1509.

5-Ethyl-2-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (3x): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (t, J = 8.0 Hz, 3H), 2.50 (s, 3H), 2.87 (q, J = 8.0 Hz, 2H), 6.44 (s, 1H), 6.69 (s, 1H), 7.54 (t, J = 3.2 Hz, 3H), 8.02 (d, J = 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.2, 14.8, 31.5, 95.3, 106.5, 128.6, 129.2, 130.8, 131.5, 145.9, 150.3, 154.9, 163.2. HRMS calcd for $C_{15}H_{16}N_3$: 238.1344 [M + H], found: 238.1348.

2-Cyclopropyl-5-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (3y): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85–0.87 (m, 2H), 0.95–0.99 (m, 2H), 2.06–2.10 (m, 1H), 2.50 (s, 3H), 6.20 (s, 1H), 6.56 (s, 1H), 7.44 (d, J = 2.4 Hz, 3H), 7.97–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.3, 10.2, 24.6, 91.2, 107.2, 128.4, 129.3, 130.7, 131.3, 145.2, 150.4, 158.2, 161.3. HRMS calcd for $C_{16}H_{16}N_3$: 250.1344 [M + H], found: 250.1341.

7-(3-Chlorophenyl)-2-cyclopropyl-5-methylpyrazolo[1,5-*a*]-pyrimidine (3z): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.81–0.85 (m, 2H), 0.96–1.00 (m, 2H), 2.04–2.08 (m, 1H), 2.51 (s, 3H), 6.18 (s, 1H), 6.55 (s, 1H), 7.33–7.41 (m, 2H), 7.84 (d, J = 7.2 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.5, 10.2, 24.6, 91.4, 107.3, 127.4, 129.3, 129.7, 130.7, 132.9, 134.4, 143.6, 150.2, 158.2, 161.5. HRMS calcd for $C_{16}H_{15}ClN_3$: 284.0955 [M + H], found: 284.0953.

2-Cyclopropyl-7-(4-methoxyphenyl)-5-methylpyrazolo[1,5-*a*]-pyrimidine (3aa): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.81–0.84 (m, 2H), 0.93–0.97 (m, 2H), 2.03–2.08 (m, 1H), 2.46 (s, 3H), 3.75 (s, 3H), 6.14 (s, 1H), 6.50 (s, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.3, 10.2, 24.6, 55.3, 90.9, 106.3, 113.8, 123.3, 130.9, 144.9, 150.4, 158.0, 161.1, 161.5. HRMS calcd for $C_{17}H_{18}N_3O$: 280.1450 [M + H], found: 280.1453.

4-(2-Cyclopropyl-5-methylpyrazolo[1,5-*a*]pyrimidin-7-yl)-benzonitrile (3bb): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.81–0.83 (m, 2H), 0.97–1.01 (m, 2H), 2.03–2.07 (m, 1H), 2.56 (s, 3H), 6.20 (s, 1H), 6.64 (s, 1H), 7.76 (d, J = 7.6 Hz, 2H), 8.13 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.5, 10.2, 24.7, 91.8, 107.7, 114.2, 118.2, 129.9, 132.2, 135.6, 143.0, 143.0, 150.2, 158.3, 161.8, 161.8. HRMS calcd for $C_{17}H_{15}N_4$: 275.1297 [M + H], found: 275.1295.

2-Cyclopropyl-5-methyl-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (3cc): yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.98–1.07 (m, 4H), 2.12–2.15 (m, 1H), 2.53 (s, 3H), 6.27 (s, 1H), 6.91 (s, 1H), 7.15 (t, J = 4.0 Hz, 1H), 7.60 (d, J = 4.8 Hz, 1H), 8.19 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.7, 10.2, 24.7, 92.0, 103.3, 127.3, 130.9, 131.6, 131.9, 138.5, 150.1, 157.4, 161.0. HRMS calcd for $C_{14}H_{14}N_3S$: 256.0908 [M + H], found: 256.0903.

7-Benzyl-2-cyclopropyl-5-methylpyrazolo[1,5-*a*]pyrimidine (3dd): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90–0.94 (m, 2H), 1.01–1.06 (m, 2H), 2.11–2.15 (m, 1H), 2.41 (s, 3H), 4.38 (s, 2H), 6.06 (s, 1H), 6.20 (s, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.3, 10.2, 24.6, 36.1, 91.5, 106.5, 127.3, 128.8, 129.9, 135.0, 147.6, 149.2, 158.1, 161.0. HRMS calcd for $C_{17}H_{18}N_3$: 264.1501 [M + H], found: 264.1505.

2-Cyclopropyl-5-methyl-7-phenethylpyrazolo[1,5-*a*]pyrimidine (3ee): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90–0.91 (m, 2H), 1.02 (d, J = 8.4 Hz, 2H), 2.09–2.12 (m, 1H), 2.44 (s, 3H), 3.10 (t, J = 8.4 Hz, 2H), 3.31 (t, J = 8.0 Hz, 2H), 6.18 (s, 1H), 6.28 (s, 1H), 7.17 (d, J = 6.8 Hz, 2H), 7.25 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.4, 10.2, 24.6, 31.8, 32.1, 91.3, 106.2, 126.4, 128.4, 128.5, 140.4, 147.2, 149.3, 157.9, 160.9. HRMS calcd for $C_{18}H_{19}N_3$: 278.1657 [M + H], found: 278.1653.

2-Cyclopropyl-5-ethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (3ff): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86–0.90 (m, 2H), 1.01–1.06 (m, 2H), 1.37 (t, J = 7.6 Hz, 3H), 2.11–2.15 (m, 1H), 2.86 (q, J = 7.6 Hz, 2H), 6.24 (s, 1H), 6.68 (s, 1H), 7.54 (t, J = 7.6 Hz, 3H), 8.04–8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.4, 10.2, 13.2, 31.4, 91.1, 106.3, 128.5, 129.3, 130.8, 131.5, 145.7, 150.3, 161.6, 163.1. HRMS calcd for $C_{17}H_{18}N_3$: 264.1501 [M + H], found: 264.1508.

5-Methyl-2,7-diphenylpyrazolo[1,5-*a*]pyrimidine (3gg): yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ: 2.61 (s, 3H), 6.71 (s, 1H), 6.94 (s, 1H), 7.36 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.2 Hz, 2H), 7.53–7.56 (m, 3H), 8.00–8.02 (m, 2H), 8.11–8.14 (m, 2H); 13C NMR (100 MHz, $CDCl_3$) δ: 24.8, 92.5, 108.2, 126.6, 128.5, 128.7, 128.8, 129.5, 130.9, 131.1, 133.1, 145.6, 150.8, 155.6, 158.6. HRMS calcd for $C_{19}H_{16}N_3$: 286.1344 [M + H], found: 286.1348.

7-(4-Bromophenyl)-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (3hh): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.62 (s, 3H), 6.71 (s, 1H), 6.92 (s, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 8.0 Hz, 2H), 7.68–7.70 (m, 2H), 7.96–7.98 (m, 2H), 8.01–8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.8, 92.7, 107.9, 125.4, 126.5, 128.7, 128.9, 129.9, 131.0, 131.8, 132.9, 144.5, 150.7, 155.7, 158.6. HRMS calcd for $C_{19}H_{15}BrN_3$: 364.0449 [M + H], found: 364.0455.

5,6-Dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (3ii): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.14 (s, 3H), 2.62 (s, 3H), 6.58 (d, J = 2.0 Hz, 1H), 7.45–7.47 (m, 2H), 7.53–7.57 (m, 3H), 7.95 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.1, 24.1, 95.5, 114.9, 128.9, 129.4, 129.9, 130.9, 144.0, 147.4, 159.6. HRMS calcd for $C_{14}H_{14}N_3$: 224.1188 [M + H], found: 224.1185.

2,5,6-Trimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (3jj): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (s, 3H), 2.39 (s,

3H), 2.57 (s, 3H), 6.35 (s, 1H), 7.44–7.54 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9, 15.1, 24.1, 94.8, 113.9, 128.8, 129.6, 129.8, 131.0, 143.5, 148.2, 154.0, 159.1. HRMS calcd for $C_{15}H_{16}N_3$: 238.1344 [M + H], found: 238.1342.

2-Cyclopropyl-5,6-dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (3kk): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.74–0.77 (m, 2H), 0.93–0.96 (m, 2H), 2.01–2.03 (m, 1H), 2.08 (d, J = 1.2 Hz, 3H), 2.55 (d, J = 2.0 Hz, 3H), 6.11 (s, 1H), 7.45–7.54 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.4, 10.2, 15.1, 24.0, 90.0, 113.7, 128.6, 129.7, 129.7, 130.9, 143.4, 148.2, 159.0, 160.7. HRMS calcd for $C_{17}H_{18}N_3$: 264.1501 [M + H], found: 264.1498.

6-Ethyl-2,5-dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (3ll): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (t, J = 7.6 Hz, 3H), 2.39 (s, 3H), 2.47 (q, J = 7.2 Hz, 2H), 2.64 (s, 3H), 6.36 (s, 1H), 7.41–7.43 (m, 2H), 7.53–7.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 14.8, 21.7, 23.2, 94.7, 120.7, 128.9, 129.1, 129.6, 131.1, 143.9, 148.1, 154.3, 158.6. HRMS calcd for $C_{16}H_{18}N_3$: 252.1501 [M + H], found: 252.1503.

6,7-Dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (4ii): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 2.86 (s, 3H), 6.67 (d, J = 2.0 Hz, 1H), 7.46–7.53 (m, 5H), 8.10 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ; 14.1, 15.5, 96.7, 113.4, 128.4, 128.7, 128.7, 128.9, 139.7, 144.0, 146.9, 159.5. HRMS calcd for $C_{14}H_{14}N_3$: 224.1188 [M + H], found: 224.1181.

2,6,7-Trimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (4jj): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 2.52 (s, 3H), 2.80 (s, 3H), 6.43 (s, 1H), 7.43–7.51 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 14.7, 15.5, 95.8, 112.5, 128.3, 128.6, 128.7, 139.7, 143.4, 147.6, 154.2, 159.1. HRMS calcd for $C_{15}H_{16}N_3$: 238.1344 [M + H], found: 238.1351.

2-Cyclopropyl-6,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (4kk): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88–0.92 (m, 2H), 1.02–1.07 (m, 2H), 2.12–2.16 (m, 1H), 2.24 (s, 3H), 2.79 (s, 3H), 6.25 (s, 1H), 7.40–7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.2, 10.2, 14.1, 15.5, 91.8, 112.3, 128.3, 128.6, 128.7, 139.8, 143.4, 147.6, 159.0, 160.8. HRMS calcd for $C_{17}H_{18}N_3$: 264.1501 [M + H], found: 264.1505.

6-Ethyl-2,7-dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (4ll): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (t, J = 7.2 Hz, 3H), 2.54 (s, 3H), 2.68 (q, J = 7.2 Hz, 2H), 2.84 (s, 3H), 6.44 (s, 1H), 7.44–7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.7, 15.1, 21.6, 95.8, 119.1, 128.2, 128.3, 128.5, 139.9, 143.3, 147.4, 154.4, 159.3. HRMS calcd for $C_{16}H_{18}N_3$: 252.1501 [M + H], found: 252.1504.

1-Butyl-5-(5-methylpyrazolo[1,5-*a*]pyrimidin-7-yl)-4-(methylthio)pyrimidin-2(1*H*)-one (7): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, J = 8.0 Hz, 3H), 1.35 (sext, J = 7.2 Hz, 2H), 1.73 (quint, J = 7.2 Hz, 2H), 2.47 (s, 3H), 2.58 (s, 3H), 3.86 (t, J = 7.2 Hz, 2H), 6.57 (d, J = 2.4 Hz, 1H), 6.86 (s, 1H), 7.99 (d, J = 2.4 Hz, 1H), 8.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.5, 13.7, 19.7, 24.8, 30.8, 51.2, 96.6, 107.1, 110.6, 138.5, 144.5, 146.9, 149.1, 153.1, 158.4, 175.6. HRMS calcd for $C_{16}H_{20}N_5OS$: 330.1389 [M + H], found: 330.1382.

((2*R*,3*S*,5*R*)-3-Acetoxy-5-(5-(2,5-dimethylpyrazolo[1,5-*a*]pyrimidin-7-yl)-4-(methylthio)-2-oxopyrimidin-1(2*H*)-yl)tetrahydrofuran-2-yl)methyl acetate (11): yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54 (s, 3H), 2.00 (s, 3H), 2.13–2.20 (m, 1H), 2.32 (s, 3H), 2.42 (s, 3H), 2.49 (s, 3H), 2.71–2.77 (m, 1H), 4.17 (d, J = 2.8 Hz, 2H), 4.23–4.25 (m, 1H), 5.12–5.13 (m, 1H), 6.21 (t, J = 6.8 Hz, 1H), 6.30 (s, 1H), 6.70 (s, 1H), 8.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.5, 14.6, 20.0, 20.8, 24.6, 38.8, 63.5, 74.0, 82.9, 87.3, 95.9, 107.7, 109.6, 137.9, 141.6, 149.7, 152.1, 154.8, 157.9, 169.9, 170.2, 176.4. HRMS calcd for $C_{22}H_{26}N_5O_6S$: 488.1604 [M + H], found: 488.1609.

General procedure for the preparation of nucleoside-pyrazolo-[1,5-*a*]pyrimidine chimeras 8 and 12

A sealed tube (50 mL) containing compound **7** or **11** (0.5 mmol), i-PrOH (5 mL), $NH_3{\cdot}H_2O$ (1 mL) and a magnetic stirring bar was heated to 90 °C for 8 h. The resulting mixture was then concentrated under vacuum, and the residue was purified by chromatography on silica gel to afford the nucleoside-pyrazolo[1,5-*a*]pyrimidine chimera **8** or **12**.

4-Amino-1-butyl-5-(5-methylpyrazolo[1,5-*a*]pyrimidin-7-yl)-pyrimidin-2(1*H*)-one (8): white solid. ^{1}H NMR (400 MHz, DMSO) δ: 0.88 (t, J = 7.2 Hz, 3H), 1.22–1.30 (m, 2H), 1.55–1.62 (m, 2H), 2.52 (s, 3H), 3.70 (t, J = 7.6 Hz, 2H), 6.58 (s, 1H), 6.94 (s, 1H), 8.09 (s, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ: 14.1, 19.7, 24.7, 31.3, 49.1, 95.9, 98.1, 111.0, 140.3, 144.4, 149.0, 149.1, 155.2, 158.8, 162.8. HRMS calcd for $C_{15}H_{19}N_6O$: 299.1620 [M + H], found: 299.1656.

4-Amino-5-(2,5-dimethylpyrazolo[1,5-*a*]pyrimidin-7-yl)-1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-pyrimidin-2(1*H*)-one (12): white solid. ^{1}H NMR (400 MHz, DMSO) δ: 2.02–2.08 (m, 1H), 2.18–2.22 (m, 1H), 2.35 (s, 3H), 2.48 (s, 3H), 3.46–3.54 (m, 2H), 3.77 (s, 1H), 4.19 (s, 1H), 4.90 (t, J = 4.4 Hz, 1H), 5.22 (d, J = 2.8 Hz, 1H), 6.18 (t, J = 6.0 Hz, 1H), 6.37 (s, 1H), 6.69 (br., 1H), 6.81 (s, 1H), 7.48 (br., 1H), 8.28 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ: 14.9, 24.7, 41.2, 61.5, 70.5, 85.8, 87.9, 95.2, 99.3, 110.1, 139.8, 143.7, 149.8, 153.7, 154.5, 158.5, 162.5. MS: m/z 373 $(MH)^+$. HRMS calcd for $C_{17}H_{21}N_6O_4$: 373.1624 [M + H], found: 373.1628.

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