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ARTICLE

Palladium-catalyzed C-H olefination of uracils and caffeines using molecular oxygen as the sole oxidant

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The palladium-catalyzed oxidative C-H olefination of uracils or caffeines with alkenes using atmospheric pressure of molecular oxygen as the sole oxidant has been disclosed. This novel strategy offers an efficient and environmentally friendly way to biologically important C5-alkene uracils derivatives or C8-alkene caffeines derivatives.

Introduction

There has been great interest in caffeines or uracil-scaffold-containing compounds because of their potential biological activity and pharmaceutical significance.[1] Besides, their derivatives have numerous applications as fluorescent biological probes,[2] organic light emitting diodes (OLEDs),[3] advance materials,[4] heavy metal sensor,[5] and nucleobase functionalized π-conjugated oligomers.[6] Therefore, the development of efficient and clean methodologies for the synthesis of caffeine or uracil derivatives is highly desirable.[7]

Since Fujiwara and Moritani's pioneering work,[8] transition-metal-catalyzed oxidative aryl C-H olefination has drawn considerable attention.[9] Various transition-metal complexes such as palladium, rhodium, and ruthenium can be applied for oxidative Heck reaction, and a variety of substrates such as simple arene with directing groups, O-heteroarenes, N-heteroarenes, and S-heteroarenes were successfully coupled with olefin for delivering arylalkenes. However, most these methods required stoichiometric amounts of the oxidants such as copper(II) salt,[10] silver (I) salt,[11] HFIP,[12] benzoquinone,[13] etc to drive the reaction forward. In order to fulfill the requirements of green chemistry, there is an increasing demand to use ecologically benign oxidants such as molecular oxygen. Recent developments of our group and others have demonstrated that the catalytic amount of polyoxometalates (POMs) can act as relay species in oxidative Heck reactions in which O_2 serves as the terminal oxidant.[14] Nevertheless, copious POMs need to be added in the reaction system due to its large molecular weights. Hence, using molecular oxygen as the sole oxidant is considered as the ideal alternative because the formation of C-C bond via oxidative Heck reaction occurs with only the generation of water as a by-product. Typical examples , to name a few, include Pd(II)-catalyzed olefination of electron-deficient arenes using 2,6-dialkylpyridine ligands with molecular oxygen as the sole oxidant,[15] regioselective palladium-catalyzed olefination of coumarins,[16] palladium-catalyzed C3 alkenylation of indoles,[17] enantioselective metal/organo-catalyzed aerobic oxidative sp^3 C-H olefination of tertiary amines,[18] aerobic dehydrogenative Heck reaction of ferrocene with a $Pd(OAc)_2$/4,5-diazafluoren-9-one catalyst,[19] palladium-catalyzed oxidative olefination of phenol derivatives,[20] Rh(III)-catalyzed C-H olefination of N-pentafluoroaryl benzamides.[21] In 2015, our group also disclosed palladium-catalyzed cross-dehydrogenative-coupling (CDC) reaction of polyfluoroarenes with alkenes and arenes using atmospheric pressure of molecular oxygen as the sole oxidant.[22] Despite these advances, the transition-metal-catalyzed oxidative Heck reaction using molecular oxygen as the sole oxidant still in its infancy, and there is much new territory such as larger substrate scope to be explored.

In 2012, You et al. reported a dehydrogenative Heck coupling of caffeine with alkenes using $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.) and $CuCl_2$ (15 mol%) as the oxidants.[23] In 2013, Yu et al. reported the palladium-catalyzed dehydrogenative alkenylation of uracils using AgOAc (3 equiv.) as the oxidant.[24] However, stoichiometric amounts of metal oxidants are still required in reaction system. In our continuous interests in this area, we herein describe the palladium-catalyzed oxidative Heck reaction of uracils and caffeines with alkenes using the atmospheric molecular oxygen as the sole oxidant.

Results and discussion

Our initial studies involved the oxidative Heck reaction of 1,3-dimethyluracil (**1a**) with *n*-butyl acrylate (**2a**) employing the conditions of $Pd(OAc)_2$ (10 mol%), DL-pGlu-OH (10 mol%) and PivOH (2 equiv.) in DMA at 100 ^oC using O_2 (1atm) as the sole oxidant. As shown in Table 1, this leads to the generation of C-5-alkenylated product **3a** in 72% yield with completely E-stereoselectivity. (Table 1, entry 1). Yu and co-workers have discovered that mono-N-protected amino acids

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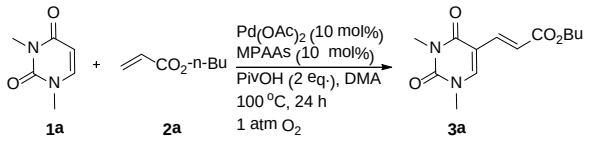
Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

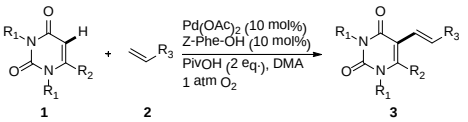
Entry	MPAAs	yield[b](%)
1	DL-pGlu-OH	72
2	Boc-Leu-OH	78
3	Boc-Val-OH	41
4	Boc-Ala-OH	80
5	Fmoc-Leu-OH	67
6	Fmoc-Ile-OH	60
7	Fmoc-Ala-OH	35
8	Ac-DL-Leu-OH	70
9	Z-Phe-OH	92 (88)
10[c]	Z-Phe-OH	56
11[d]	Z-Phe-OH	70
12[e]	Z-Phe-OH	0
13[f]	Z-Phe-OH	0

[a] Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1 equiv.), **2a** (0.4 mmol, 2 equiv.), solvent (1 mL), O_2 (1 atm) at 100 °C for 24 h. DMA = *N*,*N*-dimethylacetamide, PivOH = pivalic acid. [b] Yield according to GC based on the amount of **2a** used. Number in parenthesis is isolated yield. [c] The reaction time is 8 h. [d] The reaction time is 16 h. [e] The reaction was carried out in the absence of $Pd(OAc)_2$. [f] The reaction was carried out under a nitrogen atmosphere.

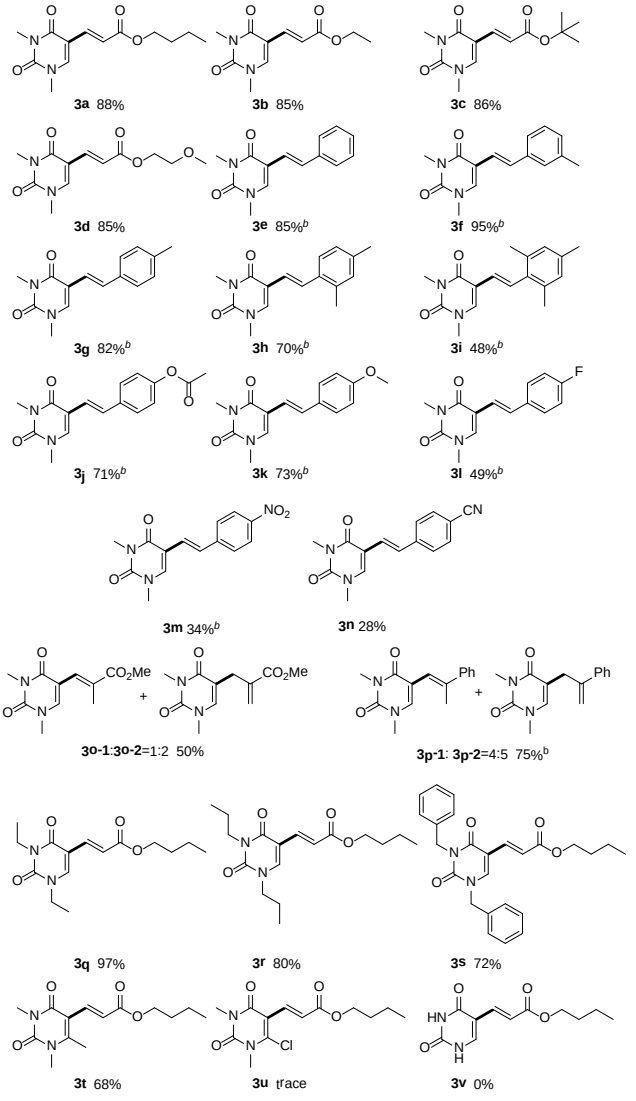
(MPAAs) could enable the acceleration of Pd(II)-catalyzed oxidative heck reactions.[25] With this research in mind, the effect of MPAAs was investigated intensively to further boost the yield. Z-Phe-OH (92%; Table 1, entry 9) was found to be superior to others such as Boc-Leu-OH (78%;Table 1, entry 2), Boc-Val-OH (41%; Table 1, entry 3), Boc-Ala-OH (80%; Table 1, entry 4), Fmoc-Leu-OH (67%; Table 1, entry 5), Fmoc-Lle-OH (60%; Table 1, entry 6), Fmoc-Ala-OH (35%; Table 1, entry 7)and Ac-DL-Leu-OH (70%; Table 1, entry 8). Additionally, shortening the reaction time led to a decreased conversion of **1a** to some degree (Table 1, entries 10-11). Finally, Control experiments revealed that no **3a** was formed in the absence of a palladium catalyst or molecular oxygen (Table 1, entries 12-13).

With the identification of the optimal MPAA, the substrate scope with respect to direct olefination of 1,3-dimethyluracil was illustrated in Table 2 (see **3a-p**). The present protocol was successfully extended to other acrylate of various alcohols. *n*-Butylacrylate, *t*-butyl acrylate, ethyl acrylate and 2-methoxyethyl acrylate reacted efficiently with caffeine to give corresponding products (see **3a-d**) in 72%, 59%, 68% and 54% yield, respectively. In addition, styrenes were also found to be competent coupling partners. Whereas, the reaction required higher temperature (120 °C) and external base (K_2CO_3). The effect of substituents in different position of the styrene was examined then. It is clear that the steric effect of the substituents was very significant. Styrene, 3- methylstyrene and 4-methylstyrene were good substrates, and delivered the

Table 2 Oxidative olefination of uracils with alkenes[a]



1 2 3



[a] Reaction conditions: **1** (0.2 mmol),**2** (2 equiv.), $Pd(OAc)_2$ (10 mol%), Z-Phe-OH (10 mol%), DMA (1 mL), O_2 (1 atm), 100 °C, 24 h; Isolated yields. [b] 120 °C, K_2CO_3 (40 mol%).

desired products in excellent yields (see **3e-g**). The direct olefination of 1,3-dimethyluracil with 2,-4-dimethylstyene also occurred, but afforded relatively low yield of the product (see **3h**). In contrast, for 2,4,6- trimethylstyrene, the olefination reaction is sluggish and **3i** was isolated in 48% yield (see **3i**). styrenes bearing an electron-donating groups (alkyl, methoxy or acetoxyl group) showed better reactivity compared with that bearing an electron-withdrawing group (F, CN, NO_2, see **3l-n**). α-substituted such as N-phthaloyl dehydroalanine was not suitable for the process,[26] since the desired product were not isolated, and starting materials were recovered. However, the reaction of 1,3-dimethyluracil with α-substituted olefines such

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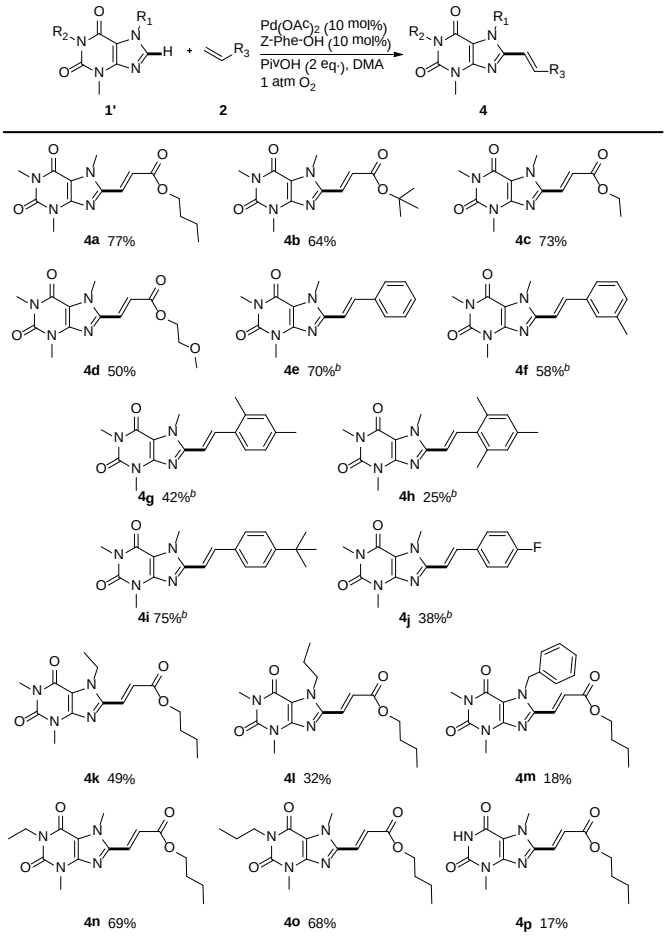
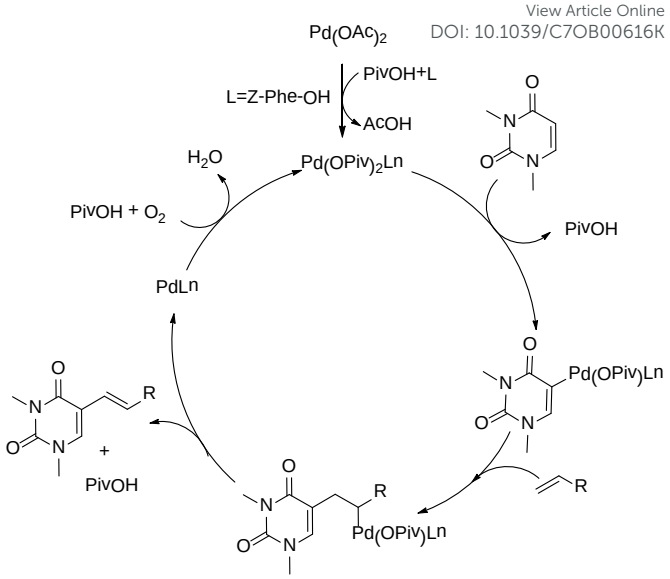
as methyl methacrylate and α-methylstyrene could afforded a mixture of olefinated products in mild to good yields. (see **3o**-**p**). 1,3-dialkyluracils could be olefinated to give the desired products in good yields (see **3q**-**s**). Treatment of 1,3,6-trimethyluracil also afforded the desired product **3t** in good yield. However, when using 6-chloro-1,3-dimethyluracil as the substrate, the desired transformation did not occur and starting materials were recovered (see **3u**). It is presumed that this low yield seems to be due to the decreased nucleophilicity of the C(5)-H bond of uracil. Unfortunately, the free (NH)-uracil was not suitable substrate for the reaction, since the desired product was not isolated.

To demonstrate the versatility of this methodology for oxidative Heck reaction using O_2 as the sole oxidant, we further investigated the direct C-H olefination of caffeines with above-mentioned reaction conditions (Table 1, entry 9). Delightedly, the current catalytic system was also effective for the caffeines and the results are summarized in Table 3. Both acrylates and styrenes took part in the alkenylation reaction with good yields and excellent E-stereoselectivity. Similarly,

Table 3. Oxidative olefination of caffeines with alkenes[a]



[a] Reaction conditions: **1'** (0.2 mmol), **2** (2 equiv.), $Pd(OAc)_2$ (10 mol%), Z-Phe-OH (10 mol%), DMA (1 mL), O_2 (1 atm), 120 ^{0}C, 24 h; Isolated yields. [b] 140 °C, K_2CO_3 (40 mol%).



Scheme 1 A plausible mechanism

the steric and electronic effect of the substituents on the styrene is very significant. (see **4e**-**j**) 3-Ethyl or 3-propyl substituted caffeines underwent olefination with *n*-butyl acrylate to give the desired products in good yields (see 4**n**-**o**).However, moderate or low yield was observed in the reaction of 7-ethyl, 7-propyl or 7-benzyl substituted caffeines presumably due to steric reasons (see **4k**-**m**). Because of the poor solubility of 3-NH caffeine in DMA, only 17% of the target product **4p** was obtained.

Base on the observed results and pioneering reports,[27] the mechanism for the direct C-H olefination of uracils with alkenes was proposed in Scheme 1. It is thought that $Pd(OAc)_2$ first coordinates with Ac-Gly-OH and PivOH to form the activated palladium (II) catalyst, and then the reaction mechanism involves the electrophilic attack of Pd(II) to uracil or caffeine, followed by insertion into the olefin and the subsequent reductive elimination to give product and Pd(0). Finally, the reoxidation of Pd(0) to Pd(II) by molecular oxygen to complete the catalytic cycle.

Conclusion

In conclusion, we have developed the palladium-catalyzed oxidative Heck reaction of uracil or caffeine using O_2 as the sole oxidant. This simple and efficient approach provides an economical and environmentally benign process for the preparation of a variety of vinyl or styryl-substituted uracil/caffeine scaffolds.

Experimental section

Materials and methods

All reagents are analytically pure and used without further purification, or prepared as described in the literature. 1H and 13C NMR spectra were recorded on a Bruker advance III 400 spectrometer at 400 MHz and 100 MHz, respectively. 1H

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chemical shifts (δ) were referenced to TMS, and 13C NMR chemical shifts (δ) were referenced to internal solvent resonance. GC analyses of organic compounds were performed on an Agilent Technologies 6890N GC (with a SGE-OV1701 25m capillary column) instrument. ESI-HRMS spectra were recorded on a Bruker micrOTO II equipment (ESI-QTOF). Column chromatography was performed using silica gel (230-400 mesh). Thin layer chromatography (TLC) was performed using silica gel GF254, 0.25 mm thickness.

A Representative Procedure for the oxidative coupling of 1,3-dimethyluracil (1a) with n-butyl acrylate (2a)

Formation of (E)-butyl 3-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acrylate **3a**: 1,3-dimethyluracil **1a** (28 mg, 0.2 mmol), *n*-butyl acrylate **2a** (58 μl, 0.4 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), Z-Phe-OH (6.0 mg, 0.02 mmol), PivOH (41 mg, 0.4 mmol) and DMA (1 mL) were placed in a 50 mL Schlenk tube. The reaction solution was degassed twice and refilled with O_2 (1.0 atm).The mixture was heated in oil bath at 100 °C with stirring for 24 h. After the reaction vessel was cooled to room temperature, the crude reaction mixture was diluted with CH_2Cl_2 to 5 mL and $C_{28}H_{58}$ (0.2 mmol) was added as an internal standard for GC analysis. After GC analysis of the reaction mixture, volatiles were removed under reduced pressure, and the residue was subjected to silica gel column chromatography [eluting with petroleum ether/ethyl acetate=2:1] to afford **3a** in 88% yield. The GC analyses of the reaction mixture disclosed the formation of **3a** in 92% yield.

(E)-butyl 3-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acrylate (3a) [24]**:** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (s, 1H), 7.27 (d, *J* = 15.8 Hz, 1H), 6.97 (d, *J* = 15.8 Hz, 1H), 4.15 (t, *J* = 6.6 Hz, 2H), 3.47 (s, 3H), 3.37 (s, 3H), 1.68 – 1.59 (m, 2H), 1.45 – 1.34 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.8, 161.4, 150.8, 144.8, 136.3, 119.3, 109.0, 64.4, 37.6, 30.86, 28.2, 19.3, 13.8.

(E)-ethyl 3-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acrylate (3b): 1H NMR (400 MHz, Chloroform-d) δ 7.43 (s, 1H), 7.30 (d, J = 15.8 Hz, 1H), 6.98 (d, J = 15.8 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.48 (s, 3H), 3.39 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). 13C NMR (101 MHz, Chloroform-d) δ 167.6, 161.4, 150.8, 144.8, 136.3, 119.3, 109.0, 60.5, 37.6, 28.2, 14.4. HRMS: Calculated for C11H15N2O4+ [M+H]+:239.1026; Found: 239.1030.

(E)-tert-butyl 3-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acrylate (3c) [24]**:** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (s, 1H), 7.20 (d, *J* = 15.8 Hz, 1H), 6.89 (d, *J* = 15.8 Hz, 1H), 3.47 (s, 3H), 3.39 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.9, 161.5, 150.9, 144.3, 135.1, 121.4, 109.2, 80.5, 37.6, 28.3, 28.2.

(E)-2-methoxyethyl 3-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acrylate (3d): 1H NMR (400 MHz, Chloroform-d) δ 7.42 (s, 1H), 7.31 (d, J = 15.8 Hz, 1H), 7.03 (d, J = 15.8 Hz, 1H), 4.34 – 4.29 (m, 2H), 3.66 – 3.62 (m, 2H), 3.47 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H). 13C NMR (101 MHz, Chloroform-d) δ 167.6, 161.4, 150.8, 144.9, 136.9, 118.9, 109.0, 70.7, 63.7, 59.2, 37.6, 28.3. HRMS: Calculated for C12H16N2NaO5+ [M+Na]+:291.0951; Found: 291.0953.

(E)-1,3-dimethyl-5-styrylpyrimidine-2,4(*1H,3H*)-dione (3e) [24]**:** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.42 (m, 2H), 7.37 (d, *J* = 16.4 Hz, 1H), 7.35 – 7.30 (m, 3H), 7.26 – 7.23 (m, 1H), 6.82 (d, *J* = 16.4 Hz, 1H), 3.44 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.3, 151.0, 139.3, 137.3, 129.3, 128.6, 127.6, 126.3, 120.0, 111.4, 37.2, 28.1.

(E)-1,3-dimethyl-5-(3-methylstyryl)pyrimidine-2,4(*1H,3H*)-dione (3f): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 (d, *J* = 16.3 Hz, 1H), 7.32 (s, 1H), 7.28 (s, 1H), 7.26 – 7.19 (m, 3H), 7.06 (d, *J* = 6.9 Hz, 1H), 6.83 (d, *J* = 16.3 Hz, 1H), 3.46 (s, 3H), 3.41 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.4, 151.2, 139.2, 138.3, 137.4, 129.5, 128.7, 128.6, 127.2, 123.7, 119.8, 111.7, 37.3, 28.3, 21.5. HRMS: Calculated for $C_{15}H_{17}N_2O_2^+$ $[M+H]^+$:257.1285; Found: 257.1280.

(E)-1,3-dimethyl-5-(4-methylstyryl)pyrimidine-2,4(*1H,3H*)-dione (3g): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.30 (m, 4H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 16.4 Hz, 1H), 3.45 (s, 3H), 3.40 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.4, 151.2, 139.0, 137.7, 134.6, 129.5, 129.3, 126.4, 119.0, 111.8, 37.3, 28.3, 21.4. HRMS: Calculated for $C_{15}H_{17}N_2O_2^+$ $[M+H]^+$:257.1285; Found: 257.1287.

(E)-5-(2,4-dimethylstyryl)-1,3-dimethylpyrimidine-2,4(*1H,3H*)-dione (3h): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 16.1 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.29 (s, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.98 (s, 1H), 6.67 (d, *J* = 16.1 Hz, 1H), 3.46 (s, 3H), 3.41 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.5, 151.2, 139.3, 137.5, 135.8, 133.7, 131.3, 127.5, 127.0, 125.1, 120.4, 112.1, 37.28, 28.2, 21.2, 20.0. HRMS: Calculated for $C_{16}H_{19}N_2O_2^+$ $[M+H]^+$:271.1441; Found: 271.1424.

(E)-1,3-dimethyl-5-(2,4,6-trimethylstyryl)pyrimidine-2,4(*1H,3H*)-dione (3i): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 16.6 Hz, 1H), 6.88 (s, 2H), 6.30 (d, *J* = 16.6 Hz, 1H), 3.47 (s, 3H), 3.41 (s, 3H), 2.31 (s, 6H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.5, 151.3, 139.0, 136.5, 136.1, 134.2, 128.9, 128.3, 125.1, 111.9, 37.3, 28.2, 21.2, 21.1. HRMS: Calculated for $C_{17}H_{21}N_2O_2^+$ $[M+H]^+$:285.1598; Found: 285.1596.

(E)-4-(2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)vinyl)phenyl acetate (3j) [24]**:** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.43 (m, 2H), 7.39 (d, *J* = 16.3 Hz, 1H), 7.33 (s, 1H), 7.09 – 7.03 (m, 2H), 6.78 (d, *J* = 16.3 Hz, 1H), 3.47 (s, 3H), 3.41 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.6, 162.4, 151.2, 150.2, 139.5, 135.4, 128.5, 127.4, 121.9, 120.4, 111.5, 37.4, 28.3, 21.3. HRMS: Calculated for $C_{16}H_{17}N_2O_4^+$ $[M+H]^+$:301.1183; Found: 301.1176.

(E)-5-(4-methoxystyryl)-1,3-dimethylpyrimidine-2,4(*1H,3H*)-dione (3k): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.36 (m, 2H), 7.30 (d, *J* = 16.3 Hz, 1H), 7.30 (s, 1H), 6.90 – 6.85 (m, 2H), 6.71 (d, *J* = 16.3 Hz, 1H), 3.82 (s, 3H), 3.46 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.5, 159.5, 151.2, 138.6, 130.3, 129.1, 127.8, 117.9, 114.3, 112.0, 55.5, 37.3, 28.3. HRMS: Calculated for $C_{15}H_{17}N_2O_3^+$ $[M+H]^+$:273.1234; Found: 273.1240.

(E)-5-(4-fluorostyryl)-1,3-dimethylpyrimidine-2,4(*1H,3H*)-dione (3l): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.39 (m,

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2H), 7.36 (d, *J* = 16.3 Hz, 1H), 7.32 (s, 1H), 7.06 – 6.98 (m, 2H), 6.73 (d, *J* = 16.3 Hz, 1H), 3.47 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.5 (d, $^{1}J_{C\text{-}F}$= 247.4 Hz), 162.4, 151.1, 139.4, 133.7 (d, $^{3}J_{C\text{-}F}$ = 3.2 Hz), 128.4, 128.0 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 119.9 (d, $^{3}J_{C\text{-}F}$= 1.9 Hz), 115.7 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz), 111.5, 37.3, 28.3. HRMS: Calculated for $C_{14}H_{14}FN_2O_2^+$ $[M+H]^+$:261.1034; Found: 261.1043.

(E)-1,3-dimethyl-5-(4-nitrostyryl)pyrimidine-2,4(1*H*,3*H*)-dione (3m): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.63 – 7.52 (m, 3H), 7.41 (s, 1H), 6.94 (d, *J* = 16.2 Hz, 1H), 3.50 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.1, 150.9, 146.8, 144.2, 141.5, 127.2, 126.8, 124.9, 124.3, 110.6, 37.6, 28.3. HRMS: Calculated for $C_{14}H_{14}N_3O_4^+$ $[M+H]^+$:288.0979; Found: 288.0975.

(E)-4-(2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)vinyl)benzonitrile (3n): 1H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 7.58 (m, 2H), 7.54 – 7.48 (m, 3H), 7.39 (s, 1H), 6.89 (d, J = 16.3 Hz, 1H), 3.49 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.1, 151.0, 142.2, 141.12, 132.6, 127.7, 126.8, 124.0, 119.2, 110.7, 110.7, 37.52, 28.33. HRMS: Calculated for $C_{15}H_{14}N_3O_2^+$ $[M+H]^+$: 268.1081; Found: 268.1083.

(E)-methyl 3-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-methylacrylate (3o-1) and methyl 2-((1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)acrylate (3o-2): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.54 (s, 1H, **3o-1**), 7.36 (s, 1H, **3o-1**), 7.15 (s, 1H, **3o-2**), 6.27 (s, 1H, **3o-2**), 5.82 (s, 1H, **3o-2**), 3.79 (s, 3H, **3o-1**), 3.75 (s, 3H, **3o-2**), 3.49 (s, 3H, **3o-1**), 3.39 (s, 6H, **3o-1**+**3o-2**), 3.34 (s, 5H, **3o-2**), 2.05 (s, 3H, **3o-1**). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.3, 167.2, 163.4, 162.4, 151.8, 151.1, 142.4, 141.1, 136.8, 129.7, 128.1, 128.0, 110.5, 109.8, 52.2, 52.0, 37.7, 37.0, 29.7, 28.3, 28.0, 14.8. HRMS: Calculated for $C_{11}H_{15}N_2O_4^+$ $[M+H]^+$: 239.1026; Found: 239.1033.

(E)-1,3-dimethyl-5-(2-phenylprop-1-en-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (3p-1) and 1,3-dimethyl-5-(2-phenylallyl)pyrimidine-2,4(1*H*,3*H*)-dione (3p-2): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.52 – 7.41 (m, 2H, **3p-1**; 2H, **3p-2**), 7.38 – 7.26 (m, 4H, **3p-1**; 3H, **3p-2**), 6.84 (s, 1H, **3p-2**), 6.58 (s, 1H, 3p-1), 5.57 (s, 1H, 3p-2), 5.17 (s, 1H, 3p-2), 3.59 (s, 2H, 3p-2), 3.47 (s, 3H, 3p-1), 3.40 (s, 3H, 3p-1), 3.37 (s, 3H, 3p-3), 3.28 (s, 3H, 3p-2), 2.21 (s, 3H, 3p-2). ^{13}C NMR (101 MHz, Chloroform-d) δ 163.6, 163.3, 151.7, 151.4, 144.3, 143.1, 140.5, 140.3, 139.5, 138.3, 128.6, 128.4, 128.0, 127.6, 126.1, 126.0, 118.2, 115.3, 111.6, 111.5, 37.4, 37.0, 32.2, 28.3, 28.2, 18.0. HRMS: Calculated for $C_{15}H_{17}N_2O_2^+$ $[M+H]^+$: 257.1285; Found: 257.1289.

(E)-butyl 3-(1,3-diethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acrylate (3q): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (s, 1H), 7.29 (d, *J* = 15.8 Hz, 1H), 6.99 (d, *J* = 15.8 Hz, 1H), 4.17 (t, *J* = 6.6 Hz, 2H), 3.48 (s, 3H), 3.39 (s, 3H), 1.69 – 1.62 (m, 2H), 1.48 – 1.35 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.8, 161.4, 150.8, 144.8, 136.3, 119.3, 109.0, 64.4, 37.6, 30.9, 28.2, 19.3, 13.9. HRMS: Calculated for $C_{15}H_{23}N_2O_4^+$ $[M+H]^+$:295.1652; Found: 295.1650.

(E)-butyl 3-(2,4-dioxo-1,3-dipropyl-1,2,3,4-tetrahydropyrimidin-5-yl)acrylate (3r): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 (s, 1H), 7.29 (d, *J* = 15.8 Hz, 1H), 7.00 (d, *J* = 15.8 Hz, 1H), 4.17 (t, *J* = 6.6 Hz, 2H), 3.97 – 3.91 (m, 2H), 3.80 – 3.75 (m, 2H), 1.81 – 1.71 (m, 2H), 1.70 – 1.61 (m, 4H), 1.47 – 1.36 (m, 2H), 1.00 – 0.92 (m, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.9, 161.2, 150.4, 144.4, 136.5, 119.2, 109.1, 64.4, 52.0, 43.3, 30.9, 22.5, 20.9, 19.3, 13.8, 11.4, 11.0. HRMS: Calculated for $C_{17}H_{27}N_2O_4^+$ $[M+H]^+$:323.1965; Found: 323.1962.

(E)-butyl 3-(1,3-dibenzyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acrylate (3s): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.46 (m, 2H), 7.41 – 7.34 (m, 4H), 7.34 – 7.25 (m, 5H), 7.21 (d, *J* = 15.8 Hz, 1H), 6.98 (d, *J* = 15.8 Hz, 1H), 5.17 (s, 2H), 4.96 (s, 2H), 4.13 (t, *J* = 6.6 Hz, 2H), 1.68 – 1.57 (m, 2H), 1.45 – 1.33 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.7, 160.9, 150.7, 143.9, 136.5, 136.3, 134.7, 129.4, 129.2, 128.9, 128.6, 128.3, 127.9, 119.5, 109.6, 64.4, 52.8, 45.0, 30.8, 19.2, 13.8. HRMS: Calculated for $C_{25}H_{27}N_2O_4^+$ $[M+H]^+$:419.1965; Found: 419.1965.

(E)-butyl 3-(1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acrylate (3t): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 15.6 Hz, 1H), 7.11 (d, *J* = 15.6 Hz, 1H), 4.18 (t, *J* = 6.6 Hz, 2H), 3.54 (s, 3H), 3.39 (s, 3H), 2.47 (s, 3H), 1.70 – 1.64 (m, 2H), 1.46 – 1.38 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.4, 161.0, 152.8, 151.3, 135.5, 121.5, 107.3, 64.4, 32.9, 30.9, 28.5, 19.3, 17.0, 13.9. HRMS: Calculated for $C_{14}H_{21}N_2O_4^+$ $[M+H]^+$:281.1496; Found: 281.1509.

(E)-butyl 3-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)acrylate (4a) [23]**:** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 15.3 Hz, 1H), 7.04 (d, *J* = 15.3 Hz, 1H), 4.25 (t, *J* = 6.6 Hz, 2H), 4.09 (s, 3H), 3.59 (s, 3H), 3.41 (s, 3H), 1.74 – 1.66 (m, 2H), 1.47 – 1.40 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.1, 155.4, 151.7, 148.5, 146.9, 126.5, 126.5, 109.4, 65.2, 32.0, 30.8, 29.9, 28.2, 19.3, 13.8.

(E)-tert-butyl 3-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)acrylate (4b) [23]**:** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 15.3 Hz, 1H), 6.97 (d, *J* = 15.3 Hz, 1H), 4.07 (s, 3H), 3.58 (s, 3H), 3.41 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.2, 155.4, 151.6, 148.5, 147.1, 128.6, 125.6, 109.2, 81.7, 31.9, 29.8, 28.2, 28.1.

(E)-ethyl 3-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)acrylate (4c): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 15.3 Hz, 1H), 7.03 (d, *J* = 15.3 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.09 (s, 3H), 3.59 (s, 3H), 3.41 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.0, 155.4, 151.7, 148.5, 146.9, 126.5, 126.5, 109.4, 61.3, 32.0, 29.9, 28.2, 14.4. HRMS: Calculated for $C_{13}H_{17}N_4O_4^+$ $[M+H]^+$:293.1244; Found: 293.1250.

(E)-2-methoxyethyl 3-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)acrylate (4d): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 15.3 Hz, 1H), 7.06 (d, *J* = 15.3 Hz, 1H), 4.40 – 4.35 (m, 2H), 4.06 (s, 3H), 3.68 – 3.63 (m, 2H), 3.55 (s, 3H), 3.42 – 3.38 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.9, 155.3, 151.6, 148.4, 146.7, 126.9, 126.0, 109.3, 70.4, 64.2, 59.1, 31.9, 29.8, 28.1. HRMS: Calculated for $C_{14}H_{19}N_4O_5^+$ $[M+H]^+$:323.1350; Found: 323.1333.

(E)-1,3,7-trimethyl-8-styryl-1*H*-purine-2,6(3*H*,7*H*)-dione (4e) [23]**:** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 15.8 Hz, 1H),

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7.58 (d, *J* = 7.0 Hz, 2H), 7.45 – 7.34 (m, 3H), 6.92 (d, *J* = 15.8 Hz, 1H), 4.07 (s, 3H), 3.63 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.4, 151.8, 150.1, 148.7, 138.5, 135.6, 129.7, 129.1, 127.5, 111.3, 108.1, 31.7, 29.9, 28.1.

(E)-1,3,7-trimethyl-8-(3-methylstyryl)-1*H*-purine-2,6(3*H*,7*H*)-dione (4f): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 15.8 Hz, 1H), 7.40 (s, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 15.8 Hz, 1H), 4.07 (s, 3H), 3.63 (s, 3H), 3.42 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.5, 151.8, 149.2, 148.3, 139.7, 138.3, 135.3, 130.0, 128.6, 128.1, 125.9, 114.4, 107.5, 32.6, 29.9, 28.1, 21.5. HRMS: Calculated for $C_{17}H_{19}N_4O_2^+$ $[M+H]^+$:311.1503; Found: 311.1498.

(E)-8-(2,4-dimethylstyryl)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (4g): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 15.6 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.04 (s,1H), 6.79 (d, *J* = 15.6 Hz, 1H), 4.04 (s, 3H), 3.63 (s, 3H), 3.41 (s, 3H), 2.46 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.4, 151.9, 150.5, 148.7, 139.7, 137.2, 136.2, 131.8, 131.8, 127.3, 125.7, 111.5, 107.9, 31.6, 29.9, 28.1, 21.4, 20.0. HRMS: Calculated for $C_{18}H_{21}N_4O_2^+$ $[M+H]^+$:325.1659; Found: 325.1659.

(E)-1,3,7-trimethyl-8-(2,4,6-trimethylstyryl)-1*H*-purine-2,6(3*H*,7*H*)-dione (4h): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 16.0 Hz, 1H), 6.93 (s, 2H), 6.53 (d, *J* = 16.0 Hz, 1H), 3.99 (s, 3H), 3.64 (s, 3H), 3.42 (s, 3H), 2.40 (s, 6H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.5, 151.7, 149.4, 148.5, 138.3, 137.5, 135.5, 132.7, 128.5, 117.2, 107.5, 32.3, 29.6, 28.0, 21.1, 20.4. HRMS: Calculated for $C_{19}H_{23}N_4O_2^+$ $[M+H]^+$:339.1816; Found: 339.1816.

(E)-8-(4-(tert-butyl)styryl)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (4i): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 15.7 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 15.7 Hz, 1H), 4.05 (s, 3H), 3.63 (s, 3H), 3.41 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.3, 153.2, 151.8, 150.3, 148.7, 138.4, 132.9, 127.3, 126.0, 110.5, 107.9, 35.0, 31.6, 31.3, 29.9, 28.0. HRMS: Calculated for $C_{20}H_{25}N_4O_2^+$ $[M+H]^+$:353.1972; Found: 353.1971.

(E)-8-(4-fluorostyryl)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (4j) [23]**:** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 15.7 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.14 – 7.06 (m, 2H), 6.83 (d, *J* = 15.7 Hz, 1H), 4.06 (s, 3H), 3.62 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.5 (d, $^{1}J_{C-F}$ = 250.6 Hz), 155.4, 151.8, 149.9, 148.7, 137.2, 131.9, 129.2 (d, $^{3}J_{C-F}$ = 8.3 Hz), 116.2 (d, $^{2}J_{C-F}$ = 21.9 Hz), 111.1, 108.1, 31.6, 29. 9, 28.1.

(E)-butyl 3-(7-ethyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)acrylate (4k): 1H NMR (400 MHz, Chloroform-d) δ 7.50 (d, J = 15.3 Hz, 1H), 7.06 (d, J = 15.3 Hz, 1H), 4.52 (q, J = 7.1 Hz, 2H), 4.25 (t, J = 6.6 Hz, 2H), 3.59 (s, 3H), 3.42 (s, 3H), 1.70 (p, J = 6.9 Hz, 2H), 1.53 – 1.41 (m, 5H), 0.97 (t, J = 7.4 Hz, 3H). 13C NMR (101 MHz, Chloroform-d) δ 166.2, 155.0, 151.7, 148.7, 146.0, 126.6, 126.5, 108.6, 65.2, 40.6, 30.7, 29.8, 28.2, 19.2, 17.1, 13.8. HRMS: Calculated for C16H23N4O4+ [M+H]+:335.1714; Found: 335.1706.

(E)-butyl 3-(1,3-dimethyl-2,6-dioxo-7-propyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)acrylate (4l): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 15.3 Hz, 1H), 6.98 (d, *J* = 15.3 Hz, 1H), 4.34 (t, *J* = 7.4 Hz, 2H), 4.17 (t, *J* = 6.6 Hz, 2H), 3.52 (s, 3H), 3.34 (s, 3H), 1.86 – 1.71 (m, 2H), 1.69 – 1.57 (m, 2H), 1.42 – 1.30 (m, 2H), 0.93 – 0.84 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.2, 155.0, 151.7, 148.6, 146.5, 126.7, 126.4, 108.9, 65.2, 46.8, 30.7, 29.8, 28.2, 25.0, 19.2, 13.8, 10.9. HRMS: Calculated for $C_{17}H_{25}N_4O_4^+$ $[M+H]^+$:349.1870; Found: 349.1863.

(E)-butyl 3-(7-benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)acrylate (4m): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 15.3 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.26 – 7.19 (m, 2H), 7.04 (d, *J* = 15.3 Hz, 1H), 5.69 (s, 2H), 4.22 (t, *J* = 6.6 Hz, 2H), 3.60 (s, 3H), 3.41 (s, 3H), 1.72 – 1.64 (m, 2H), 1.49 – 1.35 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.0, 155.2, 151.6, 148.7, 146.9, 135.7, 129.3, 128.6, 127.2, 126.9, 126.8, 108.8, 65.2, 48.4, 30.8, 29.9, 28.3, 19.3, 13.8. HRMS: Calculated for $C_{21}H_{25}N_4O_4^+$ $[M+H]^+$:397.1870; Found: 397.1870.

(E)-butyl 3-(1-ethyl-3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)acrylate (4n): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 15.3 Hz, 1H), 7.03 (d, *J* = 15.3 Hz, 1H), 4.25 (t, *J* = 6.6 Hz, 2H), 4.13 – 4.03 (m, 5H), 3.58 (s, 3H), 1.73 – 1.66 (m, 2H), 1.49 – 1.39 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.2, 155.2, 151.3, 148.5, 146.8, 126.5, 126.4, 109.5, 65.2, 36.7, 32.0, 30.8, 29.8, 19.3, 13.8, 13.4. HRMS: Calculated for $C_{16}H_{23}N_4O_4^+$ $[M+H]^+$:335.1714; Found: 335.1708.

(E)-butyl 3-(3,7-dimethyl-2,6-dioxo-1-propyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)acrylate (4o): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 15.3 Hz, 1H), 7.03 (d, *J* = 15.3 Hz, 1H), 4.25 (t, *J* = 6.7 Hz, 2H), 4.09 (s, 3H), 4.02 – 3.91 (m, 2H), 3.58 (s, 3H), 1.75 – 1.61 (m, 4H), 1.44 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.1, 155.3, 151.4, 148.5, 146.8, 126.5, 126.4, 109.4, 65.2, 43.1, 31.9, 30.7, 29.7, 21.4, 19.2, 13.8, 11.4. HRMS: Calculated for $C_{17}H_{25}N_4O_4^+$ $[M+H]^+$:349.1870; Found: 349.1872.

(E)-butyl 3-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)acrylate (4p): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 7.50 (d, *J* = 15.3 Hz, 1H), 7.05 (d, *J* = 15.3 Hz, 1H), 4.25 (t, *J* = 6.7 Hz, 2H), 4.07 (s, 3H), 3.55 (s, 3H), 1.74 – 1.67 (m, 2H), 1.44 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). HRMS: Calculated for $C_{14}H_{19}N_4O_4^+$ $[M+H]^+$:307.1401; Found: 307.1400.

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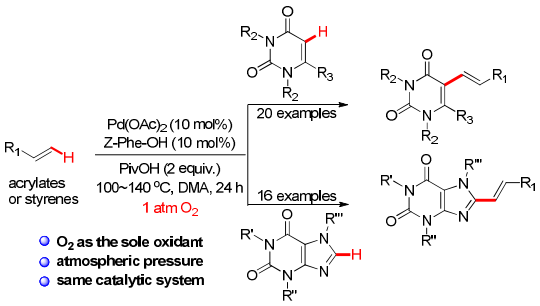

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