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Synthesis of 2-arylpyridopyrimidinones, 6-aryluracils and tri- and tetra-substituted conjugated alkenes via Pd-catalyzed enolic C–O bond activation-arylation

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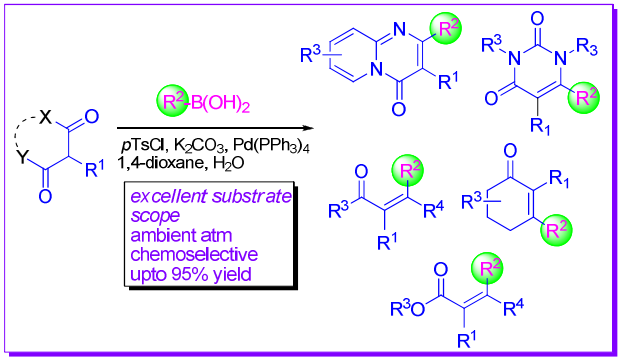


Abstract:

A new and efficient approach for synthesis of biologically important 2-aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and 6-aryluracils via previously unknown Pd-catalyzed enolic C–OH activation-arylation of pyridopyrimidin-2,4-diones and barbituric acids, respectively with boronic acids is reported. The starting materials are readily available and products are obtained in high yields. An efficient and chemo- and stereo-selective access to various tri- and tetra-substituted conjugated alkenones and alkenoates is also obtained in this arylation approach. Interestingly, the procedure for construction of such diverse molecular frameworks is general and featured with excellent substrates scope, tolerance of a broad range of functionalities, unusual viability of performing reaction under open air and in aqueous co-

solvent and the amenability to a scale up synthesis, which have been found to be common limitations in the conventional/classical routes. The application of the protocol in a simple one-step high-yielding route to pharmaceutically important poly-arylated pyridopyrimidinone demonstrates its further synthetic utility.

Introduction

The importance of nitrogen heterocycles in drug discovery processes has long been known. Major prescription drugs comprise of these scaffolds. Pyrimidinone motif is one of the important N-heterocycles that occupy privileged positions in drug discovery. In particular, its pyridine-annulated analogs, pyrido[1,2-*a*]pyrimidin-4-ones have been found to possess various biological activities.[1] Risperidone[2] and Paliperidone[3] are used as atypical oral antipsychotic drugs.[4] The recent studies have explored a particular derivative-set of this structural motif 2-aryl substituted pyrido[1,2-*a*]pyrimidin-4-one as medicinally valuable. They have been attributed a diverse range of bioactivities, such as selective aldose reductase inhibition,[5] hepatitis C virus NS3 protease inhibition,[6] improving the transcriptional functions of estrogen-related receptors,[7] Quorum sensing inhibition,[8] and MexAB-OprM specific efflux pump inhibition.[9] 2-Arylpyridopyrimidinones are prepared by a classical reaction of 2-aminopyridine with 3-aryl-3-oxopropanoate, but the method is non-flexible in incorporating versatile aryl moieties and poor to moderate yielding in major cases.[5] Another approach involves the preparation of 2-chloropyridopyrimidinone by deoxychlorination of pyridopyrimidin-2,4-dione using excess $POCl_3$ or $SOCl_2$[10] and subsequently the Suzuki coupling with arylboronic acid. However, such deoxychlorination process is notorious and hazardous, generating enormous waste materials, while, on the other hand, as part of the current momentum of minimizing global environment-concern the research with development of green synthesis has been realized as an essential practice by chemists in both industry and academia.[11,12] Moreover, the reaction in $POCl_3$/$SOCl_2$ solvent is detrimental for tolerating numerous functionalities and, thus, limits the potential in generating the substitutions-diversity in the products-library.

One more well-known important motif of pyrimidinones family is uracil. Its derivatives are present in uridine nucleosides and naturally occurring thymidine, are used as probes in

indentifying the interactions between nucleosides/nucleotides and proteins,[13] and have showed a wide range of biological activities.[14,15] In recent years, C6-arylated uracil derivatives have received significant attention because of their various biological applications.

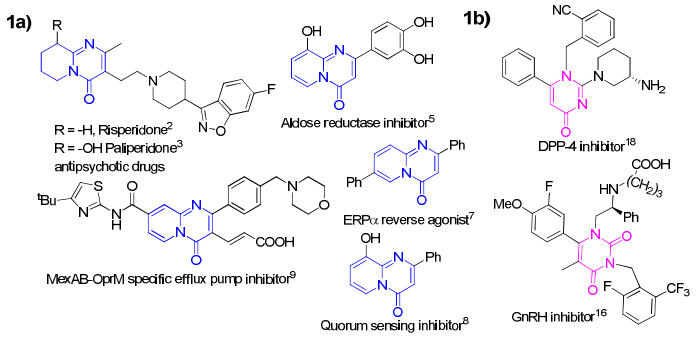


Figure 1: A representative bioactive **a)** pyridopyrimidinones and **b)** 6-aryluracils

6-Aryluracils have been reported as versatile pharmacologically active agents, e.g., GnRH antagonist,[16] anti-inflamatory agents,[17] dipeptidyl peptidase IV (DPP-4) inhibitors[18] antiviral agents and sirtuin inhibitors.[19-22] However, the synthetic methods of 6-aryluracils are limited. They include arylation of 6-iodouracils by photochemical reaction,[23] and Stille[24] or Suzuki-Miyaura[25] coupling. The limitations in preparation of 6-iodouracils that are usually obtained by lithiation of uracils using LDA and iodination,[26] such as inflexibility, low-yielding and requirement of stringent anhydrous conditions,[27] make these photochemical/coupling methods non-practical. Therefore, towards development of an alternative approach devoid of using 6-iodouracil as precursor, recent efforts have been made for direct C6-H arylation of 1,3-dimethyluracil.[28-30] Nevertheless, the methodologies suffer from low reaction conversions and yields of products, feasibility of reactions limited to electron-rich arylating substrates only, and the use of strong base. Ricart *et al* has documented an interesting approach towards direct construction of C6-aryluracils, which involves formal [3+3] cycloaddition of metal carbene complexes with substituted ureas followed by oxidation.[31]

In transition-metal-catalyzed cross-couplings, the recent attractive trend is, among others, the discovery of new variants[32,33] of reaction towards convenient preparation of versatile molecular frameworks,[34] not limiting to biaryl only. Significant attention on the catalyzed arylation via C–O bond cleavage has been focussed for synthesis of biaryls,[35,36] but its conceptual variation in the direction of arylation via enolic C–O bond activation leading to preparation of biologically important N-heterocyclic motifs has not been yet documented.[37,38] Herein, we report a new approach for synthesis of 2-aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and 6-aryluracils from pyridopyrimidin-2,4-diones and barbituric acids, respectively, via Pd-catalyzed enolic C–O bond activation-arylation (Figure 2). Notably, pyridopyrimidin-2,4-diones are easily accessible and barbituric acid is much economical compared to uracil[39] used as synthetic precursor in previous methods. Moreover, this approach represents a one-step strategy of converting an N-heterocyclic scaffold to other. An efficient and chemo- and stereo-selective route to various tri- and tetra-substituted conjugated alkenone and alkenoate has also been accomplished.

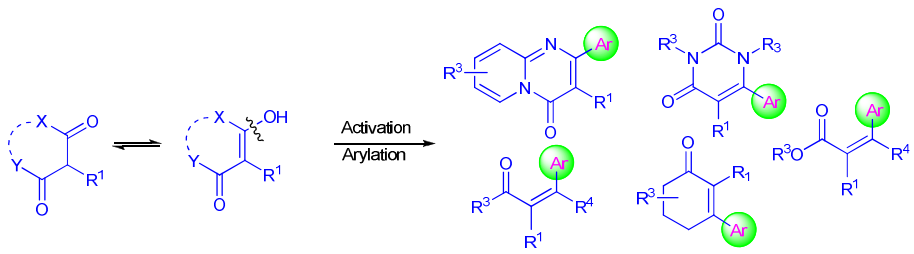
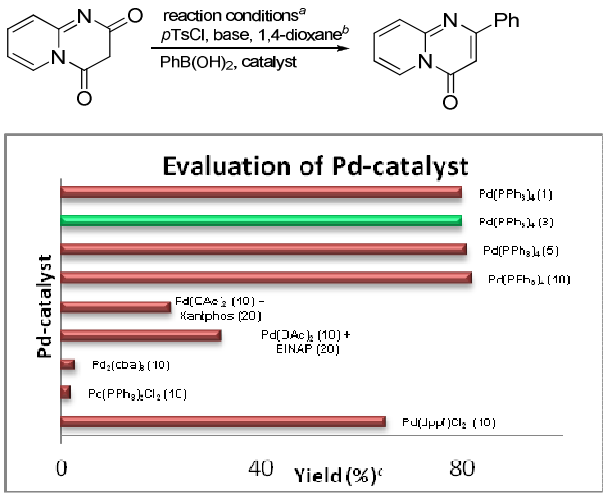


Figure 2: Access to 2-arylpyridopyrimidinones, 6-aryluracils and tri- and tetra-substituted conjugated alkenes

Results and Discussion

At the outset of our studies for a model enolic activation-arylation reaction of pyridopyrimidin-2,4-dione with phenylboronic acid, we screened a number of Pd-catalytic conditions involving different solvents at varying temperatures with a few selected inexpensive activating agents, *p*-TsCl, $(EtO)_2P(O)Cl$, and *tert*-butoxycarbonyl anhydride.

$Pd(PPh_3)_2Cl_2$ catalyst and *p*-TsCl in 1,4-dioxane provided the desired product, although in poor yield (maximally 11%), while other activating agents were found to be ineffective. Pd-sources were then examined (Figure 3). Varied yields of the product were obtained with different Pd-catalysts. $Pd(PPh_3)_4$ as catalyst was proved to be best and its 3 mol% quantity was found to be optimal. The desired product did not form when the reaction was done in the absence of Pd-catalyst.



[a]Substrates, reagents and condtions: Pyridopyrimidine-2,4-dione (1 mmol), *p*TsCl (1.3 eq), K_2CO_3 (5 eq), 1,4-dioxane (2 mL), H_2O (0.8 mL), then $ArB(OH)_2$ (2 eq), catalyst, 100 °C; [b]solvent used as received commercially without further distillation; [c]yield for maximum conversion in optimum time.

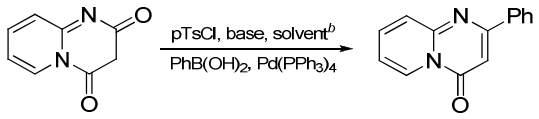
Figure 3 Evaluation of Pd-catalysts

Among the bases tested, K_2CO_3 was most effective (Table 1). 1,4-Dioxane was found to be superior than other evaluated solvents ranging from weakly polar to polar aprotic. Remarkably, the reaction did not require any inert atmosphere and proceeded smoothly in the presence of water as co-solvent (optimal quantity) which was proved to be essential plausibly for dissolving K_2CO_3 (entries 11-14).

To check the generality of the method, we investigated the reactions of various substituted pyridopyrimidinones with different arene boronic acids (Table 2). Pleasingly, the method was found to be flexible in accommodating the varied substrates. The successful synthesis of 2-arylpyridopyrimidin-4-one prompted us to consider other enolizable motif-containing

heterocyclic scaffold, barbituric acid, towards synthesis of biologically important 6-arylated uracils. Delightfully, barbituric acid underwent arylation smoothly with various arene boronic acids and afforded 6-aryluracils in high yields. Compared to the conventional/classical methods known for synthesis of 2-arylpyridopyrimidin-4-one and 6-aryluracils, the present enolic activation-arylation approach is step-economical, convenient and high-yielding, uses easily accessible or economical starting materials, and avoids hazardous reagents and stringent anhydrous conditions.

Table 1 Evaluation of base, additive and solvent[a]

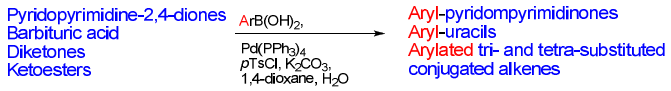


#	$PhB(OH)_2$ (eq)	Base (eq)	Solvent[b]	water (mL)	Yield (%)[c]
1	2	K_3PO_4 (5)	1,4-dioxane	0.8	55
2	2	Et_3N (5)	1,4-dioxane	0.8	NR[d]
3	2	Na_2CO_3 (5)	1,4-dioxane	0.8	43
4	2	Cs_2CO_3 (5)	1,4-dioxane	0.8	35
5	2	K_2CO_3 (2.5)	1,4-dioxane	0.8	81
6	2	K_2CO_3 (1.5)	1,4-dioxane	0.8	65
7	2	K_2CO_3 (2.5)	Toluene	0.8	NR[d]
8	2	K_2CO_3 (2.5)	DMF	0.8	22
9	2	K_2CO_3 (2.5)	MeCN	0.8	15
10[e]	2	K_2CO_3 (2.5)	THF	0.8	35
11	2	K_2CO_3 (2.5)	1,4-dioxane	0	25
12	2	K_2CO_3 (2.5)	1,4-dioxane	0.4	55
13	2	K_2CO_3 (2.5)	1,4-dioxane	1	88
14	2	K_2CO_3 (2.5)	1,4-dioxane	1.2	80
15	1.5	K_2CO_3 (2.5)	1,4-dioxane	1	89
16	1.2	K_2CO_3 (2.5)	1,4-dioxane	1	90

[a]Substrates, reagents and condtions: Pyridopyrimidine-2,4-dione (1 mmol), *p*TsCl (1.3 eq), base, solvent (2 mL), H_2O, then $ArB(OH)_2$,$Pd(PPh_3)_4$ (3 mol %), 100 °C;[b]solvent used as received commercially without further distillation;
[c]yield for maximum conversion in optimum time;
[d]No reaction; [e]80 °C;

We were pleased to find that our developed approach provided also a useful access to acyclic/cyclic and alkyl/aryl tri- and tetra-substituted conjugated alkenes (carbonyl/ester) (Table 2, **9a-d**; **10a**,**b**; **11a**,**b**).[40,41] Importantly, excellent stereoselectivity (90 to 100 : 5 to 0) for acyclic alkenes was obtained.

Table 2 Enolic–OH arylation of versatile motifs[a]



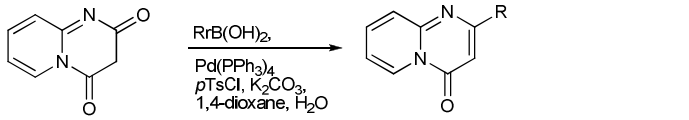
Substrates	Products
1a, R=H **1b**, R=Me **1c**, R=Ph **1d**, R=*p*-ClC$_6$H$_4$	(**7a**, 92%); (**7b**, 88%); (**7c**, 84%); (**7d**, 78%); (**7e**, 71%)
2[c]	(**8a**, 88%); (**8b**, 78%); (**8c**,76%); (**8d**, 67%)
3a, R=H **3b**, R=Ph	(**9a**, 92%); (**9b**, 85%); (**9c**, 55%)[d]; (**9d**, 62%)[d]
4a, R^1,R^2=Me **4b**, R^1,R^2=Ph	(**10a**, 75%)[e] (*E*:*Z* = 100:0)[f]; (**10b**, 73%)[e] (*E*:*Z* = 1:19)[f]
5a, R=Me **5b**, R=Ph	(**11a**, 84%)[e] (*E*:*Z* = 9:1)[f]; (**11b**, 75%)[e]

[a]Substrate (1 mmol), *p*TsCl (1.3 eq), K_2CO_3 (2.5 eq), 1,4-dioxane (2 mL), H_2O (1 mL), then $RB(OH)_2$ (1.2-1.5 eq), $Pd(PPh_3)_4$ (3 mol %), 100 °C,1-1.5 h (24 h for **9c** and **9d**); [b]yield; [c]KOH (1.5 eq) replacing K_2CO_3 was added; [d]$Pd(PPh_3)_4$ (10 mol %); [e]DABCO (1.5 eq) replacing K_2CO_3 was added; [f]Determined by ^{1}H NMR.

The stereoselectivity (*E*/*Z*) of tosyl-intermediates in a representative example (**11a**) was found to retain in the final arylated products. This as well as the requirement of a Pd-catalyst indicates that the addition-elimination pathway is not involved in the reaction. These tri- and tetra-substituted conjugated alken-ones/oates have been, in general, prepared by classical approach of addition of Grignard reagent to 1,3-dicarbonyl followed by dehydration,[42] and later by Heck coupling,[43] diarylation of α-oxo- ketene dithioacetal,[44] or Meyer-Schuster rearrangement of propargylic alcohol.[45] In comparison, the present approach represents a simple and high yielding methodology, enables the incorporation of versatile aryl units in products, and is functional compatible.

Next, we investigated the flexibility of the method for versatile boronic acids (Table 3). We found that a variety of aryl, heteroaryl and arylalkenyl boronic acids containing both electron-donating and electron-withdrawing functionalities were feasible substrates in the arylation of pyridopyrimidin-2,4-dione. The reaction conversions were complete and the products were obtained in high to excellent yields. The tolerance of several functional groups on both aryl boronic acids and pyridopyrimidin-2,4-diones, including aldehyde, acetyl, and phenolic and alcoholic hydroxyl groups in the reaction is remarkable (Tables 2 and 3). In the

Table 3 Arylation with various boronic acids[a]



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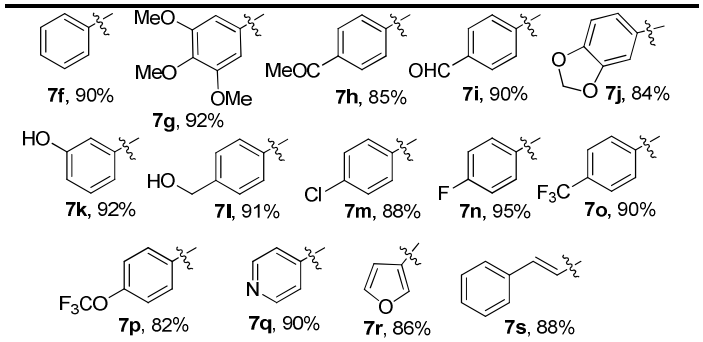
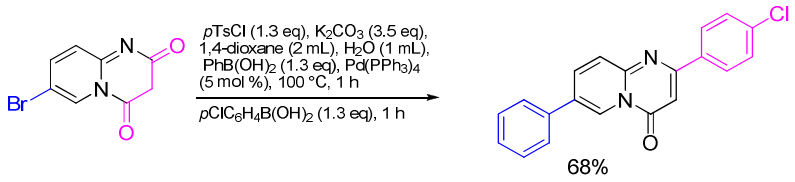


[a]Substrates, reagents and condtions: Pyridopyrimidine-2,4-dione (1 mmol), *p*TsCl (1.3 eq), K_2CO_3 (2.5 eq), 1,4-dioxane (2 mL), H_2O (1 mL), then $RB(OH)_2$ (1.2-1.5 eq), $Pd(PPh_3)_4$ (3 mol %), 100 °C, 1-1.5 h; [b]yield

previously known methods, the preparation of 2-arylpyridopyrimidinones with numerous substitutions/funtionalities on fused pyridine ring[46] (e.g., methyl, benzyloxy) or 2-aryl moieties[45] have been found to be poor-yielding. In contrast, our developed approach has comfortably accommodated these variations in the scaffold, affording high yields. The protocol has showed excellent substrates scope, tolerance of a broad range of functionalities and high-yielding access of products. The reaction conditions proved also amenable to a scale-up synthesis (investigated upto 20 mmol).

Poly-arylated pyridopyrimidinones are known to enhance the transcriptional functions of nuclear estrogen-related receptor α (ERRα).[7] These compounds have been prepared before via multi-reaction steps,[7] whereas, interestingly, can now be readily accessible in high yields using the present approach via one-pot chemoselective poly-arylation. The reaction of 7-bromo-pyridopyrimidin-2,4-dione with two similarly reactive arylboronic acids proceeded chemoselective arylations and provided 2,7-diaryl substituted pyrido[1,2-*a*]pyrimidin-4-one in high yield (Scheme 1). This demonstrates the further synthetic utility of our developed method. The arylation takes place chemoselectively first at C7-Br and subsequently at C2-OH. The only intermediate formed was isolated from the resultant mixture obtained by stopping the reaction at intermediate time (after 40 min). It was found to be 7-Phenyl-2-(4-methylbenzenesulphonyloxy)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**7c1**).



Scheme 1 One-pot synthesis of multi-arylated heterocycle

In conclusion, a new and efficient method for the synthesis of biologically important 2-aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and 6-aryluracils from pyridopyrimidin-2,4-diones and barbituric acids, respectively, via Pd-catalyzed enolic C–OH activation-arylation with

boronic acids has been established. This method opens up a practical strategy of generating a valuable N-heterocyclic unit in high yield from readily available scaffold of completely different class of N-heterocycle that contains enolizable moiety. In this approach, versatile cyclic/acyclic aryl/alkyl tri- and tetra-substituted conjugated carbonyls/esters are accessible in high yields with chemo- and stereo-selectivities. The method has also been successfully applied to a simple high-yielding synthesis of pharmaceutically important poly-arylated pyridopyrimidinone. This protocol is quite resourceful in broad applications to the synthesis of biologically/synthetically important motifs.

Experimental Section:

General information: Infrared (IR) spectra were recorded on a FTIR with ATR & IR Microscope spectrometer. ^{1}H NMR spectra were measured on a 400 MHz spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$/CD_3OD/DMSO-d_6 integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, td = triplet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, br = broad), and coupling constants (Hz). ^{13}C NMR spectra were measured on a 100 MHz spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High-resolution mass spectra (HRMS) were performed on a high resolution LCMS/MS instrument with "Q-TOF" mass analyser. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. The products were purified by column chromatography silica gel 60-120 (Merck, silica gel 60-120 mesh, neutral, spherical) or neutral alumina column chromatography.

The starting materials and solvents were used as received from commercial suppliers without further purification.

Typical experimental procedure for direct C-OH bond arylation of enolizable/tautomerizable motifs: *p*-TsCl (1.3 eq, 124 mg, 0.65 mmol) was added to a mixture of the substrate (0.5 mmol), and K_2CO_3 (2.5 eq, 173 mg, 1.25 mmol) in 1,4-dioxane (2 mL) and H_2O (1 mL) taken in a round-bottomed flask. The mixture was stirred under open air for 1h at rt (25-28 °C). The boronic acid (1.2 eq, 0.6 mmol) and $Pd(PPh_3)_4$ (3 mol %, 17 mg, 0.015 mmol) were subsequently added and the mixture was heated at 100 °C under open air. For compounds (**8a-8d**) KOH (1.5 eq, 42 mg, 0.65 mmol) and for compounds (**10a-11b**) DABCO (1.5 eq, 84 mg, 0.65 mmol) in place of K_2CO_3 (2.5 eq) was added after substrate and K_2CO_3 (1 eq, 69 mg, 0.5 mmol) was added after Pd-catalyst. Upon completion of reaction as indicated by TLC (1-1.5 h), the resultant mixture was cooled to rt and extracted with EtOAc (2x25 mL). The combined organic solution was washed with water (2x5 mL) and brine (1x5 mL), dried with anhyd. Na_2SO_4, and concentrated under reduced pressure. The column chromatographic purification of crude mass was performed on neutral alumina (for compounds **7a-7s**, **8a-8d)** using EtOAc-hexane (30-40%) as eluting solvent and on silica gel (for compounds **9a-11b**) eluting with EtOAc-hexane (2-10%) to afford the arylated products.

Characterization data for arylated products (7a-11b)

2-(4-Methoxyphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[5] (7a): Light yellow solid, 116 mg, 92% yield, m.p. 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (d, J = 7.1 Hz, 1H), 8.09 (d, J = 8.7 Hz, 2H), 7.76-7.70 (m, 2H), 7.11 (dd, J = 6.8 Hz, J = 5.8 Hz, 1H), 7.02 (d, J = 8.7 Hz, 2H), 6.87 (s, 1H), 3.89 (s, 3H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 161.8, 161.5, 158.6, 150.9, 136.0, 129.5, 128.9, 127.2, 126.6, 114.9, 114.1, 98.7, 55.4 ppm; IR: ν_{max} 3037, 1667, 1637, 1253, 1027 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{15}H_{13}N_2O_2$ $[M+H]^+$ 253.0977, found: 253.0979.

2-(4-Chlorophenyl)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7b): Light yellow solid, 119 mg, 88%, m.p. 210-212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.64-7.58 (m, 2H), 7.43 (d, J = 8.5 Hz, 2H), 6.83 (s, 1H), 2.43 (s, 3H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 160.2, 158.4, 149.9, 139.3, 136.7, 135.7, 128.9, 128.6, 126.1, 125.7, 124.7, 99.5, 18.4 ppm; IR: ν_{max} 2924, 1686, 1645, 823 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{15}H_{12}ClN_2O$ [M(^{35}Cl)+H]$^+$ 271.0638, found: 271.0639.

2-(4-Chlorophenyl)-7-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7c): Greenish-yellow solid, 139 mg, 84%, m.p. 195-197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26 (d, J = 1.9 Hz, 1H), 8.06-8.02 (m, 3H), 7.77 (d, J = 9.2 Hz, 1H), 7.68-7.64 (m, 2H), 7.53-7.49 (m, 2H), 7.48-7.44 (m, 3H), 6.88 (s, 1H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 160.4, 158.6, 150.1, 136.9, 136.3, 135.6, 135.4, 129.40, 129.36, 129.0, 128.9, 128.7, 126.88, 126.79, 124.2, 99.8 ppm; IR: ν_{max} 3071, 2922, 1682, 1633, 822 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{20}H_{13}ClN_2ONa$ [M(^{35}Cl)+Na]$^+$ 355.0614, found: 355.0609.

2,7-bis(4-Chlorophenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7d): Greenish-yellow solid, 143 mg, 78%, m.p. 208-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (d, J = 1.9 Hz, 1H), 8.02 (d, J = 8.6 Hz, 2H), 7.97 (dd, J = 9.3 Hz, J = 2.2 Hz, 1H), 7.77 (dd, J = 9.2 Hz, J = 0.4 Hz, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.50-7.43 (m, 4H), 6.88 (s, 1H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 160.5, 158.4, 149.9, 137.0, 135.9, 135.5, 135.2, 133.8, 129.6, 129.0, 128.7, 128.13, 128.09, 127.0, 124.2, 99.9 ppm; IR: ν_{max} 3089, 1690, 1634, 813 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{20}H_{13}Cl_2N_2O$ [M(^{35}Cl^{35}Cl)+H]$^+$ 367.0405, found: 367.0399.

9-(Benzyloxy)-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7e): White solid, 116 mg, 71%, m.p. 180-184 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (dd, J = 7.1 Hz, J = 1.3 Hz, 1H), 8.18-8.14 (m, 2H), 7.54-7.34 (m, 8H), 7.05 (dd, J = 7.6 Hz, J = 1.2 Hz, 1H), 6.98-6.95 (m, 2H), 5.38 (s, 2H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 160.7, 158.9, 151.5, 145.8, 137.3, 135.7, 130.6, 128.80, 128.78, 128.3, 127.5, 127.1, 119.6, 114.3, 114.1, 100.6, 71.7 ppm; IR:

ν_{max} 1687, 1376, 1275, 1171 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{21}H_{17}N_2O_2$ $[M+H]^+$ 329.1280, found: 329.1282.

6-(4-methoxyphenyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione[28] (8a): Light yellow solid, 108 mg, 88%, m.p. 107-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 5.68 (s, 1H), 3.87 (s, 3H), 3.40 (s, 3H), 3.25 (s, 3H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 162.5, 160.9, 154.6, 152.8, 129.3, 125.6, 114.3, 102.4, 55.4, 34.6, 28.0 ppm; IR: ν_{max} 2956, 1697, 1645, 1249, 1177 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{13}H_{14}N_2O_3Na$ $[M+Na]^+$ 269.0902, found: 269.0906.

1,3-Dimethyl-6-phenylpyrimidine-2,4(1*H*,3*H*)-dione[28] (8b): White solid, 84 mg, 78%, m.p. 142-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.46 (m, 3H), 7.34-7.32 (m, 2H), 5.70 (s, 1H), 3.41 (s, 3H), 3.22 (s, 3H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 162.5, 154.6, 152.7, 133.4, 130.2, 129.0, 127.8, 102.5, 34.6, 28.0 ppm; IR: ν_{max} 3057, 1689, 1637 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{12}H_{12}N_2O_2Na$ $[M+Na]^+$ 239.0797, found: 239.0791.

6-(4-Chlorophenyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione[30] (8c): White solid, 96 mg, 76%, m.p. 122-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.68 (s, 1H), 3.40 (s, 3H), 3.22 (s, 3H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 162.2, 153.4, 152.6, 136.6, 131.7, 129.4, 129.2, 102.7, 34.6, 28.1 ppm; IR: ν_{max} 3084, 1697, 1651, 838 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{12}H_{11}ClN_2O_2Na$ $[M+Na]^+$ 273.0407, found: 273.0400.

6-(4-Acetylphenyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (8d): Off-white solid, 86 mg, 67%, m.p. 126-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 5.69 (s, 1H), 3.39 (s, 3H), 3.20 (s, 3H), 2.64 (s, 3H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 192.2, 157.4, 148.7, 147.7, 133.5, 132.8, 124.1, 123.4, 97.9, 29.8, 23.3, 21.9 ppm; IR: ν_{max} 3060, 2959, 1697, 1682, 1650 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{15}N_2O_3$ $[M+H]^+$ 259.1082, found: 259.1079.

3-(4-Methoxyphenyl)-5,5-dimethylcyclohex-2-enone[48] (9a): Yellow oil, 106 mg, 92%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 6.39 (t, J = 1.3 Hz, 1H), 3.85 (s, 3H), 2.62 (d, J = 1.2 Hz, 2H), 2.32 (s, 2H), 1.13 (s, 6H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 200.1, 161.2, 156.9, 135.0, 131.1, 128.1, 126.8, 122.6, 114.1, 55.4, 50.9, 42.1, 33.7, 28.5 ppm; IR: ν_{max} 2956, 1653, 1596, 1239, 1179 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{15}H_{19}O_2$ $[M+H]^+$ 231.1385, found: 231.1389.

3-(4-Formylphenyl)-5,5-dimethylcyclohex-2-enone (9b): Light yellow solid, 97 mg, 85%, m.p. 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 6.68 (d, J = 8.3 Hz, 2H), 6.46 (s, 1H), 2.67 (d, J = 1.2 Hz, 2H), 2.37 (s, 2H), 1.15 (s, 6H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 199.7, 191.5, 155.9, 144.9, 136.9, 130.0, 126.8, 126.2, 50.9, 42.3, 33.8, 28.4 ppm; IR: ν_{max} 3103, 1689, 1637 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{15}H_{17}O_2$ $[M+H]^+$ 229.1228, found: 229.1221.

3-(4-Methoxyphenyl)-5,5-(dimethyl)-2-phenylcyclohex-2-enone (9c): White solid, 84 mg, 55%, m.p. 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.12 (m, 3H), 6.96-6.93 (m, 4H), 6.66 (d, J = 8.9 Hz, 2H), 3.72 (s, 3H), 2.71 (s, 2H), 2.51 (s, 2H), 1.19 (s, 6H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 198.5, 159.1, 155.0, 136.1, 135.8, 133.1, 131.0, 130.0, 129.8, 127.7, 126.6, 113.3, 55.2, 51.7, 47.0, 33.0, 28.2 ppm; IR: ν_{max} 3010, 2958, 1655, 1605, 1252, 1175 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{21}H_{23}O_2$ $[M+H]^+$ 307.1698, found: 307.1698.

2,3-(Diphenyl)-5,5-(dimethylcyclohex-2-enone (9d): White solid, 86 mg, 62%, m.p. 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.11 (m, 6H), 7.01-6.99 (m, 2H), 6.93-6.91 (m, 2H), 2.72 (s, 2H), 2.53 (s, 2H), 1.20 (s, 6H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 198.5, 155.5, 141.0, 136.7, 135.4, 130.9, 128.0, 127.9, 127.7, 127.6, 126.8, 51.7, 47.1, 33.2, 28.22 ppm; IR: ν_{max} 3031, 2949, 1658 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{20}H_{21}O$ $[M+H]^+$ 277.1592, found: 277.1592.

(*E*)-4-(4-Methoxyphenyl)pent-3-en-2-one[49] (10a): White solid, 71 mg, 75%, m.p. 69-71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 6.49 (d, J = 0.6 Hz, 1H), 3.83 (s, 3H), 2.52 (d, J = 1.1 Hz, 1H), 2.27 (s, 3H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 198.8, 160.6, 153.3, 134.5, 127.9, 122.9, 113.9, 55.3, 32.2, 18.0 ppm; IR: ν_{max} 2925, 1673, 1584, 1246, 1172 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{12}H_{14}O_2Na$ $[M+ Na]^+$ 213.0892, found: 213.0891.

(*Z*)-3-(4-methoxyphenyl)-1,3-diphenylprop-2-en-1-one[50] (10b): Fluorescent yellow oil, 114 mg, 73%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 7.1 Hz, 2H), 7.47 (tt, J = 7.4 Hz, J = 1.3 Hz, 1H), 7.41-7.34 (m, 7H), 7.11 (d, J = 8.8 Hz, 2H), 7.00 (s, 1H), 6.77 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H), ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 192.9, 159.9, 154.8, 141.9, 138.4, 132.6, 131.5, 131.2, 129.7, 128.84, 128.76, 128.40, 128.36, 123.4, 113.5, 55.2 ppm; IR: ν_{max} 3057, 1655, 1598, 1579, 1246, 1174 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{22}H_{18}O_2Na$ $[M+Na]^+$ 337.1205, found: 337.1205.

(*E*)-Ethyl 3-(4-chlorophenyl)but-2-enoate[51] (11a): Clear oil, 94 mg, 84%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 6.11 (q, J = 1.2 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.54 (d, J = 1.2 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 166.7, 154.0, 140.6, 134.9, 128.7, 127.6, 117.5, 59.9, 17.8, 14.3 ppm; IR: ν_{max} 2929, 1712, 1629, 827 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{12}H_{14}ClO_2$ $[M+H]^+$ 225.0682, found: 225.0673.

Ethyl 3,3-diphenylacrylate[52] (11b): Clear oil, 94 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.36 (m, 3H), 7.35-7.27 (m, 5H), 7.23-7.19 (m, 2H), 6.36 (s, 1H), 4.04 (q, J = 7.1 Hz, 2H), 1.10 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 166.2, 156.5, 140.8, 139.0, 129.4, 129.1, 128.4, 128.3, 128.1, 127.9, 117.5, 60.1, 14.0 ppm; IR: ν_{max} 3028, 2979, 1720, 1700, 1262, 1149 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{17}O_2$ $[M+H]^+$ 253.1228, found: 253.1225.

2-Phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[5] (7f): Light yellow solid, 100 mg, 90%, m.p. 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (d, J = 7.1 Hz, 1H), 8.10-8.08 (m, 2H), 7.74-7.73 (m, 2H), 7.53-7.49 (m, 3H), 7.14-7.11 (m, 1H), 6.92 (s, 1H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 162.0, 158.6, 151.0, 137.3, 136.1, 130.6, 128.8, 127.4, 127.3, 126.8, 115.2, 100.1 ppm; IR: ν_{max} 3131, 1678, 1634 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{10}N_2ONa$ $[M+Na]^+$ 245.0691, found: 245.0687.

2-(3,4,5-Trimethoxyphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7g): Light yellow solid, 144 mg, 92%, m.p. 188-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (dt, J = 7.1 Hz, J = 1.1 Hz, 1H), 7.76-7.75 (m, 2H), 7.35 (s, 2H), 7.16-7.12 (m, 1H), 6.87 (s, 1H), 3.98 (s, 6H), 3.92 (s, 3H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 161.6, 158.6, 153.4, 150.9, 140.4, 136.2, 132.6, 127.3, 126.7, 115.2, 104.7, 99.7, 60.9, 56.3 ppm; IR: ν_{max} 2917, 2849, 1674, 1629, 1230, 1119 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{17}N_2O_4$ $[M+H]^+$ 313.1188, found: 313.1189.

2-(4-Acetylphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7h): Off-white solid, 112 mg, 85%, m.p. 205-207 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (d, J = 7.1 Hz, 1H), 8.18 (d, J = 8.0 Hz, 2H), 8.08 (d, J = 8.0 Hz, 2H), 7.81-7.75 (m, 2H), 7.17 (dd, J = 6.8 Hz, J = 5.8 Hz, 1H), 6.95 (s, 1H), 2.66 (s, 3H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 197.6, 160.6, 158.5, 151.1, 141.5, 138.3, 136.5, 128.7, 127.6, 127.3, 126.8, 115.6, 100.8, 26.8 ppm; IR: ν_{max} 3124, 1685, 1669, 1634 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{12}N_2O_2Na$ $[M+Na]^+$ 287.0797, found: 287.0799.

2-(4-Formylphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7i): Off-white solid, 112 mg, 90%, m.p. >200 °C; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 10.1 (s, 1H), 9.09 (d, J = 7.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 2H), 8.03 (d, J = 8.0 Hz, 2H), 7.86-7.79 (m, 2H), 7.23 (dd, J = 6.3 Hz, J = 6.2 Hz, 1H), 6.97 (s, 1H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ

192.1, 160.7, 158.7, 151.1, 142.8, 137.5, 136.8, 130.1, 128.1, 127.3, 126.8, 115.9, 101.0 ppm; IR: ν_{max} 3118, 2852, 2755, 1699, 1685, 1632, 1605 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{15}H_{10}N_2O_2Na$ $[M+Na]^+$ 273.0640, found: 273.0642.

2-(Benzo[*d*][1,3]dioxol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7j): Off-white solid, 112 mg, 84%, m.p. 213-215 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (d, J = 7.1 Hz, 1H), 7.74 (ddd, J = 9.0 Hz, J = 6.2 Hz, J = 1.6 Hz, 1H), 7.69 (ddd, J = 9.0 Hz, J = 1.7 Hz, J = 0.9 Hz, 1H), 7.66 (dd, J = 8.2 Hz, J = 1.8 Hz, 1H), 7.61(d, J = 1.8 Hz, 1H), 7.12 (ddd, J = 6.3 Hz, J = 1.7 Hz, J = 0.9 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.81 (s, 1H), 6.05 (s, 2H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 161.4, 158.6, 150.9, 149.9, 148.3, 136.2, 131.5, 127.3, 126.6, 122.2, 115.0, 108.5, 107.6, 101.6, 99.1 ppm; IR: ν_{max} 2912, 1682, 1629, 1478, 1249, 1036 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{15}H_{11}N_2O_3$ $[M+H]^+$ 267.0769, found: 267.0763.

2-(3-Hydroxyphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7k): Off-white solid, 109 mg, 92% yield, m.p. 242-244 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.98 (d, J = 6.8 Hz, 1H), 7.98 (dt, J = 6.8 Hz, J = 1.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.64-7.60 (m, 2H), 7.38-7.34 (m, 1H), 7.32 (d, J = 7.9 Hz, 1H), 6.94 (dd, J = 7.9 Hz, J = 1.9 Hz, 1H), 6.91 (s, 1H), ppm; ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6): δ 160.9, 158.15, 158.13, 151.0, 138.5, 138.1, 130.3, 127.4, 126.6, 118.5, 118.2, 116.6, 114.4, 99.0 ppm; IR: ν_{max} 3296, 1673, 1633, 1454, 1280 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{11}N_2O_2$ $[M+H]^+$ 239.0820, found: 239.0818.

2-(4-(Hydroxymethyl)phenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7l): White solid, 115 mg, 91% yield, m.p. 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 9.01 (d, J = 6.9 Hz, 1H), 8.10 (d, J = 7.7 Hz, 2H), 7.87 (dd, J = 8.0 Hz, J = 7.3 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 7.7 Hz, 2H), 7.25 (dd, J = 6.8 Hz, J = 6.7 Hz, 1H), 6.86 (s, 1H), 5.18 (t, J = 5.6 Hz, O<u>H</u>), 4.65 (d, J = 5.6 Hz, 2H) ppm; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 161.9, 158.7, 151.6, 146.1, 137.6, 136.2, 127.9, 127.8, 127.5, 127.3, 116.4, 99.6, 64.0 ppm;

IR: ν_{max} 3315, 3115, 1652, 1629, 1471, 1444 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{15}H_{12}N_2O_2Na$ $[M+Na]^+$ 275.0803, found: 275.0803.

2-(4-Chlorophenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[53] (7m): White solid, 113 mg, 88%, m.p. 195-197 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.07 (d, J = 7.1 Hz, 1H), 8.05 (d, J = 8.6 Hz, 2H), 7.79-7.71 (m, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.15 (ddd, J = 6.0 Hz, J = 5.8 Hz, J = 1.4 Hz, 1H), 6.88 (s, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 160.7, 158.5, 151.0, 136.9, 136.4, 135.6, 129.0, 128.7, 127.3, 126.7, 115.3, 99.8 ppm; IR: ν_{max} 2916, 1679, 1625, 819 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{14}H_9ClN_2ONa$ $[M(^{35}Cl)+Na]^+$ 279.0301, found: 279.0300.

2-(4-Fluorophenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[53] (7n): White solid, 114 mg, 95%, m.p. 185-187 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.06 (d, J = 7.1 Hz, 1H), 8.09 (dd, J = 8.8 Hz, J = 5.4 Hz, 2H), 7.75 (dt, J = 8.8 Hz, J = 1.4 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.17 (t, J = 8.8 Hz, 2H), 7.12 (d, J = 6.2 Hz, 1H), 6.85 (s, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 164.5 (d, $J_{C\text{-}F}$ = 249 Hz), 160.9, 158.5, 151.0, 136.3, 133.3 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3 Hz), 129.5 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 9 Hz), 127.3, 126.7, 115.8 (d, $J_{C\text{-}C\text{-}F}$ = 21 Hz), 115.3, 99.6 ppm; IR: ν_{max} 3042, 1681, 1633, 1233 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{14}H_9FN_2ONa$ $[M+Na]^+$ 263.0597, found: 263.0601.

2-(4-(Trifluoromethyl)phenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[10] (7o): Crystal white solid, 131 mg, 90%, m.p. 196-198 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.08 (dd, J = 6.1 Hz, J = 0.9 Hz, 1H), 8.20 (d, J = 8.1 Hz, 2H), 7.81-7.74 (m, 4H), 7.18 (ddd, J = 6.4 Hz, J = 1.8 Hz, J = 0.8 Hz, 1H), 6.93 (s, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 160.3, 158.4, 151.1, 140.6, 136.5, 132.1 (q, $J_{C\text{-}C\text{-}F}$ = 32 Hz), 127.7, 127.3, 126.8, 125.6 (q, $J_{C\text{-}C\text{-}C\text{-}F}$ = 4 Hz), 123.9 (q, $J_{C\text{-}F}$ = 271 Hz), 115.6, 100.6 ppm; IR: ν_{max} 3055, 1692, 1637, 1107 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{15}H_9F_3N_2ONa$ $[M+Na]^+$ 313.0565, found: 313.0561.

2-(4-(Trifluoromethoxy)phenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7p): Crystal white solid, 125 mg, 82%, m.p. 152-154 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.08 (d, J = 7.1 Hz,

1H), 8.14 (d, J = 8.8 Hz, 2H), 7.80-7.72 (m, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.16 (dt, J = 7.1 Hz, J = 1.7 Hz, 1H), 6.88 (s, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 160.6, 158.5, 151.0 (dd, $J_{C\text{-}O\text{-}C\text{-}F}$ = 8 Hz, $J_{C\text{-}O\text{-}C\text{-}F}$ = 2 Hz), 136.4, 135.8, 129.1, 127.3, 126.8, 120.9, 120.2 (q, $J_{C\text{-}F}$ = 270 Hz), 115.4, 100.0 ppm; IR: ν_{max} 3081, 1683, 1633, 1250, 1209, 1144 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{15}H_9F_3N_2O_2Na$ $[M+Na]^+$ 329.0514, found: 329.0520.

2-(Pyridin-4-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[10] (7q): Off-white solid, 100 mg, 90%, m.p. 212-214 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.10 (d, J = 7.1 Hz, 1H), 8.78 (d, J = 5.7 Hz, 2H), 7.95 (dd, J = 4.6 Hz, J = 1.5 Hz, 2H), 7.84-7.80 (m, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.21 (dt, J = 7.2 Hz, J = 1.6 Hz, 1H), 6.96 (s, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 159.4, 158.5, 151.3, 150.6, 144.6, 136.7, 127.4, 126.9, 121.3, 115.9, 100.9 ppm; IR: ν_{max} 3119, 1697, 1630 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{13}H_{10}N_3O$ $[M+H]^+$ 224.0824, found: 224.0821.

2-(Furan-3-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7r): Cream solid, 91 mg, 86%, m.p. 130-132 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.03 (dd, J = 6.6 Hz, J = 0.4 Hz, 1H), 8.16 (dd, J = 1.4 Hz, J = 0.8 Hz, 1H), 7.74-7.70 (m, 1H), 7.63 (td, J = 8.9 Hz, J = 0.9 Hz, 1H), 7.52 (t, J = 1.7 Hz, 1H), 7.10 (dt, J = 7 Hz, J = 1.4 Hz, 1H), 6.87 (dd, J = 1.8 Hz, J = 0.8 Hz, 1H), 6.61 (s, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 158.4, 156.7, 151.3, 144.3, 143.8, 136.2, 127.3, 126.3, 125.7, 114.9, 108.5, 99.4 ppm; IR: ν_{max} 2916, 1676, 1628, 1442, 1115 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{12}H_8N_2O_2Na$ $[M+Na]^+$ 235.0484, found: 235.0470.

(*E*)-2-Styryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7s): Light yellow solid, 109 mg, 88%, m.p. 139-141 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.01 (d, J = 7.0 Hz, 1H), 7.88 (d, J = 15.8 Hz, 1H), 7.71 (dt, J = 6.6 Hz, J = 1.4 Hz, 1H), 7.66-7.61 (m, 3H), 7.42-7.33 (m, 3H), 7.07 (dt, J = 7.2 Hz, J = 1.4 Hz, 1H), 7.02 (d, J = 15.8 Hz, 2H), 6.49 (s, 1H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 160.1, 158.5, 150.9, 137.3, 136.2, 135.8, 129.3, 128.8, 127.7, 127.3, 126.33,

126.28, 114.7, 102.4 ppm; IR: ν_{max} 3081, 1683, 1633, 1607 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{12}N_2ONa$ $[M+Na]^+$ 271.0848, found: 271.0852.

Spectral data for the intermediates 7c1 and 11a1

7-Phenyl-2-(4-methylbenzenesulphonyloxy)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7c1): Yellow solid, 161 mg, 82%, m.p. >200 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.24 (d, J = 2.0 Hz, 1H), 8.10 (dd, J = 9.1 Hz, J = 2.2 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.66-7.62 (m, 3H), 7.54-7.47 (m, 3H), 7.38 (d, J = 8.2 Hz, 2H), 6.13 (s, 1H), 2.47 (s, 3H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 161.8, 159.2, 149.3, 145.8, 138.0, 134.9, 133.6, 130.5, 129.8, 129.5, 129.2, 128.8, 126.9, 125.9, 124.8, 91.6, 21.8 ppm; IR: $\bullet_{max}$ 1704, 1637, 1371, 1165 cm^{-1}; HRMS (ESI) m/z: calcd. for $C_{21}H_{17}N_2O_4S$ $[M+H]^+$ 393.0909, found: 393.0902.

(*E*)-Ethyl 3-(tosyloxy)but-2-enoate[54] (11a1): Colorless oil, 122 mg, 86%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 5.71 (q, J = 0.9 Hz, 1H), 4.14 (q, J = 9.1 Hz, 2H), 2.47 (s, 3H), 2.27 (d, J = 0.9 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 165.4, 162.3, 145.7, 132.9, 130.0, 128.2, 111.0, 60.5, 21.7, 18.6, 14.1 ppm; IR: $\bullet_{max}$ 2926, 1717, 1657, 1367, 1177 cm^{-1}; HRMS (ESI) m/z: calcd. for $C_{13}H_{16}O_5SNa$ $[M+Na]^+$ 307.0616, found: 307.0615.

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Supporting Information Available: scanned ^1H and ^{13}C spectra for products **7a-11b.** This material is available free of charge via the Internet at http://pubs.acs.org.

References:

(1) Hermecz, I.; Mészáros, Z.; *Med. Res. Rev.* **1988**, *8*, 203–230.

(2) Fenton, C.; L. J. Scott,*CNSDrugs*, **2005**, *19*, 429–444

(3) Harrison, T. S.; Goa, K. L. *CNS Drugs* **2004**, *18*, 113–132.

(4) For the palmitate ester prodrug of Paliperidone that is currently under evaluation by the USFDA for the treatment of schizophrenia, see: Hoy, S. M.; Scott, L. J.; Keating, G. M. *CNS Drugs* **2010**, *24*, 227–244.

(5) Motta, C. L.; Sartini, S.; Mugnaini, L.; Simorini, F.; Taliani, S.; Salerno, S.; Marini, A. M.; Settimo, F. D.; Lavecchia, A.; Novellino, E.; Cantore, M.; Failli, P.; Ciuffi, M. *J. Med. Chem.* **2007**, *50*, 4917–4927.

(6) Sin, N.; Good, A.; Venables, B.; Scola, P.; Meanwell, N. Hepatitis C Virus Inhibitors. PCT Int. Appl. 2006086381, 17 Aug 2006.

(7) Peng, L.; Gao, X.; Duan, L.; Ren, X.; Wu, D.; Ding, K. *J. Med. Chem.* **2011**, *54*, 7729–7733.

(8) Suga, H.; Igarashi, J. Quorum Sensing Inhibitor. (JP)PCT Int. Appl., 2009063901, 22 May 2009.

(9) Yoshida, K.; Nakayama, K.; Yokomizo, Y.; Ohtsuka, M.; Takemura, M.; Hoshino, K.; Kanda, H.; Namba, K.; Nitanai, H.; Zhang, J. Z.; Lee V. J.; Watkins, W. J. *Bioorg. Med. Chem.* **2006**, *14*, 8506–8518.

(10) Molnár, A.; Kapros, A.; Párkányi, L.; Mucsi, Z.; Vláda, G.; Hermecz, I. *Org. Biomol. Chem.* **2011**, *9*, 6559 –6565.

(11) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010,** *39*, 301-312.

(12) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L. Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang T. Y. *Green Chem.* **2007**, *9*, 411-420.

(13) Birnbaum, G. I.; Hruska, F. E.; Niemczura, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 5586–5590.

(14) Bello, A. M.; Konforte, D.; Poduch, E.; Furlonger, C.; Wei, L.; Liu, Y.; Lewis, M.; Pai, E. F.; Paige, C. J.; Kotra, L. P. *J. Med. Chem.* **2009**, *52*, 1648–1658.

(15) Krajewska, E.; Shugar, D. *Biochem. Pharmacol.* **1982**, *31*, 1097–1102.

(16) Chen, C.; Wu, D.; Guo, Z.; Xie, Q.; Reinhart, G. J.; Madan, A.; Wen, J.; Chen, T.; Huang, C. Q.; Chen, M.; Chen, Y.; Tucci, F. C.; Rowbottom, M.; Pontillo, J.; Zhu, Y.-F.; Wade, W.; Saunders, J.; Bozigian, H.; Struthers, R. S. *J. Med. Chem.* **2008**, *51*, 7478–7485.

(17) Skulnick, H. I.; Ludens, J. H.; Wendling, M. G.; Glenn, E. M.; Rohloff, N. A.; Smith, R. J.; Wierenga, W. *J. Med. Chem.* **1986**, *29*, 1499–1504.

(18) Zhang, Z.; Wallace, M. B.; Feng, J.; Stafford, J. A.; Skene, R. J.; Shi, L.; Lee, B.; Aertgeerts, K.; Jennings, A.; Xu, R.; Kassel, D. B.; Kaldor, S. W.; Navre, M.; Webb, D. R.; Gwaltney, S. L. *J. Med. Chem.*, **2011**, *54*, 510–524.

(19) Regan, C. F.; Guo, Z.; Chen, Y.; Huang, C. Q.; Chen, M.; Jiang, W.; Rueter, J. K.; Coon, T.; Chen, C.; Saunders, J.; Brown, M. S.; Betz, S. F.; Struthers, R. S.; Yang, C.; Wen, J.; Madan, A.; Zhu, Y.-F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4503–4507.

(20) Medda, F.; Russell, R. J. M.; Higgins, M.; McCarthy, A. R.; Campbell, J.; Slawin, A. M. Z.; Lane, D. P.; Lain, S.; Westwood, N. J. *J. Med. Chem.* **2009**, *52*, 2673–2683.

(21) Wang, X.; Zhang, J.; Huang, Y.; Wang, R.; Zhang, L.; Qiao, K.; Li, L.; Liu, C.; Ouyang, Y.; Xu, W.; Zhang, Z.; Zhang, L.; Shao, Y.; Jiang, S.; Ma, L.; Liu, J. *J. Med. Chem.* **2012**, *55*, 2242–2250.

(22) Taher, A. T.; Abou-Seri, S. M. *Molecules* **2012**, *17*, 9868–9886.

(23) Ikehira, H.; Matsuura, T.; Saito, I. *Tetrahedron Lett.* **1985**, *26*, 1743–1746.

(24) Palmisano, G.; Santagostino, M. *Tetrahedron* **1993**, *49*, 2533–2542.

(25) Nencka, R.; Sinnaeve, D.; Karalic, I.; Martins, J. C.; Van Calenbergh, S. *Org. Biomol. Chem.* **2010**, *8*, 5234–5246

(26) Shih, Y. –C.; Yang, Y. –Y.; Lin, C. –C.; Chien T. –C. *J. Org. Chem.* **2013**, *78*, 4027−4036.

(27) Shih, Y. –C.; Chien, T. –C. *Tetrahedron* **2011**, *67*, 3915–3923.

(28) Čerňová, M.; Pohl, R.; Hocek**,** M. *Eur. J. Org. Chem.* **2009**, 3698–3701

(29) Cheng, C.; Shih, Y. –C.; Chen, H. –T.; Chien, T. –C.; *Tetrahedron* **2013**, *69*, 1387–1396.

(30) Mondal, B.; Hazra, S.; Roy, B. Tetrahedron Lett. **2014,** *55*, 1077–1081.

(31) Polo, R.; Moretó, J. M.; Schick, U.; Ricart, S. *Organometallics*, **1998**, *17*, 2135–2137.

(32) Lee, D.; Ryu, T.; Park, Y.; Lee, P. H. *Org. Lett.* **2014**, *16*, 1144–1147.

(33) Tobisu, M.; Imoto, S.; Ito, S.; Chatani, N. *J. Org. Chem.* **2010**, *75*, 4835–4840.

(34) Seechurn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.

(35) Leowanawat, P.; Zhang, N.; Percec, V. *J. Org. Chem.* **2012**, *77*, 1018 –1025.

(36) Chen, H.; Huang, Z.; Hu, X.; Tang, G.; Xu, P.; Zhao, Y.; Cheng, C. –H. *J. Org. Chem.* **2011**, *76*, 2338–2344.

(37) For arylation of tautomerizable heterocycles (tautomerization of amide to hydroxylimine in heteroaromatic scaffolds), see this article and an article mentioned in the ref. 38. Kang, F.-A.; Sui, Z.; Murray, W. V. *J. Am. Chem. Soc.* **2008**, *130*, 11300 –11302.

(38) Shi, C.; Aldrich, C. C. *Org. Lett.* **2010**, *12*, 2286–2289.

(39) The cost for 5g of 1,3-dimethyluracil is 12,832 INR while 50g of 1,3-dimethylbarbituric acid costs only 4,593 INR.

(40) Baxter, J. M.; Steinhuebel, D.; Palucki, M.; Davies, I. W. *Org. Lett.* **2005**, *7*, 215–218.

(41) Steinhuebel, D.; Baxter, J. M.; Palucki, M.; Davies, I. W. *J. Org. Chem.* **2005**, *70*, 10124-10127.

(42) Freeman, J. P. *J. Am. Chem. Soc.* **1958**, *80*, 1926–1930.

(43) Ying, C. –H.; Yan, S. –B.; Duan, W. –L. *Org. Lett.* **2014**, *16*, 500–503.

(44) Jin, W.; Du, W.; Yang, Q.; Yu, H.; Chen, J.; Yu, Z. *Org. Lett.* **2011**, *13*, 4272–4275.

(45) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027–4029.

(46) D'Andrea, S.; Scola, P. Inhibitors of Hepatitis C Virus. U.S. Pat. Appl. Publ. 20080107623, 08 May 2008

(47) Lochead, A.; Saady M.; Yaiche, P. *Eur. Pat. Appl.* 2,138,493, 2009.

(48) Walker, S. E.; Boehnke, J.; Glen, P. E.; Levey, S.; Patrick, L.; Jordan-Hore, J. A.; Lee, A. –L. *Org. Lett.* **2013**, *15*, 1886–1889.

(49) Dabrowski, J. A.; Villaume, M. T.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 8156–8159.

(50) Smith, M. R.; Jang, Y. J.; Kim, J. Y.; Ciufolini, M. A. *Tetrahedron* **2013**, *69*, 10139–10151.

(51) Chen, Y.; Huang, L.; Zhang, X. P. *Org. Lett.* **2003**, *5*, 2493–2496.

(52) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097–2100.

(53) Bonacorso, H. G.; Righi, F. J.; Rodrigues, I. R.; Cechinel, C. A.; Costa, M. B.; Wastowski, A. D.; Martins, M. A. P.; Zanatta, N. *J. Heterocycl. Chem.* 2006, **43**, 229 –233.

(54) Hansen, A. L.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 5997–6003.