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CATALYST-FREE MULTICOMPONENT FORMATION OF NOVEL ACYLPYRROLE-CONTAINING 6-IMINOHEXAHYDRO-1*H*-PYRIDO-[1,2-*a*]PYRIMIDINE DERIVATIVES

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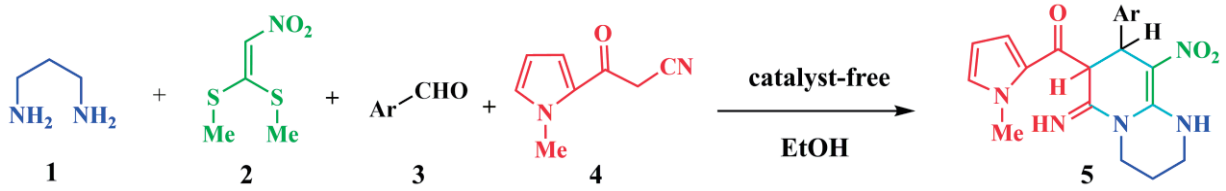
Abstract – A simple and green synthesis of acylpyrrole-containing 6-iminohexahydro-1*H*-pyrido[1,2-*a*]pyrimidine derivatives were successfully prepared via four-component reaction of 1,1-bis(methylthio)-2-nitroethene, propane-1,3-diamine, 3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile and aromatic aldehydes in ethanol under microwave irradiation. This method offers several significant advantages, including green solvent, avoidance of catalysts, high-speed reaction, outstanding selectivity, tremendous substrate diversity and no column chromatographic purification.

During the last decade, functionalized nitrogen-containing heterocycles have been found to be widely distributed in nature, and have become major synthetic targets owing to their high structural diversity and utility as scaffolds for drug development.[1] Among these heterocycles, pyridopyrimidine derivatives are an important class because of their diverse biological and pharmacological activity.[2] For example, ranirestat and diazasugars represent a novel class of selective aldose reductase inhibitors, acting against glycosidases for the treatment of diabetes,[3] while TGX221 has appeared as a novel, valid and selective inhibitor of Vps34 for the therapy of solid tumors.[4] Acylpyrrole derivatives are considered as an essential core for the design and synthesis of new anti-inflammatory agents and the synthesis of the natural antibiotic distamycin.[5,6] In addition, substituted pyrroles are important compounds broadly, being used not only in material science but also as building blocks for the assembly of polycyclic heterocycles.[7] Hence, it is highly desirable to synthesize a new class of compound containing both acylpyrrole and pyrido[1,2-*a*]pyrimidine frameworks.

A number of synthetic methods for the construction of pyrido[1,2-*a*]pyrimidine derivatives have been reported.[8-11] Sivakumar's group reported a highly efficient and facile three-component reaction to afford

pyrido[1,2-*a*]pyrimidines in the presence of Et_3N,[12] and Sun's group has developed a route to multisubstituted 1,8-naphthyridine derivatives via a one-pot, three-component protocol using a co-catalyst.[13] These three-component methods have some inevitable features, requiring bases or acids as catalysts and time-consuming and severe reaction conditions. Bayat and co-workers have also reported an efficient synthesis of 6-amino derivatives of pyrido[1,2-*a*]pyrimidines via a four-component reaction in short reaction times and the absence of catalyst.[14] However, the main structure of the product 6-amino-pyrido[1,2-*a*]pyrimidine may not have enough novelty and distinctiveness in similar reaction systems.[15]

Consequently, an appropriate strategy to construct novel and distinct structures of acylpyrrole-containing pyrido[1,2-*a*]pyrimidines is not only a huge challenge but an urgent requirement. In recent years, an efficient class of synthetic methods has been developed for the selective construction of complex heterocyclic compounds, in which portions of three or more reactants are combined in a single synthetic operation, known as multi-component domino reactions (MDRs).[16-19] Herein, an efficient and catalyst-free, one-pot four-component domino cyclization for the formation of novel acylpyrrole-containing 6-iminohexahydro-1*H*-pyrido[1,2-*a*]pyrimidine derivatives is reported (Scheme 1). To the best of our knowledge, few reports on the synthesis of these imino structures by green methods of this type have appeared in the literature.



Scheme 1. Synthesis of acylpyrrole-containing 6-iminohexahydro-1*H*-pyrido[1,2-*a*]pyrimidines

Initially, the reaction of propane-1,3-diamine **1** and 1,1-bis(methylthio)-2-nitroethene **2** were heated at 80 °C under microwave irradiation (200 W) for 1 h, after completion of the reaction (confirmed by TLC). Then 4-bromobenzaldehyde **3d** and 3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile **4** were added to the reaction mixture directly. We choose this as a model substrate to investigate the feasibility of the strategy and to optimize the reaction conditions leading to the formation of acylpyrrole-containing pyrido[1,2-*a*]pyrimidines. This model reaction was examined in the presence of different solvents under MWI conditions at different temperatures and times. The results are represented in Table 1.

Table 1. Optimization of reaction conditions

Entry	Solvent	T (°C)	Time[a] (min)	Yield[c] (%)
1	H_2O	90	10	none
2	THF	65	10	18
3	DMF	120	10	20
4	MeCN	70	10	23
5	$CHCl_3$	60	10	27
6	MeOH	60	10	44
7	EtOH	60	10	70
8	EtOH	rt	20	38
9	EtOH	80	10	84
10	EtOH	80	15	82
11	EtOH	80	20	80
12	EtOH	80	60[b]	75

[a] Microwave (MW) irradiation, [b] Conventional heating conditions, [c] Isolated yields.

At first, we investigated the efficacy of different solvents for the synthesis of acylpyrrole-containing pyrido[1,2-*a*]pyrimidines under MWI for 10 min. We found that when we use H_2O as solvent and the product was not produced because the reactants were not dissolved in this solvent (Table 1, entry 1). Then the effect of various polar and non-polar solvents on the product yields was studied with THF, DMF, MeCN, $CHCl_3$, MeOH and EtOH, although they offered an outcome in terms of reaction media (Table 1, entries 2-6), however, EtOH gave the best yield (Table 1, entry 7). Subsequently, the model reaction was carried out at room temperature under similar conditions for 20 min, which formed product only at 38% yield (Table 1, entry 8). When we conducted the model reaction at 80 °C under similar conditions for 10 min, 15 min and 20 min, we found that 10 min reaction time was the most suitable and afforded the product at 84% yield (Table 1, entries 9-11). Finally we made a comparison of microwave irradiation and conventional heating, when the ingredients **1** and **2** were was stirred at reflux for 6 h in EtOH, then ingredients **3d** and **4** were added to the reaction mixture for 1 h. We find the yield of product is low than under microwave irradiation, because of the efficiency of microwave irradiation is higher than conventional heating (Table 1, entry 12).

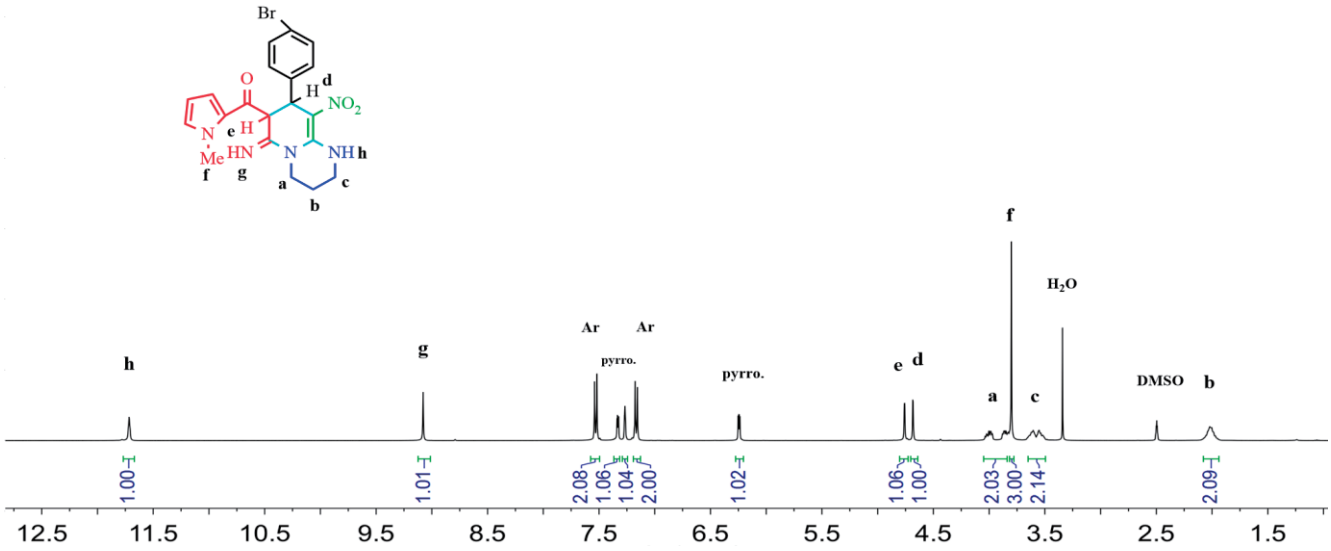


Figure 1. The ^{1}H NMR spectrum of **5d**

On the basis of the above experimental results, the optimized reaction conditions for the synthesis of acylpyrrole-containing pyrido[1,2-*a*]pyrimidines were identified. The probable structures of the products were characterized on the basis of ^{1}H NMR, ^{13}C NMR, IR and mass spectra. For example, the ^{1}H NMR spectrum of **5d** showed (Figure 1) multiplets for three CH_2 groups H_b, H_c and H_a (δ 1.98-2.02, 3.54-3.62, 3.85-4.02 ppm), one singlet for the CH_3 of pyrrole H_f (δ 3.80 ppm), two doublets for the CH groups H_d (δ 4.68 ppm, J = 1.5 Hz) and H_e (δ 4.76 ppm, J = 1.7 Hz), multiplets in the central region of the spectrum (δ 6.24-7.54 ppm) for the aromatic and pyrrole moieties and two singlets for the NH groups H_g and H_h (δ 9.08, 11.72 ppm), on which basis the structure **5d** (imino structure) was determined as the most feasible. The structure of the compound **5d** was further established by single crystal X-ray diffraction analysis (Figure 2).

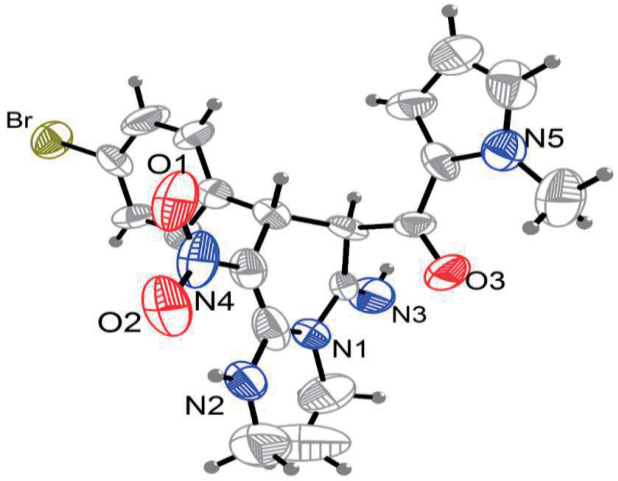
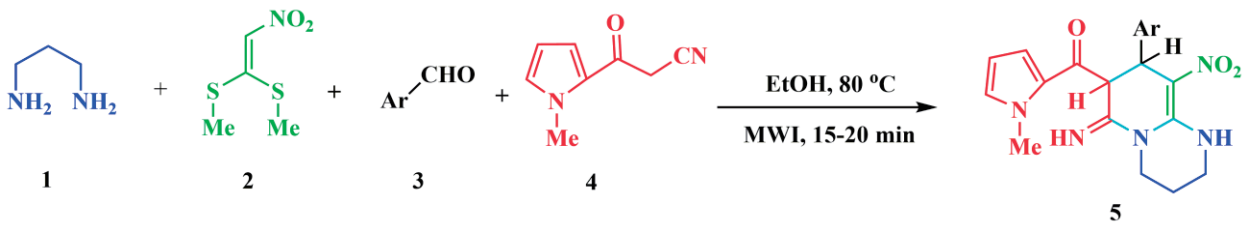


Figure 2. X-Ray crystal structure (ORTEP) of **5d**

With the optimized conditions in hand, the applicable scope of various aromatic aldehydes was investigated to provide acylpyrrole-containing 6-iminohexahydro-1*H*-pyrido[1,2-*a*]pyrimidine derivatives, summarized in (Table 2). It is obviously noting that aromatic aldehydes bearing electron-neutral (-H, -Me, -Et), electron-donating (-OMe), electron-withdrawing (-NO_2) and halogenated (-Cl, -Br, -F) substituents in the ortho position, meta position or the para position were smoothly converted to the heterocyclic products **5a-5o** in excellent yields (79-89%; Table 2). In addition, naphthaldehyde as the hugeness aldehyde was produced the desired acylpyrrole-containing pyrido[1,2-*a*]pyrimidine **5p** in decentyield (76%; Table 2). In consideration of the wide scope of aldehydes tested, this special domino reaction provides a new route for constructing acylpyrrole-containing pyridopyrimidines motif in an economical fashion, which is a valuable synthetic strategy to discover new bioactive compounds.

Table 2. One-pot, four-component synthesis of **5a-5p**



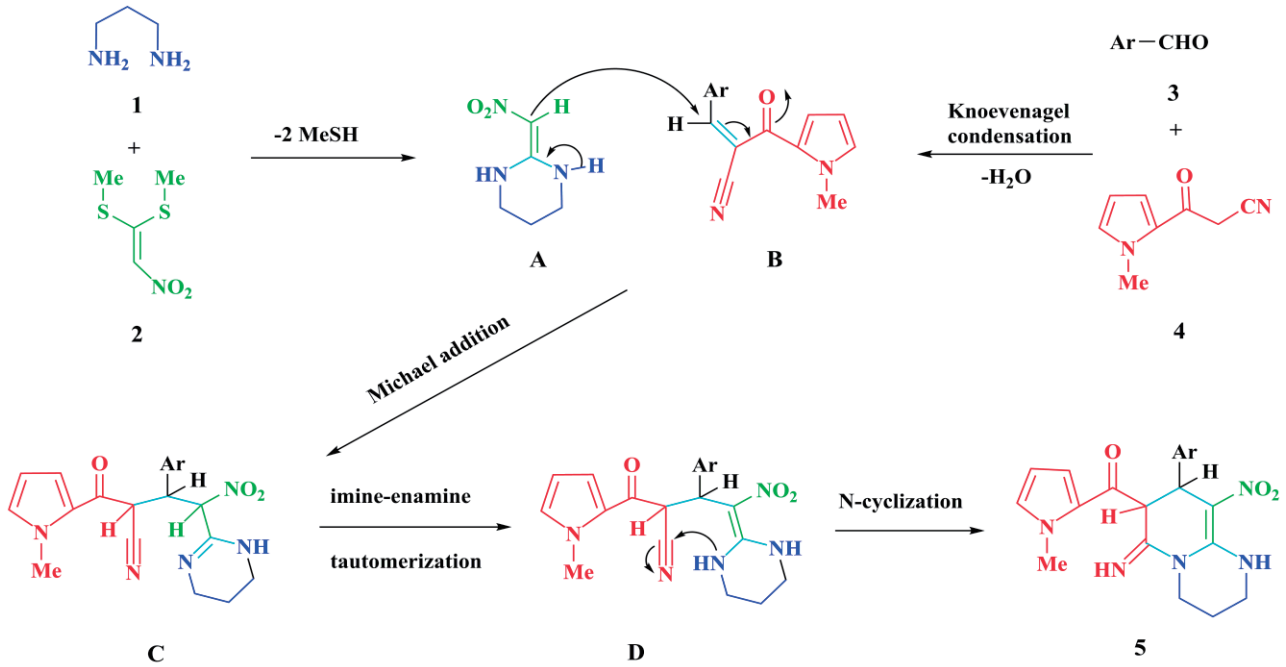
1 2 3 4 5

Entry	Ar	Time (min)	Yield (%)	Entry	Ar	Time (min)	Yield (%)
5a	C_6H_5	15	81	**5i**	4-ClC_6H_4	10	84
5b	2,4-$(Cl)_2C_6H_3$	15	83	**5j**	2-BrC_6H_4	10	85
5c	4-$MeOC_6H_4$	10	82	**5k**	2-$MeOC_6H_4$	10	88
5d	4-BrC_6H_4	10	84	**5l**	2-MeC_6H_4	15	80
5e	4-EtC_6H_4	20	79	**5m**	3-ClC_6H_4	10	89
5f	4-MeC_6H_4	15	80	**5n**	3-$NO_2C_6H_4$	15	87
5g	2-ClC_6H_4	10	86	**5o**	3,4-$(F)_2C_6H_3$	20	81
5h	4-$NO_2C_6H_4$	10	85	**5p**	1-$C_{10}H_7$	20	76

Equal amounts of the reactants **1-4** (1 mmol) were used in EtOH at 80 °C under MWI without any catalyst for 15-20 min.

In accordance with all the above-mentioned experimental results, we temporarily proposed a plausible mechanism[12] which is decipted in Scheme 2. Initially, the reaction of 1,1-bis(methylthio)-2-nitroethylene

2 and propane-1,3-diamine **1** produces heterocyclic nitroketene aminal **A**, afterward, the Knoevenagel condensation between 3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile **4** and aromatic aldehydes **3** obtains intermediate **B**. In the next step, intermediate **B**, as acceptor, undergoes Michael addition with nitroketene aminal **A** to affords the intermediate **C**, which then undergoes an imine-enamine and tautomerization to give intermediate **D**. Ultimately, the intramolecular N-cyclization of intermediate **D** can occur with CN to form the imino **5**, which is a stably final structure, hence not lead to a tautomerization.



Scheme 2. Plausible mechanism for the formation of **5**

In summary, we have illustrated a facile and reliable one-pot four-component domino reaction for efficient synthesis of a series of novel acylpyrrole-containing 6-iminohexahydro-1*H*-pyrido[1,2-*a*]pyrimidine derivatives. It is noteworthy that few reports on the synthesis of these imino structures by green methods of this type have appeared in the literature. Furthermore, the important advantages of this methodology is conspicuous like outstanding selectivity, mild conditions, high-speed synthesis, green solvent, absence of catalysts and column chromatographic purification processes avoided.

EXPERIMENTAL

General information: Microwave reaction was carried out in WF-4000C model microwave system and all reactions were investigated under the power of 200 W. ^{1}H and ^{13}C NMR (400 MHz) spectra were

recorded in DMSO-d_6 at room temperature using a Bruker Ultra Shield Plus 400 MHz instrument with reference tetramethylsilane (TMS). Melting points (mp) were taken on a Gallenkamp apparatus. FTIR spectra were measured using a Germany Bruker Vertex 80v FT-IR spectrometer by incorporating samples in KBr disks. High resolution mass spectra were operated on Aglient 6550 iFunnel Q-TOF. All of the reagents were purchased from chemical reagent Crop. in China and used without further purification.

(Conventional heating) synthesis of acylpyrrole-containing pyrido[1,2-*a*]pyrimidine 5b:

A mixture of propane-1,3-diamine **1** (0.074 g, 1 mmol), 1,1-bis(methylthio)-2-nitroethene **2** (1 mmol, 0.165 g) and 5 mL EtOH in a 50 mL flask was stirred at reflux for 6 h. After completion of the reaction (monitored by TLC), 3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile **4** (0.148 g, 1 mmol) and 2,4-dichlorobenzaldehyde **3b** (0.174 g, 1 mmol) were added to the reaction mixture, and the mixture was stirred at reflux for 1 h. Then, the reaction mixture was allowed to cool to rt, and the precipitates were filtered and washed with EtOH to give product **5b** in yield of 75% (as showed in Table 1).

(Microwave irradiation) synthesis of acylpyrrole-containing pyrido[1,2-*a*]pyrimidines 5:

In a 20 mL reaction vessel, a mixture of 1,1-bis(methylthio)-2-nitroethene **2** (0.165 g, 1mmol), propane-1,3-diamine **1** (0.074 g, 1 mmol) and 5 mL EtOH were heated at 80 ^{o}C under microwave irradiation (200 W) for 1 h. After completion of the reaction (confirmed by TLC), aromatic aldehydes **3** (1 mmol) and 3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile **4** (0.148 g, 1 mmol) were added to the reaction mixture for 10-15 min at 80 ^{o}C under microwave irradiation (200 W). Then, the reaction mixture was cooled to rt and the precipitated solid was filtered by Buchner funnel, afterward washed with little cold EtOH and dried under vacuum to acquire product **5** in yield of 76-89% (as showed in Table 1).

(6-Imino-9-nitro-8-phenyl-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5a): Pale yellow powder: mp 179-181 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.76 (s, 1H), 9.05 (s, 1H), 7.34 (s, 1H), 7.33 (dt, J = 2.8, 1.7 Hz, 2H), 7.27 (dq, J = 4.4, 2.4, 1.9 Hz, 2H), 7.20 (d, J = 1.6 Hz, 1H), 7.19-7.16 (m, 1H), 6.25 (dd, J = 4.2, 2.5 Hz, 1H), 4.78 (d, J = 1.7 Hz, 1H), 4.71 (d, J = 1.5 Hz, 1H), 4.06-3.98 (m, 1H), 3.90-3.83 (m, 1H), 3.80 (s, 3H), 3.66-3.51 (m, 2H), 2.04-1.99 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.8, 157.3, 152.9, 141.2, 133.5, 128.8, 127.4, 127.1, 126.7, 120.7, 108.6, 106.9, 56.0, 42.5, 41.0, 38.8, 37.2, 19.5. IR (KBr, ν, cm^{-1}): 3244, 1651, 1603, 1407, 1513, 1383, 1313, 1226, 1151, 1108, 1016, 974, 747, 700. HRMS (ESI) *m/z*: calcd. for: $C_{20}H_{21}N_5O_3$, 379.1644 $[M+Na]^+$, found: 379.1700.

(8-(2,4-Dichlorophenyl)-6-imino-9-nitro-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5b): White powder: mp 213-215 ^{o}C, ^{1}H NMR (400 MHz,

DMSO-d_6) δ (ppm) 11.76 (s, 1H), 9.16 (s, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.53 (dd, J = 4.3, 1.7 Hz, 1H), 7.34 (dd, J = 8.4, 2.2 Hz, 1H), 7.27 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.20 (dd, J = 4.2, 2.4 Hz, 1H), 4.93 (d, J = 1.4 Hz, 1H), 4.66 (d, J = 1.6 Hz, 1H), 3.96-3.85 (m, 2H), 3.80 (s, 3H), 3.60-3.56 (m, 2H), 2.09-1.94 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 183.5, 156.7, 153.4, 137.6, 134.2, 133.6, 132.5, 129.2, 129.1, 127.7, 127.7, 122.0, 108.4, 106.6, 53.1, 41.3, 38.8, 38.7, 37.3, 19.4. IR (KBr, ν, cm^{-1}): 3268, 3129, 1655, 1612, 1526, 1456, 1397, 1295, 1318, 1141, 1015, 968, 745. HRMS (ESI) *m/z*: calcd. for: $C_{20}H_{19}Cl_2N_5O_3$, 447.0865 $[M+Na]^+$, found: 447.0734.

(6-Imino-8-(4-methoxyphenyl)-9-nitro-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5c): White powder: mp 205-207 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.77 (s, 1H), 9.04 (s, 1H), 7.30 (dd, J = 4.3, 1.6 Hz, 1H), 7.26 (s, 1H), 7.10 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.25 (dd, J = 4.2, 2.4 Hz, 1H), 4.75 (d, J = 1.9 Hz, 1H), 4.66 (d, J = 1.5 Hz, 1H), 4.06-3.97 (m, 1H), 3.90-3.82 (m, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.65-3.57 (m, 1H), 3.57-3.49 (m, 1H), 2.04-1.98 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.9, 158.3, 157.5, 152.8, 133.4, 133.0, 127.8, 127.5, 120.7, 114.2, 108.6, 107.2, 56.3, 55.1, 41.7, 41.0, 38.8, 37.2, 19.5. IR (KBr, ν, cm^{-1}): 3265, 2948, 1638, 1509, 1401, 1363, 1242, 1174, 1015, 969, 776, 734. HRMS (ESI) *m/z*: calcd. for: $C_{21}H_{23}N_5O_4$, 409.1750 $[M+Na]^+$, found: 409.1613.

(8-(4-Bromophenyl)-6-imino-9-nitro-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5d): White powder: mp 209-211 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.72 (s, 1H), 9.08 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.33 (dd, J = 4.3, 1.6 Hz, 1H), 7.27 (s, 1H), 7.17 (d, J = 8.5 Hz, 2H), 6.24 (dd, J = 4.2, 2.4 Hz, 1H), 4.76 (d, J = 1.7 Hz, 1H), 4.68 (d, J = 1.5 Hz, 1H), 4.06-3.96 (m, 1H), 3.87 (dd, J = 7.3, 4.6 Hz, 1H), 3.80 (s, 3H), 3.66-3.58 (m, 1H), 3.55 (t, J = 4.5 Hz, 1H), 2.08-1.94 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.4, 157.1, 152.8, 140.6, 133.6, 131.7, 129.1, 127.4, 120.9, 120.2, 108.7, 106.6, 55.6, 42.0, 41.1, 38.8, 37.2, 19.4. IR (KBr , ν, cm^{-1}): 3262, 3011, 2947, 1643, 1609, 1524, 1443, 1363, 1240, 1160, 1050, 973, 745. HRMS (ESI) *m/z*: calcd. for: $C_{20}H_{20}BrN_5O_3$, 457.0750 $[M+Na]^+$, found: 457.0648.

(8-(4-Ethylphenyl)-6-imino-9-nitro-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5e): White powder: mp 190-191 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.77 (s, 1H), 9.04 (s, 1H), 7.34-7.28 (m, 1H), 7.26 (s, 1H), 7.17 (d, J = 7.9 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 6.25 (dd, J = 4.1, 2.4 Hz, 1H), 4.77 (d, J = 1.7 Hz, 1H), 4.68 (s, 1H), 4.08-3.96 (m, 1H), 3.91-3.81 (m, 1H), 3.80 (s, 3H), 3.68-3.49 (m, 2H), 2.57 (q, J = 7.6 Hz, 2H), 2.07-1.96 (m, 2H), 1.15 (t, J = 7.6 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.9, 157.4, 152.9, 142.5, 138.4, 133.4, 128.2, 127.5, 126.7, 120.7, 108.6, 107.0, 56.1, 42.1, 41.0, 38.8, 37.2, 27.7, 19.5, 15.6. IR (KBr, ν, cm^{-1}): 3266, 2962, 1643, 1607, 1523, 1359, 1315, 1289, 1141, 1016, 969, 738. HRMS (ESI) *m/z*: calcd. for: $C_{22}H_{25}N_5O_3$, 407.1957 $[M+Na]^+$, found: 407.1861.

(6-Imino-9-nitro-8-(*p*-tolyl)-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5f): Pale yellow powder: mp 177-179 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.76 (s, 1H), 9.02 (s, 1H), 7.31 (dd, *J* = 4.2, 1.7 Hz, 1H), 7.27 (t, *J* = 2.0 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.25 (dd, *J* = 4.2, 2.4 Hz, 1H), 4.75 (d, *J* = 1.8 Hz, 1H), 4.67 (d, *J* = 1.6 Hz, 1H), 4.05-4.01(m, 1H), 3.89-3.82 (m, 1H), 3.80 (s, 3H), 3.62 (s, 1H), 3.58-3.50 (m, 1H), 2.27 (s, 3H), 2.06-1.97 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.9, 157.4, 152.9, 138.1, 136.2, 133.4, 129.3, 127.4, 126.6, 120.7, 108.6, 106.9, 56.2, 42.1, 40.9, 38.8, 37.2, 20.5, 19.5. IR (KBr, ν, cm^{-1}): 3221, 2972, 1633, 1610, 1526, 1408, 1366, 1318, 1212, 1170, 1037, 973, 746. HRMS (ESI) *m/z*: calcd. for: $C_{21}H_{23}N_5O_3$, 393.1801 $[M+Na]^+$, found: 393.1713.

(8-(2-Chlorophenyl)-6-imino-9-nitro-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5g): White powder: mp 194-196 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.81 (s, 1H), 9.16 (s, 1H), 7.55 (dd, *J* = 4.3, 1.7 Hz, 1H), 7.51 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.35-7.27 (m, 2H), 7.27 (s, 1H), 7.03 (dd, *J* = 7.2, 2.2 Hz, 1H), 6.20 (dd, *J* = 4.2, 2.4 Hz, 1H), 4.98 (d, *J* = 1.5 Hz, 1H), 4.68 (d, *J* = 1.7 Hz, 1H), 3.99-3.84 (m, 2H), 3.80 (s, 3H), 3.67-3.53 (m, 2H), 2.12-1.93 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 183.8, 156.8, 153.5, 138.3, 134.1, 132.7, 129.8, 128.9, 127.8, 127.7, 127.6, 122.0, 108.3, 106.9, 53.4, 41.2, 39.0, 38.8, 37.3, 19.4. IR (KBr, ν, cm^{-1}): 3291, 2948, 1642, 1604, 1572, 1525, 1405, 1328, 1281, 1149, 1021, 967, 750. HRMS (ESI) *m/z*: calcd. for: $C_{20}H_{20}ClN_5O_3$, 413.1255 $[M+Na]^+$, found: 413.1313.

(6-Imino-9-nitro-8-(4-nitrophenyl)-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5h): Pale yellow powder: mp 195-197 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.69 (s, 1H), 9.12 (s, 1H), 8.20 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.38 (dd, *J* = 4.3, 1.6 Hz, 1H), 7.29 (s, 1H), 6.26 (dd, *J* = 4.2, 2.4 Hz, 1H), 4.84 (d, *J* = 1.4 Hz, 1H), 4.81 (d, *J* = 1.7 Hz, 1H), 4.04-3.95 (m, 1H), 3.93-3.85 (m, 1H), 3.82 (s, 3H), 3.68-3.52 (m, 2H), 2.12-1.95 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.0, 156.8, 152.8, 148.9, 146.7, 133.7, 128.3, 127.3, 123.9, 121.1, 108.7, 106.2, 55.0, 42.3, 41.2, 38.9, 37.3, 19.4. IR (KBr, ν, cm^{-1}): 3234, 2940, 1656, 1612, 1516, 1367, 1319, 1242, 1170, 1021, 972, 744. HRMS (ESI) *m/z*: calcd. for: $C_{20}H_{20}N_6O_5$, 424.1495 $[M+Na]^+$, found: 424.1394.

(8-(4-Chlorophenyl)-6-imino-9-nitro-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5i): White powder: mp 208-210 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.72 (s, 1H), 9.08 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.33 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.27 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.24 (dd, *J* = 4.2, 2.5 Hz, 1H), 4.76 (d, *J* = 1.7 Hz, 1H), 4.70 (d, *J* = 1.5 Hz, 1H), 4.05-3.97 (m, 1H), 3.90-3.82 (m, 1H), 3.66-3.58 (m, 1H), 3.54 (dd, *J* = 10.9, 5.1 Hz, 1H), 2.08-1.95 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.5, 157.1, 152.8, 140.1, 133.6, 131.7, 128.7, 127.4, 120.9, 108.7, 106.6, 55.7, 41.9, 41.0, 38.8, 37.2, 19.4. IR (KBr, ν, cm^{-1}): 3259, 2945, 1660, 1609 1566,

1524, 1488, 1318, 1241, 1108, 1053, 971, 743. HRMS (ESI) *m/z*: calcd. for: $C_{20}H_{20}ClN_5O_3$, 413.1255 $[M+Na]^+$, found: 413.1113.

(8-(2-Bromophenyl)-6-imino-9-nitro-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5j): White powder: mp 209-211 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.70 (s, 1H), 9.15 (s, 1H), 8.17-8.12 (m, 1H), 8.01 (s, 1H), 7.71-7.63 (m, 2H), 7.40 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.28 (d, *J* = 2.0 Hz, 1H), 6.26 (dd, *J* = 4.2, 2.4 Hz, 1H), 4.86 (s, 2H), 4.03-3.83 (m, 2H), 3.82 (s, 3H), 3.68-3.51 (m, 2H), 2.02 (q, *J* = 6.6, 6.1 Hz, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.0, 157.0, 152.8, 148.0, 143.3, 133.7, 133.6, 130.4, 127.5, 122.2, 121.6, 121.1, 108.7, 106.5, 55.1, 41.8, 41.2, 38.9, 37.3, 19.5. IR (KBr, ν, cm^{-1}): 3253, 3089, 2951, 1660, 1606, 1580, 1533, 1453, 1348, 1313, 1173, 1025, 978, 734. HRMS (ESI) *m/z*: calcd. for: $C_{20}H_{20}BrN_5O_3$, 457.0750 $[M+Na]^+$, found: 457.0613.

(6-Imino-8-(2-methoxyphenyl)-9-nitro-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5k): White powder: mp 206-208 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.78 (s, 1H), 8.89 (s, 1H), 7.58 (dd, *J* = 4.3, 1.7 Hz, 1H), 7.28-7.22 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 5.8 Hz, 1H), 6.28 (dd, *J* = 4.2, 2.4 Hz, 1H), 5.02 (d, *J* = 1.8 Hz, 1H), 4.72 (d, *J* = 1.9 Hz, 1H), 4.02-3.95 (m, 1H), 3.94 (s, 3H), 3.85-3.81 (m, 1H), 3.80 (s, 3H), 3.69-3.51 (m, 2H), 2.06-1.99 (m , 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 185.2, 157.8, 156.6, 153.6, 133.4, 128.4, 127.9, 127.9, 126.2, 121.1, 120.5, 111.1, 108.3, 106.1, 55.2, 54.5, 40.9, 38.8, 37.2, 37.2, 19.5. IR (KBr, ν, cm^{-1}): 3239, 2942, 1639, 1606, 1523, 1435, 1392, 1314, 1240, 1152, 1019, 971, 757. HRMS (ESI) *m/z*: calcd. for: $C_{21}H_{23}N_5O_4$, 409.1750 $[M+Na]^+$, found: 409.1623.

(6-Imino-9-nitro-8-(*o*-tolyl)-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5l): White powder: mp 200-202 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.92 (s, 1H), 9.05 (s, 1H), 7.45 (dd, *J* = 4.3, 1.7 Hz, 1H), 7.27 (s, 1H), 7.24-7.18 (m, 1H), 7.17-7.06 (m, 2H), 6.91-6.81 (m, 1H), 6.20 (dd, *J* = 4.2, 2.4 Hz, 1H), 4.71 (d, *J* = 1.3 Hz, 1H), 4.60 (d, *J* = 1.5 Hz, 1H), 4.03-3.85 (m, 2H), 3.80 (s, 3H), 3.68-3.52 (m, 2H), 2.38 (s, 3H), 2.12-1.93 (m, 2H).^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.3, 157.3, 153.4, 139.7, 135.3, 134.1, 130.6, 127.9, 126.9, 126.3, 125.6, 121.3, 108.5, 108.2, 53.8, 41.1, 38.7, 38.0, 37.3, 19.5, 19.2. IR (KBr, ν, cm^{-1}): 3279, 3094, 1644, 1614, 1509, 1358, 1234, 1164, 1017, 968, 763. HRMS (ESI) *m/z*: calcd. for: $C_{21}H_{23}N_5O_3$, 393.1801 $[M+Na]^+$, found: 393.1677.

(8-(3-Chlorophenyl)-6-imino-9-nitro-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-a]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5m): Pale yellow powder: mp 177-179 °C, ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.73 (s, 1H), 9.12 (s, 1H), 7.44-7.37 (m, 1H), 7.37-7.34 (m, 2H), 7.28 (t, *J* = 2.0 Hz, 1H), 7.24 (t, *J* = 1.9 Hz, 1H), 7.19-7.15 (m, 1H), 6.26 (dd, *J* = 4.2, 2.4 Hz, 1H), 4.81 (d, *J* = 1.8 Hz, 1H), 4.72 (d, *J* = 1.6 Hz, 1H), 4.02 (ddd, *J* = 12.5, 7.2, 4.7 Hz, 1H), 3.86 (td, *J* = 8.9, 7.9, 3.5 Hz, 1H), 3.81 (s, 3H), 3.67-3.53 (m, 2H), 2.08-1.96 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.3, 157.1, 152.8,

143.6, 133.6, 133.3, 130.7, 127.4, 127.2, 126.7, 125.5, 121.0, 108.7, 106.6, 55.4, 42.0, 41.0, 38.8, 37.2, 19.4. IR (KBr, ν, cm^{-1}): 3224, 3110, 2969, 1630, 1608, 1525, 1406, 1366, 1319, 1168, 1025, 972, 739. HRMS (ESI) *m/z*: calcd. for: $C_{20}H_{20}ClN_5O_3$, 413.1255 $[M+Na]^+$, found: 413.1155.

(6-Imino-9-nitro-8-(3-nitrophenyl)-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5n): White powder: mp 200-202 °C, ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.86 (s, 1H), 9.24 (s, 1H), 7.68 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.62 (dd, *J* = 4.3, 1.6 Hz, 1H), 7.33 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.27 (s, 1H), 7.22 (td, *J* = 7.6, 1.7 Hz, 1H), 7.03 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.19 (dd, *J* = 4.2, 2.4 Hz, 1H), 4.93 (d, *J* = 1.3 Hz, 1H), 4.66 (d, *J* = 1.7 Hz, 1H), 3.97-3.84 (m, 2H), 3.82 (s, 3H), 3.68-3.53 (m, 2H), 2.13-1.90 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.1, 157.1, 153.9, 140.5, 134.6, 133.6, 129.6, 128.6, 128.4, 128.3, 124.2, 122.9, 108.8, 107.9, 53.9, 41.8, 39.3, 37.9, 19.9. IR (KBr, ν, cm^{-1}): 3292, 2979, 1632, 1602, 1564, 1524, 1439, 1349, 1285, 1156, 1022, 971, 740. HRMS (ESI) *m/z*: calcd. for: $C_{20}H_{20}N_6O_5$, 424.1495 $[M+Na]^+$, found: 424.1365.

(8-(3,4-Difluorophenyl)-6-imino-9-nitro-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5o): Pale yellow powder: mp 190-192 °C, ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.72 (s, 1H), 9.11 (s, 1H), 7.45-7.29 (m, 3H), 7.28 (d, *J* = 2.2 Hz, 1H), 7.09-7.01 (m, 1H), 6.25 (dd, *J* = 4.2, 2.4 Hz, 1H), 4.78 (d, *J* = 1.7 Hz, 1H), 4.72 (d, *J* = 1.5 Hz, 1H), 4.06-3.97 (m, 1H), 3.86 (dt, *J* = 9.7, 4.5 Hz, 1H), 3.81 (s, 3H), 3.65-3.50 (m, 2H), 2.10-1.94 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.7, 157.6, 153.3, 139.3, 134.1, 127.9, 121.6, 118.3, 118.1, 116.6, 116.5, 109.2, 107.1, 55.9, 42.0, 41.5, 37.8, 35.3, 19.9. IR (KBr, ν, cm^{-1}): 3260, 2982, 1639, 1607, 1408, 1384, 1333, 1297, 1226, 1161, 1110, 975, 948, 766. HRMS (ESI) *m/z*: calcd. for: $C_{20}H_{19}F_2N_5O_3$, 415.1456 $[M+Na]^+$, found: 415.1378.

(6-Imino-8-(naphthalen-1-yl)-9-nitro-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5p): Pale yellow powder: mp 189-191 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 9.07 (s, 1H), 8.12-8.04 (m, 1H), 8.03-7.97 (m, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.63-7.54 (m, 2H), 7.43-7.35 (m, 2H), 7.32 (s, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 6.24 (dd, *J* = 4.2, 2.4 Hz, 1H), 5.38 (s, 1H), 4.75 (d, *J* = 1.4 Hz, 1H), 4.02-3.94 (m, 1H), 3.86 (s, 3H), 3.71-3.57 (m, 2H), 2.14-1.97 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ (ppm) 184.1, 157.0, 153.7, 137.0, 134.2, 133.9, 130.3, 129.1, 128.1, 127.6, 126.4, 125.9, 125.6, 123.1, 122.7, 121.6, 108.5, 107.6, 54.3, 41.2, 38.8, 37.6, 37.3, 19.5. IR (KBr, ν, cm^{-1}): 3288, 2958, 1613, 1525, 1355, 1259, 1157, 1032, 970, 782, 734, 697, 603. HRMS (ESI) *m/z*: calcd. for: $C_{24}H_{23}N_5O_3$, 429.1801 $[M+Na]^+$, found: 429.1672.

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