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Three-component domino reaction synthesis of highly functionalized bicyclic pyrrole derivatives

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ABSTRACT

An efficient one-pot synthesis of highly functionalized bicyclic pyrrole derivatives by a three-component domino reaction of heterocyclic ketene aminals (HKAs), arylglyoxal monohydrate, and indoles in ethanol medium catalyzed by acetic acid is described. In this procedure, three sigma bonds were formed simultaneously. The present synthesis features excellent regio-selectivity, easy purification as well as simple starting materials.

1. Introduction

Multicomponent reactions (MCRs)[1] are powerful tools in the modern drug discovery and development process as they allow rapid access to structural variation and complexity within single-step conversions. The features of such reactions[2] include rapidity, diversity, efficiency, atom-economy, and environmental amiability. Because of these advantages, developing new MCRs with environmentally benign protocols has been recognized as one of the most important topics of synthetic chemistry.[3] In this article, we provide a novel multicomponent domino reaction for heterocyclic construction.

The indole skeleton is one of the most abundant and relevant heterocycles in natural products and it can perhaps be considered as the most important single class of heterocyclic systems.[4] A vast number of natural and synthetic indoles have found applications as pharmaceuticals.[5] Amongst them, 3-substituted indole is a 'privileged medicinal scaffold' found in many natural products and biologically active compounds.[6] Furthermore, they are important building blocks for the synthesis of various biologically active molecules.[7] Consequently, the development of new synthetic methodologies for the construction of the 3-substituted indole scaffold is very important in organic synthesis.[8]

On the other hand, the pyrrole core is featured in a number of natural products as well as medicinally relevant compounds;[9] as cholesterol-lowering agent (Atorvastatin, Fig. 1),[9a] myosin ATPase inhibitor (Fig. 1),[9b] and a human topoisomerase I inhibitor (Lamellarin D, Fig. 1), etc.[9c] Substituted bicyclic pyrrole nucleoside derivatives are reported to have various biological activities, i.e., antitumor,[10] anti-HIV type 1,[11] antiviral,[12] antifungal,[13] anti-HCV,[14] and antibacterial activity;[15] they could also include inhibitors of PI3K,[16] Janus kinases,[17] glycosidase,[18] firefly luciferase,[19] gastric acid pumps,[20] dihydrofolate reductase (DHFR),[21] and so on.[22] The importance of such molecules has stimulated many synthetic chemists to develop novel, efficient synthetic routes for the synthesis of

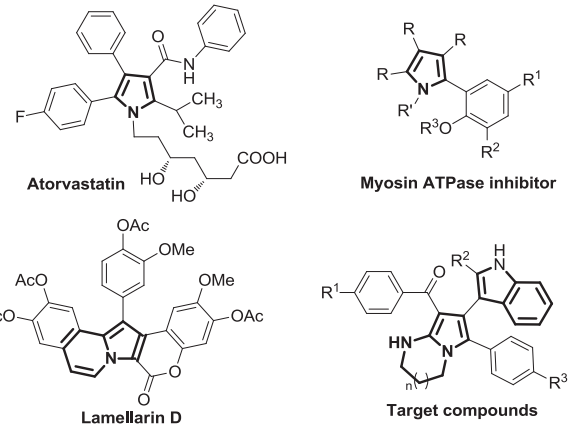

Fig. 1. Biological activity pyrroles and bicyclic pyrroles.

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these kinds of bicyclic pyrroles. Although various approaches[23] for the preparation of bicyclic pyrroles containing a ring-junction nitrogen framework have been developed, preparation of these indole ketene-containing bicyclic pyrroles via an environmentally friendly and highly regioselective domino procedure has rarely been studied.

As a type of versatile synthetic intermediate, HKAs have been used for the synthesis of a wide variety of heterocyclic and fused heterocyclic compounds.[24] Furthermore, a number of efficient approaches for bicyclic pyrrole derivatives through HKAs have been explored.[25] Despite so many synthetic approaches for bicyclic pyrrole derivatives, the development of efficient access to highly functionalized bicyclic pyrroles via multicomponent domino reaction is very limited. Arylglyoxal monohydrate,[26] as a readily available 1,2-biacceptor,[27] can provide two active sites that can be attacked by nucleophilic reagents; this molecule has been shown to be an important synthon in the construction of heterocyclic systems.[26,28] Accordingly, we turned our attention to simultaneously utilizing these two fascinating synthons to develop a new strategy for the synthesis of bicyclic pyrroles.

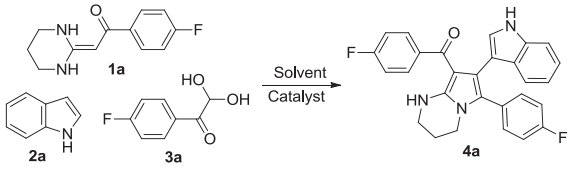
HKAs possess two nucleophilic centers (α-C atom and NH group). Similarly, indoles contain three nucleophilic centers; C-nucleophilicity at the C3 position is stronger than that of the C2 position and the NH group. As a readily available 1,2-biacceptor, arylglyoxal monohydrate can provide two electrophilic centers that can be attacked by the indole C3 atom as well as the HKA β-C and NH group for the formation of the C–C and C–N bonds.

Herein, we developed a synthetic method to synthesize such a pyrrolo[1,2-*a*]pyrimidine ring by simply heating HKA **1**, indole **2**, and arylglyoxal monohydrate **3**, catalyzed by HOAc in ethanol, to obtain the target compounds in good to excellent yields (72–95%).

2. Result and discussion

In the preliminary experiments, for the synthesis of pyrrolo-[1,2-*a*]pyrimidines **4**, the heterocyclic ketene aminals **1a**, indole **2a**, and arylglyoxal monohydrate **3a** in the green solvent ethanol were selected as model reactants for the optimization process (Table 1).

Table 1
Optimization of the reaction conditions[a]



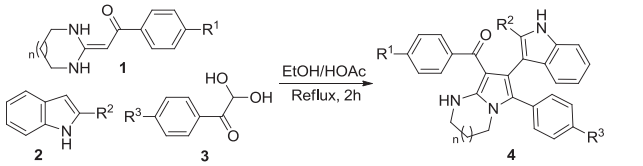
Entry	Solvent	Catalyst	*t* (°C)	Time (h)	Yield[e] (%)
1	EtOH	—	rt	6	n.r.
2	EtOH	—	Reflux	6	n.r.
3	EtOH	Piperidine[b]	Reflux	6	n.r
4	EtOH	Et_3N[b]	Reflux	6	n.r.
5	EtOH	DABCO[b]	Reflux	6	n.r.
6	EtOH	HOAc[b]	Reflux	1	88
7	EtOH	*p*-TSA[b]	Reflux	1	81
8	EtOH	L-Proline[b]	Reflux	2	n.r.
9	EtOH	TFA[b]	Reflux	2	25
10	CH_3CN	HOAc[b]	Reflux	2	50
11	Dioxane	HOAc[b]	Reflux	2	Trace
12	DMF	HOAc[b]	110 °C	2	n.r.
13	EtOH	HOAc[c]	Reflux	2	83
14	EtOH	HOAc[d]	Reflux	2	81

[a] The reaction was performed with **1a** (1 mmol), **2a** (1.1 mmol), **3a** (1.1 mmol), and the solvent (15 mL).
[b] Catalyst (0.1 mmol).
[c] Catalyst (0.2 mmol).
[d] Catalyst (0.3 mmol).
[e] Isolated yields based on HKA **1a**. n.r.=no reaction.

No transformation occurred in the presence of a basic catalyst or without a catalyst, even within 6 h (Table 1, entries 1–5). However, when 10 mol % acetic acid was added to the ethanol in reflux, the yield of **4a** reached 88% (Table 1, entry 6). Inspired by this result, we continued to optimize the reaction conditions to further improve the chemical yield; *p*-TSA, L-proline, and TFA were used as protic acids to catalyze the domino reaction; however, the reactions carried out using these acids did not give better results than using acetic acid as the catalyst (Table 1, entries 7–9). Subsequently, we performed the model reaction in other solvents, such as acetonitrile, dioxane, and DMF. The results revealed that those solvents were completely ineffective for the formation of **4a** (Table 1, entries 10–12). Next, the amount of acetic acid was screened, and 0.1 equiv was found to be the best (Table 1, entries 6, 13 & 14). Briefly, the optimum results were obtained when the HKAs, arylglyoxal monohydrate, and indole in ethanol were treated with 10 mmol% of acetic acid as the catalyst at reflux for 2 h.

Based on the success of the model system, a series of products **4a**–**z** were constructed in order to evaluate the applicability of this reaction sequence (Table 2). A wide variety of HKAs **1a**–**f**, indole **2a**–**c**, and arylglyoxal monohydrate **3a**,**b** were explored and the results are summarized in Table 2.

Table 2
Domino reaction synthesis of products **4** from various of **1**–**3**[a]



Entry	**1** *n*/R^1	**2**/R^2	**3**/R^3	**4**	Yield[b] (%)
1	**1a** (1/*p*-F)	**2a**/H	**3a**/F	**4a**	88
2	**1a** (1/*p*-F)	**2a**/H	**3b**/H	**4b**	86
3	**1a** (1/*p*-F)	**2b**/CH_3	**3a**/F	**4c**	91
4	**1a** (1/*p*-F)	**2b**/CH_3	**3b**/H	**4d**	91
5	**1a** (1/*p*-F)	**2c**/Ph	**3a**/F	**4e**	94
6	**1a** (1/*p*-F)	**2c**/Ph	**3b**/H	**4f**	92
7	**1b** (1/*o*-F)	**2b**/CH_3	**3a**/F	**4g**	93
8	**1b** (1/*o*-F)	**2b**/CH_3	**3b**/H	**4h**	91
9	**1c** (1/*p*-Cl)	**2a**/H	**3b**/H	**4i**	83
10	**1c** (1/*p*-Cl)	**2b**/CH_3	**3a**/F	**4j**	89
11	**1c** (1/*p*-Cl)	**2b**/CH_3	**3b**/H	**4k**	87
12	**1c** (1/*p*-Cl)	**2c**/Ph	**3a**/F	**4l**	93
13	**1c** (1/*p*-Cl)	**2c**/Ph	**3b**/H	**4m**	91
14	**1d** (1/*o*-Cl)	**2a**/H	**3a**/F	**4n**	91
15	**1d** (1/*o*-Cl)	**2a**/H	**3b**/H	**4o**	90
16	**1d** (1/*o*-Cl)	**2b**/CH_3	**3a**/F	**4p**	93
17	**1d** (1/*o*-Cl)	**2b**/CH_3	**3b**/H	**4q**	90
18	**1d** (1/*o*-Cl)	**2c**/Ph	**3a**/F	**4r**	95
19	**1d** (1/*o*-Cl)	**2c**/Ph	**3b**/H	**4s**	92
20	**1e** (1/*p*-H)	**2a**/H	**3b**/H	**4t**	83
21	**1e** (1/*p*-H)	**2b**/CH_3	**3a**/F	**4u**	86
22	**1e** (1/*p*-H)	**2b**/CH_3	**3b**/H	**4v**	84
23	**1e** (1/*p*-H)	**2c**/Ph	**3a**/F	**4w**	91
24	**1e** (1/*p*-H)	**2c**/Ph	**3b**/H	**4x**	88
25	**1f** (1/*p*-CH_3)	**2b**/CH_3	**3b**/H	**4y**	72
26	**1g** (2/*p*-Cl)	**2c**/Ph	**3a**/F	**4z**	94

[a] The reaction was performed with **1** (1 mmol), **2** (1.1 mmol), **3** (1.1 mmol), and HOAc (0.1 mmol) in EtOH (15 mL) under reflux.
[b] Isolated yields based on HKA **1**.

As shown in Table 2, HKAs bearing different groups (F, Cl, H, CH_3) and indoles with different groups at the C2 position (H, CH_3, Ph) could also smoothly give the corresponding products; the yields ranged from 72% to 95%. This confirmed that the electronic nature of the aromatic rings of HKAs has a significant impact on the reaction yield. It was clearly demonstrated that the electron-

withdrawing aromatic rings of HKAs **1** could encourage the yield of the reaction (Table 2, compare entries 2, 9 & 20). Furthermore, the HKAs with substituents at *ortho*-positions afforded higher yields than those counterparts at the *para*-position (Table 2, entries 7 vs 3). The indole C2 position with electron-donating groups afforded a much higher yield (Table 2, entries 9, 11 & 13). We speculated that an electron-donating group can increase the nucleophilicity of the C3 position, which facilitated nucleophilic addition.

In order to further investigate the scope of HKAs, the seven-membered HKA (n=2) **1g** also was employed in this process (Table 2, entry 26), and giving the corresponding product with higher yields than that of six-membered HKAs. Moreover, the bulkiness of 2-phenyl indole **2c** did not hamper the reaction process.

It is noteworthy that all of the isolated products needed only washing with ethanol instead of column chromatography or recrystallization for the work-up. The easy purification makes this protocol facile, environmentally benign, and rapid to execute.

All compounds were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopy. The structure of product **4l** was further confirmed by X-ray crystallographic analysis (Fig. 2).

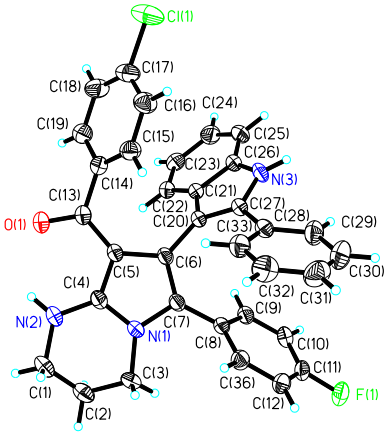
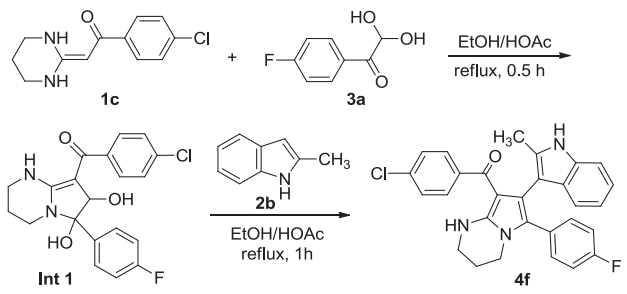


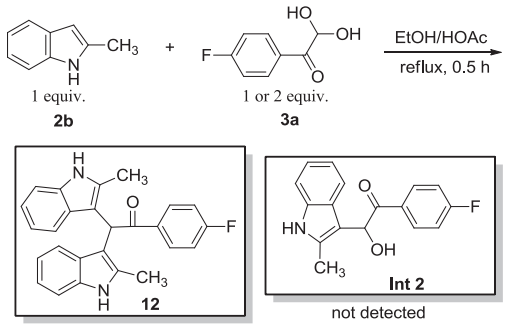
Fig. 2. X-ray crystal structures of **4l**; ellipsoids are drawn at 30% probability level.

Both HKAs and indoles possesses nucleophilic centers, for example, the arylglyoxal monohydrate can provide two electrophilic centers that can be attacked by the C3 of the indole or the β-C and NH of the HKA. Thus, the domino reaction might occur in two directions. To propose a plausible reaction mechanism, some additional experiments were performed. As an initial attempt, we began our investigation by testing the reaction of **1c** and **3a**. An intermediate (**Int 1**) (see Supplementary data) was obtained after half an hour. Then, **2b** was added to the resulting mixture, our desired target molecule **4f** was obtained with the consumption of **1c** (Scheme 1). Moreover, **Int 1** can be separated and further reacted with **2b** in the same condition. To our delight, the product **4f** was afforded in excellent yield (97%).



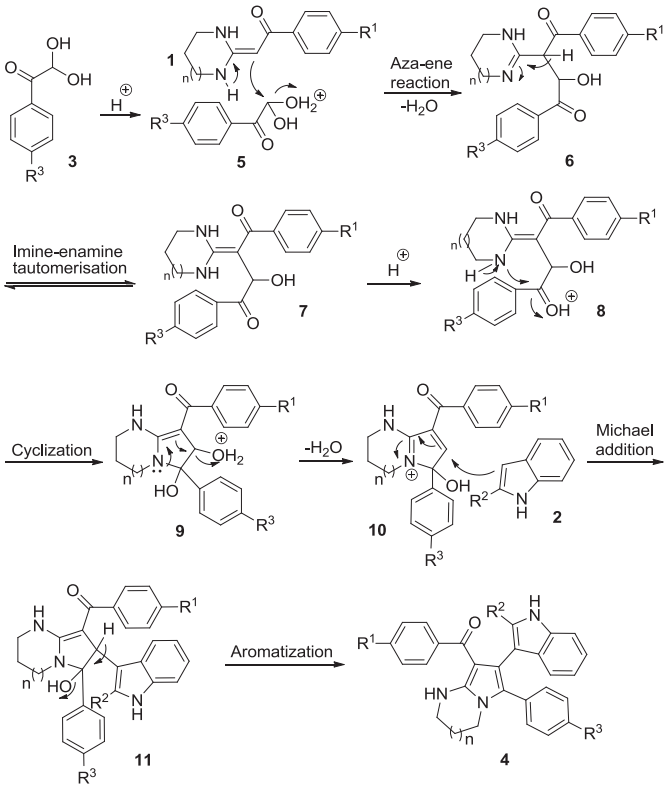
Scheme 1. Verification of reaction mechanism: starting from **1** and **3**.

Comparing with the previous results, we next changed the sequence of adding initial substrates. For example, we added **2b** and **3a** first. The expected intermediate (**Int 2**) was not detected when the above reaction mixtures were heat, instead the compound **12** was afforded. This phenomenon was also observed even if the arylglyoxal monohydrate was residual (Scheme 2).



Scheme 2. Verification of reaction mechanism: starting from **2** and **3**.

According to the experimental outcomes, a mechanism hypothesis for this domino reaction is proposed as shown in Scheme 3. First, the hydroxyl of arylglyoxal monohydrate **3** accepts one proton to form **5**. With the strong electron-withdrawing keto-carbonyl group at the α-position of the HKA and the electron-donating diamino groups of HKA, HKA **4** serves as a heteroene component to react with compound **5** accompanying the loss of one molecule of H_2O to obtain the intermediate **6** via an aza-ene reaction. Then, compound **6** is followed by imine–enamine tautomerisation[29] to produce **7**. The keto-carbonyl group acquires one proton to give **8**. The NH group of intermediate **8** attacks the intramolecular carbonyl



Scheme 3. Plausible mechanism for the formation of **4**.

group via a cyclization reaction to afford **9**, which followed by dehydration to give intermediate **10**. Next, the intermediate **11** is formed by intermolecular Michael addition between **10** and **2**. Finally, intermediate **11** loses a molecule of H_2O leads to the formation of bicyclic pyrrolo **4**.

3. Conclusion

In summary, we have successfully developed a procedure for the facile synthesis of a variety of potentially biologically active highly functionalized bicyclic pyrrole derivatives based on a novel regioselective domino reaction. This is the first report of the preparation of the highly functional title compounds. The features of this strategy include environmentally friendly conditions, convenient one-pot operation, excellent regioselectivity, and easy purification. Moreover, this series of bicyclic pyrroles may provide new classes of biologically active compounds for biomedical screening. Further investigations into the in vitro biological activities of compounds **4** are in progress.

4. Experimental

4.1. General information

All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker DRX400 & DRX500, chemical shifts (δ) are expressed in parts per million, and J values are given in Hertz, and deuterated DMSO-d_6 was used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using KBr pellet. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF_{254}. The melting points were determined on XT-4A melting point apparatus and are uncorrected. HRMS were performed on an Agilent LC/Msd TOF instrument. All chemicals and solvents were used as received without further purification unless otherwise stated. Compounds **1** were prepared according to the literature.[30] The materials **2a**–**c** and **3a**,**b** were purchased from Aldrich Corporation Limited.

4.2. General procedure for the synthesis of 1,3-diazaheterocycle-fused[1,2-*a*]indoles 4

HKAs **1** (1.0 mmol), indole **2** (1.1 mmol), arylglyoxal monohydrate **3** (1.1 mmol), solvent EtOH (15 mL), and HOAc (0.1 mmol) were charged into a 25 mL round-bottom flask, and the mixture was stirred at reflux until HKA **1** was completely consumed. The mixture was cooled to room temperature. Then, the precipitation was filtered and recrystallized by ethanol to afford the pure products **4** in good yield (72%–95%). The products were further identified by FT-IR, NMR, and HRMS, and were in good agreement with the assigned structures.

4.2.1. (4-Chlorophenyl)(6-(4-fluorophenyl)-7-(1H-indol-2-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4a***. Yellow solid; mp >300 °C; IR (KBr): 3342, 1602, 1523, 1417, 1219, 1151, 842, 738 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.59 (br, 1H, NH), 7.99 (br, 1H, NH), 7.23–7.27 (m, 2H, ArH), 6.06–6.10 (m, 1H, ArH), 6.98–7.08 (m, 4H, ArH), 6.92 (d, J=7.9 Hz, 1H, ArH), 6.83–6.88 (m, 1H, ArH), 6.60–6.66 (m, 1H, ArH), 6.63 (d, J=1.8 Hz, 1H, ArH), 6.35–6.41 (m, 2H, ArH), 3.76–3.80 (m, 2H, NCH_2), 3.44–3.52 (m, 2H, NCH_2), 1.97–2.07 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ=187.8, 163.0 (d, J=89.0 Hz), 160.6 (d, J=88.0 Hz), 148.4, 138.0, 135.8, 132.5 (d, J=8.0 Hz), 132.4 (d, J=8.0 Hz), 129.8 (d, J=8.0 Hz), 129.7 (d, J=8.0 Hz), 128.4, 127.9, 125.5, 124.3, 120.8, 119.4, 118.5, 118.3, 115.3 (d, J=21.0 Hz), 115.1 (d, J=21.0 Hz), 112.9 (d, J=21.0 Hz), 112.7 (d, J=21.0 Hz), 112.1, 111.1, 109.5, 102.9, 42.0, 38.3, 21.5; HRMS (TOF ES^+): m/z calcd for $C_{28}H_{23}F_2N_3O$ [$(M+H)^+$], 454.1725; found, 454.1723.

4.2.2. (7-(1H-Indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)(4-fluorophenyl)methanone ***4b***. Yellow solid; mp >300 °C; IR (KBr): 3279, 1602, 1529, 1417, 1219, 1153, 841, 746 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ=10.60 (br, 1H, NH), 8.00 (br, 1H, NH), 7.23 (d, J=7.6 Hz, 2H, ArH), 7.19 (t, J=7.4 Hz, 2H, ArH), 7.12–7.15 (m, 1H, ArH), 7.07 (d, J=8.0 Hz, 1H, ArH), 7.01 (t, J=6.7 Hz, 2H, ArH), 6.92 (d, J=7.9 Hz, 1H, ArH), 6.85 (t, J=7.4 Hz, 1H, ArH), 6.64–6.70 (m, 2H, ArH), 6.38 (t, J=8.5 Hz, 2H, ArH), 3.76–3.84 (m, 2H, NCH_2), 3.45–3.51 (m, 2H, NCH_2), 1.97–2.06 (m, 2H, NCH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ=188.3, 161.6 (d, J=243.8 Hz), 148.8, 138.5, 136.2, 132.4, 130.9, 130.9, 130.1, 128.6, 128.6, 127.3, 125.9, 121.1, 119.8, 118.8, 113.3 (d, J=21.3 Hz), 113.1 (d, J=21.3 Hz), 112.3, 111.4, 110.0, 103.4, 42.6, 38.7, 22.0; HRMS (TOF ES^+): m/z calcd for $C_{28}H_{23}FN_3O$ [$(M+H)^+$], 436.1820; found, 436.1822.

4.2.3. (4-Fluorophenyl)(6-(4-fluorophenyl)-7-(2-methyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4c***. Yellow solid; mp 279–281 °C; IR (KBr): 3348, 1601, 1523, 1410, 1221, 1152, 842, 607 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.40 (br, 1H, NH), 8.00 (br, 1H, NH), 7.11–7.15 (m, 2H, ArH), 6.97–7.03 (m, 3H, ArH), 6.90–6.96 (m, J=4.7 Hz, 2H, ArH), 6.87 (d, J=7.8 Hz, 1H, ArH), 6.80 (t, J=7.4 Hz, 1H, ArH), 6.68 (t, J=7.3 Hz, 1H, ArH), 6.33 (d, J=8.8 Hz, 2H, ArH), 3.79–3.86 (m, 2H, NCH_2), 3.43–3.49 (m, 2H, NCH_2), 1.97–2.09 (m, 2H, NCH_2), 1.74 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ=187.8, 162.2 (d, J=244.0 Hz), 161.1 (d, J=243.0 Hz), 148.5, 137.7, 135.4, 133.1, 131.8, 131.7, 129.6, 129.5, 129.3, 128.7, 124.7, 120.0, 118.4, 118.3, 115.4 (d, J=21.0 Hz), 115.2 (d, J=21.0 Hz), 112.5 (d, J=21.0 Hz), 112.3 (d, J=21.0 Hz), 111.6, 110.1, 106.7, 102.5, 42.0, 38.2, 21.5, 12.2; HRMS (TOF ES^+): m/z calcd for $C_{29}H_{24}F_2N_3O$ [$(M+H)^+$], 468.1882; found, 468.1885.

4.2.4. (4-Fluorophenyl)(7-(2-methyl-1H-indol-3-yl)-6-phen-yl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4d***. Yellow solid; mp 285–286 °C; IR (KBr): 3332, 1601, 1525, 1413, 1220, 1154, 742, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.34 (br, 1H, NH), 7.97 (br, 1H, NH), 7.15 (t, J=7.0 Hz, 2H, ArH), 7.08–7.11 (m, 3H, ArH), 6.86–6.97 (m, 4H, ArH), 6.76–6.80 (m, 1H, ArH), 6.64–6.68 (m, 1H, ArH), 6.33 (t, J=8.6 Hz, 2H, ArH), 3.77–3.87 (m, 2H, NCH_2), 3.43–3.51 (m, 2H, NCH_2), 1.96–2.05 (m, 2H, CH_2), 1.73 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ=188.0, 162.2 (d, J=244.0 Hz), 148.6, 137.8, 135.5, 133.2, 132.3, 139.8, 129.6, 129.5, 128.4, 126.7, 125.8, 120.0, 118.4, 112.6 (d, J=21.0 Hz), 112.3 (d, J=21.0 Hz), 111.6, 110.2, 107.0, 102.6, 42.3, 38.3, 21.6, 12.2; HRMS (TOF ES^+): m/z calcd for $C_{29}H_{25}FN_3O$ [$(M+H)^+$], 450.1976; found, 450.1981.

4.2.5. (4-Fluorophenyl)(6-(4-fluorophenyl)-7-(2-phenyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4e***. Yellow solid; mp 281–283 °C; IR (KBr): 3325, 1603, 1525, 1418, 1221, 1153, 840, 748 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ=10.92 (br, 1H, NH), 8.11 (br, 1H, NH), 7.39 (d, J=7.4 Hz, 2H, ArH), 7.29 (t, J=7.3 Hz, 2H, ArH), 7.17–7.23 (m, 2H, ArH), 7.11 (d, J=4.9 Hz, 2H, ArH), 7.03–7.07 (m, 1H, ArH), 6.92–6.99 (m, 3H, ArH), 6.79–6.82 (m, 1H, ArH), 6.63 (d, J=5.2 Hz, 2H, ArH), 6.27 (t, J=8.5 Hz, 2H, ArH), 3.80–3.90 (m, 2H, NCH_2), 3.48–3.56 (m, 2H, NCH_2), 2.00–2.10 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ=187.8, 161.9 (d, J=241.0 Hz), 161.5 (d, J=242.5 Hz), 148.9, 137.8, 136.1, 134.7, 132.8, 131.5, 130.1, 128.7, 128.5, 128.3, 127.0, 126.4, 124.9, 121.7, 119.3, 119.0, 115.2 (d, J=20.0 Hz), 115.0 (d, J=20.0 Hz), 112.5 (d, J=21.3 Hz), 112.3 (d, J=21.3 Hz), 111.6, 110.9, 107.4, 101.6, 42.0, 38.1, 21.4; HRMS (TOF ES^+): m/z calcd for $C_{34}H_{26}F_2N_3O$ [$(M+H)^+$], 530.2038; found, 530.2036.

4.2.6. (4-Fluorophenyl)(6-phenyl-7-(2-phenyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone

4f. Yellow solid; mp 294–297 °C; IR (KBr): 3303, 1603, 1524, 1422, 1221, 909, 744, 697 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.84 (br, 1H, NH), 8.07 (br, 1H, NH), 7.36 (d, *J*=7.7 Hz, 2H, ArH), 7.26 (t, *J*=7.5 Hz, 2H, ArH), 7.01–7.19 (m, 8H, ArH), 6.94 (t, *J*=7.5 Hz, 1H, ArH), 6.78 (t, *J*=7.4 Hz, 1H, ArH), 6.55–6.59 (m, 2H, ArH), 6.22 (t, *J*=8.8 Hz, 2H, ArH), 3.78–3.91 (m, 2H, NCH_2), 3.45–3.54 (m, 2H, NCH_2), 1.97–2.05 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ=187.9, 161.9 (d, *J*=243.0 Hz), 149.1, 138.0, 136.1, 134.9, 132.9, 132.0, 130.4, 129.6, 128.8, 128.7, 128.6, 128.2, 127.0, 126.8, 126.5, 126.1, 121.2, 119.4, 119.1, 112.6 (d, *J*=21.0 Hz), 112.4 (d, *J*=21.0 Hz), 111.6, 111.0, 107.7, 101.8, 42.3, 38.2, 21.5; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{34}H_{29}FN_3O$ [(M+H)$^+$], 512.2133; found, 512.2131.

4.2.7. (2-Fluorophenyl)(6-(4-fluorophenyl)-7-(2-methyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4g***. Yellow solid; mp 288–290 °C; IR (KBr): 3320, 1609, 1526, 1271, 1157, 1055, 838, 747 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.25 (br, 1H, NH), 8.06 (br, 1H, NH), 7.07–7.11 (m, 2H, ArH), 6.88–7.00 (m, 4H, ArH), 6.68–6.79 (m, 4H, ArH), 6.30–6.39 (m, 2H, ArH), 3.87–3.93 (m, 1H, NCH_2), 3.72–3.77 (m, 1H, NCH_2), 3.34–3.58 (m, 2H, NCH_2), 1.94–2.10 (m, 2H, CH_2), 1.80 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ=184.2, 161.1 (d, *J*=242.0 Hz), 158.2 (d, *J*=243.0 Hz), 148.4, 135.3, 133.3, 131.6 (d, *J*=8.0 Hz), 131.5 (d, *J*=8.0 Hz), 129.9, 129.7, 129.3, 129.2, 128.5, 128.3, 125.3, 121.9, 119.8, 118.5, 118.1, 115.4 (d, *J*=21.0 Hz), 115.2 (d, *J*=21.0 Hz), 113.9 (d, *J*=22.0 Hz), 113.7 (d, *J*=22.0 Hz), 111.8, 110.0, 105.6, 103.9, 42.0, 38.2, 21.4, 12.1; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{29}H_{24}F_2N_3O$ [(M+H)$^+$], 468.1882; found, 468.1883.

4.2.8. (2-Fluorophenyl)(7-(2-methyl-1H-indol-3-yl)-6-phen-yl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)-methanone ***4h***. Yellow solid; mp 295–298 °C; IR (KBr): 3329, 1609, 1530, 1415, 1259, 744, 546, 439 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.20 (br, 1H, NH), 8.04 (br, 1H, NH), 7.05–7.16 (m, 5H, ArH), 6.93 (d, *J*=7.7 Hz, 1H, ArH), 6.87 (d, *J*=7.9 Hz, 1H, ArH), 6.64–6.78 (m, 4H, ArH), 6.30–6.36 (m, 2H, ArH), 3.89–3.92 (m, 1H, NCH_2), 3.73–3.77 (m, 1H, NCH_2), 3.45–3.55 (m, 2H, NCH_2), 1.98–2.06 (m, 2H, CH_2), 1.77 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ=184.2, 158.2 (d, *J*=243.0 Hz), 148.4, 135.3, 133.2, 132.0, 130.1, 129.9, 129.8, 129.5, 129.2, 128.3, 126.6, 126.4, 121.9, 119.7, 118.5, 118.0, 113.9 (d, *J*=21.0 Hz), 113.7 (d, *J*=21.0 Hz), 111.7, 109.9, 105.7, 104.0, 42.1, 38.2, 21.4, 12.1; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{29}H_{25}FN_3O$ [(M+H)$^+$], 450.1976; found, 450.1981.

4.2.9. (7-(1H-Indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a] pyrimidin-8-yl)(4-chlorophenyl)methanone ***4i***. Yellow solid; mp >300 °C; IR (KBr): 3277, 1600, 1528, 1417, 1275, 1098, 741, 690 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ=10.68 (br, 1H, NH), 8.01 (br, 1H, NH), 7.22–7.26 (m, 2H, ArH), 7.19 (t, *J*=7.4 Hz, 2H, ArH), 7.13 (t, *J*=7.1 Hz, 1H, ArH), 7.06 (d, *J*=8.1 Hz, 1H, ArH), 6.94 (d, *J*=8.3 Hz, 2H, ArH), 6.91 (d, *J*=7.9 Hz, 1H, ArH), 6.85 (t, *J*=7.5 Hz, 1H, ArH), 6.67 (d, *J*=4.4 Hz, 2H, ArH), 6.60 (d, *J*=8.3 Hz, 1H, ArH), 3.75–3.85 (m, 2H, NCH_2), 3.42–3.52 (m, 2H, NCH_2), 1.98–2.06 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ=188.1, 148.9, 140.6, 136.2, 133.5, 132.3, 130.8, 129.5, 128.6, 127.3, 126.4, 126.0, 121.1, 119.8, 118.8, 112.3, 111.4, 109.9, 103.5, 42.6, 38.7, 21.9; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{28}H_{23}ClN_3O$ [(M+H)$^+$], 452.1542; found, 452.1541.

4.2.10. (4-Chlorophenyl)(6-(4-fluorophenyl)-7-(2-methyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4j***. Yellow solid; mp 282–285 °C; IR (KBr): 3313, 1602, 1526, 1410, 1213, 837, 747, 666 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ=10.46 (br, 1H, NH), 8.02 (br, 1H, NH), 7.14 (d, *J*=5.1 Hz, 2H, ArH), 6.97–7.07 (m, 3H, ArH), 6.79–6.93 (m, 4H, ArH), 6.69 (d, *J*=6.9 Hz, 1H, ArH), 6.59 (d, *J*=7.9 Hz, 2H, ArH), 3.80–3.90 (m, 2H, NCH_2), 3.44–3.54 (m, 2H, NCH_2), 1.96–2.96 (m, 2H, CH_2), 1.78 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ=187.6, 161.0 (d, *J*=243.7 Hz), 148.5, 139.8, 135.3, 133.0, 131.6, 129.3, 128.8, 128.5, 125.5, 124.7, 119.9, 118.3, 118.2, 115.3 (d, *J*=21.2 Hz), 115.1 (d, *J*=21.2 Hz), 111.4, 110.0, 106.6, 102.5, 42.0, 38.2, 21.4, 12.1; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{29}H_{25}ClFN_3O$ [(M+H)$^+$], 484.1586; found, 484.1585.

4.2.11. (4-Chlorophenyl)(7-(2-methyl-1H-indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4k***. Yellow solid; mp 273–275 °C; IR (KBr): 3291, 1602, 1526, 1412, 1166, 1090, 743, 692 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ=10.40 (br, 1H, NH), 8.01 (br, 1H, NH), 7.17 (t, *J*=7.3 Hz, 2H, ArH), 7.11–7.13 (m, 3H, ArH), 6.96 (d, *J*=7.9 Hz, 1H, ArH), 6.79–6.92 (m, 4H, ArH), 6.65–6.69 (m, 1H, ArH), 6.58 (d, *J*=8.0 Hz, 2H, ArH), 3.79–3.90 (m, 2H, NCH_2), 3.44–3.54 (m, 2H, NCH_2), 1.96–2.08 (m, 2H, CH_2), 1.75 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ=188.1, 149.0, 140.3, 135.8, 133.5, 132.6, 130.1, 129.9, 129.2, 128.7, 127.0, 126.2, 126.0, 120.4, 118.7, 111.8, 110.5, 107.3, 103.1, 42.6, 38.6, 21.9, 12.6; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{29}H_{25}ClN_3O$ [(M+H)$^+$], 466.1681; found, 466.1687.

4.2.12. (4-Chlorophenyl)(6-(4-fluorophenyl)-7-(2-phenyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4l***. Yellow solid; mp >300 °C; IR (KBr): 3303, 1603, 1525, 1420, 1216, 1091, 835, 745 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.92 (br, 1H, NH), 8.10 (br, 1H, NH), 7.37 (d, *J*=7.8 Hz, 2H, ArH), 7.37 (d, *J*=7.6 Hz, 2H, ArH), 7.15–7.20 (m, 2H, ArH), 7.08–7.14 (m, 2H, ArH), 7.02 (d, *J*=7.9 Hz, 1H, ArH), 6.97 (d, *J*=7.2 Hz, 1H, ArH), 6.89–6.95 (m, 3H, ArH), 6.92 (t, *J*=8.9 Hz, 3H, ArH), 6.80 (t, *J*=7.4 Hz, 1H, ArH), 6.55 (d, *J*=8.3 Hz, 2H, ArH), 3.79–3.88 (m, 2H, NCH_2), 3.47–3.56 (m, 2H, NCH_2), 2.00–2.08 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ=187.7, 161.2 (d, *J*=243.0 Hz), 149.1, 140.1, 136.1, 134.8, 132.9, 131.6, 131.6, 130.2, 128.6, 128.3, 128.2, 127.1, 126.5, 125.7, 125.1, 121.8, 119.4, 119.1, 115.3 (d, *J*=22.0 Hz), 115.1 (d, *J*=22.0 Hz), 111.7, 111.0, 107.3, 101.8, 42.1, 38.2, 21.4; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{34}H_{26}ClFN_3O$ [(M+H)$^+$], 546.1743; found, 546.1739.

4.2.13. (4-Chlorophenyl)(6-phenyl-7-(2-phenyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4m***. Yellow solid; mp 174–177 °C; IR (KBr): 3343, 1603, 1524, 1417, 1219, 1151, 842, 739 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ=10.90 (br, 1H, NH), 8.11 (br, 1H, NH), 7.39 (d, *J*=7.6 Hz, 2H, ArH), 7.28 (t, *J*=7.7 Hz, 2H, ArH), 7.15–7.20 (m, 2H, ArH), 6.97–7.12 (m, 6H, ArH), 6.96 (t, *J*=7.3 Hz, 1H, ArH), 6.76–6.82 (m, 1H, ArH), 6.53 (d, *J*=8.2 Hz, 2H, ArH), 6.47 (d, *J*=8.3 Hz, 2H, ArH), 3.80–3.88 (m, 2H, NCH_2), 3.47–3.53 (m, 2H, NCH_2), 1.97–2.06 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ=187.6, 149.1, 140.1, 136.0, 134.8, 132.8, 132.6, 131.8, 130.4, 129.5, 128.5, 128.1, 128.0, 127.0, 126.7, 126.5, 126.2, 125.6, 121.6, 119.3, 119.0, 111.5, 110.9, 107.5, 101.9, 42.2, 38.2, 21.4; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{34}H_{27}ClN_3O$ [(M+H)$^+$], 528.1837; found, 528.1839.

4.2.14. (2-Chlorophenyl)(6-(4-fluorophenyl)-7-(1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4n***. Yellow solid; mp 282–284 °C; IR (KBr): 3365, 1608, 1529, 1413, 1156, 743, 653, 548 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.42 (br, 1H, NH), 8.12 (br, 1H, NH), 7.17–7.25 (m, 2H, ArH), 6.93–7.03 (m, 4H, ArH), 6.80–6.88 (m, 2H, ArH), 6.60–6.75 (m, 4H, ArH), 3.76–3.84 (m, 2H, NCH_2), 3.47–3.53 (m, 2H, NCH_2), 1.98–2.06 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ=186.1, 161.3 (d, *J*=243.0 Hz), 148.5, 140.8, 135.7, 132.1, 130.0, 128.6, 128.4, 128.1, 125.4, 125.3, 125.0, 120.6, 119.5, 118.3, 115.2 (d, *J*=21.0 Hz), 115.0 (d, *J*=21.0 Hz), 111.9, 110.9, 108.1, 103.9, 42.0, 38.2, 21.4; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{28}H_{22}ClFN_3O$ [(M+H)$^+$], 470.1430; found, 470.1435.

4.2.15. (7-(1H-Indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a] pyrimidin-8-yl)(2-chlorophenyl)methanone ***4o***. Yellow solid; mp

>300 °C; IR (KBr): 3345, 1606, 1531, 1418, 1279, 1103, 742, 693 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ=10.41 (br, 1H, NH), 8.13 (br, 1H, NH), 7.18 (d, J=7.2 Hz, 2H, ArH), 7.13 (t, J=7.1 Hz, 2H, ArH), 7.09 (d, J=6.9 Hz, 1H, ArH), 6.97–7.03 (m, 2H, ArH), 6.82–6.86 (m, 2H, ArH), 6.71 (d, J=6.3 Hz, 2H, ArH), 6.61–6.67 (m, 2H, ArH), 3.76–3.84 (m, 2H, NCH_2), 3.45–3.53 (m, 2H, NCH_2), 1.98–2.06 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ=186.5, 149.0, 141.2, 136.1, 132.2, 130.4, 129.2, 128.8, 128.6, 128.4, 128.4, 127.2, 126.9, 125.7, 125.3, 121.0, 120.0, 118.6, 112.2, 111.2, 108.7, 104.4, 42.5, 38.7, 21.9; HRMS (TOF ES^+): m/z calcd for $C_{28}H_{23}ClN_3O$ [$(M+H)^+$], 452.1542; found, 452.1533.

4.2.16. (2-Chlorophenyl)(6-(4-fluorophenyl)-7-(2-methyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4p***. Yellow solid; mp 271–273 °C; IR (KBr): 3344, 1609, 1525, 1369, 1269, 1157, 748, 542 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.23 (br, 1H, NH), 8.12 (br, 1H, NH), 7.06–7.11 (m, 2H, ArH), 6.97 (t, J=8.7 Hz, 3H, ArH), 6.88 (d, J=7.8 Hz, 1H, ArH), 6.79 (t, J=7.3 Hz, 2H, ArH), 6.66–6.73 (m, 3H, ArH), 6.54–6.62 (m, 1H, ArH), 3.87–3.91 (m, 1H, NCH_2), 3.72–3.76 (m, 1H, NCH_2), 3.42–3.59 (m, 2H, NCH_2), 1.99–2.06 (m, 2H, CH_2), 1.83 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ=186.0, 161.2 (d, J=242.0 Hz), 148.8, 140.2, 135.3, 131.6, 131.5, 130.2, 128.4, 127.9, 125.7, 124.4, 119.8, 118.8, 118.1, 115.4 (d, J=21.0 Hz), 115.1 (d, J=21.0 Hz), 111.6, 110.0, 109.9, 103.5, 42.0, 38.2, 21.4, 12.3; HRMS (TOF ES^+): m/z calcd for $C_{29}H_{24}ClFN_3O$ [$(M+H)^+$], 484.1586; found, 484.1593.

4.2.17. (2-Chlorophenyl)(7-(2-methyl-1H-indol-3-yl)-6-phen-yl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4q***. Yellow solid; mp 289–290 °C; IR (KBr): 3325, 1607, 1528, 1471, 1276, 1166, 742, 696 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ=10.20 (br, 1H, NH), 8.13 (br, 1H, NH), 7.12 (d, J=7.3 Hz, 2H, ArH), 7.04–7.09 (m, 3H, ArH), 6.98 (d, J=6.9 Hz, 1H, ArH), 6.87 (d, J=7.7 Hz, 1H, ArH), 6.78 (t, J=7.3 Hz, 2H, ArH), 6.63–6.75 (m, 3H, ArH), 6.55–6.61 (m, 1H, ArH), 3.89–3.93 (m, 1H, NCH_2), 3.73–3.79 (m, 1H, NCH_2), 3.50–3.58 (m, 1H, NCH_2), 3.43–3.47 (m, 1H, NCH_2), 2.05–2.11 (m, 1H, CH_2), 1.98–2.02 (m, 1H, CH_2), 1.73 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ=186.4, 149.3, 140.6, 135.7, 132.4, 130.7, 129.9, 128.7, 128.7, 128.3, 127.1, 124.8, 120.2, 119.2, 118.4, 111.9, 110.3, 104.0, 42.5, 38.6, 21.8, 12.8; HRMS (TOF ES^+): m/z calcd for $C_{29}H_{25}ClN_3O$ [$(M+H)^+$], 466.1681; found, 466.1679.

4.2.18. (2-Chlorophenyl)(6-(4-fluorophenyl)-7-(2-phenyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4r***. Yellow solid; mp >300 °C; IR (KBr): 3325, 1611, 1527, 1420, 1222, 1021, 743, 552 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.78 (br, 1H, NH), 8.21 (br, 1H, NH), 7.46 (d, J=7.7 Hz, 2H, ArH), 7.28–7.33 (m, 2H, ArH), 7.17–7.22 (m, 1H, ArH), 7.12 (d, J=7.8 Hz, 1H, ArH), 7.01–7.09 (m, 3H, ArH), 6.85–6.95 (m, 4H, ArH), 6.78–6.82 (m, 1H, ArH), 6.69–6.74 (m, 1H, ArH), 6.32–6.36 (m, 2H, ArH), 3.78–3.88 (m, 2H, NCH_2), 3.50–3.58 (m, 2H, NCH_2), 2.00–2.08 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ=186.0, 161.2 (d, J=242.0 Hz), 149.3, 140.1, 136.0, 133.1, 131.3, 131.0, 129.7, 128.7, 128.3, 128.1, 127.0, 126.5, 125.6, 124.3, 121.6, 119.8, 118.8, 115.3 (d, J=21.0 Hz), 115.1 (d, J=21.0 Hz), 111.8, 110.7, 106.7, 102.8, 42.1, 38.3, 21.4; HRMS (TOF ES^+): m/z calcd for $C_{34}H_{26}ClFN_3O$ [$(M+H)^+$], 546.1743; found, 546.1741.

4.2.19. (2-Chlorophenyl)(6-phenyl-7-(2-phenyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4s***. Yellow solid; mp >300 °C; IR (KBr): 3307, 1607, 1525, 1323, 1215, 1104, 745, 694 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.76 (br, 1H, NH), 8.22 (br, 1H, NH), 7.44–7.52 (m, 2H, ArH), 7.26–7.34 (m, 2H, ArH), 6.90–7.23 (m, 10H, ArH), 6.71–6.81 (m, 3H, ArH), 6.31–6.35 (m, 1H, ArH), 3.80–3.89 (m, 2H, NCH_2), 3.49–3.58 (m, 2H, NCH_2), 2.00–2.06 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ=186.0, 149.3, 140.2, 136.0, 133.2, 131.8, 131.2, 129.7, 129.4, 128.8, 128.2, 128.2, 127.0, 126.9, 126.7, 126.5, 124.3, 121.6, 119.9, 118.8, 111.7, 110.7, 107.0, 102.3, 42.2, 38.3, 21.4; HRMS (TOF ES^+): m/z calcd for $C_{34}H_{27}ClN_3O$ [$(M+H)^+$], 528.1837; found, 528.1833.

4.2.20. (7-(1H-Indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)(phenyl)methanone ***4t***. Yellow solid; mp >300 °C; IR (KBr): 3277, 1602, 1526, 1415, 1276, 1105, 742, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.45 (br, 1H, NH), 8.01 (br, 1H, NH), 7.09–7.22 (m, 5H, ArH), 6.97–7.04 (m, 3H, ArH), 6.94 (d, J=7.9 Hz, 1H, ArH), 6.80–6.88 (m, 2H, ArH), 6.57–6.68 (m, 4H, ArH), 3.77–3.83 (m, 2H, NCH_2), 3.44–3.52 (m, 2H, NCH_2), 1.97–2.07 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ=189.3, 148.4, 141.7, 135.8, 132.1, 130.4, 128.6, 128.2, 128.0, 127.5, 126.8, 126.2, 125.5, 125.3, 120.6, 119.5, 118.3, 112.1, 111.0, 109.6, 103.1, 42.2, 38.3, 21.6; HRMS (TOF ES^+): m/z calcd for $C_{28}H_{25}N_3O$ [$(M+H)^+$], 418.1914; found, 418.1913.

4.2.21. (6-(4-Fluorophenyl)-7-(2-methyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)(phenyl)methanone ***4u***. Yellow solid; mp 246–247 °C; IR (KBr): 3363, 1604, 1526, 1400, 1218, 1158, 837, 740 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.29 (br, 1H, NH), 8.02 (br, 1H, NH), 7.12–7.16 (m, 2H, ArH), 7.00 (d, J=8.8 Hz, 2H, ArH), 6.79–6.96 (m, 5H, ArH), 6.78 (t, J=7.4 Hz, 1H, ArH), 6.67 (t, J=7.4 Hz, 1H, ArH), 6.59 (t, J=7.6 Hz, 2H, ArH), 3.80–3.86 (m, 2H, NCH_2), 3.44–3.52 (m, 2H, NCH_2), 1.96–2.96 (m, 2H, CH_2), 1.75 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ=189.2, 161.1 (d, J=242.0 Hz), 148.5, 141.2, 135.4, 133.2, 131.8 (d, J=8.0 Hz), 131.7 (d, J=8.0 Hz), 129.3, 128.8, 128.6, 127.3, 125.8, 124.6, 119.8, 118.3, 115.3 (d, J=21.0 Hz), 115.1 (d, J=21.0 Hz), 111.7, 110.2, 106.8, 102.6, 42.0, 38.2, 21.5, 12.2; HRMS (TOF ES^+): m/z calcd for $C_{29}H_{25}FN_3O$ [$(M+H)^+$], 450.1976; found, 450.1971.

4.2.22. (7-(2-Methyl-1H-indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)(phenyl)methanone ***4v***. Yellow solid; mp >300 °C; IR (KBr): 3311, 1601, 1525, 1406, 1273, 1052, 742, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.29 (br, 1H, NH), 8.02 (br, 1H, NH), 7.08–7.16 (m, 5H, ArH), 6.85–6.94 (m, 5H, ArH), 6.73–6.79 (m, 1H, ArH), 6.62–6.68 (m, 1H, ArH), 6.58 (t, J=7.3 Hz, 3H, ArH), 3.82–3.88 (m, 2H, NCH_2), 3.45–3.53 (m, 2H, NCH_2), 2.17–2.27 (m, 2H, CH_2), 1.73 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ=189.2, 148.5, 141.3, 135.4, 133.1, 132.4, 129.8, 129.5, 128.6, 128.3, 127.4, 126.5, 125.8, 125.6, 119.7, 118.4, 118.2, 111.6, 110.1, 106.9, 102.6, 42.2, 38.2, 21.6, 12.2; HRMS (TOF ES^+): m/z calcd for $C_{29}H_{26}N_3O$ [$(M+H)^+$], 432.2070; found, 432.2068.

4.2.23. (6-(4-Fluorophenyl)-7-(2-phenyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)(phenyl)methanone ***4w***. Yellow solid; mp 286–287 °C; IR (KBr): 3353, 1602, 1525, 1410, 1219, 1021, 751, 696 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ=10.79 (br, 1H, NH), 8.11 (br, 1H, NH), 7.35 (d, J=7.4 Hz, 2H, ArH), 7.27 (t, J=7.3 Hz, 2H, ArH), 7.16–7.20 (m, 1H, ArH), 7.07–7.14 (m, 3H, ArH), 7.05 (d, J=7.8 Hz, 1H, ArH), 6.89–6.95 (m, 3H, ArH), 6.85 (t, J=7.1 Hz, 1H, ArH), 6.79 (t, J=7.2 Hz, 1H, ArH), 6.61 (d, J=7.3 Hz, 2H, ArH), 6.49 (t, J=7.3 Hz, 2H, ArH), 3.79–3.88 (m, 2H, NCH_2), 3.46–3.56 (m, 2H, NCH_2), 2.00–2.08 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ=189.2, 161.0 (d, J=242.5 Hz), 148.9, 141.4, 136.0, 134.8, 132.9, 131.6, 130.2, 128.4, 128.1, 126.9, 126.6, 126.5, 125.7, 124.7, 121.5, 119.3, 118.9, 115.2 (d, J=21.3 Hz), 115.0 (d, J=21.3 Hz), 111.9, 110.9, 107.4, 101.8, 42.0, 38.1, 21.4; HRMS (TOF ES^+): m/z calcd for $C_{34}H_{27}FN_3O$ [$(M+H)^+$], 512.2133; found, 512.2128.

4.2.24. Phenyl(6-phenyl-7-(2-phenyl-1H-indol-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)methanone ***4x***. Yellow solid; mp >300; IR (KBr): 3306, 1603, 1522, 1413, 1215, 1173, 744, 692 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ=10.76 (br, 1H, NH), 8.12

(br, 1H, NH), 7.36 (d, J=7.7 Hz, 2H, ArH), 7.27 (t, J=7.5 Hz, 2H, ArH), 7.15–7.19 (m, 1H, ArH), 7.01–7.12 (m, 7H, ArH), 6.93 (t, J=7.4 Hz, 1H, ArH), 6.84 (t, J=7.2 Hz, 1H, ArH), 6.78 (t, J=7.4 Hz, 1H, ArH), 6.58 (d, J=7.6 Hz, 1H, ArH), 6.48 (t, J=7.4 Hz, 2H, ArH), 6.32–6.36 (m, 2H, ArH), 3.89 (q, J=5.8 Hz, 1H, NCH_2), 3.80–3.92 (m, 2H, NCH_2), 3.46–3.56 (m, 2H, NCH_2), 2.00–2.07 (m, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ=189.2, 149.0, 141.4, 136.0, 134.8, 133.0, 132.0, 130.1, 129.6, 128.4, 128.1, 126.8, 126.8, 126.5, 125.9, 125.7, 121.4, 119.4, 118.9, 111.8, 110.9, 107.6, 101.9, 42.2, 38.2, 21.5; HRMS (TOF ES$^+$): m/z calcd for $C_{34}H_{28}N_3O$ [(M+H)$^+$], 494.2227; found, 494.2226.

4.2.25. (7-(2-Methyl-1H-indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidin-8-yl)(p-tolyl)methanone ***4y***. Yellow solid; mp >300; IR (KBr): 3288, 1602, 1526, 1410, 1272, 1168, 744, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.29 (br, 1H, NH), 7.96 (br, 1H, NH), 7.13 (d, J=7.2 Hz, 2H, ArH), 7.07–7.11 (m, 3H, ArH), 6.94 (d, J=8.0 Hz, 1H, ArH), 6.86 (d, J=7.8 Hz, 1H, ArH), 6.74–6.81 (m, 3H, ArH), 6.62–6.66 (m, 1H, ArH), 6.36 (d, J=7.8 Hz, 2H, ArH), 3.86 (t, J=5.7 Hz, 2H, NCH_2), 3.44–3.50 (m, 2H, NCH_2), 2.01 (t, J=5.0 Hz, 2H, CH_2), 1.98 (s, 3H, CH_3), 1.72 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ=189.2, 148.3, 138.5, 137.9, 135.4, 133.1, 132.4, 130.0, 129.5, 128.3, 127.5, 126.5, 126.3, 125.5, 119.7, 118.4, 118.2, 111.7, 109.9, 107.1, 102.7, 42.2, 38.2, 21.6, 21.3, 12.2; HRMS (TOF ES$^+$): m/z calcd for $C_{30}H_{28}N_3O$ [(M+H)$^+$], 446.2227; found, 446.2229.

4.2.26. (4-Chlorophenyl)(7-(4-fluorophenyl)-8-(2-methyl-1H-indol-3-yl)-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,3]diazepin-9-yl)methanone ***4z***. Yellow solid; mp >300; IR (KBr): 3348, 1542, 1412, 1225, 1086, 836, 738, 671 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=10.44 (br, 1H, NH), 7.91 (br, 1H, NH), 7.06 (d, J=7.2 Hz, 4H, ArH), 6.90–6.96 (m, 3H, ArH), 6.79–6.83 (m, 2H, ArH), 6.62–6.69 (m, 3H, ArH), 3.73–3.79 (m, 1H, NCH_2), 3.57–3.63 (m, 1H, NCH_2), 3.33–3.37 (m, 1H, NCH_2), 3.17–3.23 (m, 1H, NCH_2), 1.79–1.94 (m, 4H, CH_2), 1.74 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ=190.2, 161.1 (d, J=243.0 Hz), 155.1, 138.7, 135.4, 134.1, 132.9, 131.8 (d, J=8.0 Hz), 131.7 (d, J=8.0 Hz), 129.4, 129.1, 127.0, 125.8, 118.4, 118.2, 115.8 (d, J=21.0 Hz), 115.6 (d, J=21.0 Hz), 113.1, 110.2, 106.5, 106.2, 47.9, 46.5, 30.1, 27.3, 12.1; HRMS (TOF ES$^+$): m/z calcd for $C_{30}H_{26}ClFN_3O$ [(M+H)$^+$], 498.1743; found, 498.1742.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.12.062.

References and notes

1. (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (b) Hulme, C.; Gore, V. V. *Curr. Med. Chem.* **2003**, *10*, 51–80; (c) Lieby-Muller, F.; Constantieux, T.; Rodriguez Jean, J. *J. Am. Chem. Soc.* **2005**, *127*, 17176–17177.
2. (a) Pando, O.; Stark, S.; Dnkert, A.; Porzel, A.; Preusentanz, R.; Wessjohann, L. A. *J. Am. Chem. Soc.* **2011**, *133*, 7692–7695; (b) Singh, M. S.; Chowdhury, S. *RSC Adv.* **2012**, *2*, 4547–4592; (c) Shaabani, A.; Rezayan, A. H.; Keshipour, S.; Sarvary, A.; Ng, S. W. *Org. Lett.* **2009**, *11*, 3342–3345; (d) Nair, V.; Rajesh, C.; Vinod, A.; Bindu, U. S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899–907.
3. (a) Cheng, C.; Jiang, B.; Tu, S.-J.; Li, G.-G. *Green Chem.* **2011**, *13*, 2107–2115; (b) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472; (c) Aditya, K.; Béla, T. *Green Chem.* **2010**, *12*, 875–878; (d) Barry, B. T.; Dennis, G. H. *Chem. Rev.* **2009**, *109*, 4439–4486; (e) Kumaravel, K.; Vasuki, G. *Green Chem.* **2009**, *11*, 1945–1947; (f) Candeias, N. R.; Veiros, L. F.; Afonso, C. A. M.; Gois, P. M. P. *Eur. J. Org. Chem.* **2009**, *12*, 1859–1863; (g) Ma, N.; Jiang, B.; Zhang, G.; Tu, S.-J.; Wever, W.; Li, G.-G. *Green Chem.* **2010**, *12*, 1357–1361; (h) Jiang, B.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G.-G. *J. Am. Chem. Soc.* **2009**, *131*, 11660–11661.
4. (a) Saxton, J. E. *Nat. Prod. Rep.* **1997**, *14*, 559–590; (b) Toyota, M.; Ihara, N. *Nat. Prod. Rep.* **1998**, *15*, 327–340; (c) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev.* **2009**, *109*, 3080–3098; (d) Ishikura, M.; Yamada, K. *Nat. Prod. Rep.* **2009**, *26*, 803–852; (e) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843–868; (f) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761–765; (g) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.
5. (a) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489–4497; (b) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508–3549; (c) Yamashita, T.; Kawai, N.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 15038–15039; (d) Van Zandt, M. C.; Jones, M. L.; Gunn, D. E.; Geraci, L. S.; Jones, J. H.; Sawicki, D. R.; Sredy, J.; Jacot, J. L.; DiCioccio, A. T.; Petrova, T.; Mitschler, A.; Podjarny, A. D. *J. Med. Chem.* **2005**, *48*, 3141–3152; (e) Estevão, M. S.; Carvalho, L. C. R.; Freitas, M.; Gomes, A.; Viegas, A.; Manso, J.; Erhardt, S.; Fernandes, E.; Cabrita, E. J.; Marques, M. M. B. *Eur. J. Med. Chem.* **2012**, *54*, 823–833.
6. (a) Wu, Y.-S.; Coumar, M. S.; Chang, J.-Y.; Sun, H.-Y.; Kuo, F.-M.; Kuo, C.-C.; Chen, Y.-J.; Chang, C.-Y.; Hsiao, C. L.; Liou, J.-P.; Chen, C.-P.; Yao, H. T.; Chiang, Y. K.; Tan, U. K.; Chen, C.-T.; Chu, C.-Y.; Wu, S.-Y.; Yeh, T. K.; Lin, C.-Y.; Hsieh, H. P. *J. Med. Chem.* **2009**, *52*, 4941–4945; (b) Thirumurugan, P.; Nandakumar, A.; Muralidharan, D.; Perumal, P. T. *J. Comb. Chem.* **2010**, *12*, 161–167; (c) Zhu, S.; Ji, S.; Su, X.; Sun, C.; Liu, Y. *Tetrahedron Lett.* **2008**, *49*, 1777–1781; (d) Liu, W.-G.; Liu, K.; Wood, H. B.; McCann, M. E.; Doebber, T. W.; Chang, C.-H.; Akiyama, T. E.; Einstein, M.; Berger, J. P.; Meinke, P. T. *J. Med. Chem.* **2009**, *52*, 4443–4453.
7. (a) Yadav, J. S.; Subba- Reddy, B. V.; Praneeth, K. *Tetrahedron Lett.* **2008**, *49*, 2815–2819; (b) Amat, M.; Llor, N.; Checa, B.; Molins, E.; Bosch, J. *J. Org. Chem.* **2010**, *75*, 178–189; (c) Mason, J. J.; Bergman, J.; Janosik, T. *J. Nat. Prod.* **2008**, *71*, 1447–1450; (d) Garr, A. N.; Luo, D.-H.; Brown, N.; Cramer, C. J.; Buszek, K. R.; Velde, D. V. *Org. Lett.* **2010**, *12*, 96–99.
8. (a) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469–6480; (b) Regina, G. L.; Coluccia, A.; Brancale, A.; Piscitelli, F.; Gatti, V.; Maga, G.; Samuele, A.; Pannecouque, C.; Schols, D.; Balzarini, J.; Novellino, E.; Silvestri, R. *J. Med. Chem.* **2011**, *54*, 1587–1589.
9. (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402–4421; (b) Preller, M.; Chinthalapudi, K.; Martin, R.; Knölker, H.-J.; Manstrin, D. J. *J. Med. Chem.* **2011**, *54*, 3675–3685; (c) Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. *J. Med. Chem.* **2005**, *48*, 3796–3807.
10. (a) Wang, L.; Cherian, C.; Desmoulin, S. K.; Mitchell-Ryan, S.; Hou, Z.-J.; Matherly, L. H.; Gangjee, A. *J. Med. Chem.* **2012**, *55*, 1758–1770; (b) Gangjee, A.; Jain, H. D.; Queener, S. F.; Kisliuk, R. L. *J. Med. Chem.* **2008**, *51*, 4589–4600; (c) Deng, Y.-J.; Wang, Y.-Q.; Cherian, C.; Hou, Z.-J.; Buck, S. A.; Matherly, L. H.; Gangjee, A. *J. Med. Chem.* **2008**, *51*, 5052–5063; (d) Soares, M. L.; Brito, A. F.; Laranjo, M.; Paixão, J. A.; Botelho, M. F.; Melo, T. M. V. D. P. *Eur. J. Med. Chem.* **2013**, *60*, 254–262; (e) Wang, L.; Desmoulin, S.; Cherian, K. C.; Polin, L.; White, K.; Kushner, J.; Fulterer, A.; Chang, M.-H.; Mitchell-Ryan, S. M.; Romero, M. F.; Hou, Z.-J.; Matherly, L. H.; Gangjee, A. *J. Med. Chem.* **2011**, *54*, 7150–7164; (f) Tangeda, S. J.; Garlapati, A. *Eur. J. Med. Chem.* **2010**, *45*, 1453–1458.
11. Regueiro-Ren, A.; Xue, Q.-M.; Swidorski, J. J.; Gong, Y.-F.; Mathew, M.; Parker, D. D.; Yang, Z.; Eggers, B.; D'Arienzo, C.; Sun, Y.-N.; Malinowski, J.; Gao, Q.; Wu, D.-D.; Langley, D. R.; Colonno, R. J.; Chien, C.; Grasela, D. M.; Zheng, M.; Lin, P.-F.; Meanwell, N. A.; Kadow, J. F. *J. Med. Chem.* **2013**, *56*, 1656–1669.
12. (a) Pudio, J. S.; Saxena, N. K.; Nassiri, M. R.; Turk, S. R.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1988**, *31*, 2086–2092; (b) Saxena, N. K.; Hagenow, B. M.; Genzlinger, G.; Turk, S. R.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1988**, *31*, 1501–1506.
13. E1-Gaby, M. S. A. A.; Gaber, M.; Atalla, A. A.; Abd Al-Wahab, K. A. *IL Farmaco* **2002**, *57*, 613–617.
14. Varaprasad, C. V. N. S. S.; Ramasamy, K.; Girardet, J. L.; Gunic, E.; Lai, V.; Zhong, Z.; An, H.; Hong, Z. *Bioorg. Chem.* **2007**, *35*, 25–34.
15. Trzoss, M.; Bensen, D. C.; Lia, X.-M.; Chen, Z.-Y.; Lam, T.; Zhang, J.-Z.; Creighton, C. J.; Cunningham, M. L.; Kwan, B.; Stidham, M.; Nelson, K.; Brown-Driver, V.; Castellano, A.; Shaw, K. J.; Lightstone, F. C.; Wong, S.-E.; Nguyen, T. B.; Finn, J.; Tari, L. W. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1537–1543.
16. Chen, Z.-C.; Venkatesan, A. M.; Dehnhardt, C. M.; Ayral-Kaloustian, S.; Brooijmans, N.; Mallon, R.; Feldberg, L.; Hollander, I.; Lucas, J.; Yu, K.; Kong, F.-M.; Mansour, T. S. *J. Med. Chem.* **2010**, *53*, 3169–3682.
17. (a) Clark, M. P.; George, K. M.; Bookland, R. G.; Chen, J.; Laughlin, S. K.; Thakur, K. D.; Lee, W.; Davis, J. R.; Cabrera, E. J.; Brugel, T. A.; VanRens, J. C.; Laufersweiler, M. J.; Maier, J. A.; Sabat, M. P.; Golebiowski, A.; Easwaran, V.; Webster, M. E.; Dea, B.; Zhang, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1250–1253; (b) Weinberg, L. R.; Albom, M. S.; Angeles, T. S.; Breslin, H. J.; Gingrich, D. E.; Huang, Z.-Q.; Lisko, J. G.; Mason, J. L.; Milkiewicz, K. L.; Thieu, T. V.; Underiner, T. L.; Wells, G. J.; Wells-Knecht, K. J.; Dorsey, B. D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7325–7330.
18. Lindsay, K. B.; Pyne, S. G. *Tetrahedron* **2004**, *60*, 4173–4176.
19. Liu, Y.; Fang, J.-P.; Cai, H.-Y.; Xiao, F.; Ding, K.; Hua, Y.-H. *Bioorg. Med. Chem.* **2012**, *20*, 5473–5482.
20. Palmer, A. M.; Münch, G.; Brehm, C.; Zimmermann, P. J.; Buhr, W.; Feth, M. P.; Simon, W. A. *Bioorg. Med. Chem.* **2008**, *16*, 1511–1530.
21. Taylor, E. C.; Kuhnt, D.; Shih, C.; Rinzel, S. M.; Grindey, G. B.; Barredo, J.; Jannatipour, M.; Moran, G. R. *J. Med. Chem.* **1992**, *35*, 4450–4454.

22. (a) Kaspersen, S. J.; Sundby, E.; Charnock, C.; Hoff, B. H. *Bioorg. Chem.* **2012**, *44*, 35–41; (b) Bernotas, R. C.; Lenicek, S.; Antane, S.; Cole, D. C.; Harrison, B. L.; Robichaud, A. J.; Zhang, G.-M.; Smith, D.; Platt, B.; Lin, Q.; Li, P.; Coupet, J.; Rosenzweig-Lipson, S.; Beyer, C. E.; Schechter, L. E. *Bioorg. Med. Chem.* **2009**, *17*, 5153–5183; (c) Oguro, Y.; Miyamoto, N.; Okada, K.; Takagi, T.; Iwata, H.; Awazu, Y.; Miki, H.; Hori, A.; Kamiyama, K.; Imamura, S. *Bioorg. Med. Chem.* **2010**, *18*, 7260–7263; (d) Pittalà, V.; Siracusa, M. A.; Modica, M. N.; Salerno, L.; Pedretti, A.; Vistoli, G.; Cagnotto, A.; Mennini, T.; Romeo, G. *Bioorg. Med. Chem.* **2011**, *19*, 5260–5276.
23. (a) Taylor, E.; Patel, H.; Jun, J.-G. *J. Org. Chem.* **1995**, *60*, 6684–6687; (b) Cobo, J.; Nogueras, M. *Tetrahedron* **1998**, *54*, 5753–5762; (c) Hopkins, C. R.; Collar, N. *Tetrahedron Lett.* **2005**, *46*, 1845–1848; (d) Chen, W.-T.; Hu, M.; Wu, J.-W.; Zou, H.-B.; Yu, Y.-P. *Org. Lett.* **2010**, *12*, 3863–3865; (e) Chen, Y.-H.; Xiang, H.-Y.; Tan, C.; Xie, Y.-Y.; Yang, C.-H. *Tetrahedron* **2013**, *69*, 2714–2719.
24. (a) Yu, F.-C.; Yan, S.-J.; Hu, L.; Wang, Y.-C.; Lin, J. *Org. Lett.* **2011**, *13*, 4782–4785; (b) Yan, S.-J.; Chen, Y.-L.; Liu, L.; He, N.-Q.; Lin, J. *Green Chem.* **2010**, *12*, 2043–2045; (c) Chen, X.-B.; Zhu, D.-D.; Wang, X.-Y.; Yan, S.-J.; Lin, J. *Tetrahedron* **2013**, *69*, 9224–9236; (d) Yan, S.-J.; Chen, Y.-L.; Liu, L.; Tang, Y.-J.; Lin, J. *Tetrahedron Lett.* **2011**, *52*, 465–467; (e) Chen, X.-B.; Liu, X.-M.; Huang, R.; Yan, S.-J.; Lin, J. *Eur. J. Org. Chem.* **2013**, *69*, 4607–4613; (f) Yan, S.-J.; Niu, Y.-F.; Huang, R.; Lin, J. *Synlett* **2009**, 2821–2824.
25. (a) Wang, L.-B.; Yu, C.-Y.; Huang, Z.-T. *Synthesis* **1994**, 1441–1444; (b) Nie, X.-P.; Wang, M.-X.; Huang, Z. T. *Synthesis* **2000**, *17*, 1439–1448; (c) Alizadeh, A.; Rezvanian, A.; Deng, Y. *Tetrahedron* **2010**, *66*, 9933–9937.
26. Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev.* **2013**, *113*, 2958–3034.
27. Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. *J. Org. Chem.* **2008**, *73*, 2090–2095.
28. (a) Quiroga, J.; Acosta, P. A.; Cruz, S.; Abonía, R.; Insuasty, B.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2010**, *51*, 5443–5447; (b) Fu, L.-P.; Shi, Q.-Q.; Shi, Y.; Jiang, B.; Tu, S.-J. *ACS Comb. Sci.* **2013**, *15*, 135–140; (c) Jiang, B.; Li, Q.-Y.; Zhang, H.; Tu, S.-J.; Pindi, S.; Li, G.-G. *Org. Lett.* **2012**, *14*, 700–703; (d) Li, Y.; Li, Q.-Y.; Xu, H.-W.; Fan, W.; Jiang, B.; Wang, S.-L.; Tu, S.-J. *Tetrahedron* **2013**, *69*, 2941–2964.
29. Yu, C.-Y.; Yang, P.-H.; Zhao, M.-X.; Huang, Z.-T. *Synlett* **2006**, 1835–1840.
30. (a) Huang, Z.-T.; Wang, M.-X. *Synthesis* **1992**, *12*, 1273–1275; (b) Li, Z.-J.; Charles, D. *Synth. Commun.* **2001**, *31*, 527–533; (c) Huang, Z.-T.; Liu, Z.-R. *Synth. Commun.* **1989**, *19*, 943–958.