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Synthesis of novel oxindolylpyrrolo[2,3-*d*]pyrimidines via a three-component sequential tandem reaction

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ABSTRACT

A novel one-pot three-component reaction of 6-amino-uracil, isatin, and acetophenone was accomplished through a programmed pH variation for the synthesis of 5-(2-oxoindolin-3-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione derivatives. The reaction was conducted in a sequential tandem manner to give the oxindole substituted pyrrolo[2,3-*d*]pyrimidine products in good to excellent yields. Despite of timing all the processes were carried out in one pot. Most of these novel compounds show narrow to good spectrum of antimicrobial activities in vitro.

1. Introduction

The invention of concise synthetic methodologies for the construction of complex molecules is a pivotal focal point of researches aiming to facilitate the preparation of compound libraries and elaborate syntheses in the field of modern medicinal chemistry. Natural and biologically relevant systems are diverse and often complex molecules, which encourage organic chemists to emulate nature's efficiency in the development of new synthetic methods and reactions for assembling novel compounds. A potential approach toward this goal is to combine two or more distinct reactions into a single transformation, thereby effecting tandem reactions.[1] Tandem reactions widely occur in living organisms and many were discovered by chemists on mimicry to save synthetic operations while maximizing the build-up of structural and functional complexity using simple starting materials.[2] As such, tandem reactions are of increasing importance in modern organic chemistry. One-pot tandem reactions by virtue of their convergence, elegance, and highly step-economy are particularly appealing in the context of rapid target-oriented synthesis.[3] These reactions fall under the fold of green chemistry, as they obviate the isolation and purification of intermediates leading to a reduction in pollution.[4]

3-Substituted indoles are the structural units of many natural and biologically interesting compounds possessing various pharmacological properties.[5–8] A number of indole derivatives have shown antibacterial,[9] antiviral,[10] protein kinase inhibitory[11] as well as potential anticancer activities; indole-3-carbinols have been reported to exhibit anticancer activities against a number of human cancers through acting on different cellular signaling pathways.[12] 1-Aroylindoles and 3-aroylindoles have shown potent cytotoxicity against different human cancer cell lines.[13] Indole alkaloids are quite prevalent in nature and form a prominent class of bioactive natural products.[14] Two diastereoisomeric tris–indole alkaloids, occurring as enantiomeric pairs, designated as (±)-gelliusinus A and B I represent the major components of a deep water Caledonian sponge[15] and vibrindole A II is a metabolite of the marine bacterium, *Vibrio parahaemalyticus*, which is isolated from the toxic mucus of the boxfish *Ostracion cubicus*[16] (Scheme 1).

Prompted by the biological activities of indoles,[17–24] and in line with our interest in the synthesis of heterocyclic compounds,[25–29] herein we report a novel and efficient method for the assembling of 5-(2-oxoindolin-3-yl)-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione derivatives. These compounds belong to the class of oxindolyl-7-deazapurines and to the best of our knowledge this is the first report on their synthesis.

2. Results and discussion

To approach the synthesis of the oxindolylpyrrolo[2,3-*d*]pyrimidines **4**, we based our experiments on a three-component reaction between the model substrates 6-amino-1,3-dimethyluracil **1a**, isatin **2a**, and acetophenone **3a**. Our initial trials centered on

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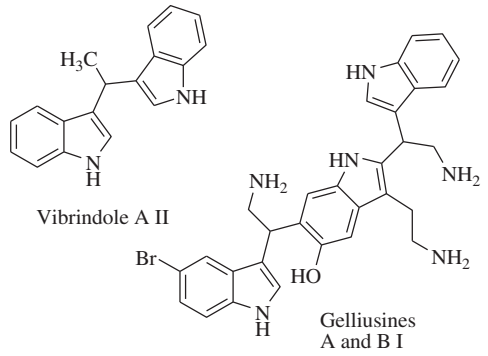


Scheme 1. Instances of the indole alkaloids.

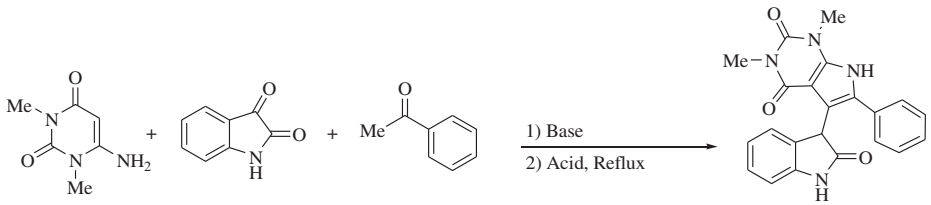
effecting the reaction in the absence of any catalyst, but resulted in low conversions even under prolonged (15 h) refluxing in ethanol (Table 1, entry 1).

the pH of the reaction mixture to be acidic, as we expected, led to condensation of the in situ obtained oxindole intermediate with 6-amino-1,3-dimethyluracil **1a** to give the product **4a**. Certainly, the choice of an appropriate reaction medium is of crucial importance for effecting a successful tandem reaction. In this regard, we attempted to determine the optimum conditions by examining the effect of solvent and catalyst variations on progress of the model reaction. The results were collected in Table 1. It could be seen that the best yield of the product is obtained by the sequential use of piperidine (10 mol %) and *p*-toluenesulfonic acid (*p*-TSA, 40 mol %) in refluxing ethanol at 80 °C (Table 1, entry 8).

After determination of piperidine and *p*-toluenesulfonic acid as suitable catalysts, a variety of isatin derivatives, acetophenones, and amino-uracils were employed under similar conditions to evaluate the substituent scope of this reaction. As Table 2 shows, all the cyclocondensation reactions proceeded efficiently and afforded the products **4a**–**p** in fairly high yields.

Encouraged by these results, we attempted to expand the scope of this synthetic method by using naphthalenamines in place of

Table 1
Optimization of the reaction conditions[a]



1a **2a** **3a** **4a**

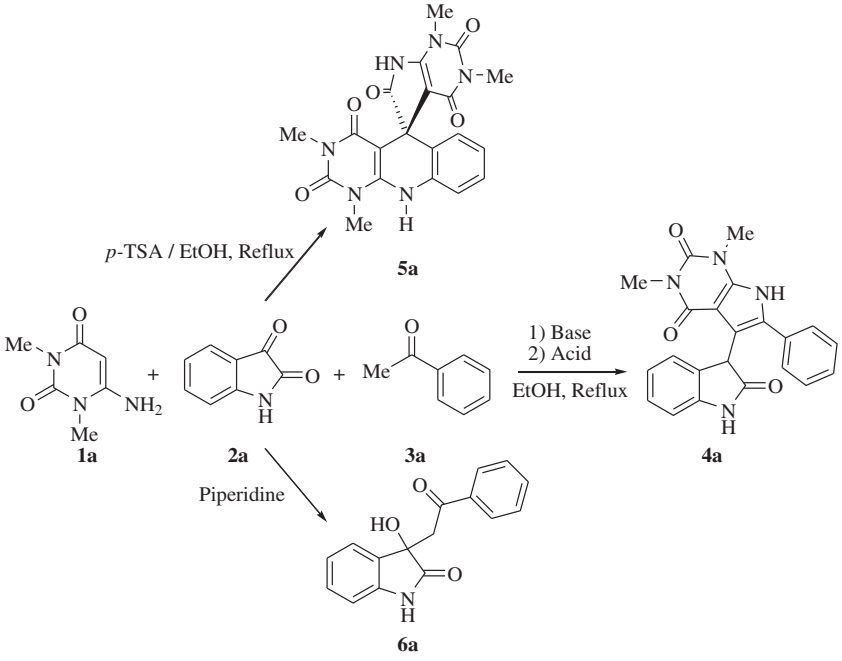
Entry	Solvent	Base catalyst	Acid catalyst	Time (h)	Yield[b] (%)
1	EtOH	—	—	15	23[c]
2	EtOH	—	*p*-TSA	7	73[c]
3	H_2O	—	*p*-TSA	6	80[c]
4	THF	Piperidine	*p*-TSA	8	30
5	CH_3CN	Piperidine	*p*-TSA	8	24
6	H_2O/EtOH	Piperidine	*p*-TSA	5	68
7	H_2O	Piperidine	*p*-TSA	7	46
8	EtOH	Piperidine	*p*-TSA	2	94
9	EtOH	Et_2NH	*p*-TSA	3	75
10	EtOH	Piperidine	HCl	7	60
11	EtOH	Piperidine	CH_3COOH	6	65
12	EtOH	Piperidine	L-Proline	4	74
13	EtOH	Piperidine	—	8	93[d]

[a] A mixture of 6-amino-1-methyluracil (1 mmol), acetophenone (1.5 mmol), isatin (1 mmol), and the catalysts (10 mol % of the base and 40 mol % of the acid).
[b] Isolated yields of **4a**.
[c] The side product **5** is formed.
[d] Product **6** is formed.

A short course of experimentations indicated that under acidic conditions the desired reaction is superseded by a three-component condensation between two molecules of 6-amino-1,3-dimethyluracil **1a** and isatin **2a** to give the 1,1′,3,3′-tetramethyl-1*H*-spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]-2,2′,4,4′,6′(1′*H*,3*H*,3′*H*,7′*H*,10*H*)-pentaone **5a** (Scheme 2).[30] Moreover, under mild basic conditions the reaction no longer proceeds beyond the addition of acetophenone **3a** on isatin **2a**, leaving 6-amino-1,3-dimethyluracil **1a** completely unreacted aside. Upon these observations, we thought to bring the three components into a sequential tandem reaction in one pot to synthesize the oxindolylpyrrolo[2,3-*d*]pyrimidines simply by inverting the pH of the reaction medium. The key-step validating this protocol is the quick base-catalyzed addition of acetophenone on isatin, which goes to completion in a few minutes to give the intermediate 3-hydroxy-3-benzoylmethylindolin-2-one. Afterward, by changing amino-uracil partner. However, naphthalenamines remained entirely unreactive when we tried to enter them into a similar reaction. This failure may be ascribed to the aromatic character of 1- and 2-naphthalenamines restricting their action as enamines, in comparison with amino-uracils. Similar endeavors we made to employ 1- or 2-naphthols in place of amino-uracils also remained unsuccessful to give the corresponding compounds comprising of naphthofuran moiety.

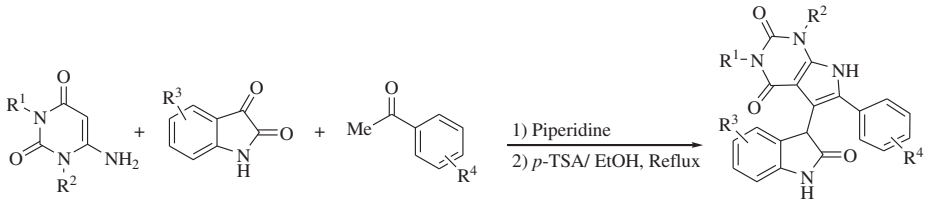
Attempts to bring acenaphthoquinone, ninhydrin, or phenanthrene-9,10-dione into the sequential tandem reactions with acetophenone and amino-uracils were unsatisfactory as they gained multiple of products polluted with unreacted substrates or otherwise completely remained unreactive.

A plausible mechanism for the formation of 5-(2-oxoindolin-3-yl)-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-diones **4a**–**p** from the three components is depicted in Scheme 3. Compounds **4a**–**p** are



Scheme 2. The competing reactions of the three components and their relative conditions.

Table 2
Synthesis of 2-oxoindolin-3-yl-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-diones **4a**–**p** under the optimized conditions



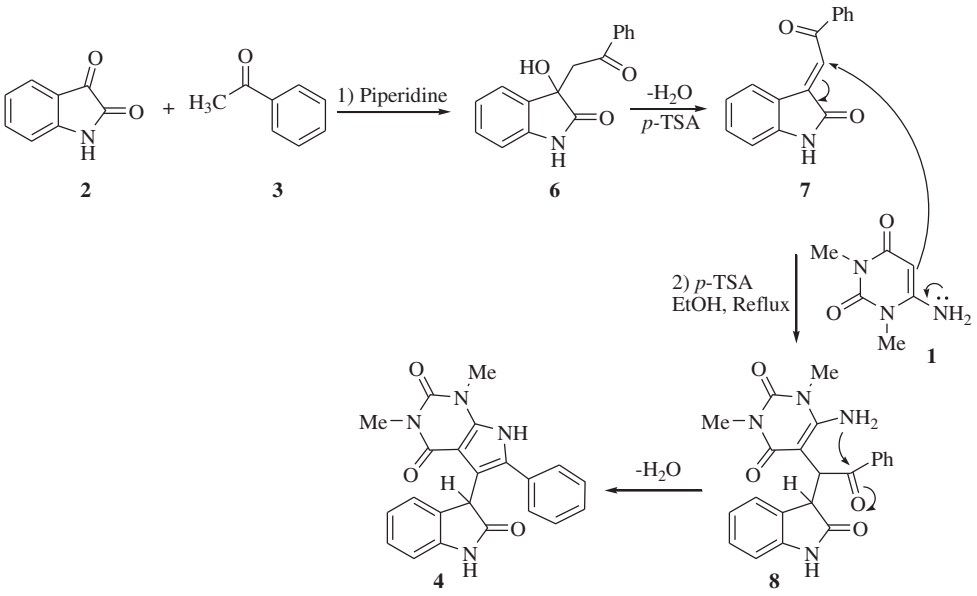
R^1, R^2 = Me / H (**1**) R^3 = H / Cl (**2**) R^4 = H / Cl / F / OCH_3 (**3**) (82–95%) **4a-p**

Product	R^1	R^2	R^3	R^4	Time (h)	Yield[a] (%)
4a	Me	Me	H	H	2	94
4b	Me	Me	H	Cl	2	88
4c	Me	Me	H	F	2	91
4d	Me	Me	Cl	H	2.5	89
4e	Me	Me	Cl	Cl	2.5	92
4f	Me	Me	Cl	F	2	86
4g	Me	Me	H	OCH_3	2	90
4h	H	H	Cl	OCH_3	2.5	87
4i	H	H	H	H	3	84
4j	H	H	H	Cl	2.5	92
4k	H	H	H	F	2	85
4l	H	H	H	OCH_3	2	89
4m	H	Me	H	H	3	95
4n	H	Me	H	Cl	2.5	86
4o	H	Me	Cl	F	2	92
4p	H	Me	Cl	H	2	82

[a] Isolated yields.

thought to be formed through a sequence of reactions initiated by a quick nucleophilic addition of acetophenones onto isatins under piperidine catalysis to afford 3-hydroxy-3-aroylmethylindolin-2-ones **6**. Upon addition of *p*-TSA to the reaction mixture, the 3-hydroxyindolin-2-ones **6** undergo dehydration to give the intermediate 3-aryloylmethylideneindolin-2-ones **7**. These intermediates are comprised of an exocyclic alkenyl bond being polarized by the dominant electron-withdrawing impact of indolin-2-one moiety, whereupon they undergo Michael addition preferably at the olefinic methine carbon atom. The Michael adduct **8** follows an intramolecular condensation to form the product **4**.

Only a trace of the side product **9**, resulting from the regioisomeric Michael adduct of amino-uracil and the intermediate **7**, was detected by ^{1}H NMR spectrum of the reaction mixture. This side product was readily distinguished by the characteristic signal of its single olefinic proton resonating around δ_H 5.6. Assigning of all the ^{1}H NMR signals of this side product is very difficult since they appear so weak and commonly overlapping with the signals of the main

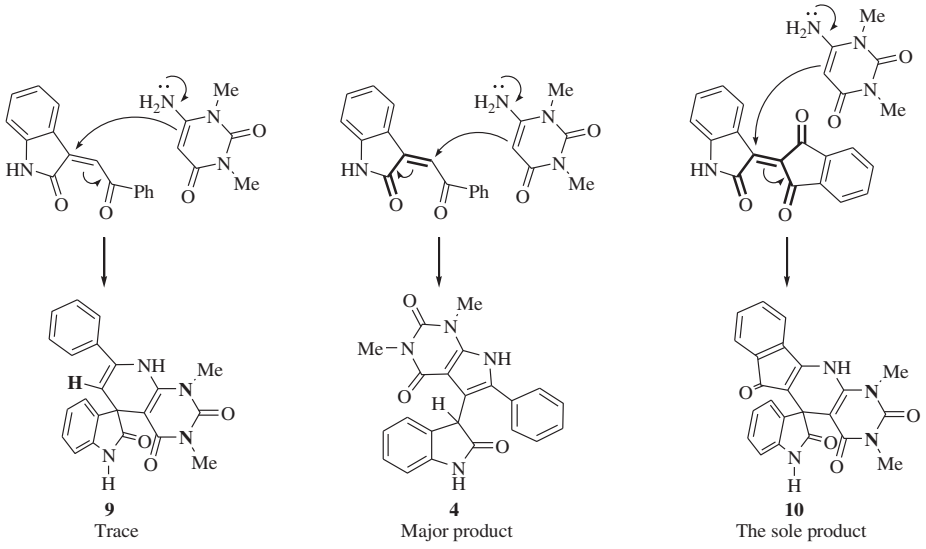


Scheme 3. A proposed mechanism for the sequential tandem reactions.

product. Reasonably, orientation of the Michael addition onto intermediate **7** is predominantly directed by the oxindole carbonyl group, owing to rigid coplanar configuration of this group with the olefinic bond. As we have previously reported,[28,29] the direction of the Michael addition is completely reversed when two rigidly coplanar carbonyl groups compete with the oxindole carbonyl group at the opposing conjugation terminal of the olefinic bond (Scheme 4).

sharp signal of the methine proton at δ 4.60. In addition, there are two singlet signals appeared at δ 10.37 and 11.88 in the spectrum accounting for the presence of two N–H groups in the molecule. The ^{13}C NMR spectrum of **4a** displays 20 distinct lines with appropriate chemical shifts corresponding to the structure of this compound.

Finally, the synthesized products **4a**–**p** were screened for antimicrobial activity. The microorganisms used in this study



Scheme 4. The favored Michael additions emerging as the determinants of selectivity.

The structures of compounds **4a**–**p** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The IR spectrum of compound **4a**, for example, shows absorption bands at 3356, 3108, 1682, and 1643 cm^{-1} indicating the presence of N–H and C=O groups in this molecule. Aromatic protons of this compound were seen at δ 6.83–7.61 in its ^{1}H NMR spectrum resonating with proper integrals and splittings. Aliphatic region of this spectrum exhibits two singlet peaks at δ 3.04 and 3.49 arising from protons of the two methyl groups along with the characteristic

were *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 85327 (as gram-negative bacteria), *Bacillus subtilis* ATCC465, and *Staphylococcus aureus* ATCC 25923 (as gram-positive bacteria). The minimum inhibitory concentrations (MICs) of compounds **4a**–**p** were determined by microdilution method[31] (Table 3). As can be seen from Table 3, good antibacterial activities were observed for most of the compounds against all species of gram-positive and gram-negative bacteria used in this study.

Table 3
MIC (mg/mL) values of products **4a**–**p**

Product	*Escherichia coli*	*Pseudomonas aeruginosa*	*Bacillus subtilis*	*Staphylococcus aureus*
4a	a	16	64	32
4b	a	8	8	4
4c	a	8	32	8
4d	a	8	16	64
4e	a	16	8	64
4f	128	8	64	128
4g	16	8	8	32
4h	a	8	128	32
4i	8	a	128	128
4j	a	128	16	32
4k	128	8	a	8
4l	a	a	a	16
4m	64	16	32	8
4n	16	128	8	32
4o	a	8	128	64
4p	128	32	8	16
Norfloxacin	<2	20	2	16
Tetracycline	a	a	4	4

a: not active.

3. Conclusion

In summary, we have developed a sequential tandem protocol for facile preparation of a new class of oxindolyl-7-deazapurine derivatives in one pot via a novel cyclocondensation reaction between acetophenones, isatins, and 6-amino-uracils in refluxing ethanol. The synthesis occurs selectively subject to a sequential application of two catalysts and we anticipate being prone to automation by using a pH-gradient reactor. These products were evaluated in vitro for their antibacterial activities. Almost all of the obtained oxindolylpyrrolo[2,3-*d*]pyrimidine products exhibited good to excellent antibacterial activities against the tested strains.

4. Experimental

4.1. General

All of the solvents and reagents were purchased from Fluka or Merck chemical companies. Melting points were measured on an Electrothermal apparatus and are uncorrected. IR spectra were obtained in KBr disks on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Brucker DRX-400 AVANCE spectrometer. Chemical shifts of ^{1}H and ^{13}C NMR spectra were expressed in parts per million downfield from tetramethylsilane. Mass spectra were recorded on a Shimadzu QP1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a Foss Heraus CHN–O-rapid analyzer.

4.2. Typical experimental procedure for synthesis of 4a

A mixture of isatin (0.147 g, 1 mmol), acetophenone (0.09 mL, 1.5 mmol), and piperidine (two drops, 0.1 mmol) in ethanol (95.5%, 1 mL) was heated at 80 °C for about 5 min. To the solid obtained at this stage was added 6-amino-1,3-dimethyluracil (0.155 g, 1 mmol), *p*-toluenesulfonic acid monohydrate (0.076 g, 0.04 mmol), and EtOH (95.5%, 2 mL). The mixture was stirred and heated gently at 80 °C. After completion of the reaction (115 min), as monitored by TLC using 5:1 ratio of ethyl acetate/*n*-hexane, the reaction mixture was cooled to room temperature and then filtered. The separated solids were washed twice with 10 mL of water and 3 mL of hot ethanol (95.5%) to obtain the pure product **4a**.

*4.2.1. 1,3-Dimethyl-5-(2-oxoindolin-3-yl)-6-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4a**).* White powder (0.362 g, 94%). Mp 350 °C decomp. IR (KBr): 3356, 3108, 3035, 1682, 1643, 1551 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 3.04 (3H, s, CH_3), 3.49 (3H, s, CH_3), 4.60 (1H, s, CH), 6.83 (1H, t, ^{3}J 7.2 Hz), 6.83 (1H, d, ^{3}J 7.6 Hz), 7.14 (1H, t, ^{3}J 7.6 Hz), 7.43 (1H, t, ^{3}J 7.4 Hz), 7.53 (2H, t, ^{3}J 7.6 Hz), 7.62 (2H, d, ^{3}J 7.2 Hz), 10.37 (1H, s, NH), 11.88 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 27.8 (CH_3), 31.0 (CH_3), 44.2, 97.8, 109.5, 111.3, 121.2, 123.4, 127.7, 128.2, 128.3, 128.8, 129.3, 131.0, 131.2, 140.2, 144.0, 151.1, 157.8, 178.0. MS (EI, 70 eV) *m*/*z*: 386 (M^{+}, 17), 381 (17), 368 (58), 313 (50), 260 (77), 236 (56), 183 (37), 152 (41), 83 (64), 57 (100). Anal. Calcd for $C_{22}H_{18}N_4O_3$ (386.14): C, 68.38; H, 4.70; N, 14.50%. Found: C, 68.32; H, 4.65; N, 14.57%.

*4.2.2. 6-(4-Chlorophenyl)-1,3-dimethyl-5-(2-oxoindolin-3-yl)-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4b**).* Cream powder (0.369 g, 88%). Mp 355 °C decomp. IR (KBr): 3362, 3296, 3138, 3050, 1693, 1642, 1535 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 3.03 (3H, s, CH_3), 3.49 (3H, s, CH_3), 4.61 (1H, s, CH), 6.81–6.86 (2H, m), 6.89 (1H, d, ^{3}J 7.2 Hz), 7.14 (1H, t, ^{3}J 7.6 Hz), 7.58 (2H, d, *J* 8.8 Hz), 7.63 (2H, d, *J* 8.8 Hz), 10.39 (1H, s, NH), 11.91 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 27.8 (CH_3), 31.0 (CH_3), 44.1, 97.9, 109.5, 112.0, 121.2, 123.4, 127.9, 128.3, 129.3, 129.9, 130.4, 130.8, 132.9, 140.3, 144.0, 151.0, 157.8, 177.9. MS (EI, 70 eV) *m*/*z*: 422 (M^{+}, ^{37}Cl, 4), 421 (3), 420 (M^{+}, ^{35}Cl, 13), 386 (24), 368 (36), 339 (20), 313 (52), 260 (76), 236 (72), 196 (25), 149 (44), 109 (40), 83 (82), 57 (100). Anal. Calcd for $C_{22}H_{17}ClN_4O_3$ (420.10): C, 62.79; H, 4.07; N, 13.31%. Found: C, 62.68; H, 4.24; N, 13.29%.

*4.2.3. 6-(4-Fluorophenyl)-1,3-dimethyl-5-(2-oxoindolin-3-yl)-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4c**).* White powder (0.367 g, 91%). Mp 338 °C decomp. IR (KBr): 3361, 3104, 3047, 2898, 1683, 1645, 1550, 1230, 744 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 3.03 (3H, s, CH_3), 3.48 (3H, s, CH_3), 4.57 (1H, s, CH), 6.82 (1H, t, ^{3}J 7.4 Hz), 6.83 (1H, d, ^{3}J 7.6 Hz), 6.90 (1H, d, ^{3}J 7.6 Hz), 7.13 (1H, t, ^{3}J 7.8 Hz), 7.38 (2H, t, ^{3}J 8.6 Hz), 7.64 (2H, dd, $^{3}J_{HH}$ 8.6 Hz, $^{4}J_{HF}$ 5.6 Hz), 10.39 (1H, s, NH), 11.90 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 27.8 (CH_3), 31.0 (CH_3), 44.1, 97.8, 109.5, 111.4, 116.3 (d, $^{2}J_{CF}$ 22 Hz), 121.2, 123.4, 127.4 (d, ^{4}J 1 Hz) 127.8, 130.2, 130.92 (d, $^{3}J_{CF}$ 8.3 Hz), 130.93, 140.1, 144.0, 151.1, 157.8, 161.0 (d, $^{1}J_{CF}$ 243 Hz), 178.0. MS (EI, 70 eV) *m*/*z*: 404 (M^{+}, 60), 386 (21), 261 (43), 245 (100), 196 (52), 152 (39), 105 (14). Anal. Calcd for $C_{22}H_{17}FN_4O_3$ (404.13): C, 65.34; H, 4.24; N, 13.85%. Found: C, 65.41; H, 4.28; N, 13.76%.

*4.2.4. 5-(5-Chloro-2-oxoindolin-3-yl)-1,3-dimethyl-6-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4d**).* Cream powder (0.373 g, 89%). Mp 335 °C decomp. IR (KBr): 3295, 3198, 1690, 1637, 1527, 1478 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 3.04 (3H, s, CH_3), 3.49 (3H, s, CH_3), 4.67 (1H, s, CH), 6.82 (1H, d, ^{3}J 8.4 Hz), 6.88 (1H, br s), 7.18 (1H, dd, ^{3}J 8.4 Hz and ^{4}J 1.2 Hz), 7.43 (1H, t, ^{3}J 7.2 Hz), 7.53 (2H, t, ^{3}J 7.6 Hz), 7.60 (2H, d, ^{3}J 7.2 Hz), 10.52 (1H, s, NH), 11.92 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C MS (EI, 70 eV) *m*/*z*: 422 (M^{+}, ^{37}Cl, 6), 421 (M^{+}+1, 9), 420 (M^{+}, ^{35}Cl, 16), 368 (25), 313 (39), 260 (43), 236 (54), 167 (20), 149 (55), 123 (24), 83 (63), 57 (100). Anal. Calcd for $C_{22}H_{17}ClN_4O_3$ (420.10): C, 62.79; H, 4.07; N, 13.31%. Found: C, 62.70; H, 4.11; N, 13.28%.

*4.2.5. 5-(5-Chloro-2-oxoindolin-3-yl)-6-(4-chlorophenyl)-1,3-dimethyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4e**).* White powder (0.417 g, 92%). Mp 370 °C decomp. IR (KBr): 3301, 3178, 1697, 1682, 1636, 1558 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 3.04 (3H, s, CH_3), 3.48 (3H, s, CH_3), 4.68 (1H, s, CH), 6.84 (1H, d, ^{3}J 8.4 Hz), 6.88 (1H, br s), 7.18 (1H, dd, ^{3}J 8.4 Hz and ^{4}J 1.2 Hz), 7.60 (4H, s), 10.53 (1H, s, NH), 11.95 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 27.8 (CH_3), 31.0 (CH_3), 44.2, 97.8, 110.8, 111.1, 123.4, 125.2, 127.7, 129.3, 129.9, 130.2, 130.6, 133.0, 133.2,

140.4, 143.0, 151.0, 157.9, 177.6. MS (EI, 70 eV) *m*/*z*: 458 (3), 457 (7), 456 (M^+, ^{35}Cl, ^{37}Cl, 42), 455 (M^++1, ^{35}Cl, ^{35}Cl, 18), 454 (M^+, ^{35}Cl, ^{35}Cl, 61), 420 (28), 368 (17), 313 (36), 245 (86), 196 (44), 167 (36), 149 (82), 83(61), 57 (100). Anal. Calcd for $C_{22}H_{16}Cl_2N_4O_3$ (454.06): C, 58.04; H, 3.54; N, 12.31%. Found: C, 58.12; H, 3.52; N, 12.26%.

*4.2.6. 5-(5-Chloro-2-oxoindolin-3-yl)-6-(4-fluorophenyl)-1,3-dimethyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H) dione (**4f**).* White powder (0.376 g, 86%). Mp 300 °C decomp. IR (KBr): 3307, 3104, 3053, 1698, 1682, 1634, 1553, 1223, 740 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6): δ_H 3.04 (3H, s, CH_3), 3.48 (3H, s, CH_3), 4.63 (1H, s, CH), 6.83 (1H, d, ^3J 8.4 Hz), 6.89 (1H, br s), 7.18 (1H, dd, ^3J 8.4 Hz and ^4J 1.2 Hz), 7.38 (2H, t, ^3J 8.8 Hz), 7.63 (2H, dd, $^3J_{HH}$ 8.8 Hz and $^4J_{HF}$ 5.6 Hz), 10.53 (1H, s, NH), 11.93 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 27.8 (CH_3), 31.0 (CH_3), 44.2, 97.6, 110.5, 110.8, 116.2 (d, $^2J_{CF}$ 21.5 Hz), 123.4, 125.2, 127.5 (d, $^4J_{CF}$ 1 Hz), 127.7, 130.5, 131.1 (d, $^3J_{CF}$ 8.3 Hz), 133.2, 140.2, 143.0, 151.0, 157.9, 162.3 (d, $^1J_{CF}$ 244 Hz), 177.7. MS (EI, 70 eV) *m*/*z*: 440 (M^+, ^{37}Cl, 5), 439 (M^++1, ^{35}Cl, 6), 438 (M^+, ^{35}Cl, 14), 368 (40), 329 (35), 285 (18), 264 (21), 245 (49), 167 (22), 149 (56), 83 (62), 57 (100). Anal. Calcd for $C_{22}H_{16}ClFN_4O_3$ (438.09): C, 60.21; H, 3.67; N, 12.77%. Found: C, 60.14; H, 3.62; N, 12.82%.

*4.2.7. 6-(4-Methoxyphenyl)-1,3-dimethyl-5-(2-oxoindolin-3-yl)-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4g**).* White powder (0.374, 90%). Mp 360 °C decomp. IR (KBr): 3348, 3122, 3047, 1684, 1643, 1547, 1316, 1249 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6): δ_H 3.03 (3H, s, CH_3), 3.48 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 4.55 (1H, s, CH), 6.81–6.85 (2H, m), 6.90 (1H, d, ^3J 7.2 Hz), 7.09 (2H, d, ^3J 8.6 Hz), 7.15 (1H, d, ^3J 7.2 Hz), 7.53 (2H, d, ^3J 8.6 Hz), 10.36 (1H, s, NH), 11.80 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 27.7 (CH_3), 31.0 (CH_3), 44.2, 55.7 (CH_3), 97.7, 109.5, 110.4, 114.8, 121.2, 123.4, 123.6, 127.8, 130.2, 131.0, 131.1, 139.8, 143.9, 151.1, 157.8, 159.5, 178.1. MS (EI, 70 eV) *m*/*z*: 417 (M^++1, 4), 385 (7), 278 (38), 255 (19), 221 (44), 193 (23), 149 (43), 129 (41), 111 (37), 97 (36), 71 (46), 43 (100). Anal. Calcd for $C_{23}H_{20}N_4O_4$ (416.15): C, 66.34; H, 4.84; N, 13.45%. Found: C, 66.26; H, 4.86; N, 13.42%.

*4.2.8. 5-(5-Chloro-2-oxoindolin-3-yl)-6-(4-methoxyphenyl)-1,3-dimethyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4h**).* Cream powder (0.391 g, 87%). Mp 350 °C decomp. IR (KBr): 3335, 3292, 1699, 1681, 1647, 1558, 1246, 1029, 741 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6): δ_H 3.04 (3H, s, CH_3), 3.48 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 4.61 (1H, s, CH), 6.83 (1H, d, ^3J 8.4 Hz), 6.86 (1H, br s), 7.10 (2H, d, ^3J 8.6 Hz), 7.17 (1H, dd, ^3J 8.4 Hz, ^4J 1.2 Hz), 7.52 (2H, d, ^3J 8.6 Hz), 10.50 (1H, s, NH), 11.84 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 27.8 (CH_3), 31.0 (CH_3), 44.3, 55.7 (OCH_3), 97.5, 109.6, 110.8, 114.8, 123.3, 123.4, 125.1, 127.7, 130.3, 131.5, 133.4, 139.9, 143.0, 151.1, 157.9, 159.6, 177.8. MS (EI, 70 eV) *m*/*z*: 452 (M^+, ^{37}Cl, 27), 451 (M^++1, ^{35}Cl, 23) 450 (M^+, ^{35}Cl, 100), 421 (24), 337 (15), 315 (13), 259 (12), 190 (21), 134 (43), 91 (45), 57 (62), 41 (53). Anal. Calcd for $C_{23}H_{19}ClN_4O_4$ (450.11): C, 61.27; H, 4.25; N, 12.43%. Found: C, 61.33; H, 4.19; N, 12.39%.

*4.2.9. 5-(2-Oxoindolin-3-yl)-6-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4i**).* White powder (0.300 g, 84%). Mp 360 °C decomp. IR (KBr): 3284, 3189, 1702, 1681, 1646, 1618, 1560, 1314, 1177 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6): δ_H 4.58 (1H, s, CH), 6.80–6.84 (2H, m), 6.89 (1H, d, ^3J 7.6 Hz), 7.12 (1H, t, ^3J 7.6 Hz), 7.38 (1H, t, ^3J 7.2 Hz), 7.48 (2H, t, ^3J 7.6 Hz), 7.57 (2H, d, ^3J 7.8 Hz), 10.23 (1H, s, NH), 10.34 (1H, s, NH), 11.49 (1H, s, NH), 11.72 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 44.2, 109.4, 110.7, 121.2, 123.4, 127.8, 128.0, 128.2, 128.5, 129.2, 130.6, 131.1, 131.4, 140.2, 144.0, 151.5, 159.0, 178.1. MS (EI, 70 eV) *m*/*z*: 358 (M^+, 15), 327 (6), 259 (4), 180 (10), 135 (13), 127 (40), 105 (45), 97 (24), 84 (37), 55 (86), 43 (100). Anal. Calcd for $C_{20}H_{14}N_4O_3$ (358.11): C, 67.03; H, 3.94; N, 15.63%. Found: C, 67.12; H, 3.97; N, 15.57%.

*4.2.10. 6-(4-Chlorophenyl)-5-(2-oxoindolin-3-yl)-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4j**).* White powder (0.360 g, 92%). Mp 370 °C decomp. IR (KBr): 3160, 3030, 2825, 1737, 1702, 1654, 1623, 1587, 1465 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6): δ_H 4.57 (1H, s, CH), 6.78–6.82 (2H, m), 6.88 (1H, d, ^3J 7.6 Hz), 7.12 (1H, t, ^3J 7.6 Hz), 7.53 (2H, d, ^3J 8.8 Hz), 7.57 (2H, d, ^3J 8.8 Hz), 10.26 (1H, s, NH), 10.35 (1H, s, NH), 11.53 (1H, s, NH), 11.80 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 44.1, 98.3, 109.4, 111.3, 121.2, 128.1, 129.2, 129.4, 129.6, 130.1, 130.2, 131.0, 132.6, 140.4, 144.0, 151.5, 159.0, 178.0. MS (EI, 70 eV) *m*/*z*: 392 (M^+–2, ^{37}Cl, 5), 391 (3), 390 (M^+–2, ^{35}Cl, 16), 279 (14), 180 (15), 139 (55), 111 (47), 91 (16), 64 (33), 44 (100). Anal. Calcd for $C_{20}H_{13}ClN_4O_3$ (392.07): C, 61.16; H, 3.34; N, 14.26%. Found: C, 61.09; H, 3.42; N, 14.18%.

*4.2.11. 6-(4-Fluorophenyl)-5-(2-oxoindolin-3-yl)-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4k**).* White powder (0.319 g, 85%). Mp 360 °C decomp. IR (KBr): 3188, 3103, 3048, 2821, 1721, 1698, 1665, 1576, 1459, 1218, 832 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6): δ_H 4.52 (1H, s, CH), 6.79–6.83 (2H, m), 6.88 (1H, d, ^3J 7.2 Hz), 7.12 (1H, t, ^3J 7.6 Hz), 7.32 (2H, t, *J* 8.8 Hz), 7.58 (2H, dd, $^3J_{HH}$ 8.8 Hz, $^3J_{HF}$ 5.4 Hz), 10.24 (1H, s, NH), 10.35 (1H, s, NH), 11.51 (1H, s, NH), 11.75 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 44.1, 97.8, 109.4, 110.7, 116.1 (d, $^2J_{CF}$ 21.5 Hz), 121.2, 123.4, 127.7, 128.5 (d, $^4J_{CF}$ 1 Hz), 129.7, 130.7, (d, $^3J_{CF}$ 8.2 Hz), 131.1, 140.2, 144.0, 151.5, 159.0, 162.6 (d, $^1J_{CF}$ 236 Hz), 178.1. MS (EI, 70 eV) *m*/*z*: 376 (M^+, 14), 374 (M^+–2, 22), 345 (9), 279 (10), 180 (21), 153 (13), 123 (100), 95 (74), 75 (23), 44 (27). Anal. Calcd for $C_{20}H_{13}FN_4O_3$ (376.10): C, 63.83; H, 3.48; N, 14.89%. Found: C, 63.79; H, 3.39; N, 15.01%.

*4.2.12. 6-(4-Methoxyphenyl)-5-(2-oxoindolin-3-yl)-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4l**).* White powder (0.345 g, 89%). Mp 360 °C decomp. IR (KBr): 3365, 3178, 3033, 2837, 1697, 1658, 1255, 742 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6): δ_H 3.78 (3H, s, CH_3), 4.52 (1H, s, CH), 6.79–6.85 (2H, m), 6.88 (1H, d, ^3J 7.2 Hz), 7.05 (2H, d, ^3J 8.8 Hz), 7.11 (1H, t, ^3J 7.6 Hz), 7.48 (2H, d, ^3J 8.8 Hz), 10.20 (1H, s, NH), 10.33 (1H, s, NH), 11.42 (1H, s, NH), 11.62 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 44.2, 55.7, 98.0, 109.8, 113.6, 114.6, 121.2, 123.8, 127.7, 129.3, 129.9, 130.6, 131.3, 139.9, 144.0, 151.5, 159.0, 159.3, 178.3. MS (EI, 70 eV) *m*/*z*: 388 (M^+, 6), 386 (M^+–2, 16), 357 (3), 257 (61), 186 (32), 171 (28), 155 (26), 135 (100), 92 (29), 77(48), 44 (39). Anal. Calcd for $C_{21}H_{16}N_4O_4$ (388.12): C, 64.94; H, 4.15; N, 14.43%. Found: C, 64.87; H, 4.23; N, 14.39%.

*4.2.13. 1-Methyl-5-(2-oxoindolin-3-yl)-6-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4m**).* White powder (0.353 g, 95%). Mp 360 °C decomp. IR (KBr): 3332, 3140, 3048, 1698, 1684, 1667, 1618, 1542, 1317, 741 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6): δ_H 3.39 (3H, s, CH_3), 4.59 (1H, s, CH), 6.82 (1H, d, ^3J 8.0 Hz), 6.83 (1H, t, ^3J 8.0 Hz), 6.90 (1H, d, ^3J 7.2 Hz), 7.13 (1H, t, ^3J 7.6 Hz), 7.43 (1H, t, ^3J 7.6 Hz), 7.53 (2H, t, ^3J 7.6 Hz), 7.62 (2H, d, ^3J 7.6 Hz), 10.36 (1H, s, NH), 10.53 (1H, s, NH), 11.85 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_c 29.9 (CH_3), 44.2, 98.7, 110.4, 110.7, 123.4, 125.3, 127.7, 128.3, 128.4, 128.9, 129.4, 131.0, 133.3, 141.5, 142.9, 150.9, 158.3, 176.7. MS (EI, 70 eV) *m*/*z*: 372 (M^+, 9), 368 (37), 304 (29), 236 (39), 213 (24), 185 (16), 158 (70), 149 (55), 105 (91), 57 (100). Anal. Calcd for $C_{21}H_{16}N_4O_3$ (372.12): C, 67.73; H, 4.33; N, 15.05%. Found: C, 67.68; H, 4.30; N, 15.11%.

*4.2.14. 5-(5-Chloro-2-oxoindolin-3-yl)-1-methyl-6-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4n**).* White powder (0.349 g, 86%). Mp 370 °C decomp. IR (KBr): 3173, 3035, 1716, 1697, 1663, 1557, 1472 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6): δ_H 3.41 (3H, s, CH_3), 4.66 (1H, s, CH), 6.82 (1H, d, ^3J 8.0 Hz), 6.87 (1H, s, CH), 7.18

(1H, d, ^3J 8.0 Hz), 7.43 (1H, t, ^3J 7.4 Hz), 7.54 (2H, t, ^3J 7.6 Hz), 7.61 (2H, d, ^3J 7.6 Hz), 10.51 (1H, s, NH), 10.57 (1H, s, NH), 11.89 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_c 29.9 (CH_3), 44.2, 98.5, 110.5, 110.7, 123.4, 125.2, 127.6, 128.2, 128.4, 128.9, 129.3, 131.0, 133.3, 141.5, 142.9, 150.9, 158.2, 177.7. MS (EI, 70 eV) m/z: 406 (M^+, ^{35}Cl, 3), 395 (6), 379 (10), 368 (80), 353 (16), 313 (32), 236 (42), 149 (39), 111 (40), 97 (67), 57 (100). Anal. Calcd for $C_{21}H_{15}ClN_4O_3$ (406.08): C, 62.00; H, 3.72; N, 13.77%. Found: C, 61.96; H, 3.78; N, 13.74%.

*4.2.15. 5-(5-Chloro-2-oxoindolin-3-yl)-6-(4-fluorophenyl)-1-methyl-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4o**).* White powder (0.390 g, 92%). Mp 380 °C decomp. IR (KBr): 3179, 3038, 1716, 1685, 1662, 1619, 1553, 1472, 1218, 840 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 3.40 (3H, s, CH_3), 4.62 (1H, s, CH), 6.82 (1H, d, ^3J 8.4 Hz), 6.88 (1H, br s, CH), 7.17 (1H, dd, ^3J 8.4 and ^4J 1.0 Hz), 7.38 (2H, t, ^3J 8.6 Hz), 7.64 (2H, dd, $^3J_{HH}$ 8.6 Hz, $^4J_{HF}$ 5.2 Hz), 10.52 (1H, s, NH), 10.54 (1H, s, NH), 11.90 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_c 29.9 (CH_3), 44.2, 98.4, 110.6, 110.7, 116.2 (d, $^2J_{CF}$ 21.0 Hz), 123.4, 125.2, 127.5 (d, $^4J_{CF}$ 1 Hz), 127.6, 131.1 (d, $^3J_{CF}$ 8.0 Hz), 133.3, 141.4, 142.9, 150.9, 158.2, 161.1, 161.8 (d, $^1J_{CF}$ 245 Hz) 177.7. MS (EI, 70 eV) m/z: 426 (M^+, ^{37}Cl, 2), 424 (M^+, ^{35}Cl, 7), 394 (18), 368 (80), 351 (36), 313 (51), 264 (25), 236 (60), 111 (45), 83 (83), 57 (100). Anal. Calcd for $C_{21}H_{14}ClFN_4O_3$ (424.07): C, 59.37; H, 3.32; N, 13.19%. Found: C, 59.41; H, 3.35; N, 13.11%.

*4.2.16. 6-(4-Chlorophenyl)-1-methyl-5-(2-oxoindolin-3-yl)-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione (**4p**).* White powder (0.332 g, 82%). Mp 380 °C decomp. IR (KBr): 3165, 3054, 1710, 1691, 1684, 1618, 1559, 1463, 744 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 3.40 (3H, s, CH_3), 4.59 (1H, s, CH), 6.81–6.86 (3H, m), 7.13 (1H, t, ^3J 7.4 Hz), 7.59 (2H, d, ^3J 8.8 Hz), 7.63 (2H, d, ^3J 8.8 Hz), 10.38 (1H, s, NH), 10.55 (1H, s, NH), 11.88 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_c 29.9 (CH_3), 44.1, 98.8, 109.4, 112.0, 121.2, 123.4, 127.8, 128.3, 129.3, 129.9, 130.4, 130.9, 132.9, 141.6, 143.9, 150.9, 158.1, 177.8. MS (EI, 70 eV) m/z: 408 (M^+, ^{37}Cl, 4), 407 (M^+, 5), 406 (M^+, 16), 374 (6), 360 (100), 313 (20), 239 (8), 180 (24), 89 (17), 69 (20), 55 (25). Anal. Calcd for $C_{21}H_{15}ClN_4O_3$ (406.08): C, 62.00; H, 3.72; N, 13.77%. Found: C, 62.08; H, 3.74; N, 13.69%.

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