An efficient synthesis of 2,3,6,7-tetrasubstituted 4,6-dihydro-4-oxo-3*H*-pyrrolo[3,4-*d*]pyrimidin-7-carbonitrile derivatives

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Abstract

The iminophosphorane **3**, prepared by reaction of ethyl 4-amino-5-cyano-1-phenyl-1*H*-pyrrole-3-carboxylate (**2**) with triphenylphosphine, hexachloroethane and triethylamine, reacted with equimolar quantities of aromatic isocyanates to give carbodiimides **4**. Further reaction of carbodiimides **4** with various amines or phenols then gave 2,3,6,7-tetrasubstituted 4,6-dihydro-4-oxo-3*H*-pyrrolo[3,4-*d*]pyrimidin-7-carbonitrile derivatives **6** in satisfactory yields in the presence of a catalytic amount of sodium ethoxide or potassium carbonate.

Keywords: Iminophosphoranes, pyrrolo[3,4-*d*]pyrimidines, aza-Wittig reactions, isocyanates

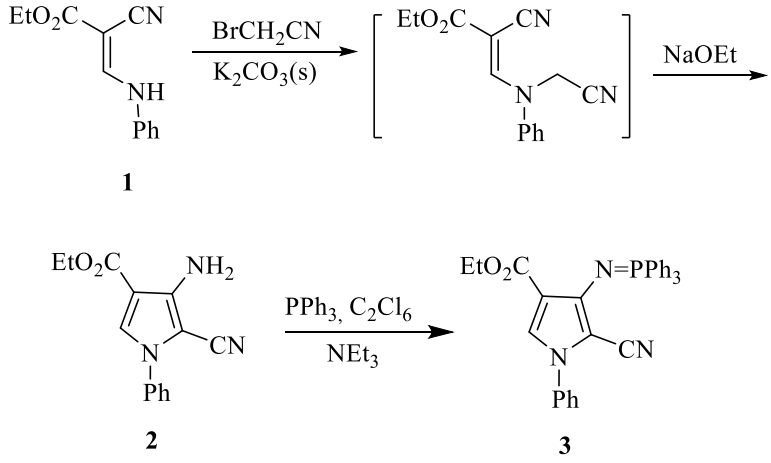
Introduction

Compounds possessing a pyrrolo[3,4-*d*]pyrimidine nucleus possess a broad range of biological activities and have been used as potent cystic fibrosis transmembrane conductance regulator inhibitors,[1] β-site APP-cleaving enzyme 1 inhibitors[2] and A_3 adenosine receptor antagonists.[3] Recent reports have also shown that some pyrrolo[3,4-*d*]pyrimidine derivatives may be used as inhibitors of heat shock protein 90 which could inhibit multiple pathways in human cancers.[4-6] There are many methods for the synthesis of fused pyrrolo[3,4-*d*]pyrimidine derivatives. One of the generally used approach is elaboration of a pyrrolo ring onto the prefabricated pyrimidine ring which bearing reactive functionalities at C-4 and C-5,[7-9] another popularly used method involved the formation of a pyrimidine ring onto the 3-aminopyrrole intermediate.[10-15] Although some pyrrolo[3,4-*d*]pyrimidine derivatives have been constructed, but the synthesis of 2,3,6,7-tetrasubstituted 4,6-dihydro-4-oxo-3*H*-pyrrolo[3,4-*d*]pyrimidin-7-carbonitrile derivatives is rarely described.

On the other hand, the aza-Wittig-mediated annulation strategy has received increased attention for the synthesis of nitrogen-containing heterocyclic compounds.[16-21] Recently we have been interested in the synthesis of fused heterocycles via aza-Wittig reaction, with the aim of evaluating their biological activities.[22-27] Herein we report an efficient synthesis of 2,3,6,7-tetrasubstituted 4,6-dihydro-4-oxo-3*H*-pyrrolo[3,4-*d*]pyrimidin-7-carbonitrile derivatives via aza-Wittig reactions, starting from the easily accessible ethyl 4-amino-5-cyano-1-phenyl-1*H*-pyrrole-3-carboxylate.

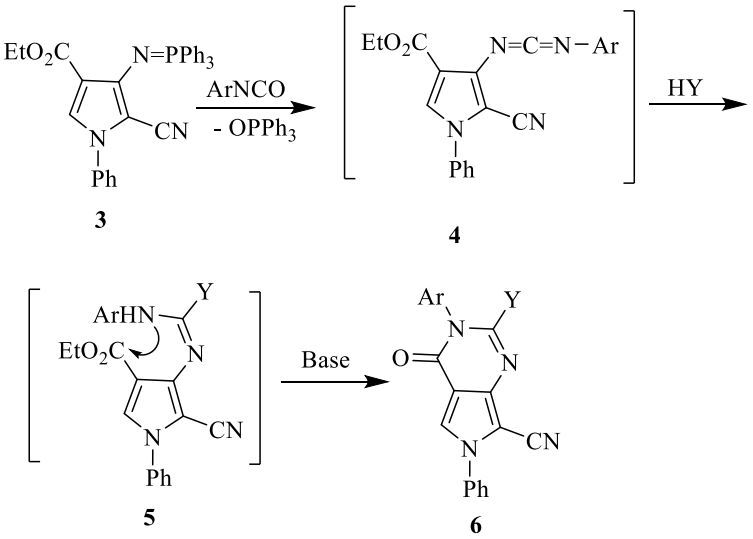
Results and Discussion

The ethyl 4-amino-5-cyano-1-phenyl-1*H*-pyrrole-3-carboxylate **2**, easily prepared by reaction of compound **1** [28] with bromoacetonitrile under basic conditions, was converted into iminophosphorane **3** via reaction with triphenylphosphine, hexachloroethane and triethylamine in dry acetonitrile in good yield (Scheme 1).



Scheme 1

Iminophosphorane **3** reacted with equimolar quantities of aromatic isocyanates to form carbodiimides **4**, which were allowed to further treated with amines to provide guanidine intermediates **5**. In the presence of a catalytic amount of sodium ethoxide in ethanol at room temperature, intermediates **5** were easily converted into 2-amino-3-aryl-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile derivatives at room temperature in satisfactory yields (Scheme 2). The results are listed in Table 1 (entry **6a**-**6l**). The cyclization reactions were achieved all in moderate to good yields whether the amines used were sterically bulky or not, and no isomers were formed such as those that have been observed in similar cases.[29-31]



Scheme 2

Table 1. Synthesis of compounds **6**

Product	Ar	Y	Time (h)	Yield (%)[a]
6a	4-FC_6H_4	morpholin-4-yl	2	85
6b	4-FC_6H_4	(*n*-Pr)$_2$N-	2	90
6c	4-FC_6H_4	(*n*-Bu)$_2$N-	2	86
6d	4-FC_6H_4	pyrrolidin-1-yl	2	89
6e	4-FC_6H_4	(*i*-Pr)$_2$N-	4	90
6f	4-FC_6H_4	piperidin-1-yl	2	80
6g	Ph	morpholin-4-yl	2	86
6h	4-FC_6H_4	(*t*-Bu)HN-	3	80
6i	Ph	(*t*-Bu)HN-	4	85
6j	4-ClC_6H_4	(*t*-Bu)HN-	3	90
6k	4-FC_6H_4	$(CH_3)_2HCHN$-	2	83
6l	4-ClC_6H_4	$C_6H_{11}HN$-	2	92
6m	Ph	3,4-2$CH_3C_6H_3O$-	4	90
6n	Ph	4-$CH_3C_6H_4O$-	4	86
6o	Ph	4-ClC_6H_4O-	6	88

[a] Isolated yields based on iminophosphorane **3**

The structures of 2-amino-3-aryl-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile derivatives **6** were confirmed by their spectral data. For example, the IR spectra of **6a** revealed the groups of CN and C=O absorption bands at 2215 and 1707 cm^{-1}, respectively.

The ^{1}H NMR spectrum of **6a** shows two triplets at 3.15 and 3.46 ppm due to the NCH_2 and OCH_2, respectively. The signals attributable to the Ar-Hs and 5-H of the pyrrole ring are found at 7.18-7.57 and 7.68 ppm as multiplet and singlet, respectively. The MS spectrum of **6a** shows molecular ion peak at *m/z* 415 with 100% abundance.

In order to extend this method of preparation of 2,3,6,7-tetrasubstituted 4,6-dihydro-4-oxo-3*H*-pyrrolo[3,4-*d*]pyrimidin-7-carbonitrile derivatives, phenols were further used to react with carbodiimides **4**. When carbodiimides **4** reacted with phenols, the presence of a catalytic amount of potassium carbonate brought about the reaction to give **6** (Y = OAr) directly in good yields. The results are listed in Table 1 (entries **6m**-**6o**). It is reasonable to assume that the reactions of carbodiimides **4** with phenols take place through an original nucleophilic addition to give the intermediates **5**, which subsequently cyclized to produce 2-aryloxy-3-aryl-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile **6** under the basic conditions. It is noteworthy that the molecules all contain a carbonitrile group, which has been shown to be of importance in the design of biologically active heterocycles.[32-37]

Conclusions

In conclusion, we have developed a new and efficient way to prepare previously unreported 2,3,6,7-tetrasubstituted 4,6-dihydro-4-oxo-3*H*-pyrrolo[3,4-*d*]pyrimidin-7-carbonitrile derivatives via reaction of carbodiimides with a variety of amines and phenols. Because of the mild reaction conditions, satisfactory yields and versatile substituents, it may well serve as an efficient route to many biologically active derivatives of this nucleus substituted as indicated.

Experimental Section

General. Melting points were determined using a X-4 model apparatus and were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 400 or 600 spectrometer and chemical shifts (δ) were given in ppm using $(CH_3)_4Si$ as an internal reference (δ = 0). IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

Preparation of ethyl 4-amino-5-cyano-1-phenyl-1*H*-pyrrole-3-carboxylate (**2**). To a solution of (*E*)-ethyl 2-cyano-3-(phenylamino)acrylate **1** (2.16g, 10 mmol) in anhydrous DMF (10 mL), was added bromoacetonitrile (1.2 g, 10 mmol) at room temperature. The reaction mixture was stirred at 70 ºC for 5 h, and then equimolar quantity of sodium ethoxide in ethanol was added, then the mixture was heated to 90 ºC for 20 minutes. After the reaction was completed, the mixture was poured into water (30 mL), and the formed solid was filtered and recrystallized from

ethanol/petroleum ether (1:1, v/v) to give compound 2 as white crystals: 2.04 g (yield: 80%); mp: 115 ºC. IR (KBr, cm^{-1}): 3440 (NH_2), 2198 (CN), 1696 (C=O), 1628, 1203, 1099, 766. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.43-7.23 (m, 5H, Ar-H), 7.06 (s, 1H, C=CH, pyrrole), 5.06 (s, 2H, NH_2), 4.10 (q, *J* 7.2 Hz, 2H, CH_2), 1.04 (t, *J* 7.2 Hz, 3H, CH_3). MS *m/z* (%): 255 (M^+, 89), 216 (100), 209 (88), 170 (96), 104 (72), 77 (68). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.81; H, 5.11; N, 16.56%.

Preparation of ethyl 5-cyano-1-phenyl-4-[(triphenylphosphoranylidene)amino]-1*H*-pyrrole-3-carboxylate (**3**). To a mixture of ethyl 4-amino-5-cyano-1-phenyl-1*H*-pyrrole-3-carboxylate (**2**) (2.04 g, 8 mmol), triphenylphosphine (3.14 g, 12 mmol) and hexachloroethane (2.84 g, 12 mmol) in dry acetonitrile (40 mL), was added dropwise triethylamine (2.42 g, 24 mmol) at room temperature. After the mixture was stirred at 25 ºC for 6 h, the solvent was removed under reduced pressure, and the residue was recrystallized from ethanol to give iminophosphorane **3** as white crystals, 3.91 g (yield: 95%), mp 126 ºC; IR (KBr, cm^{-1}): 2209 (CN), 1702 (C=O), 1630, 770. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.85-7.30 (m, 21H, 20Ar-H+1C=CH), 4.05 (q, *J* 7.2 Hz, 2H, CH_2), 1.19 (t, *J* 7.2 Hz, 3H, CH_3); MS *m/z* (%): 515 (M^+, 100), 486 (10), 468 (19), 442 (75), 346 (13), 261 (25), 201 (17), 183 (50), 77 (16); Anal. Calcd for $C_{32}H_{26}N_3O_2P$: C, 74.55; H, 5.08; N, 8.15; Found: C, 74.61; H, 5.10; N, 8.07%.

General preparation of 2-amino-3-aryl-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]-pyrimidine-7-carbonitriles (**6a-6j**)**.** To a solution of iminophosphorane **3** (1.55 g, 3 mmol) in dry methylene dichloride (15 mL), an aryl isocyanate (3 mmol) was added under nitrogen at room temperature. After the reaction mixture has stood for 1 h at room temperature, the solvent was removed under reduced pressure and a mixture of ether/petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. After filtration the solvent was removed to give carbodiimide **4**, which was used directly without further purification. To the solution of **4** prepared above in methylene dichloride (10 mL), amine (3 mmol) was added. After the reaction mixture was allowed to stand for 2-6 h, the solvent was removed and anhydrous ethanol (15 mL) with several drops of sodium ethoxide in ethanol was added. The mixture was stirred for 2-4 h at room temperature. The solution was then concentrated under reduced pressure and the residual was recrystallized from methylene dichloride/ethanol to give 2-amino-3-aryl-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile.

3-(4-Fluorophenyl)-2-morpholino-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6a**): white solid, mp: 210-211 ºC. IR (KBr, cm^{-1}): 2215 (CN), 1707 (C=N), 1606, 1581, 1563, 1506, 1217. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (s, 1H, C=CH, pyrrole), 7.57-7.18 (m, 9H, 9Ar-H), 3.46 (t, *J* 4.8 Hz, 4H, $2OCH_2$), 3.15 (t, *J* =4.8 Hz, 4H, $2NCH_2$). MS *m/z* (%): 415 (M^+, 100), 384 (13), 370 (83), 358 (87), 345 (36), 329 (86), 306 (36), 276 (17), 264 (44), 235 (20), 209 (66), 180 (37), 122 (16), 95 (27), 86 (28), 77 (28). Anal. Calcd for $C_{23}H_{18}FN_5O_2$: C, 66.50; H, 4.37; N, 16.86; Found: C, 66.54; H, 4.29; N, 16.91%.

2-(Dipropylamino)-3-(4-fluorophenyl)-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6b**): white solid, mp. 187-188 ºC. IR (KBr, cm^{-1}): 2216 (CN), 1709 (C=N), 1600, 1569. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.66 (s, 1H, C=CH, pyrrole), 7.56-7.18 (m,

9H, 9Ar-H), 3.00 (t, *J* 7.2 Hz, 4H, $2NCH_2$), 1.32-1.28 (m, 4H, $2CH_2$), 0.76 (t, *J* 7.5 Hz, 6H, $2CH_3$). MS *m/z* (%): 429 (M^+, 81), 400 (14), 386 (100), 359 (31), 344 (51), 329 (86), 306 (21), 293 (63), 277 (26), 264 (87), 251 (36), 235 (30), 209 (39), 180 (27), 100 (29), 77 (30). Anal. Calcd for $C_{25}H_{24}FN_5O$: C, 69.91; H, 5.63; N, 16.31; Found: C, 69.96; H, 5.68; N, 16.34%.

2-(Dibutylamino)-3-(4-fluorophenyl)-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-d]pyrimidine-7-carbonitrile (**6c**): white solid, mp. 140-141 ºC. IR (KBr, cm^{-1}): 2219 (CN), 1698 (C=N), 1607, 1560, 1500, 1211. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.65 (s, 1H, C=CH, pyrrole), 7.57-7.16 (m, 9H, 9Ar-H), 3.03 (t, *J* 7.2 Hz, 4H, $2NCH_2$), 1.27-1.15 (m, 8H, $2CH_2CH_2$), 0.86 (t, *J* 7.2 Hz, 6H, $2CH_3$); MS *m/z* (%): 457 (M^+, 70), 429 (21), 400 (95), 358 (100), 344 (41), 329 (91), 308 (51), 264 (49), 251 (28), 235 (29), 209 (32), 180 (19), 128 (19), 109 (23), 95 (26), 77 (39), 57 (19). Anal. Calcd for $C_{27}H_{28}FN_5O$: C, 70.88; H, 6.17; N, 15.31; Found: C, 70.82; H, 6.13; N, 15.36%.

3-(4-Fluorophenyl)-4-oxo-6-phenyl-2-(pyrrolidin-1-yl)-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6d**): white solid, mp. 275-276 ºC. IR (KBr, cm^{-1}): 2222 (CN), 1706 (C=N), 1560, 1499, 1219. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.60 (s, 1H, C=CH, pyrrole), 7.54-7.16 (m, 9H, 9Ar-H), 3.08 (t, *J* 6.6 Hz, 4H, $2NCH_2$), 1.74-1.72 (m, 4H, $2CH_2$). MS *m/z* (%): 399 (M^+, 87), 370 (31), 329 (30), 276 (37), 229 (34), 209 (26), 180 (21), 172 (19), 159 (100), 125 (23), 77 (19), 70 (27). Anal. Calcd for $C_{23}H_{18}FN_5O$: C, 69.16; H, 4.54; N, 17.53; Found: C, 69.20; H, 4.57; N, 17.49%.

2-(Diisopropylamino)-3-(4-fluorophenyl)-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]-pyrimidine-7-carbonitrile (**6e**): white solid, mp. 256-257 ºC. IR (KBr, cm^{-1}): 2211 (CN), 1703 (C=N), 1604, 1572, 1212. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.63 (s, 1H, C=CH, pyrrole), 7.57-7.15 (m, 9H, 9Ar-H), 3.55-3.51 (m, 2H, 2CH), 1.30 (d, *J* 6.6 Hz, 12H, $4CH_3$). MS *m/z* (%): 429 (M^+, 48), 400 (55), 386 (80), 343 (71), 329 (100), 293 (45), 277 (36), 251 (48), 235 (69), 209 (79), 180 (57), 77 (28). Anal. Calcd for $C_{25}H_{24}FN_5O$: C, 69.91; H, 5.63; N, 16.31; Found: C, 69.94; H, 5.57; N, 16. 40%.

3-(4-Fluorophenyl)-4-oxo-6-phenyl-2-(piperidin-1-yl)-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6f**): white solid, mp. 235-236 ºC. IR (KBr, cm^{-1}): 2209 (CN), 1697 (C=N), 1612. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.66 (s, 1H, C=C-H, pyrrole), 7.57-7.17 (m, 9H, Ar-H), 3.12 (t, *J* 5.4 Hz, 4H, $2NCH_2$), 1.46-1.27 (m, 6H, $3CH_2$). MS *m/z* (%): 413 (M^+, 94), 383 (33), 330 (24), 290 (47), 276 (41), 209 (70), 178 (100), 95 (30), 84 (71), 77 (32). Anal. Calcd for $C_{24}H_{20}FN_5O$: C, 69.72; H, 4.88; N, 16.94; Found: C, 69.76; H, 4.92; N, 17.00%.

2-Morpholino-4-oxo-3,6-diphenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6g**): white solid, mp. 260-261 ºC. IR (KBr, cm^{-1}): 2214 (CN), 1708 (C=N), 1600, 1566, 1503, 1215. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.66 (s, 1H, C=C-H, pyrrole), 7.57-7.36 (m, 10H, Ar-H), 3.40 (t, *J* 4.2 Hz, 4H, $2OCH_2$), 3.14 (t, *J* 4.2 Hz, 4H, $2NCH_2$). MS *m/z* (%): 397 (M^+, 100), 351 (49), 339 (60), 326 (48), 312 (44), 310 (38), 306 (32), 282 (21), 275 (24), 264 (32), 235 (23), 209 (61), 179 (29), 103 (27), 86 (28), 78 (34), 76 (49). Anal. Calcd for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62; Found: C, 69.50; H, 4.84; N, 17.57%.

2-(*t*-Butylamino)-3-(4-fluorophenyl)-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6h**): white solid, mp. 270-271 ºC. IR (KBr, cm^{-1}): 3445 (NH), 2210 (CN), 1704 (C=N), 1598, 1555, 1508, 1207. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.63 (s, 1H, C=CH, pyrrole), 7.55-7.27 (m, 9H, 9Ar-H), 3.94 (s, 1H, NH), 1.40 (s, 9H, $3CH_3$). MS m/z (%): 401 (M^+, 17), 345 (100), 330 (4), 235 (21), 210 (27), 180 (32), 111 (6), 95 (3), 77 (8), 57 (11). Anal. Calcd for $C_{23}H_{20}FN_5O$: C, 68.81; H, 5.02; N, 17.45; Found: C, 68.85; H, 4.99; N, 17.38%.

2-(*t*-Butylamino)-4-oxo-3,6-diphenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6i**): white solid, mp. 263-264 ºC. IR (KBr, cm^{-1}): 3441 (NH), 2210 (CN), 1699 (C=O), 1588, 1499, 761. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.63 (s, 1H, C=CH, pyrrole), 7.61-7.27 (m, 10H, 10Ar-H), 3.98 (s, 1H, NH), 1.39 (s, 9H, $3CH_3$). MS *m/z* (%): 383 (M^+, 27), 325 (100), 285 (14). Anal. Calcd for $C_{23}H_{21}N_5O$: C, 72.04; H, 5.52; N, 18.26; Found: C, 72.06; H, 5.58; N, 18.20%.

2-(t-Butylamino)-3-(4-chlorophenyl)-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6j**): white solid, mp. 279-280 ºC. IR (KBr, cm^{-1}): 3446 (NH), 2213 (CN), 1695 (C=O), 1604, 1578, 1520, 1496, 767. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.63 (s, 1H, C=C-H, pyrrole), 7.58-7.22 (m, 9H, Ar-H), 3.93 (s, 1H, NH), 1.41 (s, 9H, $3CH_3$). MS *m/z* (%): 417 (M^+, 8), 360 (54), 235 (37), 209 (28), 180 (33), 153 (16), 127 (32), 121 (19), 104 (24), 91 (21), 77 (100), 57 (89), 41 (91). Anal. Calcd for $C_{23}H_{20}ClN_5O$: C, 66.10; H, 4.82; N, 16.76; Found: C, 66.14; H, 4.86; N, 16.70%.

3-(4-Fluorophenyl)-2-(isopropylamino)-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6k**): white solid, mp. 289-290 ºC. IR (KBr, cm^{-1}): 3407 (NH), 2208 (CN), 1697 (C=O), 1603, 1564, 1506, 1413, 758. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.63 (s, 1H, C=C-H, pyrrole), 7.55-7.28 (m, 9H, Ar-H), 4.35-4.30 (m, 1H, CH), 3.82 (d, *J* 7.2 Hz, 1H, NH), 1.14 (d, *J* 6.6 Hz, 6H, $2CH_3$). MS *m/z* (%): 387 (M^+, 100), 344 (86), 235 (15), 77 (25), 58 (48). Anal. Calcd for $C_{22}H_{18}FN_5O$: C, 68.21; H, 4.68; N, 18.08; Found: C, 68.24; H, 4.62; N, 18.02%.

3-(4-Chlorophenyl)-2-(cyclohexylamino)-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]-pyrimidine-7-carbonitrile (**6l**): white solid, mp. 284-285 ºC. IR (KBr, cm^{-1}): 3437 (NH), 2207 (CN), 1706 (C=O), 1602, 1571, 1520, 1495, 759. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.61-7.25 (m, 10H, C=C-H+Ar-H), 4.01-4.00 (m, 1H, CH), 3.89 (d, *J* 7.8 Hz, 1H, NH), 1.95-1.93 (m, 2H, CH_2), 1.59-1.01 (m, 8H, $4CH_2$). MS *m/z* (%): 443 (M^+, 13), 360 (38), 325 (19), 235 (33), 180 (27), 153 (45), 127 (50), 111 (32), 83 (39), 77 (100), 55 (98), 41 (67); Anal. Calcd for $C_{25}H_{22}ClN_5O$: C, 67.64; H, 5.00; N, 15.78; Found: C, 67.69; H, 5.05; N, 15.79%.

General preparation of 2-aryloxy-3-aryl-4-oxo-6-phenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]-pyrimidine-7-carbonitriles (**6m-6o**). To the solution of carbodiimide **4** (3 mmol) prepared above in anhydrous acetonitrile (10 mL), phenol (3 mmol) and potassium carbonate (0.2 g, 1.5 mmol) were added. The mixture was stirred at 40-50 ℃ or 4-6 h. After cooling, 30 mL water was added and stir was continued until all the product was precipitated, then filtered and washed with ethanol, the residual was recrystallized from methylene dichloride/ethanol to give **6m-6o** in good yields.

2-(3,4-Dimethylphenyloxy)-4-oxo-3,6-diphenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6m**): white solid, mp. 232-233 ºC. IR (KBr, cm^{-1}): 2212 (CN), 1712 (C=O), 1618,

1586, 1494, 759. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.73 (s, 1H, C=C-H, pyrrole), 7.56-7.35 (m, 10H, Ar-H), 7.11 (d, *J* 7.8 Hz, 1H, Ar-H), 6.89 (d, *J* 8.4 Hz, 2H, Ar-H), 2.24 (s, 6H, $2CH_3$). MS *m/z* (%): 432 (M^+, 13), 314 (39), 298 (10), 119 (12), 103 (8), 91 (53), 77 (100), 51 (19); Anal. Calcd for $C_{27}H_{20}N_4O_2$: C, 74.98; H, 4.66; N, 12.95; Found: C, 74.94; H, 4.69; N, 12.90%.

4-Oxo-3,6-diphenyl-2-(*p*-tolyloxy)-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6n**): white solid, mp. 249-250 ºC. IR (KBr, cm^{-1}): 2211 (CN), 1710 (C=O), 1618, 1586, 1494, 759. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.74 (s, 1H, C=CH, pyrrole), 7.56-7.01 (m, 14H, 14Ar-H), 2.35 (s, 3H, CH_3). MS *m/z* (%): 418 (M^+, 97), 310 (24), 298 (100), 282 (30), 270 (21), 229 (10), 193 (12), 179 (11), 102 (15), 91 (12), 77 (77). $C_{26}H_{18}N_4O_2$: C, 74.63; H, 4.34; N, 13.39; Found: C, 74.65; H, 4.40; N, 13.41%.

2-(4-Chlorophenyloxy)-4-oxo-3,6-diphenyl-4,6-dihydro-3*H*-pyrrolo[3,4-*d*]pyrimidine-7-carbonitrile (**6o**): white solid, mp. 242-243 ºC. IR (KBr, cm^{-1}): 2213 (CN), 1708 (C=O), 1614, 1498, 760. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65 (s, 1H, C=CH, pyrrole), 7.53-7.19 (m, 14H, 14Ar-H). MS *m/z* (%): 438 (M^+, 80), 310 (43), 298 (100), 270 (58), 193 (23), 179 (30), 127 (39), 91 (12), 77 (77). Anal. Calcd for $C_{25}H_{15}ClN_4O_2$: C, 68.42; H, 3.45; N, 12.77; Found: C, 68.46; H, 3.39; N, 12.80%.

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