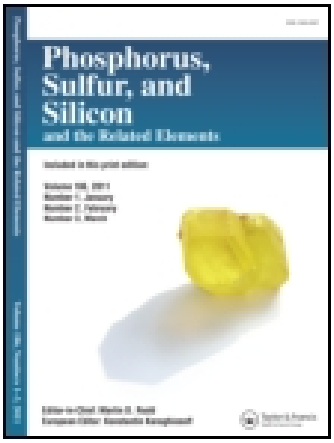

Phosphorus, Sulfur, and Silicon and the Related Elements

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Dmap-Catalyzed Synthesis of Novel Pyrrolo[2,3-D]Pyrimidine Derivatives Bearing an Aromatic Sulfonamide Moiety

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DMAP-CATALYZED SYNTHESIS OF NOVEL PYRROLO[2,3-D]PYRIMIDINE DERIVATIVES BEARING AN AROMATIC SULFONAMIDE MOIETY

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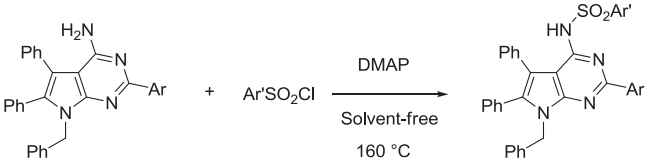
GRAPHICAL ABSTRACT



1a-1c **2a-2c** **3a-3i**

Abstract *4-(N,N-Dimethylamino)pyridine (DMAP), with a dual role as a basic nucleophilic catalyst, was shown to be a highly efficient catalyst for the synthesis of some new N-(2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzenesulfonamides through the reaction of 2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amines (7-deazaadenines) with benzenesulfonyl chlorides. It was also found that the use of DMAP under solvent-free conditions is much more effective than other catalytic systems such as pyridine as both the catalyst and solvent, t-BuOK in t-BuOH, Et_3N in ethanol (EtOH), and even DMAP in dimethylformamide (DMF). The influences of the reaction parameters, temperature, and the catalyst amount, on the catalytic performance have been studied. All synthetic compounds were characterized on the basis of their full spectral data.*

Keywords DMAP; benzenesulfonamides; pyrrolo[2,3-d]pyrimidin-4-amines; solvent-free conditions

INTRODUCTION

Sulfonamides, specially their aryl derivatives, represent a class of medicinally important compounds having interesting pharmacological activities. Many of these compounds

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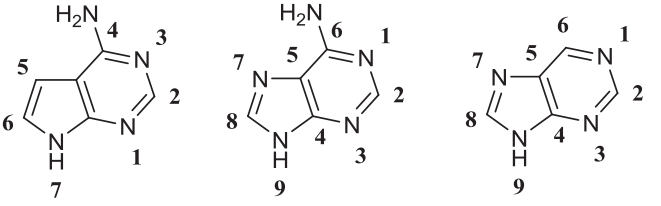
are extensively used for their antibacterial,[1] antiinflammatory,[2] hypoglycemic,[3] antifungal,[4] antidiabetic[5] activities and as anticonvulsant agents.[6,7] Also, some of them are protease,[8] and carbonic anhydrase inhibitors.[9,10] Recently, a host of structurally novel sulfonamide derivatives was reported to show substantial antitumor activity in vitro and/or in vivo.[11–14]

On the other hand, pyrrolo[2,3-d]pyrimidines are widely used as antitumor,[15] antimicrobial,[16] and antiangiogenic[17] agents with potential application as enzyme inhibitors.[18] Moreover, pyrrolo[2,3-d]pyrimidin-4-amines (**i**), which may be regarded as an analog of adenine (**ii**) in which its N-7 (purine (**iii**) numbering) has been replaced by a CH group and therefore can be named as 7-deazaadenines, are known to show antiinflammatory,[19] antifungal,[20] and antibacterial[20] activities. Also, some 4-substituted aminopyrrolo[2,3-d]pyrimidine derivatives are selective A1-adenosine receptor antagonists.[21]



(i) **(ii)** **(iiI)**

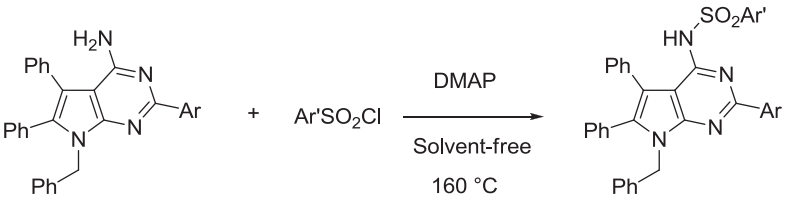
These facts prompted us to the synthesis of novel pyrrolo[2,3-d]pyrimidine derivatives bearing an aromatic sulfonamide moiety that can also be named as substituted amino-7-deazaadenines. Among the reported methods, the sulfonylation of amines with sulfonyl chlorides in the presence of a base is still the most commonly employed method for the synthesis of sulfonamides.[22,23] A perusal of the literature revealed that sulfonylation of amines with sulfonyl chlorides is commonly performed in pyridine as the base and medium.[24–28]

4-(N,N-Dimethylamino)pyridine (DMAP) is a very good nucleophilic catalyst and is more basic than pyridine. DMAP is widely used as a superb nucleophilic catalyst for many organic reactions such as Baylis–Hillman reaction,[29,30] regioselective acylation of 6-O-protected octyl β-D-glucopyranosides,[31] synthesis of electrophilic alkenes,[32] heroin synthesis,[33] and synthesis of *N*-sulfonyl monocyclic β-lactams.[34]

In continuation of our previous works in the synthesis of new heterocyclic compounds with potential biological activities,[35–45] recently, we prepared some new 2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amines (derivatives of 7-deazaadenine) by reaction of 2-amino-1-benzyl-4,5-diphenyl-1H-pyrrole-3-carbonitriles with aryl nitriles.[46] In this paper, we report the synthesis of new N-(2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzenesulfonamides **3a**–**3i** in synthetically useful yields by sulfonylation reaction of amino moiety in 2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amines **1a**–**1c** with benzenesulfonyl chlorides **2a**–**2c** in the presence of DMAP with a dual role as a base and also a nucleophilic catalyst under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

The starting materials 2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amines **1a**–**1c** were prepared according to the literature method.[46] Initially, we started the condensation of 7-benzyl-5,6-diphenyl-2-*m*-tolyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine **1b**



1a-1c **2a-2c** **3a-3i**

1a: Ar = Ph
1b: Ar = 3-MeC_6H_4
1c: Ar = 4-MeC_6H_4

2a: Ar' = Ph
2b: Ar' = 4-MeC_6H_4
2c: Ar' = 4-ClC_6H_4

3a: Ar = Ph, Ar' = Ph
3b: Ar = Ph, Ar' = 4-MeC_6H_4
3c: Ar = Ph, Ar' = 4-ClC_6H_4
3d: Ar = 3-MeC_6H_4, Ar' = Ph
3e: Ar = 3-MeC_6H_4, Ar' = 4-MeC_6H_4
3f: Ar = 3-MeC_6H_4, Ar' = 4-ClC_6H_4
3g: Ar = 4-MeC_6H_4, Ar' = Ph
3h: Ar = 4-MeC_6H_4, Ar' = 4-MeC_6H_4
3i: Ar = 4-MeC_6H_4, Ar' = 4-ClC_6H_4

Scheme 1 Synthesis of N-(2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzenesulfonamides catalyzed by DMAP.

(1 mmol) with 4-methylbenzenesulfonyl chloride **2b** (1 mmol) as a model in refluxing ethanol (EtOH) or dimethylformamide (DMF) and also under solvent-free conditions at high temperature in the absence of catalyst. No product was observed in these conditions even after prolonged reaction time (Table 1, entries 1–3). To enhance the yield of the desired product, it was thought worthwhile to carry out the reaction in the presence of a base as catalyst. Among the various tested catalyst–solvent systems such as pyridine as both catalyst and solvent, *t*-BuOK in *t*-BuOH, Et_3N in EtOH, DMAP in DMF, and also DMAP under solvent-free conditions, the reaction was proceeded to give the high yield

Table 1 Synthesis of compound **3e** in the presence of DMAP as catalyst in different reaction conditions[a]

Entry	Catalyst (amount)	Solvent	*T* (°C)	Time (h:min)	Yield (%)[b]
1	None	—	160	18:00	—
2	None	EtOH	78	18:00	—
3	None	DMF	153	18:00	—
4	Pyridine (2 mL)	—	115	10:00	Trace
5	*t*-BuOK (0.2 g)	*t*-BuOH	83	10:00	—
6	NEt_3 (0.5 mL)	EtOH	78	10:00	—
7	DMAP (0.1 g)	DMF	153	10:00	Trace
8	DMAP (0.05 g)	—	160	4:30	65
9	DMAP (0.1 g)	—	90	10:00	Trace
10	DMAP (0.1 g)	—	110	10:00	27
11	DMAP (0.1 g)	—	120	8:00	42
12	DMAP (0.1 g)	—	140	6:00	50
13	DMAP (0.1 g)	—	160	2:30	88
14	DMAP (0.1 g)	—	180	2:30	88
15	DMAP (0.2 g)	—	160	3:00	88

[a]Reaction conditions: 7-benzyl-5,6-diphenyl-2-*m*-tolyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine **1b** (1 mmol), and 4-methylbenzenesulfonyl chloride **2b** (1 mmol). [b]Isolated yields.

Table 2 Synthesis of N-(2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzenesulfonamides **3a–3i**[a]

Entry	Ar	Ar′	Product[b]	Time (h:min)	Yield (%)[c]	mp (°C)
1	C_6H_5	C_6H_5	**3a**	1:00	90	275–277
2	C_6H_5	4-MeC_6H_4	**3b**	1:30	89	233–235
3	C_6H_5	4-ClC_6H_4	**3c**	1:00	90	235–237
4	3-MeC_6H_4	C_6H_5	**3d**	2:00	85	197–199
5	3-MeC_6H_4	4-MeC_6H_4	**3e**	2:30	88	195–197
6	3-MeC_6H_4	4-ClC_6H_4	**3f**	2:00	85	206–208
7	4-MeC_6H_4	C_6H_5	**3g**	1:30	93	264–267
8	4-MeC_6H_4	4-MeC_6H_4	**3h**	1:00	97	207–209
9	4-MeC_6H_4	4-ClC_6H_4	**3i**	1:00	97	205–207

[a]Reaction conditions: 2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amines **1a–1c** (1 mmol), benzenesulfonyl chlorides **2a–2c** (1 mmol), DMAP (0.1 g), 160 °C, solvent-free.

[b]All the products were characterized according to their IR, ^{1}H NMR, ^{13}C NMR, and MASS spectral data.

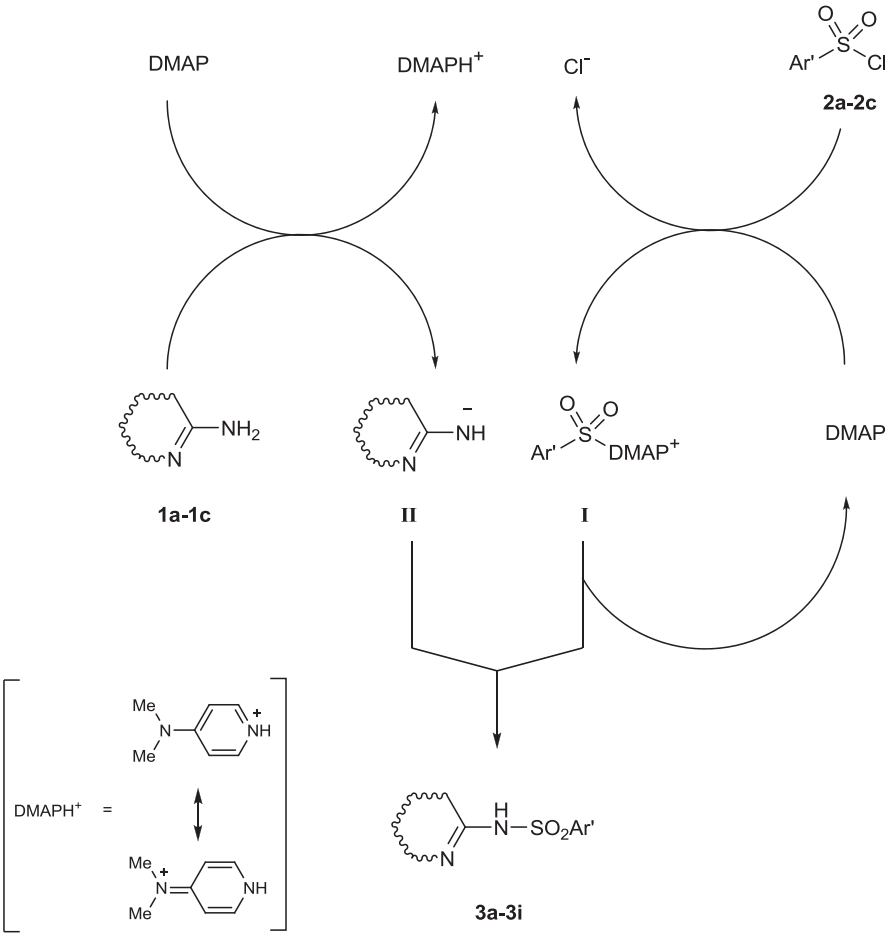
[c]Isolated yields.

of the product **3e**, using DMAP under solvent-free conditions. In order to determine the optimum conditions, we examined the influence of the reaction temperature and the amount of DMAP as catalyst. The best result was obtained when the reaction was conducted at 160 °C in the presence of 0.1 g of the catalyst under solvent-free conditions (Table 1, entry 13). A further increase in temperature and catalyst amount did not improve the product yield.

With the above result in hand, and in order to show the generality and scope of this new protocol, a range of N-(2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzenesulfonamides **3a–3i** was prepared in the presence of DMAP under optimized conditions and the results are summarized in Table 2. In all cases, the reactions proceeded to produce the corresponding products in high yields.

The structures of the new compounds **1c** and **3a–3i** were deduced from their spectral data. For example, the ^{1}H NMR spectrum of **3e** in $CDCl_3$ did not show the NH_2 signal at δ 5.18 ppm belonging to the precursor **1b**,[46] but instead showed a sharp single (1H) signal at δ 12.93 ppm for an NH group along with two sharp 3H signals at δ 2.40 and 2.51 ppm for methyl groups, a signal at δ 5.46 ppm for methylene hydrogens as well as the signals in the aromatic region due to 23 aromatic protons indicating the formation of the compound **3e**. Also, this product gave satisfactory ^{13}C NMR, mass spectrometry, and elemental analysis data corresponding to the molecular formula $C_{39}H_{32}N_4O_2S$ (Experimental section).

According to the proposed catalytic roles for DMAP in some organic reactions,[33,47–49] a plausible mechanism for the formation of products **3a–3i** using DMAP as catalyst can be depicted in Scheme 2. As shown, it is proposed that DMAP can play a dual role as a base and also nucleophilic catalyst and therefore can activate both reactants in this transformation. Since the nitrogen atom in DMAP is more nucleophilic than the amino group in compounds **1a–1c**, and also the intermediate **I** is more reactive than the benzenesulfonyl chlorides **2a–2c**, the conditions required for nucleophilic catalysis therefore exist, and the reaction is faster in the presence of DMAP than in its absence. On the other hand, DMAP can neutralize the protons generated in the reaction and prevents the development of high acid concentration. Also, DMAP as a base, can promote the reactions by the deprotonation of the amino group, enhancing the nucleophilicity of this moiety in intermediate **II**. Two intermediates **I** and **II** subsequently react together to give the final products **3a–3i**.



Scheme 2 The role of DMAP as a base and nucleophilic catalyst in the synthesis of compounds 3a–3i.

CONCLUSION

In conclusion, DMAP was found to be highly efficient catalyst for the synthesis of some new N-(2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzenesulfonamides **3a**–**3i** in high yields by the reaction of 2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amines **1a**–**1c** with benzenesulfonyl chlorides **2a**–**2c**. The use of DMAP under solvent-free conditions is much more effective than other catalytic systems such as pyridine as both the catalyst and solvent, *t*-BuOK in *t*-BuOH, Et_3N in EtOH, and even DMAP in DMF. It is proposed that DMAP can play a dual role as a base and also a nucleophilic catalyst.

EXPERIMENTAL

Melting points were recorded on a Stuart SMP3 melting point apparatus (UK). The IR spectra were obtained using a Perkin-Elmer Spectrum-1 (USA) spectrophotometer using KBr disks. The ^{1}H NMR were recorded with a Varian-400 MHz (USA) spectrometer. The

^{13}C NMR were recorded with varian-300 and 400 MHz spectrometers (USA) at 75 and 100 MHz frequencies. Mass spectra were obtained using a Thermo Finnegan LCQ DECA XP MAX (USA) mass spectrometer. Elemental analysis was performed on a Thermo Finnigan Flash EA (USA) microanalyzer.

General Procedure for the Synthesis of N-(2-Aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzenesulfonamides 3a–3i

A mixture of 2-aryl-7-benzyl-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amines **1a**–**1c** (1 mmol), benzenesulfonyl chlorides **2a**–**2c** (1 mmol), and DMAP (0.1 g) was heated in an oil bath at 160 °C for 1–2.5 h. The reaction was monitored by thin layer chromatography (TLC). Upon completion, the mixture was cooled to room temperature and hot EtOH/H_2O was added. This resulted in the precipitation of the product that was collected by filtration. The crude product was washed repeatedly with ethanol and water to give compounds **3a**–**3i** in 85%–97% yields.

Spectral Data for Compounds 1c and 3a–3i

7-Benzyl-2-(4-methylphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine 1c (Ar = 4-MeC_6H_4). This new compound was prepared according to the method reported in ref. [46]. Time 8 h, yield 95%, mp 210–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 5.04 (s br, 2H, NH_2), 5.49 (s, 2H, CH_2), 7.04–7.35 (m, 17H, arom-H), 8.38 (d, J = 8.2 Hz, 2H, arom-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4 (CH_3), 46.0 (CH_2), 100.3, 114.1, 126.7, 127.1, 127.6, 127.8, 128.1, 128.3, 128.4, 128.9, 130.4, 130.8, 131.1, 134.7, 135.1, 136.4, 138.3, 139.2, 152.3, 156.8, 158.3 (aromatics); IR (KBr disk): ν 3473, 3296, 3152, 3059, 3032, 2922, 1637, 1583, 1559, 1451, 1412, 1358, 1310, 728, 695 cm^{-1}; MS (APCI): m/z 467.43 (MH^+, 100%) (466.58 calcd. for $C_{32}H_{26}N_4$); Anal. Calcd. for $C_{32}H_{26}N_4$: C, 82.38; H, 5.62; N, 12.01; found: C, 82.06; H, 5.85; N, 11.84.

N-(7-Benzyl-2,5,6-triphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzene–sulfonamide 3a (Ar = Ph, Ar′ = Ph). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47 (s, 2H, CH_2), 6.93–7.65 (m, 21H, arom-H), 7.80 (d, J = 7.4 Hz, 2H, arom-H), 8.14–8.24 (m, 2H, arom-H), 12.97 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.4 (CH_2), 104.2, 118.9, 125.9, 126.4, 126.5, 127.0, 127.2, 127.5, 128.2, 128.4, 128.5, 128.6, 129.4, 130.1, 131.1, 131.5, 131.6, 131.8, 132.3, 136.6, 137.1, 143.4, 148.4, 148.5, 150.1 (aromatics); IR (KBr disk): ν 3434, 2925, 1630, 1445, 1260, 1021, 814 cm^{-1}; MS (APCI): m/z 593.69 (MH^+, 100%) (592.71 calcd. for $C_{37}H_{28}N_4O_2S$); Anal. Calcd. for $C_{37}H_{28}N_4O_2S$: C, 74.98; H, 4.76; N, 9.45; S, 5.41; found: C, 74.69; H, 4.54; N, 9.77; S, 5.16.

N-(7-Benzyl-2,5,6-triphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-methyl–benzenesulfonamide 3b (Ar = Ph, Ar′ = 4-MeC_6H_4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 5.46 (s, 2H, CH_2), 6.93–7.65 (m, 19H, arom-H), 7.69 (d, 2H, J = 8.1 Hz, arom-H), 8.06–8.21 (m, 3H, arom-H), 13.01 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4 (CH_3), 46.4 (CH_2), 104.1, 119.0, 125.9, 126.3, 126.5, 127.0, 127.2, 127.5, 128.3, 128.5, 128.6, 129.0, 129.4, 130.2, 130.2, 131.1, 131.6, 131.7, 132.3, 136.5, 137.9, 140.6, 142.0, 148.4, 148.4, 150.0 (aromatics); IR (KBr disk): ν 3443, 3061, 2924, 1624, 1445, 1434, 1389, 1341, 1259, 1066, 814 cm^{-1}; MS (APCI): m/z 607.26 (MH^+, 100%) (606.74 calcd. for $C_{38}H_{30}N_4O_2S$); Anal. Calcd. for $C_{38}H_{30}N_4O_2S$: C, 75.22; H, 4.98; N, 9.23; S, 5.28; found: C, 74.89; H, 5.24; N, 9.47; S, 5.56.

N-(7-Benzyl-2,5,6-triphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-chloro–benzenesulfonamide 3c (Ar = Ph, Ar′ = 4-ClC$_6$H$_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.45 (s, 2H, CH_2), 6.92–7.38 (m, 18H, arom-H), 7.55–7.62 (m, 2H, arom-H), 7.66 (d, J = 8.6 Hz, 2H, arom-H), 8.12–8.17 (m, 2H, arom-H), 12.84 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.5 (CH_2), 104.2, 118.9, 126.5, 127.1, 127.2, 127.4, 127.6, 128.4, 128.5, 128.6, 128.7, 129.4, 129.9, 131.1, 131.5, 131.6, 131.9, 132.3, 136.8, 137.1, 137.7, 142.0, 148.4, 148.5, 150.0 (aromatics); IR (KBr disk): ν 3435, 3063, 2928, 1626, 1445, 1393, 1261, 1068, 813 cm^{-1}; MS (APCI): m/z 627.21 (M$^+$, 100%), 628.28 (MH$^+$, 40%) (627.15 calcd. for $C_{37}H_{27}ClN_4O_2S$); Anal. Calcd. for $C_{37}H_{27}ClN_4O_2S$: C, 70.86; H, 4.34; N, 8.93; S, 5.11; found: C, 71.18; H, 4.59; N, 8.66; S, 4.94.

N-(7-Benzyl-5,6-diphenyl-2-m-tolyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)–benzenesulfonamide 3d (Ar = 3-MeC$_6$H$_4$, Ar′ = Ph). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 3H, CH_3), 5.46 (s, 2H, CH_2), 6.93–7.01 (m, 2H, arom-H), 7.07 (d, J = 7.5 Hz, 2H, arom-H), 7.11–7.52 (m, 16H, arom-H), 7.79 (d, J = 7.5 Hz, 2H, arom-H), 7.93–7.99 (m, 2H, arom-H), 12.91 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 (CH_3), 46.5 (CH_2), 104.2, 119.0, 123.7, 126.0, 126.4, 127.0, 127.2, 127.3, 127.6, 128.4,128.4, 128.5, 128.6, 129.3, 130.2, 131.2, 131.6, 131.7, 132.4, 132.7, 136.6, 137.2, 139.3, 143.5, 148.6, 148.7, 150.2 (aromatics); IR (KBr disk): ν 3436, 3062, 3031, 2924, 1622, 1447, 1435, 1386, 1349, 1258, 1068, 829 cm^{-1}; MS (APCI): m/z 607.34 (MH$^+$, 100%) (606.74 calcd. for $C_{38}H_{30}N_4O_2S$); Anal. Calcd. for $C_{38}H_{30}N_4O_2S$: C, 75.22; H, 4.98; N, 9.23; S, 5.28; found: C, 75.46; H, 5.15; N, 9.01; S, 5.04.

N-(7-Benzyl-5,6-diphenyl-2-m-tolyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-methylbenzenesulfonamide 3e (Ar = 3-MeC$_6$H$_4$, Ar′ = 4-MeC$_6$H$_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 5.46 (s, 2H, CH_2), 6.94–7.51 (m, 19H, arom-H), 7.68 (d, J = 8.3 Hz, 2H, arom-H), 7.93–7.98 (m, 2H, arom-H), 12.93 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4 (CH_3), 21.6 (CH_3), 46.4 (CH_2), 104.1, 118.9, 123.7, 125.9, 126.3, 127.0, 127.1, 127.2, 127.5, 128.3, 128.5, 128.6, 129.0, 129.3, 130.2, 131.1, 131.6, 132.3, 132.6, 136.5, 137.2, 139.3, 140.6, 142.0, 148.5, 148.7, 150.0 (aromatics); IR (KBr disk): ν 3435, 3061, 3028, 2920, 1625, 1434, 1390, 1354, 1301, 1259, 1127, 1069, 863, 699 cm^{-1}; MS (APCI): m/z 621.27 (MH$^+$, 100%) (620.76 calcd. for $C_{39}H_{32}N_4O_2S$); Anal. Calcd. for $C_{39}H_{32}N_4O_2S$: C, 75.46; H, 5.20; N, 9.03; S, 5.17; found: C, 75.84; H, 4.91; N, 8.74; S, 5.38.

N-(7-Benzyl-5,6-diphenyl-2-m-tolyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-chlorobenzenesulfonamide 3f (Ar = 3-MeC$_6$H$_4$, Ar′ = 4-ClC$_6$H$_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 3H, CH_3), 5.47 (s, 2H, CH_2), 6.94–7.52 (m, 19H, arom-H), 7.67 (d, J = 8.6 Hz, 2H, arom-H), 7.92–7.97 (m, 2H, arom-H), 12.79 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 (CH_3), 46.5 (CH_2), 104.2, 118.9, 123.7, 126.5, 127.1, 127.1, 127.2, 127.4, 127.6, 128.4, 128.5, 128.6, 128.7, 129.3, 130.0, 131.1, 131.5, 131.6, 132.3, 132.7, 136.8, 137.1, 137.7, 139.4, 142.0, 148.7, 150.1 (aromatics); IR (KBr disk): ν 3436, 3058, 2924, 1625, 1435, 1389, 1350, 1262, 1128, 1072, 865, 701 cm^{-1}; MS (APCI): m/z 641.37 (M$^+$, 100%), 642.38 (MH$^+$, 39%) (641.18 calcd. for $C_{38}H_{29}ClN_4O_2S$); Anal. Calcd. for $C_{38}H_{29}ClN_4O_2S$: C, 71.18; H, 4.56; N, 8.74; S, 5.00; found: C, 70.86; H, 4.37; N, 8.52; S, 5.19.

N-(7-Benzyl-5,6-diphenyl-2-p-tolyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl) benzene sulfonamide 3g (Ar = 4-MeC$_6$H$_4$, Ar′ = Ph). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 (s, 3H, CH_3), 5.45 (s, 2H, CH_2), 6.94–7.52 (m, 20H, arom-H), 7.80 (d, J = 7.4 Hz, 2H, arom-H), 8.06 (d, J = 8.1 Hz, 2H, arom-H), 12.91 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 (CH_3), 46.3 (CH_2), 103.9, 118.8, 125.9, 126.4, 126.5, 127.0, 127.2, 127.5,

128.32, 128.4, 128.4, 128.5, 130.0, 130.1, 131.1, 131.5, 132.3, 136.4, 137.2, 142.4, 143.4, 145.3, 145.7, 148.6, 150.0 (aromatics); IR (KBr disk): ν 3434, 3055, 3028, 2923, 1626, 1446, 1387, 1352, 1259, 1161, 1128, 1066, 703 cm^{-1}; MS (APCI): *m/z* 607.33 (MH^+, 100%) (606.74 calcd. for $C_{38}H_{30}N_4O_2S$); Anal. Calcd. for $C_{38}H_{30}N_4O_2S$: C, 75.22; H, 4.98; N, 9.23; S, 5.28; found: C, 75.01; H, 4.79; N, 9.48; S, 5.09.

N-(7-Benzyl-5,6-diphenyl-2-p-tolyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-methylbenzenesulfonamide 3h (Ar = 4-MeC_6H_4, Ar′ = 4-MeC_6H_4). ^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 5.45 (s, 2H, CH_2), 6.93–7.01 (m, 2H, arom-H), 7.07 (d, $J = 7.0$ Hz, 2H, arom-H), 7.12–7.36 (m, 13H, arom-H), 7.40 (d, $J = 7.0$ Hz, 2H, arom-H), 7.68 (d, $J = 8.2$ Hz, 2H, arom-H), 8.06 (d, $J = 8.2$ Hz, 2H, arom-H), 12.93 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4 (CH_3), 21.5 (CH_3), 46.4 (CH_2), 103.9, 118.9, 125.9, 126.3, 126.5, 127.0, 127.2, 127.5, 128.3, 128.5, 128.5, 128.8, 129.0, 130.1, 130.2, 131.1, 131.6, 132.4, 136.3, 137.2, 140.7, 142.0, 142.4, 148.5, 150.0 (aromatics); IR (KBr disk): ν 3434, 3063, 3032, 2921, 1619, 1430, 1382, 1348, 1263, 1160, 1123, 1096, 1067, 813, 699 cm^{-1}; MS (APCI): *m/z* 621.24 (MH^+, 100%) (620.76 calcd. for $C_{39}H_{32}N_4O_2S$); Anal. Calcd. for $C_{39}H_{32}N_4O_2S$: C, 75.46; H, 5.20; N, 9.03; S, 5.17; found: C, 75.19; H, 5.41; N, 8.72; S, 5.42.

N-(7-Benzyl-5,6-diphenyl-2-p-tolyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-chlorobenzenesulfonamide 3i (Ar = 4-MeC_6H_4, Ar′ = 4-ClC_6H_4). ^1H NMR (400 MHz, DMSO-d_6): δ 2.08 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 6.92–7.42 (m, 19H, arom-H), 7.65 (d, $J = 8.2$ Hz, 2H, arom-H), 8.02 (d, $J = 8.2$ Hz, 2H, arom-H), 12.78 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 (CH_3), 46.4 (CH_2), 104.1, 118.8, 126.5, 127.0, 127.2, 127.4, 127.6, 128.4, 128.5, 128.6, 128.7, 128.7, 130.0, 130.1, 131.1, 131.6, 132.4, 136.6, 137.1, 137.7, 142.1, 142.6, 148.6, 148.7, 150.1 (aromatics); IR (KBr disk): ν 3421, 3062, 3030, 2925, 1624, 1432, 1386, 1347, 1263, 1069, 817, 699 cm^{-1}; MS, *m/z* (APCI): 641.29 (M^+, 100%), 642.32 (MH^+, 39%) (641.18 calcd. for $C_{38}H_{29}ClN_4O_2S$); Anal. Calcd. for $C_{38}H_{29}ClN_4O_2S$: C, 71.18; H, 4.56; N, 8.74; S, 5.00; found: C, 71.55; H, 4.81; N, 8.49; S, 4.72.

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REFERENCES

1. Stokes, S. S.; Albert, R.; Buurman, E. T.; Andrews, B.; Shapiro, A. B.; Green, O. M.; McKenzie, A. R.; Otterbein, L. R. *Bioorg. Med. Chem. Lett.* **2012,** 22, 7019-7023.
2. Keche, A. P.; Hatnapure, G. D.; Tale, R. H.; Rodge, A. H.; Kamble, V. M. *Bioorg. Med. Chem. Lett.* **2012,** 22, 6611-6615.
3. Blickle, J. F.; Brogard, J. M. *Diabet. Metab.* **1998,** 24, 276-280.
4. Patel, N. B.; Patel, V. N. *Pharm. Chem. J.* **2010,** 44, 438-445.
5. Pattan, S. R.; Kekare, P.; Dighe, N. S.; Kothiwale, V. A.; Shete, R. V.; Musmade, D. S.; Parjane, S. K. *Indian Drugs* **2010,** 47, 14-19.
6. Farag, A. A.; Abd-Alrahman, S. N.; Ahmed, G. F.; Ammar, R. M.; Ammar, Y. A.; Abbas, S. Y. *Arch. Pharm.* **2012,** 345, 703-712.
7. Flaherty, P. T.; Greenwood, T. D.; Manheim, A. L.; Wolfe, J. F. *J. Med. Chem.* **1996,** 39, 1509-1513.

8. Casini, A.; Scozzafava, A.; Supuran, C. T. *Expert Opin. Ther. Pat.* **2002,** 12, 1307-1327.
9. Ann Boriack, P.; Christianson, D. W.; Kingery-Wood, J.; Whitesides, G. M. *J. Med. Chem.* **1995,** 38, 2286-2291.
10. Buyukkidan, N.; Buyukkidan, B.; Bulbul, M.; Kasimogullari, R.; Serdar, M.; Mert, S. *J. Pharm. Pharmacol.* **2013,** 65, 363-369.
11. Aly, H. M. *Phosphorus Sulfur Silicon Relat. Elem.* **2010,** 185, 211-221.
12. Rostom, S. A. *Bioorg. Med. Chem.* **2006,** 14, 6475-6485.
13. Ghorab, M. M.; Ragab, F. A.; Heiba, H. I.; Youssef, H. A.; El-Gazzar, M. G. *Med. Chem. Res.* **2012,** 21, 1376-1383.
14. El-Sayed, N. S.; El-Bendary, E. R.; El-Ashry, S. M.; El-Kerdawy, M. M. *Eur. J. Med. Chem.* **2011,** 46, 3714-3720.
15. Acs, G.; Reich, E.; Mori, M. *Proc. Nat. Sci.* **1964,** 52, 493-501.
16. Mohamed, M. S.; Rashad, A. E.; Zaki, M. E. A.; Fatahala, S. S. *Acta. Pharm.* **2005,** 55, 237-249.
17. Gangjee, A.; Namjoshi, O. A.; Yu, J.; Ihnat, M. A.; Thorpe, J. E.; Warnke, L. A. *Bioorg. Med. Chem.* **2008,** 16, 5514-5528.
18. Gibson, C. L.; Rosa, S. L.; Ohta, K.; Boyle, P. H.; Leurquin, F.; Lemacon A.; Suckling, C. J.; *Tetrahedron* **2004,** 60, 943-959.
19. Mohamed, M. S.; Kamel, R.; Fatahala, S. S. *Eur. J. Med. Chem.* **2010,** 45, 2994-3004.
20. Hassan Hilmy, K. M.; Khalifa, M. M. A.; Allah Hawata, M. A.; Aboalzeen Keshk, R. M.; El-Torgman, A. A. *Eur. J. Med. Chem.* **2010,** 45, 5243-5250.
21. Campbell, R. M.; Cartwright, C.; Chen, W.; Chen, Y.; Duzic, E.; Fu, J. M.; Loveland, M.; Manning, R.; McKibben, B.; Pleiman, C. M.; Silverman, L.; Trueheart, J.; Webb, D. R.; Wilkinson, V.; Witter, D. J.; Xie, X. B.; Castelhano, A. L. *Bioorg. Med. Chem. Lett.* **1999,** 9, 2413-2418.
22. Kim, J. G.; Jang, D. O. *Synlett* **2007,** 2501-2504.
23. Huntress, E. H.; Carten, F. H. *J. Am. Chem. Soc.* **1940,** 62, 511-514.
24. Wang, Y.; Guziec, F. S., Jr. *J. Org. Chem.* **2001,** 66, 8293-8296.
25. Da Silva, L. E.; De Sousa, P. T., Jr.; Joussef, A. C.; Piovezan, C.; Neves, A. *Quim. Nova.* **2008,** 31, 1161-1164.
26. Hangan, A.; Bodoki, A.; Oprean, L.; Crisan, O.; Mihalca, I. *Farmacia* **2012,** 60, 932-938.
27. Rai, D.; Singh, R. K. *Indian J. Chem. Sect. B Org. Med. Chem.*, **2011,** 50, 931-942.
28. Çakir, U.; Ugraş, H. I.; Ozensoy, O.; Sinan, S.; Arslan, O. *J. Enzyme Inhib. Med. Chem.* **2004,** 19, 257-261.
29. Octavio, R.; de Souza, M. A.; Vasconcellos, M. L. A. A. *Synth. Commun.* **2003,** 33, 1383-1389.
30. De Souza, R. O. M. A.; Vasconcellos, M. L. A. A. *Catal. Commun.* **2004,** 5, 21-24.
31. Muramatsu, W.; Kawabata, T. *Tetrahedron Lett.* **2007,** 48, 5031-5033.
32. Venkat Narsaiah, A.; Basak, A. K.; Visali, B.; Nagaiah, K. *Synth. Commun.* **2004,** 34, 2893-2901.
33. Klemenc, S. *Forensic Sci. Int.* **2002,** 129, 194-199.
34. Jarrahpour, A.; Zarei, M. *Molecules* **2006,** 11, 49-58.
35. Bakavoli, M.; Davoodnia, A.; Rahimizadeh, M.; Heravi, M. M. *Phosphorus Sulfur Silicon Relat. Elem.* **2002,** 177, 2303-2308.
36. Roshani, M.; Davoodnia, A.; Hedayat, M. Sh.; Bakavoli, M. *Phosphorus Sulfur Silicon Relat. Elem.* **2004,** 179, 1153-1157.
37. Seifi, N.; Zahedi-Niaki, M. H.; Barzegari, M. R.; Davoodnia, A.; Zhiani, R.; Aghaei Kaju, A. *J. Mol. Catal. A Chem.* **2006,** 260, 77-81.
38. Davoodnia, A.; Rahimizadeh, M.; Rivadeh, Sh.; Bakavoli, M.; Roshani, M. *Indian J. Heterocycl. Chem.* **2006,** 16, 151-154.
39. Davoodnia, A.; Zhiani, R.; Roshani, M.; Bakavoli, M.; Bashash, M. *Phosphorus Sulfur Silicon Relat. Elem.* **2007,** 182, 1219-1224.
40. Davoodnia, A.; Bakavoli, M.; Pooryaghoobi, N.; Roshani, M. *Heterocycl. Commun.* **2007,** 13, 323-325.

41. Davoodnia, A.; Bakavoli, M.; Bashash, M.; Roshani, M.; Zhiani, R. *Turk. J. Chem.* **2007,** 31, 599-603.
42. Davoodnia, A.; Bakavoli, M.; Mohseni, Sh.; Tavakoli-Hoseini, N. *Monatsh. Chem.* **2008,** 139, 963-965.
43. Davoodnia, A.; Zhiani, R.; Tavakoli-Hoseini, N. *Monatsh. Chem.* **2008,** 139, 1405-1407.
44. Davoodnia, A.; Rahimizadeh, M.; Atapour-Mashhad, H.; Tavakoli-Hoseini, N. *Heteroat. Chem.* **2009,** 20, 346-349.
45. Davoodnia, A.; Bakavoli, M.; Moloudi, R.; Khashi, M.; Tavakoli-Hoseini, N. *Chin. Chem. Lett.* **2010,** 21, 1-4.
46. Davoodnia, A.; Khashi, M.; Tavakoli-Hoseini, N.; Moloudi, R.; Zamani, H. A. *Monatsh. Chem.* **2013,** 144, 677-680.
47. Nair, V.; Vidya, N.; Biju, A. T.; Deepthi, A.; Abhilash, K. G.; Suresh, E. *Tetrahedron* **2006,** 62, 10136-10140.
48. Davoodnia, A.; Bakavoli, M.; Soleimany, M.; Behmadi, H. *Chin. Chem. Lett.* **2008,** 19, 685-688.
49. Shiels, R. A.; Jones, Ch. W. *J. Mol. Catal. A Chem.* **2007,** 261, 160-166.