3,4-Diaminopyrazolo[3,4-*d*]pyrimidines: A New Three-Component Microwave-Assisted Synthesis and Anti-leukemic Properties†

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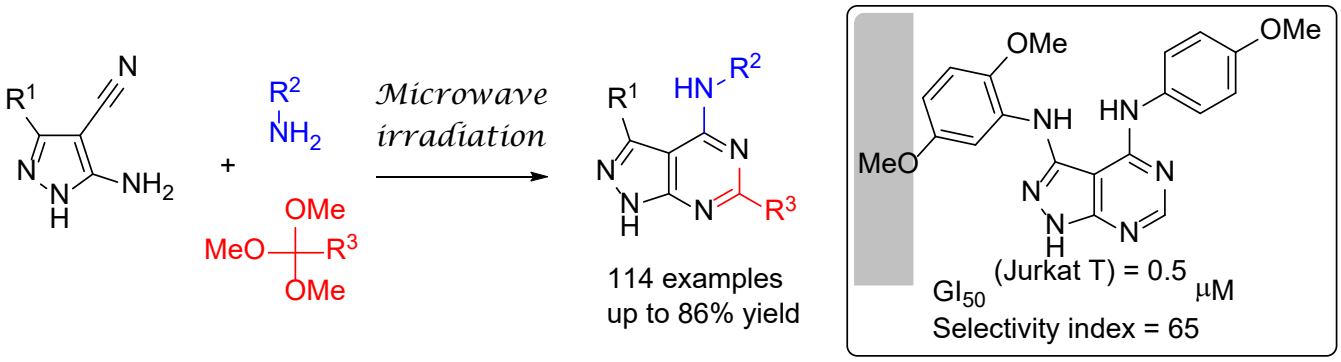
KEYWORDS

pyrimidine, aminopyrazole, anticancer, antileukemic, multicomponent reaction, microwave-assisted synthesis

Footnote

† Electronic supplementary information (ESI) available: Tables of intra- and inter-molecular geometric parameters, molecular structure diagrams and molecular packing diagrams. CCDC 2241492-2241495 contain the supplementary crystallographic data for this paper. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cexxxxxx



ABSTRACT

A convenient method for the synthesis of N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines was developed using a three-component reaction of 3,5-diaminopyrazole-4-carbonitriles with primary amines and orthoesters. The preparation of 114 examples demonstrated the good scope of the reaction, which tolerated variations in the substrate structure and was particularly efficient under microwave irradiation. The short reaction time and chromatography-free product isolation add practicality to this method. The anti-leukemic activity was assessed *in vitro* using K562 and Jurkat T cells, and the selectivity of the most active compounds was

evaluated using non-cancerous MRC5 cells. The most promising compound inhibited Jurkat T cells with a GI_{50} value of 0.5 μM and a selectivity index of 64.

1. Introduction

Purines represent the most ubiquitous of *N*-heterocyclic systems. In addition to encoding half of the genome, purines also form an integral part of the biological processes of approximately 3266 human proteins [1]. These proteins include enzymes, receptors and transporters, which can serve as targets for drug molecules. Purines play roles of substrates, cofactors or secondary messengers, thus using purine isosteres for drug? We need to specifiy discovery of what discovery is a valid strategy, which has been proven to be fruitful [2-4]. RSC superscripts references

Pyrazolo[3,4-*d*]pyrimidine is one of the heterocyclic systems isosteric with the purine ring. These heterocycles are different in the position of one nitrogen atom thus making pyrazolo[3,4-*d*]pyrimidine system an 8-aza-7-deaza-analog of purine (Figure 1). The isosterism with purine has resulted in the extensive application of pyrazolo[3,4-*d*]pyrimidines in the search for new bioactive compounds. The development of allopurinol [5] as an anti-gout drug inhibiting xanthine oxidase, an enzyme catabolizing hypoxanthine, was the first successful example of utilization of the isosteric relationship between pyrazolo[3,4-*d*]pyrimidine and purine heterocycles for drug design.

It was reported that 8-aza-7-deaza-adenine (4-aminopyrazolo[3,4-*d*]pyrimidine) exhibited *in vivo* activity against adenocarcinoma 755 and leukaemia L1210 and L5178 in mice [6]. The further optimization of substitution patterns around this scaffold resulted in the development of the first-line treatment of leukaemia and lymphoma, ibrutinib (Figure 1) [7]. Besides, there are several 4-aminopyrazolo[3,4-*d*]pyrimidines advanced to clinical trials as antineoplastic kinase inhibitors, *e.g.* sapanisertib and parsaclisib.

Sapanisertib (Figure 1) is a potent mammalian target of rapamycin (mTOR) inhibitor [8] found to be effective against retinoblastoma [9], prostate cancer [8], pancreatic cancer [10], breast cancer [11], colon cancer [12], and bone and soft-tissue sarcomas [13] in preclinical studies. Sapanisertib

has completed the Phase I clinical trials as an agent for advanced solid tumours (NCT01058707, NCT03370302 and NCT02197572) [14-16] and progressed to Phase II clinical trials for the therapy of advanced solid tumours (NCT02465060, NCT02893930 and NCT03648489) [17-19]. The structurally similar compound PP242 (Figure 1) was also found to be a more effective inhibitor of mTOR protein complex 1 than rapamycin [20].

Parsaclisib (Figure 1), targeting phosphoinositide 3-kinase δ, has entered Phase II clinical trials for relapsed B-cell malignancies (NCT02018861, NCT02998476 and NCT03314922) [21-23]. CGP57380, a potent inhibitor of MAPK-interacting kinase 1[24], demonstrated synergism with mTOR inhibitors and activity against adult T-cell acute lymphoblastic leukaemia (Jurkat cells) [24] and acute myeloid leukaemia (U937 cells) [25]. CGP57380 was found to inhibit leukaemia stem cell function in blast crisis chronic myeloid leukaemia cells [26] and overcome imatinib resistance in chronic myelogenous leukaemia [27].

Potent anti-cancer agents were also identified among 8-aza-7-deaza-adenine with the substituted amino group. For example, ZMF-10 was found to induce apoptosis in cancer cells by inhibiting P21-activated kinase 1 [28]. A selective adenosine triphosphate (ATP) competitive inhibitor of p70 S6 kinase, LY2584702, went to Phase I and Phase II clinical trials as a potential anti-cancer drug (NCT01372085, NCT01241461, NCT01394003 and NCT01115803) [29-33]. A potential anti-cancer compound, NCGC00138812, was identified as the most promising inhibitor of association between the cell division control protein 42 homolog (Cdc42) and the scaffold protein IQGAP1, which stabilises Cdc42 in its active form increasing cancer cell migration and invasion [34].

Interesting results were also obtained with N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines, which inhibited epidermal growth factor receptor protein tyrosine kinases (*e.g.* an

ATP-competitive inhibitor **1** possessing an *in vivo* anti-cancer effect in mice) [35]. The pan-kinase inhibitor **2** was found to be a good ligand for complement factor D serine protease [36].

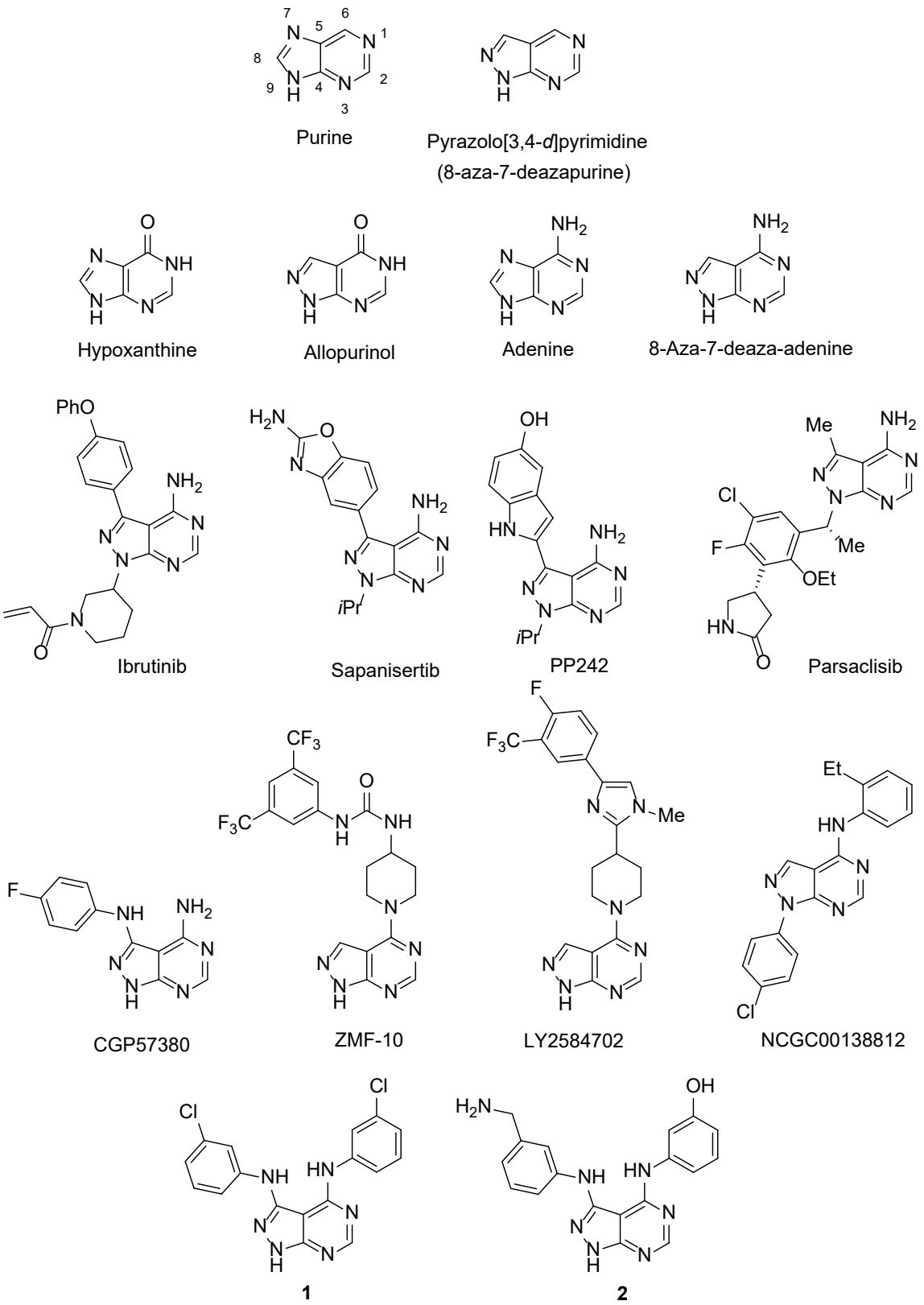
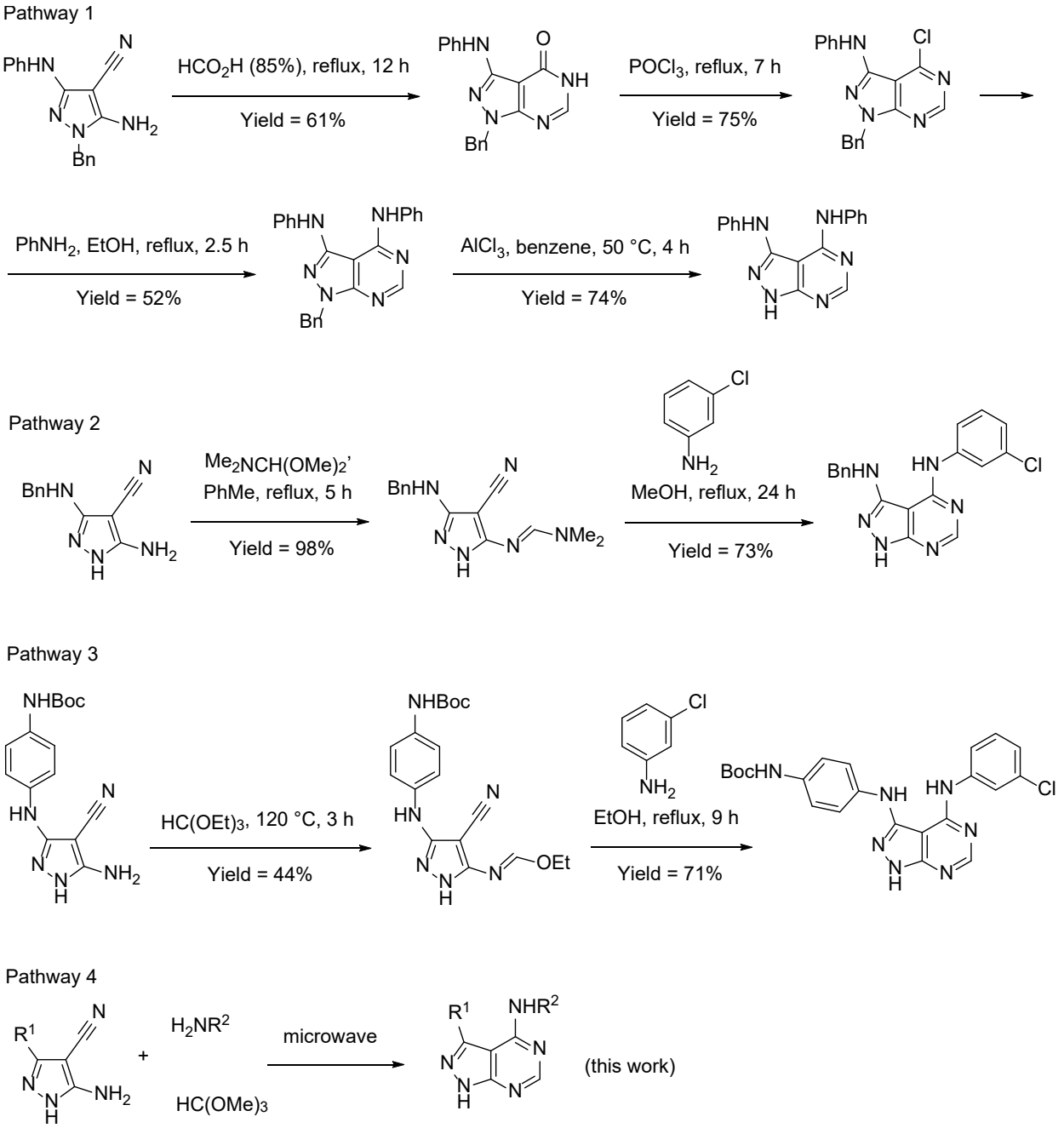


Figure 1. Isosteric replacement of purine by pyrazolo[3,4-*d*]pyrimidine in bioactive molecules.

The synthesis of 4-aminopyrazolo[3,4-*d*]pyrimidines with the alkyl- or aryl-substituted amino group has been performed using one of the following strategies: (1) amination of pyrazolo[3,4-*d*]pyrimidines possessing a leaving group in position 4, (2) pyrimidine ring closure of *N*′-(4-cyanopyrazol-5-yl)-*N,N*-dimethylformamidines in the reaction with primary amines, (3) pyrimidine ring closure of ethyl *N*-(4-cyanopyrazol-5-yl)formimidates in the reaction with primary amines and (4) arylation or alkylation of 4-aminopyrazolo[3,4-*d*]pyrimidines. The competitive reactive centres in N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines make the latter strategy not applicable to their synthesis, while the former three approaches have been explored by Traxler and colleagues [35] as exemplified in Scheme 1 (Pathways 1-3). The synthesis of targeted compounds by the amination of 4-chloro-substituted pyrazolo[3,4-*d*]pyrimidine required the presence of a protecting group and debenzylation as the final step of the transformation sequence. Although Pathways 2 and 3 appeared to be shorter, Traxler [35] mentioned that under the reported reaction conditions they were successful for a few substrates only.

Nevertheless, we decided to develop a new efficient method for the synthesis N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines using building blocks similar to those in Pathway 3: 5-aminopyrazole-4-carbonitriles, trimethyl orthoformate and amines. Recently, we reported [37] a multi-component reaction for the pyrimidinone ring annulation onto 5-aminopyrazole-4-carboxylates using microwave-assisted condensation of these compounds with primary amines and trimethyl orthoformate. It is also known [38] that the reaction of 5-aminopyrazole-4-carbonitriles with secondary amines and triethyl orthoformate under microwave irradiation resulted in the formation of formamidines structurally similar to the intermediates in the proposed synthesis of N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines. Therefore, we decided to employ controlled microwave irradiation to facilitate our proposed multi-component reaction.



Scheme 1. Methods for the synthesis of N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines.

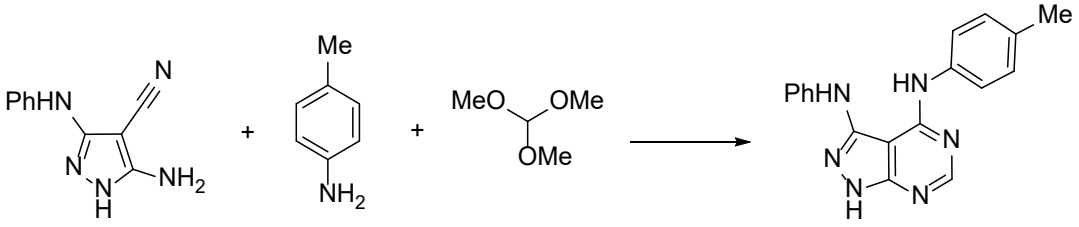
The 4-aminopyrazolo[3,4-*d*]pyrimidine precursor has been demonstrated to be a promising scaffold for the construction of new anti-cancer and particularly anti-leukemic agents. Therefore, we also assessed potential anti-leukemic properties of the newly prepared compounds.

2. Results and discussion

2.1. Synthesis

The synthesis of the starting 3-amino-substituted 5-aminopyrazole-4-carbonitriles was performed as reported previously [39,40]. The trial reaction and optimization of the reaction condition were carried out using the model reaction of 5-amino-3-phenylaminopyrazole-4-carbonitrile **3**{*1*} with trimethyl orthoformate and *p*-toluidine **4**{*7*} (Table 1). The reaction was performed under microwave irradiation in a Discover SP reactor (CEM, USA).

Table 1. Screening of reaction conditions for the microwave-assisted synthesis of N^4-(4-methylphenyl)-N^3-phenylpyrazolo[3,4-*d*]pyrimidine-3,4-diamine **5**{*1,7*}[a]



3{*1*} **4**{*7*} **5**{*1,7*}

Entry	Temperature, °C	Time, min	Solvent	Yield,[b] %
1[c]	180	20	Toluene	44
2	180	20	Toluene	48
3[d]	180	20	Toluene	48

4	180	25	Toluene	57
5	180	30	Toluene	61
6	180	35	Toluene	63
7	180	40	Toluene	61
8	170	35	Toluene	28
9	190	35	Toluene	66
10	200	35	Toluene	70
11	210	35	Toluene	69
12	220	35	Toluene	63
13	200	35	*p*-Cymene	59
14	200	35	Anisole	66
15	200	35	Eucalyptol	60
16	200	35	*n*-BuOH	53
17	200	35	*n*-PentOH	54
18[e]	200	35	Toluene	60

[a] Unless specified otherwise, the reactions were performed under microwave irradiation (maximum power = 150 W) in a Discover SP (CEM, USA) reactor using 5-amino-3-phenylaminopyrazole-4-carbonitrile **3**{*1*} (1 mmol), *p*-toluidine **4**{*7*} (3 mmol) and trimethyl orthoformate (3 mmol) in 2 mL of the specified solvent.

[b] Isolated yield calculated on the basis of **3**{*1*}.

[c] The reactions was performed using 5-amino-3-phenylaminopyrazole-4-carbonitrile **3**{*1*} (1 mmol), *p*-toluidine **4**{*7*} (2 mmol) and trimethyl orthoformate (2 mmol).

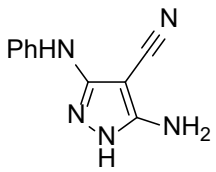
[d] The reaction was performed using 5-amino-3-phenylaminopyrazole-4-carbonitrile **3**{*1*} (1 mmol), *p*-toluidine **4**{*7*} (4 mmol) and trimethyl orthoformate (4 mmol).

[e] The reaction was performed under conventional heating in a Monowave 50 (Anton Paar, Austria) reactor.

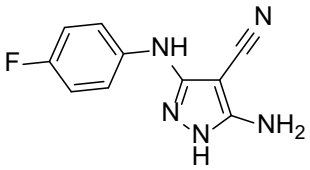
The trial reaction of 5-amino-3-phenylaminopyrazole-4-carbonitrile **3**{*1*} with trimethyl orthoformate and *p*-toluidine **4**{*7*} in toluene at 180 °C for 20 min. afforded the desired N^4-(4-methylphenyl)-N^3-phenylpyrazolo[3,4-*d*]pyrimidine-3,4-diamine **5**{*1,7*}, which was isolated by simple filtration (Entries 1-3). A better yield was achieved when 3 equiv. of the orthoester and **4**{*7*} were used (Entry 2). Using this reagent ratio, the reaction time and temperature were increased up to 200 °C for 35 min. to achieve a 70% yield (Entry 10). Further extension of the reaction time (Entry 7) or an increase in temperature (Entry 11 and 12) did not improve the reaction outcome. A series of some high-boiling point, green solvents such as *p*-cymene, anisole, eucalyptol, *n*-butanol and *n*-pentanol were also screened as media for this reaction (Entries 13-17) were less effective than toluene. To assess the microwave effect on the reaction outcome, we also tested the reaction using optimised solvent, temperature and reaction time under conventional heating in a Monowave 50 reactor (Entry 18). Without microwave irradiation, the yield decreased but remained within an acceptable range (60%), thus confirming that the thermal component of microwave irradiation played the main role in promoting the reaction.

For the exploration of the multi-component reaction scope, microwave irradiation at 200 °C for 35 min. (Table 1, entry 9) was applied as optimal conditions. The reaction scope was assessed using various combinations of 3-substituted 5-aminopyrazole-4-carbonitriles **3**{*1-18*} (Figure 2(a), Chemset 1) and primary amines **4**{*1-21*} (Figure 2(b), Chemset 2). The prepared compounds

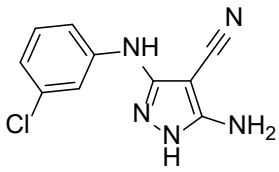
and their yields are listed in Table 2. The reaction was found to be general as illustrated by 110 - please check – 114 in the Abstract examples of prepared compounds with yields up to 86%. The aromatic and aliphatic substituents were well tolerated at both amino groups.



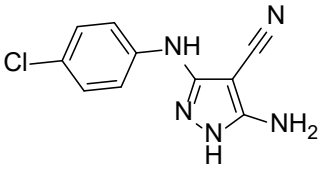
{*1*}



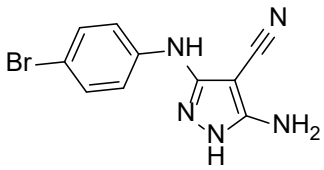
{*2*}



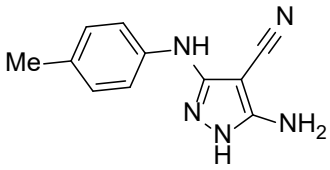
{*3*}



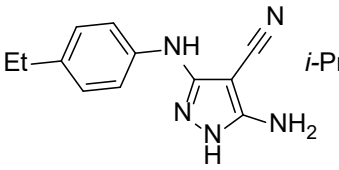
{*4*}



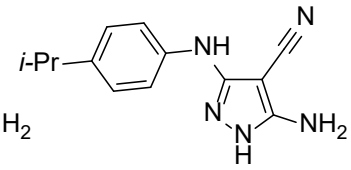
{*5*}



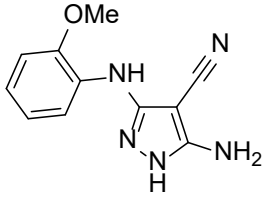
{*6*}



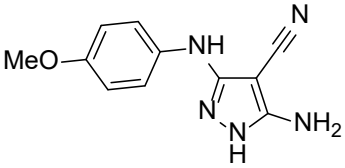
{*7*}



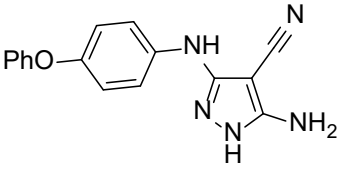
{*8*}



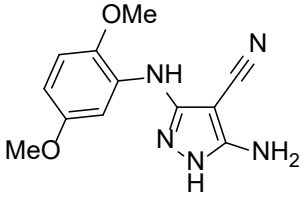
{*9*}



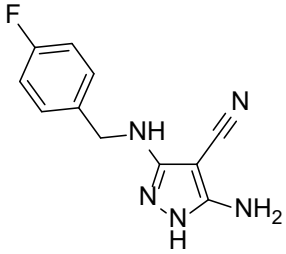
{*10*}



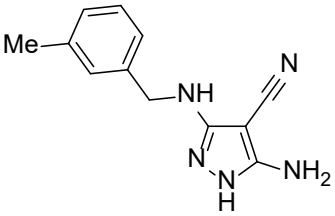
{*11*}



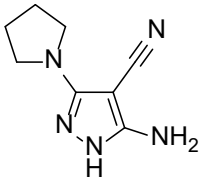
{*12*}



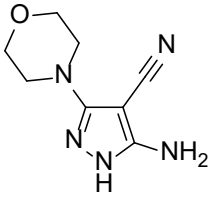
{*13*}



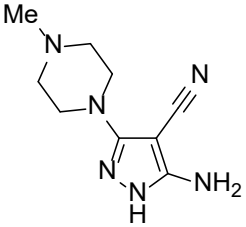
{*14*}



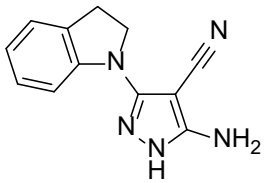
{*15*}



{*16*}

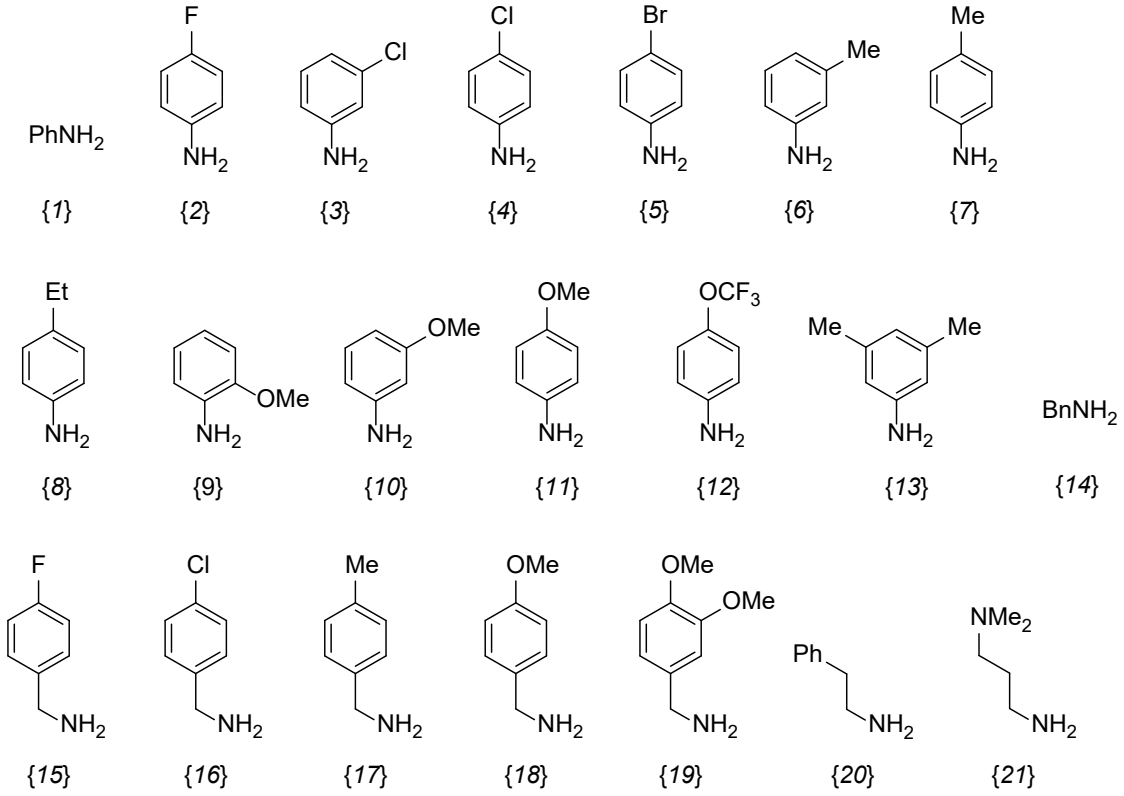


{*17*}



{*18*}

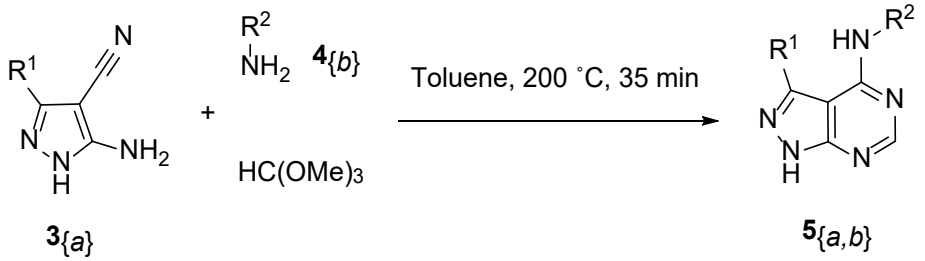
(a) Chemset 1. 5-Aminopyrazole-4-carbonitriles **3**{*a*}.



(b) Chemset 2. Primary amines **4**{*b*}.

Figure 2. Building blocks for the library of N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines **5**{*a,b*}.

Table 2. Prepared library of N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines **5**{*a,b*}[a]



Entry	Compound	Yield, %	Entry	Compound	Yield, %

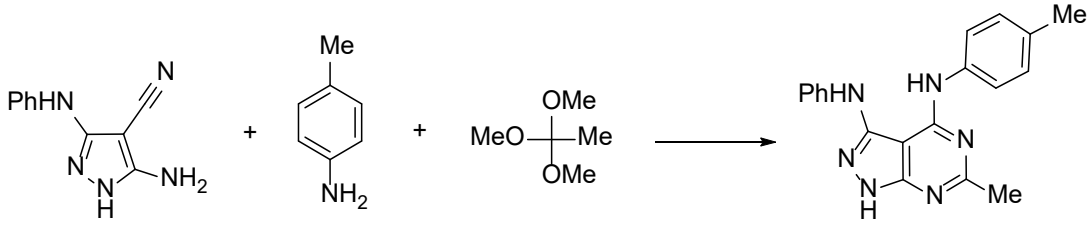
1	**5**{*1,2*}	49	57	**5**{*6,14*}	81
2	**5**{*1,4*}	35	58	**5**{*6,15*}	33
3	**5**{*1,5*}	46	59	**5**{*6,16*}	78
4	**5**{*1,6*}	52	60	**5**{*6,17*}	83
5	**5**{*1,7*}	70	61	**5**{*6,19*}	37
6	**5**{*1,8*}	38	62	**5**{*6,20*}	37
7	**5**{*1,9*}	27	63	**5**{*7,7*}	58
8	**5**{*1,11*}	51	64	**5**{*8,7*}	27
9	**5**{*1,13*}	38	65	**5**{*8,10*}	15
10	**5**{*1,14*}	83	66	**5**{*9,4*}	71
11	**5**{*1,15*}	84	67	**5**{*9,7*}	39
12	**5**{*1,16*}	81	68	**5**{*10,4*}	28
13	**5**{*1,17*}	84	69	**5**{*10,5*}	21
14	**5**{*1,18*}	86	70	**5**{*10,6*}	32
15	**5**{*1,20*}	68	71	**5**{*10,7*}	62
16	**5**{*1,21*}	60	72	**5**{*10,9*}	16
17	**5**{*2,3*}	35	73	**5**{*10,10*}	55
18	**5**{*2,7*}	56	74	**5**{*10,11*}	26
19	**5**{*2,9*}	53	75	**5**{*10,14*}	77
20	**5**{*2,10*}	37	76	**5**{*10,16*}	68
21	**5**{*3,5*}	16	77	**5**{*11,2*}	31
22	**5**{*3,7*}	54	78	**5**{*11,4*}	20
23	**5**{*4,2*}	29	79	**5**{*11,5*}	34

24	**5**{*4,3*}	24	80	**5**{*11,7*}	43
25	**5**{*4,4*}	31	81	**5**{*11,9*}	43
26	**5**{*4,5*}	57	82	**5**{*11,10*}	65
27	**5**{*4,6*}	29	83	**5**{*11,11*}	47
28	**5**{*4,7*}	52	84	**5**{*11,14*}	68
29	**5**{*4,9*}	50	85	**5**{*11,16*}	65
30	**5**{*4,10*}	36	86	**5**{*12,1*}	38
31	**5**{*4,11*}	57	87	**5**{*12,2*}	36
32	**5**{*4,13*}	44	88	**5**{*12,4*}	24
33	**5**{*4,14*}	65	89	**5**{*12,5*}	29
34	**5**{*4,15*}	62	90	**5**{*12,7*}	30
35	**5**{*4,16*}	65	91	**5**{*12,10*}	30
36	**5**{*4,17*}	72	92	**5**{*12,12*}	9
37	**5**{*5,2*}	48	93	**5**{*12,13*}	50
38	**5**{*5,3*}	26	94	**5**{*12,14*}	32
39	**5**{*5,4*}	30	95	**5**{*12,16*}	37
40	**5**{*5,5*}	68	96	**5**{*12,17*}	49
41	**5**{*5,6*}	54	97	**5**{*13,7*}	38
42	**5**{*5,7*}	70	98	**5**{*14,7*}	31
43	**5**{*5,9*}	41	99	**5**{*15,7*}	35
44	**5**{*5,10*}	67	100	**5**{*15,10*}	27
45	**5**{*5,11*}	39	101	**5**{*16,4*}	18
46	**5**{*5,13*}	47	102	**5**{*16,7*}	63

47	**5**{*5,14*}	81	103	**5**{*16,9*}	30
48	**5**{*5,16*}	33	104	**5**{*16,10*}	55
49	**5**{*6,2*}	40	105	**5**{*17,7*}	31
50	**5**{*6,3*}	35	106	**5**{*18,2*}	46
51	**5**{*6,4*}	40	107	**5**{*18,4*}	36
52	**5**{*6,5*}	55	108	**5**{*18,5*}	53
53	**5**{*6,6*}	52	109	**5**{*18,7*}	67
54	**5**{*6,7*}	64	110	**5**{*18,11*}	68
55	**5**{*6,9*}	46	111	**5**{*18,14*}	77
56	**5**{*6,10*}	80	112	**5**{*18,16*}	80

Being satisfied with the diversity of N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines **5** prepared using the developed method, we additionally explored the introduction of another substituent using the same reaction. By varying the orthoester structure in the three-component reaction, a few alkyl groups were introduced in position 6 of the heterocyclic system. Initial attempts to replicate the protocol optimised for the reaction of trimethyl orthoformate for the reaction of **3**{*1*} and **4**{*7*} with other orthoesters resulted in rather low product yields. Further optimization of the reaction conditions using the model reaction with trimethyl orthoacetate **6**{*1*} indicated that a better yield of **7**{*1,7,1*} could be obtained when the reaction time was extended to 55 min. (Table 3, Entry 3). These conditions were successfully applied for the synthesis of 6-alkyl-N^4-(4-methylphenyl)-N^3-phenylpyrazolo[3,4-*d*]pyrimidine-3,4-diamines **7**{*1,7,c*} (Scheme 2).

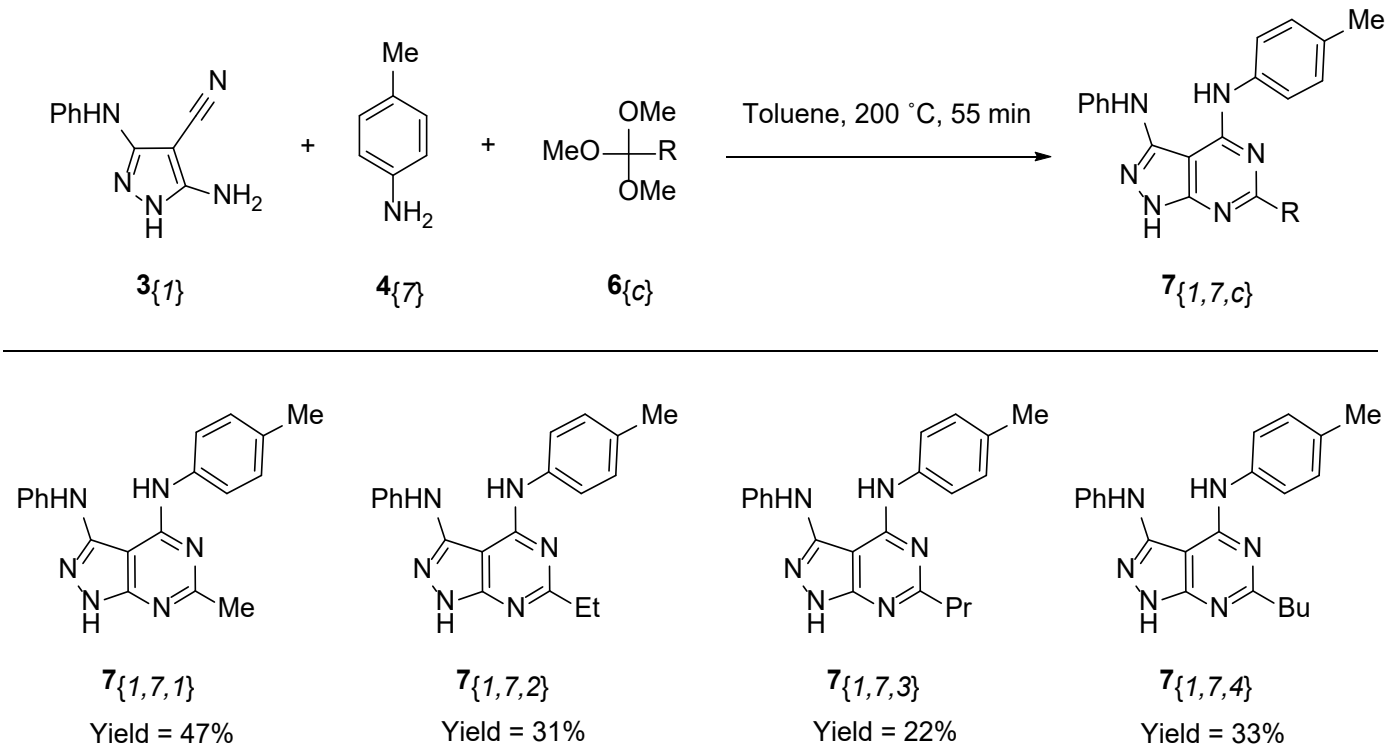
Table 3. Screening of reaction conditions for the microwave-assisted synthesis of 6-methyl-N^4-(4-methylphenyl)-N^3-phenylpyrazolo[3,4-*d*]pyrimidine-3,4-diamine **7**{*1,7,1*}[a]



3{*1*} **4**{*7*} **6**{*1*} **7**{*1,7,1*}

Entry	Temperature, °C	Time, min	Yield, %
1	200	35	26
2	200	45	27
3	200	55	47
4	200	65	32
5	210	55	41

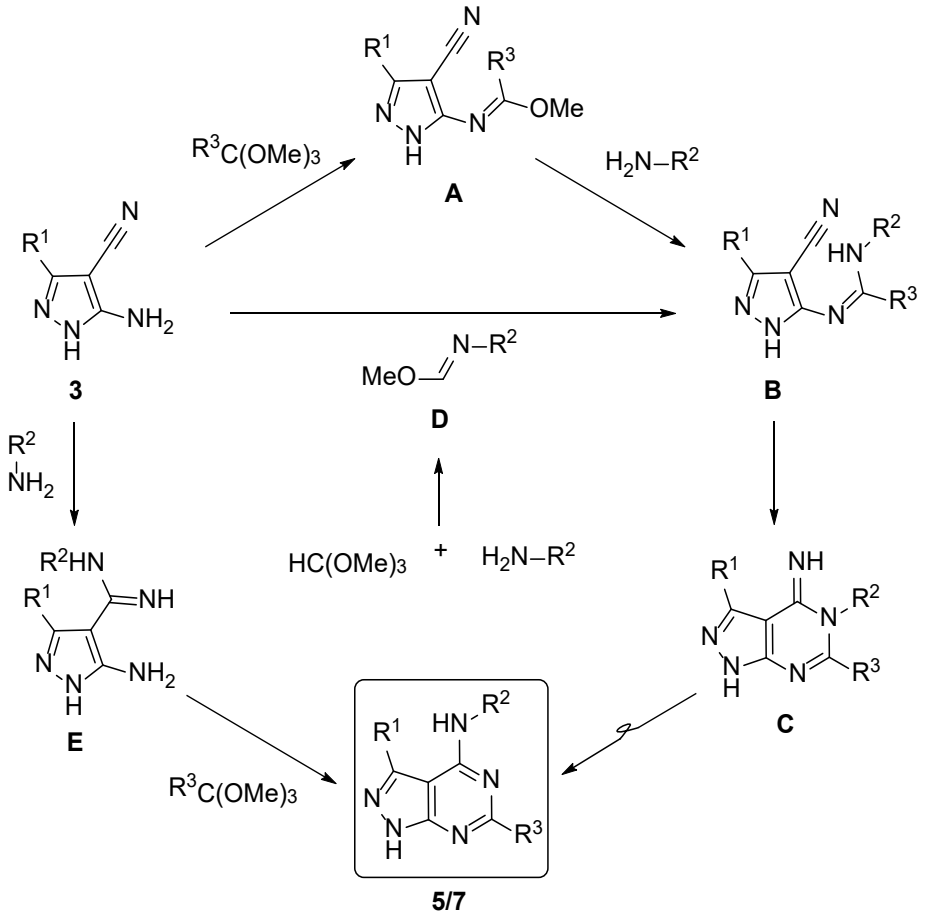
[a] The reactions were performed under microwave irradiation (maximum power = 150 W) in a Discover SP (CEM, USA) reactor using 5-amino-3-phenylaminopyrazole-4-carbonitrile **3**{*1*} (1 mmol), *p*-toluidine **4**{*7*} (3 mmol) and trimethyl orthoacetate **6**{*1*} (3 mmol) in toluene (2 mL).



Scheme 2. Synthesis of 6-alkyl-N^4-(4-methylphenyl)-N^3-phenylpyrazolo[3,4-*d*]pyrimidine-3,4-diamines **7**{*1,7,c*}

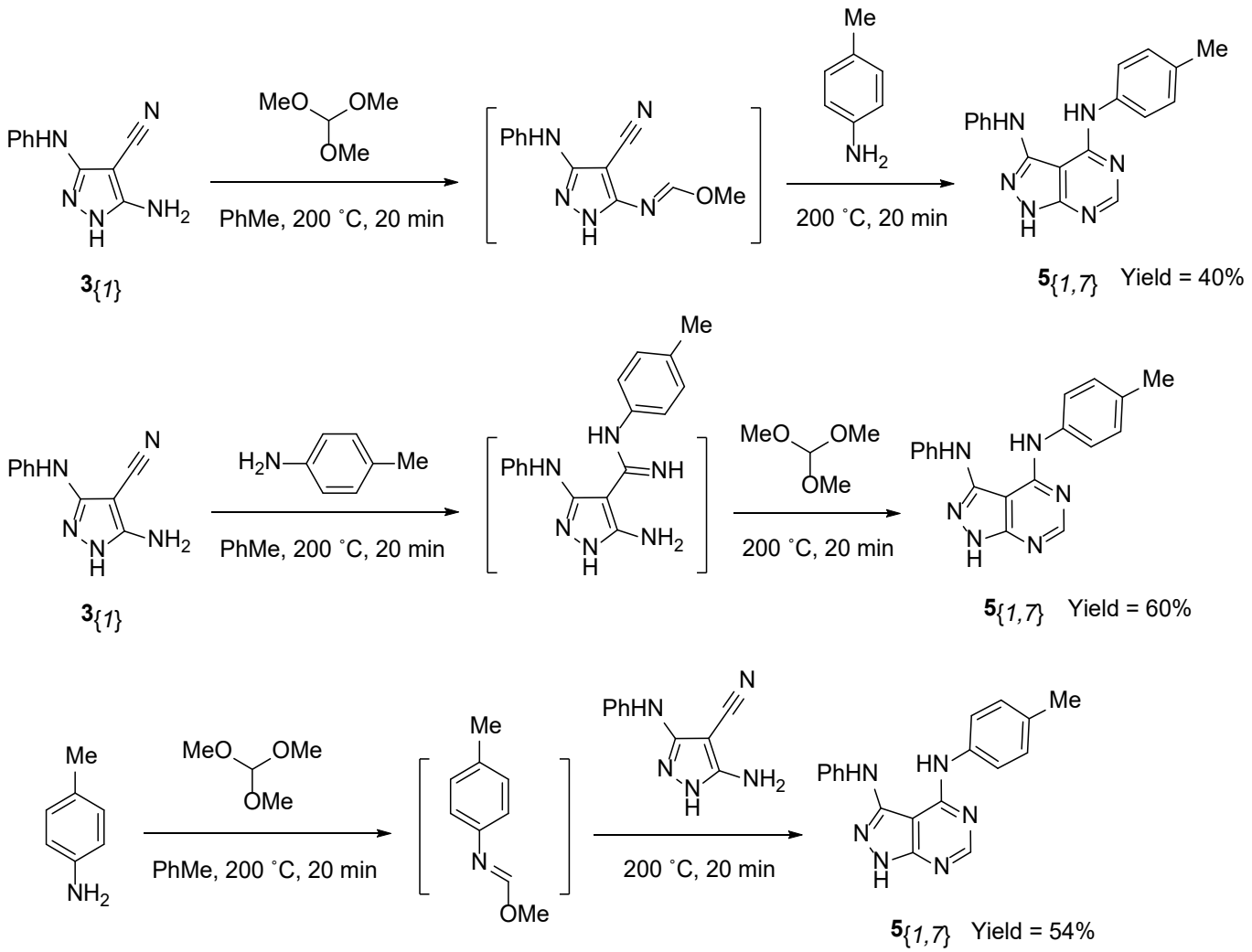
The formation of pyrazolo[3,4-*d*]pyrimidines in the developed multi-component reaction can be rationalised as depicted in Scheme 3. The initial formation of imidates **A** and their reaction with primary amines resembles the corresponding two-step synthesis (*cf.* Scheme 1, Pathway 3). The resulting amidines **B** undergo a pyrimidine ring closure and the subsequent Dimroth rearrangement of **C** to produce the desired compounds **5/7**. An alternative sequence starts with the formation of imidates **D** and then follows the same transformations. The nucleophilic attack amines on the nitrile group of **3** can potentially generate intermediates **E**, which undergo the pyrimidine ring annulation in the reaction with orthoesters. It should be noted that the addition of amines to the nitrile group of **B** followed by the cyclization is also possible; it was estimated (density functional

theory calculations) to be even more probable for the reaction of sterically hindered 1-phenyl substituted analogue of **B** (R^1 = H) with *p*-anisidine [41].



Scheme 3. Proposed mechanism of the multi-component synthesis of 3,4-diaminopyrazolo[3,4-*d*]pyrimidines.

The control experiments, using step-wise protocols (Scheme 4), suggest that the reaction may involve all the processes in the proposed mechanism and the outcome does not strongly depend on the order of the reagent introduction. Nevertheless, a higher yield (60%) was obtained when the one-pot sequence started with the reaction of **3**{*1*} with *p*-toluidine, while only a 40% yield was isolated when **3**{*1*} reacted with trimethyl orthoformate in the first step.



Scheme 4. Control reactions for the step-wise synthesis of N^4-(4-methylphenyl)-N^3-phenylpyrazolo[3,4-*d*]pyrimidine-3,4-diamine **5**{*1,7*}.

The structure of the prepared compounds was supported by ^{1}H and ^{13}C NMR spectroscopic data. The pyrimidine ring closure with the formation of compounds **5** was confirmed by the methine proton singlet at 8.13-8.42 ppm in the ^{1}H NMR spectra and the corresponding carbon atom signal at 153.7-154.9 ppm in the ^{13}C NMR spectra. In the ^{13}C NMR spectra, the signal of the amino group-bonded C-4 atom appeared at 154.7-156.0 ppm, while the NH proton of this amino group was found in the ^{1}H NMR spectra at 7.96-9.24 ppm for the N^4-aryl substituted **5**{*a,1-13*} or 6.43-

8.05 ppm for the N^4-alkyl derivatives **5**{*a,14-21*}. The multiplicity patterns of the signal for this amino group in the ^{1}H NMR spectra of **5**{*a,14-21*} also confirmed structure **5** and excluded **D**. In the NMR spectra of **7**{*1,7,c*}, the characteristic signals of the corresponding alkyl groups at C-6 of the pyrazolo[3,4-*d*]pyrimidine ring were observed, while the C-6 signal in the ^{13}C NMR spectra of these compounds is shifted downfield to 164.4-168.5 ppm. More detailed structure analysis of the prepared compounds was performed using single-crystal X-ray crystallography.

2.2 X-ray crystallography

Crystals of **5**{*1,18*}, **5**{*2,3*}, **5**{*4,10*} and **5**{*7,7*} were obtained allowing for X-ray structure determination; crystals of **5**{*2,3*} and **5**{*4,10*} were isolated as 1:1 methanol solvates. The molecular structure of **5**{*1,18*} is shown in Figure 3(a), being generally representative of the remaining molecules which are shown in ESI† Figure 1.

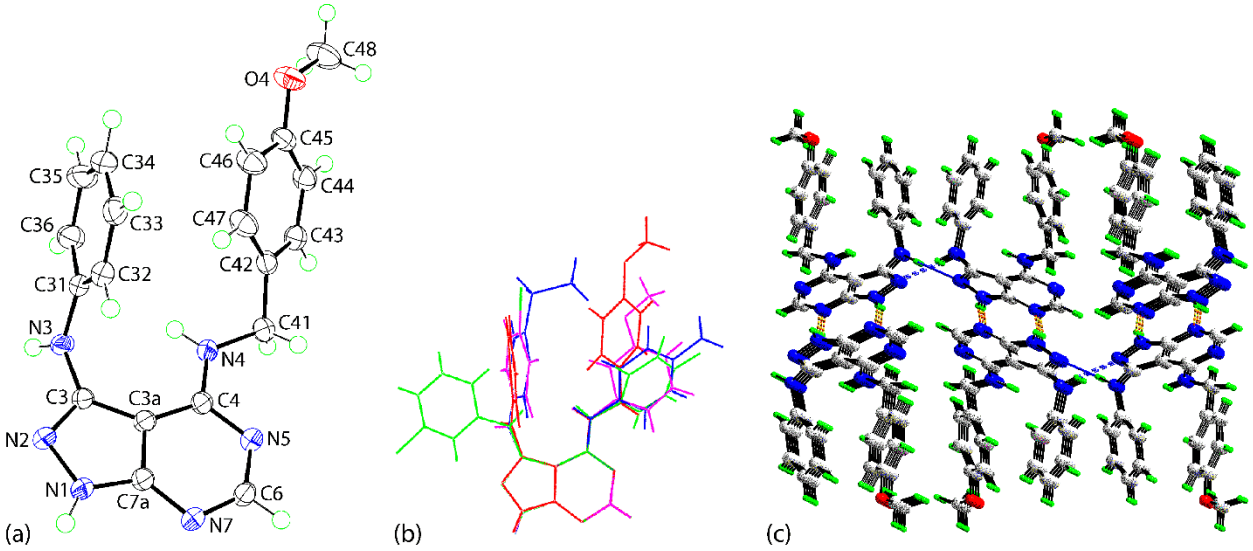


Figure 3. Crystallographic images for **5**{*1,18*}: (a) molecular structure, showing atom labelling scheme and displacement ellipsoids at the 70% probability level, (b) overlay diagram for the pyrazolopyrimidine molecules in **5**{*1,18*}, **5**{*2,3*}, **5**{*4,10*} and **5**{*7,7*}, represented by the red,

green, pink and blue images, respectively; the molecules have been overlapped so the pyrimidine residues are coincident and (c) a view of the supramolecular layer in the crystal; the pyrazole-N–H···N(pyrimidine) and (phenyl)-amino-N–H···N(pyrazole) hydrogen bonds are shown as orange and blue dashed lines, respectively.

The fused-ring system in **5**{*1*,*18*} is strictly planar with the maximum deviation from the least-squares plane through the nine atoms being 0.010(1) Å for the C3a atom. A listing of the important geometric parameters is given in ESI† Table 1. The magnitude of the C3–N2 [1.3272(13) Å] and C6–N7 [1.3335(14) Å] bond lengths are suggestive of double-bond character but other bonds, notably C7a–N2 [1.3503(14) Å] in the pyrazole ring, and C4–N5 [1.3508(13) Å] and C6–N6 [1.3440(14) Å] in the pyrimidine ring are indicative of significant delocalisation of π-electron density over the pyrazolopyrimidine residue. The delocalisation of electron-density extends to the amino-N4 substituent with evidence of the shortening of the C4–N4 [1.3394(13) Å] bond length *cf*. C3–N3 [1.3953(13) Å]. The N3-bound phenyl ring is almost perpendicular to the central fused ring system as noted from the dihedral angle of 81.87(5)° whereas the C41-bound methoxyphenyl ring is splayed forming a dihedral angle of 53.75(5)°; the dihedral angle between the terminal rings is 54.29(5)°. Globally, the molecule has an approximate U-shape.

As can be noted from ESI† Table 1, the electronic structures of molecules **5**{*2*,*3*}, **5**{*4*,*10*} and **5**{*7*,*7*} resemble closely that described for **5**{*1*,*18*} with the only exception relating to the shortening of the N4–C41(phenyl) bonds, as expected, *cf*. the N4–C41(methylene) bond in **5**{*1*,*18*}. However, significant conformational differences are in evidence as highlighted in the overlay diagram of Figure 1(b). In terms of the N3-bond groups, the exceptional conformation is noted for **5**{*2*,*3*}, where the ring is almost co-planar to the central residue [dihedral angle =

12.48(6)°]. While the differences in conformation between the terminal rings of the benzyl residue in **5**{*1*,*18*} and phenyl groups in the remaining molecules can be related to the reduced flexibility in **5**{*2*,*3*}, **5**{*4*,*10*} and **5**{*7*,*7*}, there remain significant variability in conformation between the latter with the dihedral angles between the fused-ring system and phenyl rings ranging from a low 2.20(6)° in **5**{*4*,*10*} to a high 56.40(6)° in **5**{*2*,*3*}. It is likely the dictates of molecular packing in their respective crystals are responsible for the conformational variability rather than any inherent chemical reason.

In the crystal of **5**{*1*,*18*}, intermolecular hydrogen bonding is apparent but not for the amino-N4–H atom which forms a close intramolecular contact with the amino-N3 atom; see ESI† Table 2 for geometric details for the most prominent intermolecular contacts in all four crystals. The pyrazole-N1–H atom forms a hydrogen bond with the pyrimidine-N7 atom resulting in a centrosymmetric, eight-membered $\{\cdots HNCN\}_2$ synthon. The dimeric aggregates are connected *via* (phenylamino)N3–H···N2(pyrazole) interactions, aligned along the *c*-glide plane, resulting in the formation of a supramolecular layer in the *bc*-plane; a view of the unit-cell contents is shown in ESI† Figure 2.

The centrosymmetric, eight-membered $\{\cdots HNCN\}_2$ synthons persist in the crystals of each of **5**{*2*,*3*}, **5**{*4*,*10*} and **5**{*7*,*7*}. In the crystal of **5**{*2*,*3*}, the methanol molecule of solvation sits in the bay area of the U-shaped molecule, see ESI† Figure S(a), and is held in place by (chlorophenylamino)N3–H···O51(methanol) and (fluorophenylamino)N4–H···O51(methanol) hydrogen bonds as well as a (methanol)O51–H···N2(pyrazole) hydrogen bond. The resulting centrosymmetric, four-molecule aggregates are connected into a linear chain by (pyrazole)N1–H···N7(pyrimidine) hydrogen bonds and $\{\cdots HNCN\}_2$ synthons. Further details and images are given in ESI† Figure 3. In the crystal of **5**{*4*,*10*}, the methanol molecule of solvation again plays

a prominent role in the supramolecular aggregation. Here, the (methanol)O51 molecule participates in (chlorophenylamino)N3–H···O51(methanol) and (methanol)O51–H···N2(pyrazole) hydrogen bonds. These, coupled with pyrazole-N1–H···N7(pyrimidine) hydrogen bonds, lead to supramolecular layers as detailed and illustrated in ESI† Figure 4. Finally, in the crystal of **5**{*7*,*7*} supramolecular layers are formed through (pyrazole)N1–H···N7(pyrimidine) and (ethylphenylamino)N3–H···N2(pyrazole) hydrogen bonds, with the latter propagated by a 2_1 screw axis in contrast to that noted above for **5**{*1*,*18*}; details given in ESI† Figure 5.

2.3 Anti-leukemic activity

The anti-proliferative effect of the prepared compounds was initially evaluated using the chronic myeloid leukaemia K562 cell line. The screening of compounds was performed at a concentration of 10 μM using the MTS assay. The three chemotherapeutic anticancer drugs 6-mercaptopurine, methotrexate, and cytarabine were used as positive controls. At the screening concentration, eighteen compounds out of 114 prepared and screened products decreased the K562 cell viability to less than 70% (Table 4). These compounds were selected for further concentration-response testing at concentrations ranging from 0.08 μM to 200 μM, and their 50% growth inhibitory concentrations (GI_{50}) against K562 cells were estimated (Table 5).

Overall, the most active compounds were identified among compounds with arylamino substituents in positions 3 and 4 of the pyrazolo[3,4-*d*]pyrimidine ring system (compounds **5**{*1-12*,*1-13*}. The anti-proliferative activity significantly decreased when any of the arylamino moieties was replaced by alkylamino or arylalkyamino groups (compounds **5**{*13-18*,*14-21*}. For anti-proliferative effect, the most promising substitution in position 3 of the pyrazolo[3,4-

d]pyrimidine scaffold was the 2,3-dimethoxyphenylamino group (compounds **5**{*12*,*b*}), while the 3,5-dimethylphenylamino substitution was preferred in position 4 (compounds **5**{*a*,*13*}). However, the combination of these two features in one molecule (**5**{*12*,*13*}) resulted in a significant loss of activity. The noteworthy reduction of the K562 cell growth was also observed when compounds with 4-bromophenylamino (**5**{*a*,*5*}) and *p*-toluidino (**5**{*a*,*7*}) groups were applied. The highest activity against K562 cells was identified for the pyrazolo[3,4-*d*]pyrimidine **5**{*12*,*11*} bearing 2,3-dimethoxyphenylamino group in position 3 and a *p*-anisidino group in position 4. This compound was more potent than mercaptopurine and possessed a GI_{50} value similar to that of cytarabine.

The most active compounds identified in the initial screening were also evaluated against the Jurkat T cell line (acute T cell leukaemia). The derivatives of the **5**{*12*,*b*} series bearing the 2,3-dimethoxyphenylamino moiety in position 3 significantly inhibited the Jurkat T cell growth (Table 5). However, the effects of substituents in position 4 on the compound's activity differed for the K562 and Jurkat T cell lines. The most active against Jurkat T cells was **5**{*12*,*7*} with the *p*-toluidino group in position 4 of the pyrazolo[3,4-*d*]pyrimidine core. This compound inhibited the Jurkat T cell growth with a GI_{50} value of 0.5 μM.

To assess the selectivity of the most active pyrazolo[3,4-*d*]pyrimidines, compounds possessing GI_{50} values less than 10 μM on either leukemic cell line were also tested against non-cancerous fibroblast MRC-5 cells. The majority of evaluated compounds (except **5**{*12*,*5*}) demonstrated some selectivity in their anti-proliferative effect against leukemic cells. The highest selectivity towards K562 cells was observed for the most active against this cell line compound **5**{*12*,*11*}, which was more selective than cytarabine and possessed a selectivity index similar to that of

mercaptopurine. The most active against Jurkat T cells compound **5**{*12*,*7*} was also the most selective towards this cell line and significantly exceeded the selectivity of the standard drugs.

In the series of 6-alkyl substituted compounds **7**{*1,7,c*}, activity increased with the alkyl group length. However, effectively inhibiting the growth of K562 and Jurkat T cells, compound **7**{*1,7,4*} demonstrated poor selectivity (Table 5).

Table 4. Screening of antiproliferative activity of N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines **5**{*a,b*} and **7**{*1,7,c*} against K562 cell line

Compound	Cell viability,[a] %	Compound	Cell viability,[a] %	Compound	Cell viability,[a] %
5{*1,2*}	88 ± 1.5	**5**{*5,6*}	85 ± 3.7	**5**{*11,9*}	87 ± 2.7
5{*1,4*}	65 ± 2.1	**5**{*5,7*}	78 ± 1.8	**5**{*11,10*}	80 ± 3.5
5{*1,5*}	64 ± 1.4	**5**{*5,9*}	73 ± 2.8	**5**{*11,11*}	79 ± 0.7
5{*1,6*}	88 ± 6.0	**5**{*5,10*}	91 ± 5.9	**5**{*11,14*}	98 ± 0.5
5{*1,7*}	88 ± 4.2	**5**{*5,11*}	85 ± 0.4	**5**{*11,16*}	70 ± 1.8
5{*1,8*}	89 ± 4.5	**5**{*5,13*}	66 ± 0.4	**5**{*12,1*}	62 ± 1.8
5{*1,9*}	72 ± 0.7	**5**{*5,14*}	78 ± 5.6	**5**{*12,2*}	79 ± 3.3
5{*1,11*}	76 ± 2.6	**5**{*5,16*}	73 ± 3.0	**5**{*12,4*}	65 ± 1.7
5{*1,13*}	63 ± 0.6	**5**{*6,2*}	93 ± 2.3	**5**{*12,5*}	59 ± 2.4
5{*1,14*}	98 ± 7.9	**5**{*6,3*}	78 ± 7.2	**5**{*12,7*}	50 ± 0.4
5{*1,15*}	84 ± 0.6	**5**{*6,4*}	82 ± 1.8	**5**{*12,11*}	44 ± 2.3
5{*1,16*}	80 ± 1.5	**5**{*6,5*}	87 ± 5.1	**5**{*12,12*}	69 ± 3.4
5{*1,17*}	73 ± 5.2	**5**{*6,6*}	74 ± 4.5	**5**{*12,13*}	71 ± 1.6
5{*1,18*}	75 ± 4.5	**5**{*6,7*}	82 ± 2.5	**5**{*12,14*}	82 ± 2.8
5{*1,20*}	83 ± 3.5	**5**{*6,9*}	71 ± 0.5	**5**{*12,16*}	75.6 ± 5.6
5{*1,21*}	77 ± 5.6	**5**{*6,10*}	76 ± 2.4	**5**{*12,17*}	80 ± 8.1
5{*2,3*}	98 ± 1.7	**5**{*6,14*}	93 ± 6.1	**5**{*13,7*}	84 ± 4.5
5{*2,7*}	75 ± 0.2	**5**{*6,15*}	80 ± 1.3	**5**{*14,7*}	79 ± 6.1
5{*2,9*}	71 ± 2.3	**5**{*6,16*}	90 ± 0.6	**5**{*15,7*}	83 ± 0.6
5{*2,10*}	85 ± 4.4	**5**{*6,17*}	85 ± 3.7	**5**{*15,10*}	66 ± 3.1
5{*3,5*}	87 ± 3.0	**5**{*6,19*}	72 ± 1.7	**5**{*16,4*}	74 ± 0.6
5{*3,7*}	56 ± 3.0	**5**{*6,20*}	87 ± 2.0	**5**{*16,7*}	77 ± 1.4

5{*4,2*}	72 ± 1.7	**5**{*7,7*}	90 ± 1.5	**5**{*16,9*}	77 ± 0.72
5{*4,3*}	79 ± 1.2	**5**{*8,7*}	74 ± 2.7	**5**{*16,10*}	68 ± 0.7
5{*4,4*}	86 ± 1.0	**5**{*8,10*}	75 ± 2.8	**5**{*17,7*}	89 ± 3.1
5{*4,5*}	81 ± 4.2	**5**{*9,4*}	75 ± 3.7	**5**{*18,2*}	79 ± 3.7
5{*4,6*}	76 ± 1.7	**5**{*9,7*}	68 ± 2.0	**5**{*18,4*}	73 ± 2.7
5{*4,7*}	71 ± 5.2	**5**{*10,4*}	75 ± 4.0	**5**{*18,5*}	82 ± 5.4
5{*4,9*}	81 ± 3.0	**5**{*10,5*}	96 ± 0.5	**5**{*18,7*}	85 ± 0.9
5{*4,10*}	73 ± 2.6	**5**{*10,6*}	86 ± 3.6	**5**{*18,11*}	77 ± 0.8
5{*4,11*}	77 ± 4.6	**5**{*10,7*}	93 ± 2.2	**5**{*18,14*}	97 ± 2
5{*4,13*}	66 ± 0.6	**5**{*10,9*}	90 ± 7.3	**5**{*18,16*}	77 ± 0.4
5{*4,14*}	87 ± 4.8	**5**{*10,10*}	75 ± 1.8	**7**{*1,7,1*}	79 ± 7.3
5{*4,15*}	73 ± 5.2	**5**{*10,11*}	85 ± 7.7	**7**{*1,7,2*}	80 ± 6.5
5{*4,16*}	81 ± 3.6	**5**{*10,14*}	84 ± 4.4	**7**{*1,7,3*}	73 ± 4.8
5{*4,17*}	83 ± 5.3	**5**{*10,16*}	76 ± 5.2	**7**{*1,7,4*}	57 ± 0.9
5{*5,2*}	68 ± 4.0	**5**{*11,2*}	77 ± 3.8	Methotrexate[b]	36 ± 2.9
5{*5,3*}	83 ± 0.8	**5**{*11,4*}	75 ± 0.5	Cytarabine[b]	59 ± 0.3
5{*5,4*}	78 ± 4.9	**5**{*11,5*}	67 ± 4.8	Mercaptopurine[b]	70 ± 1.5
5{*5,5*}	91 ± 5.9	**5**{*11,7*}	75 ± 2.1		

[a] Mean of three independent experiments ± standard error of the mean (SEM).

[b] Positive controls

Table 5. Antiproliferative activity of selected N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines **5**{*a,b*} and **7**{*1,7,4*} against leukemic and non-cancerous cell lines

Compound	GI_{50} [a] ± SEM, μM			Selectivity index[b]	
	K562	Jurkat T	MRC5	K562	Jurkat T
5{*1,4*}	14.9 ± 0.25	-	-	-	-
5{*1,5*}	14.6 ± 4.63	-	-	-	-
5{*1,13*}	19.9 ± 1.23	-	-	-	-
5{*3,7*}	4.9 ± 0.92	-	13.8 ± 5.36	2.8	-
5{*4,13*}	5.7 ± 0.04	-	12.6 ± 1.56	2.2	-
5{*5,2*}	17.2 ± 3.9	-	-	-	-
5{*5,13*}	6.2 ± 0.66	-	11.7 ± 3.92	1.9	-
5{*9,7*}	12.5 ± 0.08	-	-	-	-
5{*11,5*}	21.4 ± 5.51	-	-	-	-
5{*12,1*}	22.0 ± 5.58	29.6 ± 6.91	-	-	-
5{*12,4*}	16.1 ± 1.11	4.9 ± 2.41	17.1 ± 4.05	1.1	3.5
5{*12,5*}	2.1 ± 1.78	2.7 ± 0.39	1.6 ± 0.25	0.8	0.6
5{*12,7*}	12.2 ± 2.02	0.5 ± 0.06	31.6 ± 2.68	2.6	64.5
5{*12,11*}	1.6 ± 0.44	3.7 ± 0.03	8.2 ± 0.33	5.1	2.2
5{*12,12*}	17.9 ± 1.98	16.0 ± 1.22	-	-	-
5{*15,10*}	25.0 ± 3.80	-	-	-	-
5{*16,10*}	37.0 ± 0.24	11.2 ± 1.92	-	-	-
7{*1,7,4*}	6.2 ± 0.51	9.3 ± 0.05	10.2 ± 0.61	1.7	1.1
Methotrexate[c]	0.0145 ± 0.0001	0.028 ± 0.0067	0.57 ± 0.079	39.3	20.4
Cytarabine[c]	1.5 ± 0.24	0.2 ± 0.09	3.1 ± 2.16	2.1	14.2
Mercaptopurine[c]	13.2 ± 3.75	8.5 ± 0.16	76.6 ± 3.55	5.8	9.1

[a] Concentration required to inhibit tumour cell growth by 50%, values are mean of three independent experiments.

[b] Selectivity index = GI_{50}(MRC-5)/GI_{50}(leukemic cells)

[c] Positive controls

3. Conclusions

We developed a method for the synthesis of diverse N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines using a three-component reaction of 3,5-diaminopyrazole-4-carbonitriles with primary amines and orthoesters under microwave irradiation. The reaction scope is demonstrated by the synthesis of 114 representative examples. The pot- and step-economy achieved by the three-component one-pot protocol is facilitated by microwave irradiation. The reaction does not require any catalysts and allows chromatography-free product isolation.

The anti-proliferative activity evaluation of the prepared compounds identified the 2,5-dimethoxyphenylamino substitution in position 3 of the pyrazolo[3,4-*d*]pyrimidine scaffold is associated with good activities against the K562 and Jurkat T leukemic cell lines. The most promising compound in this group possessed the *p*-tolylamino group in position 4 of the heterocyclic system. This compound inhibited Jurkat T cells with a GI_{50} value of 0.5 μM and a selectivity index of 64 versus non-cancerous MRC5 cells.

4. Experimental

4.1. General

Microwave-assisted reactions were carried out using a Discover SP microwave synthesiser (CEM, USA) applying the closed vessel focused single-mode operational protocol and operating at maximal microwave power up to 150 W. The reaction temperature was automatically controlled with the equipped IR sensor. The control sealed vessel reaction under conventional heating was performed in a Monowave 50 (Anton Paar, Austria) reactor. Melting points (uncorrected) were measured using a Stuart SMP40 automatic melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Fourier NMR spectrometer (300 MHz) using DMSO-d_6 as a solvent and TMS as an internal reference.

4.2. General method for the synthesis of 5-substituted 3-arylaminopyrazolo[3,4-*d*]pyrimidin-4-ones (5)

Substituted 5-aminopyrazole-4-carboxylates **3** (1 mmol), trimethyl orthoformate (0.33 mL, 3 mmol), and a primary amine **4** (3 mmol) were added to toluene (2 mL) in a 10 mL seamless pressure vial. The reaction mixture was irradiated in a Discover SP (CEM) microwave reactor operating at a maximal microwave power of 150 W and pressure limit of 435 psi at 200 °C for 35 min. After cooling, the precipitated product was filtered and recrystallised using an appropriate solvent.

N^4-(4-Fluorophenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,2*}

Brown solid; yield 49%; m.p. 254-256 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.87 (1H, t, ^{3}J = 7.3 Hz, H-4′), 7.23 (2H, t, ^{3}J = 8.9 Hz, H-3′ and H-5′), 7.28 (2H, dd, $^{3}J_{HF}$ = 7.9 Hz, $^{3}J_{HH}$ = 7.9 Hz, H-3″ and H-5″), 7.56 (2H, d, ^{3}J = 7.7 Hz, H-2′ and H-6′), 7.68 (2H, dd, $^{4}J_{HF}$ = 5.0 Hz, $^{3}J_{HH}$ = 9.1 Hz, H-2″ and H-6″), 8.27 (1H, s, H-6), 8.63 (1H, s, NH), 8.98 (1H, s, NH), 12.83 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 91.8 (C-3a), 115.1 (d, $^{2}J_{CF}$ = 22.5 Hz, C-3″ and C-5″),

116.5 (2C), 119.8, 124.7 (d, $^{3}J_{CF}$ = 8.1 Hz, C-2″ and C-6″), 128.6 (2C), 134.9 (d, $^{4}J_{CF}$ = 3.0 Hz, C-1″), 142.7, 142.9 (C-3), 154.3 (C-6), 154.8 (C-4), 155.4 (C-7a), 158.6 (d, $^{1}J_{CF}$ = 240.7 Hz, C-4″). Anal. Calcd for $C_{17}H_{13}FN_6$: C, 63.74; H, 4.09; N, 26.24. Found: C, 63.59; H, 4.22; N, 26.03.

N^4-(4-Chlorophenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,4*}

Yellow solid; yield 35%; m.p. 273-275 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.87 (1H, t, ^{3}J = 7.3 Hz, H-4′), 7.28 (2H, t, ^{3}J = 8.0 Hz, H-3′ and H-5′), 7.44 (2H, d, ^{3}J = 8.9 Hz, H-3″ and H-5″), 7.54 (2H, d, ^{3}J = 7.7 Hz, H-2′ and H-6′), 7.75 (2H, d, ^{3}J = 9.1 Hz, H-2″ and H-6″), 8.31 (1H, s, H-6), 8.67 (1H, s, NH), 9.01 (1H, s, NH), 12.88 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 92.2 (C-3a), 116.5 (2C), 119.8, 123.8 (2C), 127.3 (2C), 128.3 (2C), 128.7, 137.8, 142.8, 142.8 (C-3), 154.0 (C-6), 154.8 (C-4), 155.3 (C-7a). Anal. Calcd for $C_{17}H_{13}ClN_6$: C, 60.63; H, 3.89; N, 24.95. Found: C, 60.48; H, 4.11; N, 24.77.

N^4-(4-Bromophenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,5*}

Yellow solid; yield 46%; m.p. 278-280 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.87 (1H, t, ^{3}J = 7.3 Hz, H-4′), 7.27 (2H, t, ^{3}J = 8.0 Hz, H-3′ and H-5′), 7.53 (2H, d, ^{3}J = 8.5 Hz, H-2′ and H-6′), 7.56 (2H, d, ^{3}J = 8.9 Hz, H-2″ and H-6″), 7.70 (2H, d, ^{3}J = 8.9 Hz, H-3″ and H-5″), 8.31 (1H, s, H-6), 8.67 (1H, s, NH), 9.00 (1H, s, NH), 12.88 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 92.2 (C-3a), 115.3 (2C), 116.5, 119.8, 124.1 (2C), 128.7 (2C), 131.2 (2C), 138.2, 142.7, 142.8 (C-3), 153.9 (C-6), 154.8 (C-4), 155.3 (C-7a). Anal. Calcd for $C_{17}H_{13}BrN_6$: C, 53.56; H, 3.44; N, 22.04. Found: C, 53.39; H, 3.53; N, 21.89.

N^4-(3-Methylphenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,6*}

Light yellow solid; yield 52%; m.p. 227-229 °C (MeOH). ^{1}H NMR (300 M Hz, DMSO-d_6): δ 2.33 (3H, s, CH_3), 6.87 (1H, t, ^{3}J = 7.3 Hz, C-4′), 6.96 (1H, d, ^{3}J = 7.5 Hz, H-4″), 7.22-7.31 (3H, m, H-3′, H-5′ and H-5″), 7.45 (1H, s, H-2″), 7.51 (3H, t, ^{3}J = 7.1 Hz, H-2′, H-6′ and H-6″), 8.29 (1H, s,

H-6), 8.66 (1H, s, NH), 8.83 (1H, s, NH), 12.85 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0 (CH_3), 92.1 (C-3a), 116.4 (2C), 119.6, 119.8, 122.9, 124.5, 128.3 (2C), 128.7, 137.7, 138.5, 142.8, 142.9 (C-3), 154.2 (C-6), 154.9 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{18}H_{16}N_6$: C, 68.34; H, 5.10; N, 26.56. Found: C, 68.08; H, 5.25; N, 26.34.

N^4-(4-Methylphenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,7*}

Yellow solid; yield 70%; m.p. 270-272 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (3H, s, CH_3), 6.88 (1H, t, ^3J = 7.3 Hz, H-4′), 7.19 (2H, d, ^3J = 8.2 Hz, H-3″ and H-5″), 7.28 (2H, t, ^3J = 7.9 Hz, H-3′ and H-5′), 7.53-7.57 (4H, m, H-2′, H-6′, H-2″ and H-6″), 8.28 (1H, s, H-6), 8.66 (1H, s, NH), 8.86 (1H, s, NH), 12.85 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 92.0 (C-3a), 116.5 (2C), 119.8, 122.7 (2C), 128.7 (2C), 128.9 (2C), 133.0, 136.1, 142.9, 142.9 (C-3), 154.4 (C-6), 154.9 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{18}H_{16}N_6$: C, 68.34; H, 5.10; N, 26.56. Found: C, 68.21; H, 5.17; N, 26.40.

N^4-(4-Ethylphenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,8*}

Light yellow solid; yield 38%; m.p. 241-243 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (3H, t, ^3J = 7.6 Hz, CH_3), 2.60 (2H, q, ^3J = 7.6 Hz, CH_2), 6.86 (1H, t, ^3J = 7.3 Hz, H-4′), 7.22 (2H, d, ^3J = 8.5 Hz, H-3″ and H-5″), 7.27 (2H, t, ^3J = 8.0 Hz, H-3′ and H-5′), 7.52 (2H, d, ^3J = 7.5 Hz, H-2′ and H-6′), 7.54 (2H, d, ^3J = 8.4 Hz, H-2″ and H-6″), 8.24 (1H, s, H-6), 8.63 (1H, s, NH), 8.86 (1H, s, NH), 12.82 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.7 (CH_3), 27.6 (CH_2), 91.9 (C-3a), 116.4 (2C), 119.7, 122.7 (2C), 127.7 (3C), 128.7 (2C), 136.2, 139.4, 142.8 (C-3), 154.3 (C-6), 154.8 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 68.94; H, 5.63; N, 25.28.

N^4-(2-Methoxyphenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,9*}

Dark yellow solid; yield 27%; m.p. 239-241 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.66 (3H, s, OCH_3), 6.83 (1H, tt, ^{4}J = 1.6 Hz, ^{3}J = 6.6 Hz, H-4′), 6.94-7.05 (2H, m, H-3″ and H-5″), 7.10 (1H, ddd, ^{4}J = 1.4 Hz, ^{3}J = 7.0 Hz, ^{3}J = 8.3 Hz, H-4″), 7.17-7.30 (4H, m, H-2′, H-3′, H-5′ and H-6′), 8.31 (1H, dd, ^{4}J = 1.4 Hz, ^{3}J = 7.9 Hz, H-6″), 8.35 (1H, s, H-6), 8.44 (1H, s, NH), 8.62 (1H, s, NH), 13.06 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.6 (OCH_3), 94.2 (C-3a), 111.0, 115.2 (2C), 119.4, 120.3, 122.4, 124.3, 127.4, 129.0 (2C), 142.3, 144.1 (C-3), 149.9, 154.2 (C-6), 154.8 (C-4), 155.8 (C-7a). Anal. Calcd for $C_{18}H_{16}N_6O$: C, 65.05; H, 4.85; N, 25.29. Found: C, 64.82; H, 5.03; N, 25.16.

N^4-(4-Methoxyphenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,11*}

Yellow solid; Yield 51%. m.p. 258-260 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.77 (3H, s, CH_3), 6.87 (1H, t, ^{3}J = 7.3 Hz, H-4′), 6.97 (2H, d, ^{3}J = 9.0 Hz, H-3″ and H-5″), 7.27 (2H, t, ^{3}J = 7.9 Hz, H-3′ and H-5′), 7.51 (2H, d, ^{3}J = 9.0 Hz, H-2″ and H-6″), 7.55 (2H, d, ^{3}J = 7.7 Hz, H-2′ and H-6′), 8.21 (1H, s, H-6), 8.59 (1H, s, NH), 8.87 (1H, s, NH), 12.77 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 91.6 (C-3a), 113.7 (2C), 116.5 (2C), 119.7, 124.8 (2C), 128.7 (2C), 131.3, 142.8, 142.9 (C-3), 154.5 (C-6), 154.8 (C-4), 155.5 (C-7a), 156.0. Anal. Calcd for $C_{18}H_{16}N_6O$: C, 65.05; H, 4.85; N, 25.29. Found: C, 64.94; H, 4.96; N, 25.19.

N^4-(3,5-Dimethylphenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,13*}

Light yellow solid; yield 38%; m.p. 241-243 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (6H, s, 2 x CH_3), 6.78 (1H, s, H-4″), 6.87 (1H, t, ^{3}J = 7.3 Hz, H-4′), 7.23-7.30 (4H, m, H-3′, H-5′, H-2″ and H-6″), 7.51 (2H, d, ^{3}J = 7.9 Hz, H-2′ and H-6′), 8.29 (1H, s, H-6), 8.65 (1H, s, NH), 8.74 (1H, s, NH), 12.85 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0 (2 x CH_3), 92.2 (C-3a), 116.5 (2C), 119.8, 120.1 (2C), 125.3, 128.7 (2C), 137.5 (2C), 138.5, 142.8, 142.9 (C-3), 154.3 (C-

6), 154.9 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 68.90; H, 5.66; N, 25.29.

N^4-Benzyl-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,14*}

White solid; yield 83%; m.p. 244-246 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.82 (2H, d, ^3J = 5.8 Hz, CH_2), 6.85 (1H, t, ^3J = 7.3 Hz, H-4′), 7.21-7.38 (7H, m, H-3′, H-5′, H-2″, H-3″, H-4″, H-5″ and H-6″), 7.55 (2H, d, ^3J = 7.7 Hz, H-2′ and H-6′), 7.99 (1H, t, ^3J = 5.8 Hz, NH), 8.17 (1H, s, H-6), 8.41 (1H, s, NH), 12.64 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2), 91.0 (C-3a), 116.5 (2C), 119.6, 126.7, 127.0 (2C), 128.2 (2C), 128.6 (2C), 139.5, 142.8, 143.1 (C-3), 154.5 (C-6), 155.8 (C-4), 156.0 (C-7a). Anal. Calcd for $C_{18}H_{16}N_6$: C, 68.34; H, 5.10; N, 26.56. Found: C, 68.23; H, 5.22; N, 26.69.

N^4-(4-Fluorobenzyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,15*}

White solid; yield 84%; m.p. 262-264 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.79 (2H, d, ^3J = 5.8 Hz, CH_2), 6.85 (1H, t, ^3J = 7.3 Hz, H-4′), 7.15 (2H, t, ^3J = 8.9 Hz, H-3′ and H-5′), 7.26 (2H, dd, $^3J_{HF}$ = 7.4 Hz, $^3J_{HH}$ = 8.5 Hz, H-3″ and H-5″), 7.40 (2H, dd, $^4J_{HF}$ = 5.6 Hz, $^3J_{HH}$ = 8.8 Hz, H-2″ and H-6″), 7.55 (2H, d, ^3J = 7.7 Hz, H-2′ and H-6′), 8.00 (1H, t, ^3J = 5.9 Hz, NH), 8.18 (1H, s, H-6), 8.40 (1H, s, NH), 12.65 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.5 (CH_2), 91.1 (C-3a), 114.9 (d, $^2J_{CF}$ = 21.4 Hz, C-3″ and C-5″), 116.6 (2C), 119.7, 129.0 (d, $^3J_{CF}$ = 8.1 Hz, C-2″ and C-6″), 129.1 (2C), 135.7 (d, $^4J_{CF}$ = 2.9 Hz, C-1″), 142.8, 143.2 (C-3), 154.6 (C-6), 155.8 (C-4), 156.0 (C-7a), 161.1 (d, $^1J_{CF}$ = 242.1 Hz, C-4″). Anal. Calcd for $C_{18}H_{15}FN_6$: C, 64.66; H, 4.52; N, 25.14. Found: C, 64.51; H, 4.63; N, 24.97.

N^4-(4-Chlorobenzyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,16*}

White solid; yield 81%; m.p. 268-270 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.79 (2H, d, ^3J = 5.9 Hz, CH_2), 6.85 (1H, t, ^3J = 7.3 Hz, H-4′), 7.25 (2H, t, ^3J = 8.0 Hz, H-3′ and H-5′), 7.37

(4H, m, H-2″, H-3″, H-5″ and H-6″), 7.54 (2H, d, ^{3}J = 7.7 Hz, H-2′ and H-6′), 8.01 (1H, t, ^{3}J = 5.9 Hz, NH), 8.16 (1H, s, H-6), 8.38 (1H, s, NH), 12.64 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.5 (CH_2), 91.0 (C-3a), 116.5 (2C), 119.7, 128.1 (2C), 128.6 (2C), 128.9 (2C), 131.2, 138.6, 142.8, 143.2 (C-3), 154.5 (C-6), 155.8 (C-4), 155.9 (C-7a). Anal. Calcd for $C_{18}H_{15}ClN_6$: C, 61.63; H, 4.31; N, 23.96. Found: C, 61.47; H, 4.55; N, 23.68.

N^4-(4-Methylbenzyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,17*}

White solid; yield 84%; m.p. 251-253 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (3H, s, CH_3), 4.77 (2H, d, ^{3}J = 5.7 Hz, CH_2), 6.85 (1H, t, ^{3}J = 7.3 Hz, H-4′), 7.12 (2H, d, ^{3}J = 8.0 Hz, H-3″ and H-5″), 7.21-7.30 (4H, m, H-3′, H-5′, H-2″ and H-6″), 7.56 (2H, d, ^{3}J = 8.1 Hz, H-2′ and H-6′), 7.95 (1H, t, ^{3}J = 5.7 Hz, NH), 8.18 (1H, s, H-6), 8.42 (1H, s, NH), 12.64 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.6 (CH_3), 42.9 (CH_2), 91.0 (C-3a), 116.6 (2C), 119.7, 127.0 (2C), 128.6 (2C), 128.8 (2C), 135.7, 136.4, 142.8, 143.2 (C-3), 154.6 (C-6), 155.8 (C-4), 156.0 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 68.86; H, 5.70; N, 25.27.

N^4-(4-Methoxybenzyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,18*}

White solid; yield 86%; m.p. 237-239 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.72 (3H, s, OCH_3), 4.74 (2H, d, ^{3}J = 5.8 Hz, CH_2), 6.84 (1H, t, ^{3}J = 7.4 Hz, H-4′), 6.88 (2H, d, ^{3}J = 8.8 Hz, H-3″ and H-5″), 7.25 (2H, t, ^{3}J = 7.9 Hz, H-3′ and H-5′), 7.28 (2H, d, ^{3}J = 8.7 Hz, H-2″ and H-6″), 7.53 (2H, d, ^{3}J = 7.7 Hz, H-2′ and H-6′), 7.89 (1H, t, ^{3}J = 5.8 Hz, NH), 8.18 (1H, s, H-6), 8.39 (1H, s, NH), 12.61 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.6 (CH_2), 55.0 (CH_3), 91.0 (C-3a), 113.7 (2C), 116.5 (2C), 119.6, 128.4 (2C), 128.6 (2C), 131.3, 142.8, 143.1 (C-3), 154.5 (C-6), 155.8 (C-4), 155.9 (C-7a), 158.2. Anal. Calcd for $C_{19}H_{18}N_6O$: C, 65.88; H, 5.24; N, 24.26. Found: C, 65.73; H, 5.38; N, 24.07.

N^4-Phenethyl-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,20*}

White solid; yield 68%; m.p. 203-205 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 2.94 (2H, t, ^{3}J = 7.6 Hz, NHCH$_2$C<u>H$_2$</u>Ph), 3.76 (2H, dt, ^{3}J = 6.5 Hz, ^{3}J = 7.6 Hz, NHC<u>H$_2$</u>CH$_2$Ph), 6.86 (1H, tt, ^{4}J = 0.9 Hz, ^{3}J = 7.3 Hz, N<u>H</u>CH$_2$CH$_2$Ph), 7.16-7.33 (7H, m, NHCH$_2$CH$_2$<u>Ph</u>, H-2″ and H-6″), 7.46-7.56 (3H, m, ^{3}J = 8.1 Hz, H-3″, H-4″ and H-5″), 8.22 (1H, s, H-6), 8.35 (1H, s, NH), 12.61 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 34.9 (NHCH$_2$<u>C</u>H$_2$Ph), 41.8 (NH<u>C</u>H$_2$CH$_2$Ph), 91.2 (C-3a), 116.4 (2C), 119.6, 126.1 (2C), 128.3 (2C), 128.6 (3C), 139.3, 142.9, 143.1 (C-3), 154.5 (C-6), 155.9 (C-4), 156.0 (C-7a). Anal. Calcd for C$_{19}$H$_{18}$N$_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 68.94; H, 5.58; N, 25.35.

N^4-[3-(N,N-Dimethylamino)propyl]-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*1,21*}

White solid; yield 60%; m.p. 173-175 °C (acetone). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 1.73 (2H, m, ^{3}J = 7.0 Hz, CH$_2$C<u>H$_2$</u>CH$_2$NH), 2.11 (6H, s, CH$_3$NCH$_3$), 2.26 (2H, t, ^{3}J = 6.9 Hz, C<u>H$_2$</u>CH$_2$CH$_2$NH), 3.55 (2H, dt, ^{3}J = 5.8 Hz, ^{3}J = 7.0 Hz, CH$_2$CH$_2$C<u>H$_2$</u>NH), 6.84 (1H, t, ^{3}J = 7.3 Hz, H-4′), 7.25 (2H, t, ^{3}J = 7.9 Hz, H-3′ and H-5′), 7.41 (1H, t, ^{3}J = 5.4 Hz, NH), 7.48 (2H, d, ^{3}J = 7.7 Hz, H-2′ and H-6′), 8.18 (1H, s, H-6), 8.34 (1H, s, NH), 12.60 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 26.8 (CH$_2$<u>C</u>H$_2$CH$_2$NH), 38.7 (CH$_3$NCH$_3$), 45.1 (<u>C</u>H$_2$CH$_2$CH$_2$NH), 56.8 (CH$_2$CH$_2$<u>C</u>H$_2$NH), 91.4 (C-3a), 116.3 (2C), 119.5, 128.6 (2C), 143.1, 143.1 (C-3), 154.5 (C-6), 155.9 (C-4), 156.0 (C-7a). Anal. Calcd for C$_{16}$H$_{21}$N$_7$: C, 61.71; H, 6.80; N, 31.49. Found: C, 61.53; H, 6.92; N, 31.36.

N^3-(3-Chlorophenyl)-N^4-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*2,3*}

Yellow solid; yield 35%; m.p. 204-206 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 6.90 (1H, dd, ^{4}J = 1.2 Hz, ^{3}J = 7.8 Hz, H-4′), 7.20-7.33 (3H, m, H-5′, H-3″ and H-5″), 7.47 (1H, dd, ^{4}J = 1.3 Hz, ^{3}J = 8.3 Hz, H-6′), 7.70 (2H, dd, 2H, dd, $^{4}J_{HF}$ = 5.0 Hz, $^{3}J_{HH}$ = 9.1 Hz, H-2″ and H-6″), 7.80

(1H, dd, ^4J = 2.0 Hz, ^4J = 2.0 Hz, H-2′), 8.28 (1H, s, H-6), 8.88 (1H, s, NH), 9.08 (1H, s, NH), 12.95 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 91.7 (C-3a), 115.0, 115.1 (d, $^2J_{CF}$ = 22.3 Hz, C-3′ and C-5′), 115.7, 119.2, 125.0 (d, $^3J_{CF}$ = 8.1 Hz, C-2′ and C-6′), 130.2, 133.2, 134.9 (d, $^4J_{CF}$ = 2.5 Hz, C-1′), 142.3, 144.1 (C-3), 154.3 (C-6), 154.8 (C-4), 155.6 (C-7a), 158.7 (d, $^1J_{CF}$ = 241.0 Hz, C-4′).

N^3-(4-Fluorophenyl)-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*2,7*}

Light yellow solid; yield 56%; m.p. 272-274 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (3H, s, CH_3), 7.11 (2H, dd, $^3J_{HH}$ = 8.9 Hz, $^3J_{HF}$ = 8.9 Hz, H-3′ and H-5′), 7.20 (2H, d, ^3J = 8.2 Hz, H-3″ and H-5″), 7.55 (2H, d, ^3J = 8.6 Hz, H-2″ and H-6″), 7.57 (2H, dd, $^4J_{HF}$ = 5.0 Hz, $^3J_{HH}$ = 9.0 Hz, H-2′ and H-6′), 8.23 (1H, s, H-6), 8.64 (1H, s, NH), 8.89 (1H, s, NH), 12.76 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 91.5 (C-3a), 115.0 (d, $^2J_{CF}$ = 22.0 Hz, C-3′ and C-5′), 118.1 (d, $^3J_{CF}$ = 7.9 Hz, C-2′ and C-6′), 122.9 (2C), 128.9 (2C), 133.0, 136.0, 139.2 (d, $^4J_{CF}$ = 2.2 Hz, C-1′), 143.1 (C-3), 154.4 (C-6), 154.8 (C-4), 155.5 (C-7a), 156.1 (d, $^1J_{CF}$ = 236.0 Hz, C-4′). Anal. Calcd for $C_{18}H_{15}FN_6$: C, 64.66; H, 4.52; N, 25.14. Found: C, 64.57; H, 4.65; N, 24.99.

N^3-(4-Fluorophenyl)-N^4-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*2,9*}

Brown solid; yield 53%; m.p. 273-275 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.72 (3H, s, OCH_3), 7.00 (1H, ddd, ^4J = 1.3 Hz, ^3J = 7.3 Hz, ^3J = 7.5 Hz, H-5″), 7.02-7.18 (4H, m, H-3′, H-5′, H-3″ and H-4″), 7.30 (2H, dd, $^4J_{HF}$ = 4.8 Hz, $^3J_{HH}$ = 9.1 Hz, H-2′ and H-6′), 8.25 (1H, dd, ^4J = 1.5 Hz, ^3J = 7.9 Hz, H-6″), 8.34 (1H, s, H-6), 8.47 (1H, s, NH), 8.65 (1H, s, NH), 13.02 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.6 (OCH_3), 93.6 (C-3a), 111.1, 115.4 (d, $^2J_{CF}$ = 22.2 Hz, 2C), 116.9 (d, $^3J_{CF}$ = 7.5 Hz, 2C), 120.4, 123.0, 124.6, 127.3, 140.4 (d, $^4J_{CF}$ = 1.9 Hz), 142.7 (C-3), 150.3, 154.4 (C-6), 154.9 (C-4), 155.8 (C-7a), 156.2 (d, $^1J_{CF}$ = 235.4 Hz). Anal. Calcd for $C_{18}H_{15}FN_6O$: C, 61.71; H, 4.32; N, 23.99. Found: C, 61.48; H, 4.51; N, 23.85.

N^3-(4-Fluorophenyl)-N^4-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*2,10*}

Brown solid; yield 37%; m.p. 233-235 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (3H, s, OCH_3), 6.73 (1H, ddd, ^3J = 6.7 Hz, ^4J = 2.5 Hz, ^4J = 2.4 Hz, H-4″), 7.12 (2H, dd, $^4J_{HF}$ = 8.9 Hz, $^3J_{HH}$ = 8.9 Hz, H-3′ and H-5′), 7.24-7.38 (3H, m, H-2″, H-5″ and H-6″), 7.56 (2H, dd, $^4J_{HF}$ = 4.8 Hz, $^3J_{HH}$ = 9.1 Hz, H-2′ and H-6′), 8.30 (1H, s, H-6), 8.69 (1H, s, NH), 8.90 (1H, s, NH), 12.83 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.0 (OCH_3), 91.9 (C-3a), 108.4, 109.0, 114.6 (d, $^2J_{CF}$ = 22.1 Hz, C-3′ and C-5′), 115.2, 117.6 (d, $^3J_{CF}$ = 7.5 Hz, C-2′ and C-6′), 129.2, 138.7 (d, $^4J_{CF}$ = 2.0 Hz, C-1′), 139.8, 143.0 (C-3), 154.2 (C-6), 154.9 (C-4), 155.5 (C-7a), 155.7 (d, $^1J_{CF}$ = 235.8 Hz, C-4′), 159.4. Anal. Calcd for $C_{18}H_{15}FN_6O$: C, 61.71; H, 4.32; N, 23.99. Found: C, 61.53; H, 4.47; N, 23.82.

N^4-(4-Bromophenyl)-N^3-(3-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*3,5*}

Light yellow solid; yield 16%; m.p. 248-250 °C (MeCN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.89 (1H, ddd, ^4J = 0.8 Hz, ^4J = 2.0 Hz, ^3J = 7.9 Hz, H-4′), 7.29 (1H, dd, ^3J = 8.1 Hz, ^3J = 8.1 Hz, H-5′), 7.44 (1H, ddd, ^4J = 0.8 Hz, ^4J = 2.1 Hz, ^3J = 8.3 Hz, H-6′), 7.57 (2H, d, ^3J = 8.9 Hz, H-2″ and H-6″), 7.72 (2H, d, ^3J = 8.9 Hz, H-3″ and H-5″), 7.76 (1H, dd, ^4J = 2.1 Hz, ^4J = 2.1 Hz, H-2′), 8.31 (1H, s, H-6), 8.93 (1H, s, NH), 9.10 (1H, s, NH), 12.99 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 92.1 (C-3a), 115.0, 115.4, 115.6, 119.2, 124.3 (2C), 130.2, 131.2 (2C), 133.1, 138.1, 142.2, 144.1 (C-3), 153.9 (C-6), 154.7 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{17}H_{12}BrClN_6$: C, 49.12; H, 2.91; N, 20.22. Found: C, 48.97; H, 3.06; N, 20.03.

N^3-(3-Chlorophenyl)-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*3,7*}

Yellow solid; yield 54%; m.p. 254-256 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (3H, s, CH_3), 6.89 (1H, ddd, ^4J = 0.9 Hz, ^4J = 2.0 Hz, ^3J = 7.8 Hz, H-4′), 7.20 (2H, d, ^3J = 8.2 Hz, H-3″

and H-5″), 7.29 (1H, t, ^{3}J = 8.2 Hz, H-5′), 7.44 (1H, ddd, ^{4}J = 0.8 Hz, ^{4}J = 2.1 Hz, ^{3}J = 8.3 Hz, H-6′), 7.56 (2H, d, ^{3}J = 8.3 Hz, H-2″ and H-6″), 7.77 (1H, dd, ^{4}J = 2.0 Hz, ^{4}J = 2.0 Hz, H-2′), 8.26 (1H, s, H-6), 8.89 (1H, s, NH), 8.96 (1H, s, NH), 12.92 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 91.7 (C-3a), 114.9, 115.6, 119.1, 123.0 (2C), 128.9 (2C), 130.2, 133.1, 133.1, 135.9, 142.2, 144.2 (C-3), 154.3 (C-6), 154.8 (C-4), 155.6 (C-7a). Anal. Calcd for $C_{18}H_{15}ClN_6$: C, 61.63; H, 4.31; N, 23.96. Found: C, 61.41; H, 4.54; N, 23.77.

N^3-(4-Chlorophenyl)-N^4-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,2*}

Brown solid; yield 29%; m.p. 260-262 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.24 (2H, dd, $^{3}J_{HH}$ = 8.8 Hz, $^{3}J_{HF}$ = 8.8 Hz, H-3″ and H-5″), 7.32 (2H, d, ^{3}J = 9.0 Hz, H-3′ and H-5′), 7.62 (2H, d, ^{3}J = 9.0 Hz, H-2′ and H-6′), 7.70 (2H, dd, $^{4}J_{HF}$ = 5.0 Hz, $^{3}J_{HH}$ = 9.1 Hz, H-2″ and H-6″), 8.27 (1H, s, H-6), 8.80 (1H, s, NH), 9.07 (1H, s, NH), 12.90 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 91.7 (C-3a), 115.1 (d, $^{2}J_{CF}$ = 22.3 Hz, C-3″ and C-5″), 118.1 (2C), 123.0, 124.9 (d, $^{3}J_{CF}$ = 8.1 Hz, C-2″ and C-6″), 128.4 (2C), 134.9 (d, $^{4}J_{CF}$ = 2.4 Hz, C-1″), 141.6, 142.6 (C-3), 154.3 (C-6), 154.8 (C-4), 155.5 (C-7a), 158.7 (d, $^{1}J_{CF}$ = 240.9 Hz, C-4″). Anal. Calcd for $C_{17}H_{12}ClFN_6$: C, 57.55; H, 3.41; N, 23.69. Found: C, 57.43; H, 3.59; N, 23.52.

N^3-(4-Chlorophenyl)-N^4-(3-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,3*}

Light yellow solid; yield 24%; m.p. 211-213 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.18 (1H, ddd, ^{4}J = 0.8 Hz, ^{4}J = 2.0 Hz, ^{3}J = 8.0 Hz, H-4″), 7.32 (2H, d, ^{3}J = 8.9 Hz, H-3′ and H-5′), 7.41 (1H, dd, ^{3}J = 8.1 Hz, ^{3}J = 8.1 Hz, H-5″), 7.60 (2H, d, ^{3}J = 8.9 Hz, H-2′ and H-6′), 7.68 (1H, ddd, ^{4}J = 0.9 Hz, ^{4}J = 2.0 Hz, ^{3}J = 8.3 Hz, H-6″), 7.95 (1H, dd, ^{4}J = 2.0 Hz, ^{4}J = 2.0 Hz, H-2″), 8.36 (1H, s, H-6), 8.84 (1H, s, NH), 9.10 (1H, s, NH), 12.98 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 92.1 (C-3a), 118.0 (2C), 120.5, 121.5, 123.0, 123.1, 128.4 (2C), 130.0, 132.7, 140.3,

141.6, 142.5 (C-3), 153.9 (C-6), 154.8 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{17}H_{12}Cl_2N_6$: C, 55.00; H, 3.26; N, 22.64. Found: C, 54.81; H, 3.43; N, 22.39.

N^3,N^4-Bis(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,4*}

Brown solid; yield 31%; m.p. 265-267 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.32 (2H, d, ^3J = 8.9 Hz, H-3′ and H-5′), 7.44 (2H, d, ^3J = 8.9 Hz, H-3″ and H-5″), 7.60 (2H, d, ^3J = 8.9 Hz, H-2′ and H-6′), 7.77 (2H, d, ^3J = 8.9 Hz, H-2″ and H-6″), 8.32 (1H, s, H-6), 8.84 (1H, s, NH), 9.09 (1H, s, NH), 12.94 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 92.0 (C-3a), 118.0 (2C), 123.0 (2C), 123.9, 127.4 (2C), 128.3 (2C), 128.4, 137.7, 141.6, 142.5 (C-3), 154.0 (C-6), 154.8 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{17}H_{12}Cl_2N_6$: C, 55.00; H, 3.26; N, 22.64. Found: C, 54.86; H, 3.38; N, 22.47.

N^4-(4-Bromophenyl)-N^3-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,5*}

Brown solid; yield 57%; m.p. 270-272 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.31 (2H, d, ^3J = 8.9 Hz, H-3′ and H-5′), 7.57 (2H, d, ^3J = 8.9 Hz, H-2′ and H-6′), 7.59 (2H, d, ^3J = 9.0 Hz, H-2″ and H-6″), 7.72 (2H, d, ^3J = 8.9 Hz, H-3″ and H-5″), 8.31 (1H, s, H-6), 8.84 (1H, s, NH), 9.07 (1H, s, NH), 12.94 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 92.0 (C-3a), 115.4 (2C), 118.0, 123.0, 124.2 (2C), 128.4 (2C), 131.2 (2C), 138.2, 141.6, 142.5 (C-3), 154.0 (C-6), 154.8 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{17}H_{12}BrClN_6$: C, 49.12; H, 2.91; N, 20.22. Found: C, 48.92; H, 3.05; N, 19.99.

N^3-(4-Chlorophenyl)-N^4-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,6*}

Light yellow solid; yield 29%; m.p. 234-236 °C (MeOH). ^{1}H NMR (300 M Hz, DMSO-d_6): δ 2.34 (3H, s, CH_3), 6.96 (1H, d, ^3J = 7.8 Hz, C-4″), 7.23-7.35 (3H, m, H-3′, H-5′ and H-5″), 7.45-7.56 (2H, m, H-2″ and H-6″), 7.59 (2H, d, ^3J = 8.9 Hz, H-2′ and H-6′), 8.29 (1H, s, H-6), 8.83 (1H, s, NH), 8.91 (1H, s, NH), 12.90 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0 (CH_3), 91.9 (C-

3a), 118.0 (2C), 119.8, 123.0, 123.0, 124.6 (2C), 128.3, 128.4, 137.7, 138.5, 141.7, 142.5 (C-3), 154.3 (C-6), 154.8 (C-4), 155.6 (C-7a). Anal. Calcd for $C_{18}H_{15}ClN_6$: C, 61.63; H, 4.31; N, 23.96. Found: C, 61.45; H, 4.48; N, 23.81.

N^3-(4-Chlorophenyl)-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,7*}

Yellow solid; yield 52%; m.p. 277-279 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (3H, s, CH_3), 7.20 (2H, d, ^3J = 8.2 Hz, H-3″ and H-5″), 7.31 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 7.55 (2H, d, ^3J = 8.5 Hz, H-2″ and H-6″), 7.58 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 8.25 (1H, s, H-6), 8.79 (1H, s, NH), 8.92 (1H, s, NH), 12.86 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 91.7 (C-3a), 118.0 (2C), 122.9 (2C), 123.0, 128.4 (2C), 128.9 (2C), 133.0, 136.0, 141.7, 142.5 (C-3), 154.3 (C-6), 154.8 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{18}H_{15}ClN_6$: C, 61.63; H, 4.31; N, 23.96. Found: C, 61.53; H, 4.43; N, 23.84.

N^3-(4-Chlorophenyl)-N^4-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,9*}

Brown solid; yield 50%; m.p. 286-288 °C (MeCN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.70 (3H, s, OCH_3), 6.99 (1H, ddd, ^4J = 1.4 Hz, ^3J = 7.5 Hz, ^3J = 7.5 Hz, H-5″), 7.02-7.20 (2H, m, H-3″ and H-4″), 7.25 (2H, d, ^3J = 9.2 Hz, H-3′ and H-5′), 7.29 (2H, d, ^3J = 9.1 Hz, H-2′ and H-6′), 8.25 (1H, dd, ^4J = 1.5 Hz, ^3J = 7.9 Hz, H-6″), 8.33 (1H, s, H-6), 8.44 (1H, s, NH), 8.79 (1H, s, NH), 13.09 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.6 (OCH_3), 93.8 (C-3a), 111.0, 116.8 (2C), 120.3, 122.8, 122.8, 124.6, 127.3 (2C), 128.7, 141.9, 143.0 (C-3), 150.1, 154.2 (C-6), 154.8 (C-4), 155.8 (C-7a). Anal. Calcd for $C_{18}H_{15}ClN_6O$: C, 58.94; H, 4.12; N, 22.91. Found: C, 58.75; H, 4.33; N, 22.67.

N^3-(4-Chlorophenyl)-N^4-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,10*}

Yellow solid; yield 36%; m.p. 227-229 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.80 (3H, s, OCH_3), 6.70-6.76 (1H, m, H-4″), 7.28-7.35 (4H, m, H-3′, H-5′, H-5″ and H-6″), 7.40 (1H, s, H-2″), 7.60 (2H, d, ^{3}J = 8.9 Hz, H-2′ and H-6′), 8.34 (1H, s, H-6), 8.87 (1H, s, NH), 8.96 (1H, s, NH), 12.96 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 92.1 (C-3a), 108.4, 109.1, 114.8, 118.0 (2C), 123.1, 128.5 (2C), 129.3, 139.8, 141.8, 142.5 (C-3), 154.2 (C-6), 154.9 (C-4), 155.5 (C-7a), 159.4. Anal. Calcd for $C_{18}H_{15}ClN_6O$: C, 58.94; H, 4.12; N, 22.91. Found: C, 58.82; H, 4.28; N, 22.75.

N^3-(4-Chlorophenyl)-N^4-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine

5{*4,11*}

Brown solid; yield 57%; m.p. 272-274 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (3H, s, OCH_3), 6.98 (2H, d, ^{3}J = 9.0 Hz, H-3″ and H-5″), 7.32 (2H, d, ^{3}J = 9.0 Hz, H-3′ and H-5′), 7.54 (2H, d, ^{3}J = 9.0 Hz, H-2″ and H-6″), 7.62 (2H, d, ^{3}J = 9.0 Hz, H-2′ and H-6′), 8.22 (1H, s, H-6), 8.76 (1H, s, NH), 8.95 (1H, s, NH), 12.83 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.4 (OCH_3), 91.7 (C-3a), 114.0 (2C), 118.3 (2C), 123.3, 125.3 (2C), 128.7 (2C), 131.5, 141.9, 142.9 (C-3), 154.9 (C-6), 155.0 (C-4), 155.9 (C-7a), 156.4. Anal. Calcd for $C_{18}H_{15}ClN_6O$: C, 58.94; H, 4.12; N, 22.91. Found: C, 58.83; H, 4.26; N, 22.75.

N^3-(4-Chlorophenyl)-N^4-(3,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine

5{*4,13*}

Yellow solid; yield 44%; m.p. 235-237 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (6H, s, (2 x CH_3), 6.79 (1H, s, H-4″), 7.28-7.34 (2H, m, H-3′, H-5′, H-2″ and H-6″), 7.57 (2H, d, ^{3}J = 8.9 Hz, H-2′ and H-6′), 8.29 (1H, s, H-6), 8.81 (2H, s, 2 x NH), 12.89 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0 (2 x CH_3), 91.9 (C-3a), 117.9 (2C), 120.3 (2C), 123.0, 125.4, 128.4 (2C),

137.5 (2C), 138.4, 141.8, 142.5 (C-3), 154.3 (C-6), 154.8 (C-4), 155.6 (C-7a). Anal. Calcd for $C_{19}H_{17}ClN_6$: C, 62.55; H, 4.70; N, 23.04. Found: C, 62.42; H, 4.57; N, 22.83.

N^4-Benzyl-N^3-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,14*}

White solid; yield 65%; m.p. 261-263 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.82 (2H, d, ^3J = 5.8 Hz, CH_2), 7.20-7.38 (7H, m, H-3′, H-5′, and Ph), 7.58 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 7.99 (1H, t, ^3J = 5.8 Hz, NH), 8.18 (1H, s, H-6), 8.57 (1H, s, NH), 12.70 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.2 (CH_2), 91.0 (C-3a), 118.0 (2C), 122.9, 126.7, 127.0 (2C), 128.2 (2C), 128.4 (2C), 139.4, 141.7, 142.8 (C-3), 154.6 (C-6), 155.9 (C-4), 156.0 (C-7a). Anal. Calcd for $C_{18}H_{15}ClN_6$: C, 61.63; H, 4.31; N, 23.96. Found: C, 61.46; H, 4.52; N, 23.79.

N^3-(4-Chlorophenyl)-N^4-(4-fluorobenzyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,15*}

White solid; yield 62%; m.p. 242-244 °C (MeCN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.80 (2H, d, ^3J = 5.7 Hz, CH_2), 7.15 (2H, dd, $^3J_{HF}$ = 8.9 Hz, $^3J_{HH}$ = 8.9 Hz, H-3″ and H-5″), 7.30 (2H, d, ^3J = 8.9 Hz, H-3′ and H-5′), 7.40 (2H, dd, $^4J_{HF}$ = 5.6 Hz, $^3J_{HH}$ = 8.7 Hz, H-2″ and H-6″), 7.58 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 8.01 (1H, t, ^3J = 5.8 Hz, NH), 8.19 (1H, s, H-6), 8.56 (1H, s, NH), 12.72 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.5 (CH_2), 91.0 (C-3a), 114.9 (d, $^2J_{CF}$ = 21.1 Hz, C-3″ and C-5″), 118.0 (2C), 122.9, 128.4 (2C), 129.0 (d, $^3J_{CF}$ = 8.1 Hz, C-2″ and C-6″), 135.6 (d, $^4J_{CF}$ = 2.9 Hz, C-1″), 141.7, 142.8 (C-3), 154.6 (C-6), 155.9 (C-4 and C-7a), 161.1 (d, $^1J_{CF}$ = 242.2 Hz, C-4″). Anal. Calcd for $C_{18}H_{14}ClFN_6$: C, 58.62; H, 3.83; N, 22.79. Found: C, 58.48; H, 4.01; N, 22.61.

N^4-(4-Chlorobenzyl)-N^3-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,16*}

White solid; yield 65%; m.p. 263-265 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.79 (2H, d, ^3J = 5.9 Hz, CH_2), 7.30 (2H, d, ^3J = 8.9 Hz, H-3′ and H-5′), 7.38 (4H, s, H-2″, H-3″, H-5″ and H-6″), 7.58 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 8.02 (1H, t, ^3J = 5.8 Hz, NH), 8.17 (1H, s, H-6),

8.55 (1H, s, NH), 12.71 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.6 (CH_2), 91.1 (C-3a), 118.1 (2C), 123.0, 128.2 (2C), 128.4 (2C), 128.9 (2C), 131.3, 138.6, 141.7, 142.9 (C-3), 154.6 (C-6), 155.9 (C-4), 156.0 (C-7a). Anal. Calcd for $C_{18}H_{14}Cl_2N_6$: C, 56.12; H, 3.66; N, 21.81. Found: C, 55.95; H, 3.80; N, 21.78.

N^3-(4-Chlorophenyl)-N^4-(4-methylbenzyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*4,15*}

White solid; yield 72%; m.p. 290-292 °C (acetone). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (3H, s, CH_3), 4.77 (2H, d, ^3J = 5.7 Hz, CH_2), 7.13 (2H, d, ^3J = 8.2 Hz, H-3″ and H-5″), 7.24 (2H, d, ^3J = 8.0 Hz, H-2″ and H-6″), 7.29 (2H, d, ^3J = 8.9 Hz, H-3′ and H-5′), 7.58 (2H, d, ^3J = 8.9 Hz, H-2′ and H-6′), 7.96 (1H, t, ^3J = 5.8 Hz, NH), 8.18 (1H, s, H-6), 8.57 (1H, s, NH), 12.70 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.6 (CH_3), 42.9 (CH_2), 90.9 (C-3a), 118.0 (2C), 122.9, 127.0 (2C), 128.4 (2C), 128.8 (2C), 135.7, 136.3, 141.7, 142.8 (C-3), 154.6 (C-6), 155.9 (C-4), 155.9 (C-7a). Anal. Calcd for $C_{19}H_{17}ClN_6$: C, 62.55; H, 4.70; N, 23.04. Found: C, 62.38; H, 4.89; N, 22.87.

N^3-(4-Bromophenyl)-N^4-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*5,2*}

Yellow solid; yield 48%; m.p. 263-265 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.24 (2H, dd, $^3J_{HF}$ = 9.0 Hz, $^3J_{HH}$ = 8.7 Hz, H-3″ and H-5″), 7.44 (2H, d, ^3J = 8.9 Hz, H-2′ and H-6′), 7.58 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 7.70 (2H, dd, $^4J_{HF}$ = 5.0 Hz, $^3J_{HH}$ = 9.1 Hz, H-2″ and H-6″), 8.27 (1H, s, H-6), 8.80 (1H, s, NH), 9.06 (1H, s, NH), 12.91 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 91.7 (C-3a), 110.7, 115.1 (d, $^2J_{CF}$ = 22.3 Hz, C-3″ and C-5″), 118.5 (2C), 124.9 (d, $^3J_{CF}$ = 7.5 Hz, C-2″ and C-6″), 131.3 (2C), 134.9 (d, $^4J_{CF}$ = 2.5 Hz, C-1″), 142.1, 142.5 (C-3), 154.3 (C-6), 154.8 (C-4), 155.5 (C-7a), 158.7 (d, $^1J_{CF}$ = 240.8 Hz, C-4″). Anal. Calcd for $C_{17}H_{12}BrFN_6$: C, 51.15; H, 3.03; N, 21.05. Found: C, 50.98; H, 3.20; N, 22.82.

N^3-(4-Bromophenyl)-N^4-(3-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*5,3*}

Yellow solid; yield 26%; m.p. 220-222 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.18 (1H, ddd, ^{4}J = 0.9 Hz, ^{4}J = 2.0 Hz, ^{3}J = 7.9 Hz, H-4″), 7.41 (1H, dd, ^{3}J = 8.2 Hz, ^{3}J = 8.2 Hz, H-5″), 7.44 (2H, d, ^{3}J = 8.9 Hz, H-2′ and H-6′), 7.55 (2H, d, ^{3}J = 8.9 Hz, H-3′ and H-5′), 7.68 (1H, ddd, ^{4}J = 0.7 Hz, ^{4}J = 1.8 Hz, ^{3}J = 8.2 Hz, H-6″), 7.95 (1H, dd, ^{4}J = 1.9 Hz, ^{4}J = 1.9 Hz, H-2″), 8.36 (1H, s, H-6), 8.85 (1H, s, NH), 9.10 (1H, s, NH), 12.99 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 92.2 (C-3a), 110.7, 118.5 (2C), 120.5, 121.5, 123.1, 130.0, 131.3 (2C), 132.7, 140.3, 142.0, 142.4 (C-3), 153.9 (C-6), 154.8 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{17}H_{12}BrClN_6$: C, 49.12; H, 2.91; N, 20.22. Found: C, 48.87; H, 3.16; N, 19.98.

N^3-(4-Bromophenyl)-N^4-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*5,4*}

Brown solid; yield 30%; m.p. 259-261 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.41-7.48 (4H, m, H-2′, H-6′, H-3″ and H-5″), 7.57 (2H, d, ^{3}J = 9.0 Hz, H-3′ and H-5′), 7.78 (2H, d, ^{3}J = 8.9 Hz, H-2″ and H-6″), 8.33 (1H, s, H-6), 8.87 (1H, s, NH), 9.11 (1H, s, NH), 12.98 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 92.0 (C-3a), 110.7, 118.5 (2C), 123.9 (2C), 127.4 (2C), 128.3 (2C), 131.3, 137.7, 142.0, 142.5 (C-3), 154.0 (C-6), 154.8 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{17}H_{12}BrClN_6$: C, 49.12; H, 2.91; N, 20.22. Found: C, 48.93; H, 3.08; N, 20.05.

N^3,N^4-Bis(4-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*5,5*}

Brown solid; yield 68%; m.p. 260-262 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.43 (2H, d, ^{3}J = 9.0 Hz, H-2′ and H-6′), 7.54 (2H, d, ^{3}J = 8.9 Hz, H-2″ and H-6″), 7.56 (2H, d, ^{3}J = 8.8 Hz, H-3′ and H-5′), 7.72 (2H, d, ^{3}J = 8.9 Hz, H-3″ and H-5″), 8.31 (1H, s, H-6), 8.85 (1H, s, NH), 9.09 (1H, s, NH), 12.95 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 92.0 (C-3a), 110.7, 115.4, 118.5 (2C), 124.2 (2C), 131.2 (2C), 131.3 (2C), 138.2, 142.0, 142.4 (C-3), 153.9 (C-6), 154.8 (C-4),

155.4 (C-7a). Anal. Calcd for $C_{17}H_{12}Br_2N_6$: C, 44.38; H, 2.63; N, 18.26. Found: C, 44.21; H, 2.79; N, 18.08.

N^3-(4-Bromophenyl)-N^4-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*5,6*}

Yellow solid; yield 54%; m.p. 236-238 °C (MeOH). ^{1}H NMR (300 M Hz, DMSO-d_6): δ 2.34 (3H, s, CH_3), 6.97 (1H, d, ^3J = 7.5 Hz, H-4″), 7.27 (1H, dd, ^3J = 7.8 Hz, ^3J = 7.8 Hz, H-5″), 7.40-7.58 (6H, m, H-2′, H-3′, H-5′, H-6′, H-2″ and H-6″), 8.30 (1H, s, H-6), 8.84 (1H, s, NH), 8.91 (1H, s, NH), 12.92 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.1 (CH_3), 92.0 (C-3a), 110.7, 118.4 (2C), 119.8, 123.0, 124.6, 128.3, 131.3 (2C), 137.7, 138.5, 142.2, 142.4 (C-3), 154.3 (C-6), 154.9 (C-4), 155.6 (C-7a). Anal. Calcd for $C_{18}H_{15}BrN_6$: C, 54.70; H, 3.83; N, 21.26. Found: C, 54.48; H, 4.05; N, 21.01.

N^3-(4-Bromophenyl)-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*5,7*}

White solid; yield 70%; m.p. 278-280 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (3H, s, CH_3), 7.20 (2H, d, ^3J = 8.5 Hz, H-3″ and H-5″), 7.43 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 7.54 (2H, d, ^3J = 9.1 Hz, H-3′ and H-5′), 7.55 (2H, d, ^3J = 8.4 Hz, H-2″ and H-6″), 8.25 (1H, s, H-6), 8.80 (1H, s, NH), 8.92 (1H, s, NH), 12.87 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 91.8 (C-3a), 110.6, 118.4 (2C), 122.9 (2C), 128.9 (2C), 131.3 (2C), 133.0, 136.0, 142.1, 142.4 (C-3), 154.3 (C-6), 154.8 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{18}H_{15}BrN_6$: C, 54.70; H, 3.83; N, 21.26. Found: C, 54.56; H, 4.00; N, 21.09.

N^3-(4-Bromophenyl)-N^4-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*5,9*}

Brown solid; yield 33%; m.p. 285-287 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.69 (3H, s, OCH_3), 6.98 (1H, ddd, ^4J= 1.3 Hz, ^3J= 7.5 Hz, ^3J= 7.5 Hz, H-5″), 7.01-7.15 (2H, m, H-3″ and H-4″), 7.20 (2H, d, ^3J = 8.9 Hz, H-3′ and H-5′), 7.40 (2H, d, ^3J = 8.9 Hz, H-2′ and H-6′), 8.25 (1H, dd, ^4J= 1.5 Hz, ^3J= 7.9 Hz, H-6″), 8.32 (1H, s, H-6), 8.42 (1H, s, NH), 8.80 (1H, s, NH), 13.10

(1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.6 (OCH_3), 93.9 (C-3a), 110.4, 111.0, 117.2 (2C), 120.3, 122.8, 124.5, 127.2, 128.1, 128.8 (2C), 131.6, 141.8, 143.4 (C-3), 150.1, 154.2 (C-6), 154.8 (C-4), 155.8 (C-7a). Anal. Calcd for $C_{18}H_{15}BrN_6O$: C, 52.57; H, 3.68; N, 20.44. Found: C, 52.41; H, 3.85; N, 20.29.

N^3-(4-Bromophenyl)-N^4-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine

5{*5,10*}

Yellow solid; yield 41%; m.p. 235-237 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (3H, s, OCH_3), 6.73 (1H, ddd, ^3J = 6.4 Hz, ^4J = 2.8 Hz, ^4J = 2.4 Hz, H-4″), 7.25-7.38 (3H, m, H-2″, H-5″ and H-6″), 7.43 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 7.53 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 8.31 (1H, s, H-6), 8.86 (1H, s, NH), 8.93 (1H, s, NH), 12.94 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.0 (OCH_3), 92.1 (C-3a), 108.3, 109.0, 110.7, 114.7, 118.4 (2C), 129.2, 131.3 (2C), 139.8, 142.1, 142.4 (C-3), 154.2 (C-6), 154.8 (C-4), 155.5 (C-7a), 159.4. Anal. Calcd for $C_{18}H_{15}BrN_6O$: C, 52.57; H, 3.68; N, 20.44. Found: C, 52.44; H, 3.81; N, 20.30.

N^3-(4-Bromophenyl)-N^4-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine

5{*5,11*}

Light green solid; yield 67%; m.p. 269-271 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.77 (3H, s, OCH_3), 6.97 (2H, d, ^3J = 9.0 Hz, H-3″ and H-5″), 7.43 (2H, d, ^3J = 9.0 Hz, H-2″ and H-6″), 7.53 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 7.57 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 8.21 (1H, s, H-6), 8.76 (1H, s, NH), 8.94 (1H, s, NH), 12.83 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.2 (OCH_3), 91.4 (C-3a), 110.6, 113.7 (2C), 118.5 (2C), 125.0 (3C), 131.3 (2C), 142.1, 142.5 (C-3), 154.5 (C-6), 154.8 (C-4), 155.6 (C-7a), 156.1. Anal. Calcd for $C_{18}H_{15}BrN_6O$: C, 52.57; H, 3.68; N, 20.44. Found: C, 52.44; H, 3.79; N, 20.32.

N^3-(4-Bromophenyl)-N^4-(3,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*5,13*}

Yellow solid; yield 39%; m.p. 240-242 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (6H, s, (2 x CH_3), 6.78 (1H, s, H-4″), 7.30 (2H, s, H-2″ and H-6″), 7.43 (2H, d, ^3J = 8.8 Hz, H-2′ and H-6′), 7.53 (2H, d, ^3J = 8.8 Hz, H-3′ and H-5′), 8.29 (1H, s, H-6), 8.83 (1H, s, NH), 8.85 (1H, s, NH), 12.90 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0 (2 x CH_3), 92.0 (C-3a), 110.6, 118.4 (2C), 120.2 (2C), 125.4, 131.3 (2C), 137.5 (2C), 138.4, 142.2, 142.4 (C-3), 154.3 (C-6), 154.8 (C-4), 155.6 (C-7a). Anal. Calcd for $C_{19}H_{17}BrN_6$: C, 55.76; H, 4.19; N, 20.53. Found: C, 55.53; H, 4.42; N, 20.28.

N^4-Benzyl-N^3-(4-Bromophenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*5,14*}

White solid; yield 81%; m.p. 265-267 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.81 (2H, d, ^3J = 5.8 Hz, CH_2), 7.20-7.35 (5H, m, H-2″, H-3″, H-4″, H-5″ and H-6″), 7.41 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 7.52 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 7.99 (1H, t, ^3J = 5.8 Hz, NH), 8.17 (1H, s, H-6), 8.57 (1H, s, NH), 12.70 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2), 91.0 (C-3a), 110.6, 118.4 (2C), 126.7, 127.0 (2C), 128.2 (2C), 131.2 (2C), 139.4, 142.1, 142.7 (C-3), 154.5 (C-6), 155.9 (C-4), 155.9 (C-7a).

N^3-(4-Bromophenyl)-N^4-(4-chlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*5,16*}

White solid; yield 47%; m.p. 264-266 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.79 (2H, d, ^3J = 5.8 Hz, CH_2), 7.37 (4H, s, H-2″, H-3″, H-5″ and H-6″), 7.41 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 7.52 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 8.02 (1H, t, ^3J = 5.8 Hz, NH), 8.16 (1H, s, H-6), 8.55 (1H, s, NH), 12.71 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.5 (CH_2), 91.0 (C-3a), 110.6, 118.4 (2C), 128.1 (2C), 128.9 (2C), 131.2, 131.2 (2C), 138.5, 142.1, 142.7 (C-3), 154.5 (C-

6), 155.9 (C-4), 155.9 (C-7a). Anal. Calcd for $C_{18}H_{14}BrClN_6$: C, 50.31; H, 3.28; N, 19.56. Found: C, 50.04; H, 3.35; N, 19.27.

N^4-(4-Fluorophenyl)-N^3-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,2*}

Yellow solid; yield 33%; m.p. 285-287 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (3H, s, CH_3), 7.09 (2H, d, ^3J = 8.9 Hz, H-3′ and H-5′), 7.23 (2H, dd, $^3J_{HH}$ = 8.9 Hz, $^3J_{HF}$ = 8.9 Hz, H-3″ and H-5″), 7.48 (2H, d, ^3J = 8.4 Hz, H-2′ and H-6′), 7.67 (2H, dd, $^4J_{HF}$ = 5.0 Hz, $^3J_{HH}$ = 9.0 Hz, H-2″ and H-6″), 8.25 (1H, s, H-6), 8.52 (1H, s, NH), 8.99 (1H, s, NH), 12.77 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 91.6 (C-3a), 115.1 (d, $^2J_{CF}$ = 22.3 Hz, C-3″ and C-5″), 116.9 (2C), 124.8 (d, $^3J_{CF}$ = 8.0 Hz, C-2″ and C-6″), 128.5, 129.1 (2C), 134.9 (d, $^4J_{CF}$ = 2.2 Hz, C-1″), 140.2, 143.3 (C-3), 154.3 (C-6), 154.8 (C-4), 155.4 (C-7a), 158.6 (d, $^1J_{CF}$ = 240.8 Hz, C-4″). Anal. Calcd for $C_{18}H_{15}FN_6$: C, 64.66; H, 4.52; N, 25.14. Found: C, 64.50; H, 4.69; N, 24.88.

N^4-(3-Chlorophenyl)-N^3-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,3*}

Yellow solid; yield 40%; m.p. 256-258 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (3H, s, CH_3), 7.09 (2H, d, ^3J = 8.3 Hz, H-3′ and H-5′), 7.17 (1H, ddd, ^4J = 0.8 Hz, ^4J = 2.0 Hz, ^3J = 8.0 Hz, H-4″), 7.40 (1H, dd, ^3J = 8.1 Hz, ^3J = 8.1 Hz, H-5″), 7.46 (2H, d, ^3J = 8.4 Hz, H-2′ and H-6′), 7.64 (1H, ddd, ^4J = 0.9 Hz, ^4J = 2.0 Hz, ^3J = 8.2 Hz, H-6″), 7.91 (1H, dd, ^4J = 2.0 Hz, ^4J = 2.0 Hz, H-2″), 8.35 (1H, s, H-6), 8.57 (1H, s, NH), 9.01 (1H, s, NH), 12.85 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 92.1 (C-3a), 116.9 (2C), 120.4, 121.4, 123.1, 128.6, 129.1 (2C), 130.0, 132.7, 140.2, 140.4, 143.2 (C-3), 153.9 (C-6), 154.9 (C-4), 155.3 (C-7a). Anal. Calcd for $C_{18}H_{15}ClN_6$: C, 61.63; H, 4.31; N, 23.96. Found: C, 61.47; H, 4.56; N, 23.70.

N^4-(4-Chlorophenyl)-N^3-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,4*}

Yellow solid; yield 35%; m.p. 297-299 °C (acetone). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (3H, s, CH_3), 7.09 (2H, d, ^3J = 8.3 Hz, H-3′ and H-5′), 7.44 (2H, d, ^3J = 8.9 Hz, H-3″ and H-5″), 7.47

(2H, d, ^{3}J = 8.4 Hz, H-2′ and H-6′), 7.75 (2H, d, ^{3}J = 8.9 Hz, H-2″ and H-6″), 8.31 (1H, s, H-6), 8.57 (1H, s, NH), 9.01 (1H, s, NH), 12.82 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 92.0 (C-3a), 116.9 (2C), 123.8 (2C), 127.3 (2C), 128.3, 128.6, 129.1 (2C), 137.8, 140.2, 143.2 (C-3), 154.0 (C-6), 154.9 (C-4), 155.3 (C-7a). Anal. Calcd for $C_{18}H_{15}ClN_6$: C, 61.63; H, 4.31; N, 23.96. Found: C, 61.50; H, 4.48; N, 23.77.

N^4-(4-Bromophenyl)-N^3-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,5*}

Yellow solid; yield 40%; m.p. 300-302 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (3H, s, CH_3), 7.09 (2H, d, ^{3}J = 8.3 Hz, H-3′ and H-5′), 7.46 (2H, d, ^{3}J = 8.4 Hz, H-2′ and H-6′), 7.56 (2H, d, ^{3}J = 8.9 Hz, H-2″ and H-6″), 7.70 (2H, d, ^{3}J = 8.9 Hz, H-3″ and H-5″), 8.30 (1H, s, H-6), 8.57 (1H, s, NH), 9.01 (1H, s, NH), 12.82 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 92.0 (C-3a), 115.3, 116.8 (2C), 124.1 (2C), 128.5, 129.1 (2C), 131.2 (2C), 138.2, 140.2, 143.2 (C-3), 153.9 (C-6), 154.8 (C-4), 155.3 (C-7a). Anal. Calcd for $C_{18}H_{15}BrN_6$: C, 54.70; H, 3.83; N, 21.26. Found: C, 54.59; H, 3.95; N, 21.12.

N^3-(4-Methylphenyl)-N^4-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,6*}

Light yellow solid; yield 55%; m.p. 221-223 °C (AcOEt). ^{1}H NMR (300 M Hz, DMSO-d_6): δ 2.25 (3H, s, CH_3), 2.33 (3H, s, CH_3), 6.95 (1H, d, ^{3}J = 7.4 Hz, H-4″), 7.09 (2H, d, ^{3}J = 8.2 Hz, H-3′ and H-5′), 7.26 (1H, dd, ^{3}J = 7.8 Hz, ^{3}J = 7.8 Hz, H-5″), 7.40-7.53 (4H, m, H-2′, H-6′, H-2″ and H-6″), 8.27 (1H, s, H-6), 8.55 (1H, s, NH), 8.80 (1H, s, NH), 12.78 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 21.0 (CH_3), 91.9 (C-3a), 116.8 (2C), 119.7, 122.9, 124.5, 128.3, 128.5, 129.1 (2C), 137.7, 138.6, 140.3, 143.2 (C-3), 154.2 (C-6), 154.9 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 68.84; H, 5.71; N, 25.18.

N^3,N^4-Bis(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,7*}

Yellow solid; yield 52%; m.p. 268-270 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (3H, s, CH_3), 2.30 (3H, s, CH_3), 7.08 (2H, d, ^{3}J = 8.5 Hz, H-3′ and H-5′), 7.19 (2H, d, ^{3}J = 8.5 Hz, H-3″ and H-5″), 7.44 (2H, d, ^{3}J = 8.5 Hz, H-2′ and H-6′), 7.52 (2H, d, ^{3}J = 8.4 Hz, H-2″ and H-6″), 8.23 (1H, s, H-6), 8.51 (1H, s, NH), 8.82 (1H, s, NH), 12.73 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 20.4 (CH_3), 91.7 (C-3a), 116.8 (C2), 122.7 (2C), 128.5, 128.9 (2C), 129.1 (2C), 132.9, 136.0, 140.3, 143.2 (C-3), 154.3 (C-6), 154.8 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 68.89; H, 5.65; N, 25.26.

N^4-(2-Methoxyphenyl)-N^3-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,9*}

Light yellow solid; yield 64%; m.p. 237-239 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (3H, s, CH_3), 3.67 (3H, s, OCH_3), 6.93-7.13 (3H, m, H-3″, H-4″ and H-5″), 7.05 (2H, d, ^{3}J = 8.8 Hz, H-3′ and H-5′), 7.15 (2H, d, ^{3}J = 8.5 Hz, H-2′ and H-6′), 8.28 (1H, dd, ^{4}J = 1.5 Hz, ^{3}J = 7.9 Hz, H-6″), 8.33 (1H, s, H-6), 8.44 (1H, s, NH), 8.50 (1H, s, NH), 12.98 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 55.6 (OCH_3), 93.9 (C-3a), 111.0, 115.5 (2C), 120.3, 122.7, 124.4, 127.4, 128.1, 129.3 (2C), 141.6, 142.7 (C-3), 150.1, 154.3 (C-6), 154.9 (C-4), 155.7 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6O$: C, 65.88; H, 5.24; N, 24.26. Found: C, 65.64; H, 5.43; N, 23.99.

N^4-(3-Methoxyphenyl)-N^3-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,10*}

Light yellow solid; yield 46%; m.p. 215-217 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 6.71 (1H, ddd, ^{4}J = 1.3 Hz, ^{4}J = 2.2 Hz, ^{3}J = 7.8 Hz, H-4″), 7.09 (2H, d, ^{3}J = 8.3 Hz, H-3′ and H-5′), 7.20-7.35 (3H, m, H-2″, H-5″ and H-6″), 7.42 (2H, d, ^{3}J = 8.4 Hz, H-2′ and H-6′), 8.29 (1H, s, H-6), 8.56 (1H, s, NH), 8.81 (1H, s, NH), 12.79 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 55.0 (OCH_3), 92.1 (C-3a), 108.2, 108.9, 114.5, 116.7

(2C), 128.5, 129.1 (2C), 129.2, 139.8, 140.3, 143.1 (C-3), 154.1 (C-6), 154.9 (C-4), 155.4 (C-7a), 159.4. Anal. Calcd for $C_{19}H_{18}N_6O$: C, 65.88; H, 5.24; N, 24.26. Found: C, 65.73; H, 5.39; N, 24.08.

N^4-Benzyl-N^3-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,14*}

Light yellow solid; yield 80%; m.p. 240-242 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.23 (3H, s, CH_3), 4.81 (2H, d, ^3J = 5.8 Hz, CH_2), 7.06 (2H, d, ^3J = 8.3 Hz, H-3′ and H-5′), 7.20-7.37 (5H, m, H-2″, H-3″, H-4″, H-5″ and H-6″), 7.46 (2H, d, ^3J = 8.5 Hz, H-2′ and H-6′), 7.95 (1H, t, ^3J = 5.8 Hz, NH), 8.16 (1H, s, H-6), 8.29 (1H, s, NH), 12.55 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 43.1 (CH_2), 90.8 (C-3a), 116.8 (2C), 126.7, 127.0 (2C), 128.2 (2C), 128.4, 129.0 (2C), 139.5, 140.2, 143.5 (C-3), 154.6 (C-6), 155.8 (C-4), 156.0 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 68.93; H, 5.67; N, 25.21.

N^4-(4-Fluorobenzyl)-N^3-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,15*}

White solid; yield 81%; m.p. 276-278 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (3H, s, CH_3), 4.79 (2H, d, ^3J = 5.7 Hz, CH_2), 7.07 (2H, d, ^3J = 8.3 Hz, H-3′ and H-5′), 7.14 (2H, dd, $^3J_{HF}$ = 8.9 Hz, $^3J_{HH}$ = 8.9 Hz, H-3″ and H-5″), 7.39 (2H, dd, $^4J_{HF}$ = 5.6 Hz, $^3J_{HH}$ = 8.6 Hz, H-2″ and H-6″), 7.46 (2H, d, ^3J = 8.6 Hz, H-2′ and H-6′), 7.97 (1H, t, ^3J = 5.8 Hz, NH), 8.17 (1H, s, H-6), 8.28 (1H, s, NH), 12.57 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 42.5 (CH_2), 90.8 (C-3a), 114.9 (d, $^2J_{CF}$ = 21.1 Hz, C-3″ and C-5″), 116.8 (2C), 128.4, 129.0 (d, $^3J_{CF}$ = 6.9 Hz, C-2″ and C-6″), 129.0 (2C), 135.7 (d, $^4J_{CF}$ = 2.9 Hz, C-1″), 140.2, 143.5 (C-3), 154.5 (C-6), 155.8 (C-4), 155.9 (C-7a), 161.1 (d, $^1J_{CF}$ = 242.1 Hz, C-4″). Anal. Calcd for $C_{19}H_{17}FN_6$: C, 65.50; H, 4.92; N, 24.12. Found: C, 65.28; H, 5.16; N, 23.86.

N^4-(4-Chlorobenzyl)-N^3-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,16*}

Yellow solid; yield 78%; m.p. 290-292 °C (BuOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (3H, s, CH_3), 4.78 (2H, d, ^3J = 5.8 Hz, CH_2), 7.06 (2H, d, ^3J = 8.3 Hz, H-3′ and H-5′), 7.37 (4H, s, H-

2″, H-3″, H-5″ and H-6″), 7.45 (2H, d, ^{3}J = 8.5 Hz, H-2′ and H-6′), 7.98 (1H, t, ^{3}J = 5.9 Hz, NH), 8.15 (1H, s, H-6), 8.26 (1H, s, NH), 12.56 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 42.5 (CH_2), 90.8 (C-3a), 116.8 (2C), 128.1 (2C), 128.4, 128.9 (2C), 129.0 (2C), 131.2, 138.6, 140.2, 143.5 (C-3), 154.5 (C-6), 155.7 (C-4), 155.9 (C-7a). Anal. Calcd for $C_{19}H_{17}ClN_6$: C, 62.55; H, 4.70; N, 23.04. Found: C, 62.34; H, 4.89; N, 22.78.

N^4-(4-Methylbenzyl)-N^3-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,17*}

White solid; yield 83%; m.p. 259-261 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.23 (3H, s, CH_3), 2.27 (3H, s, CH_3), 4.76 (2H, d, ^{3}J = 5.7 Hz, CH_2), 7.06 (2H, d, ^{3}J = 8.4 Hz, H-3′ and H-5′), 7.12 (2H, d, ^{3}J = 8.0 Hz, H-3″ and H-5″), 7.23 (2H, d, ^{3}J = 8.0 Hz, H-2″ and H-6″), 7.46 (2H, d, ^{3}J = 8.5 Hz, H-2′ and H-6′), 7.91 (1H, t, ^{3}J = 5.8 Hz, NH), 8.16 (1H, s, H-6), 8.30 (1H, s, NH), 12.55 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 20.6 (CH_3), 42.9 (CH_2), 90.8 (C-3a), 116.8 (2C), 127.0 (2C), 128.3, 128.8 (2C), 129.0 (2C), 135.7, 136.4, 140.2, 143.5 (C-3), 154.6 (C-6), 155.8 (C-4), 156.0 (C-7a). Anal. Calcd for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.40. Found: C, 69.59; H, 6.03; N, 24.18.

N^4-(3,4-Dimethoxybenzyl)-N^3-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,19*}

Yellow solid; yield 37%; m.p. 239-241 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.41 (2H, d, ^{3}J = 5.5 Hz, CH_2), 6.72 (1H, t, ^{3}J = 5.5 Hz, NH), 6.91 (1H, d, ^{3}J = 8.2 Hz, H-5″), 6.97 (1H, dd, ^{4}J = 1.8 Hz, ^{3}J = 8.2 Hz, H-6″), 7.06 (1H, d, ^{4}J = 1.8 Hz, H-2″), 7.16 (2H, d, ^{3}J = 8.3 Hz, H-3′ and H-5′), 7.51 (2H, d, ^{3}J = 8.4 Hz, H-2′ and H-6′), 8.14 (1H, s, H-6), 8.79 (1H, s, NH), 12.25 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 46.3 (CH_2), 55.4 (OCH_3), 55.5 (OCH_3), 90.1 (C-3a), 111.7, 111.9, 119.8, 122.9 (2C), 128.8 (2C), 132.6, 132.7, 136.1, 147.6, 147.7, 148.5 (C-3), 154.5 (C-6), 155.2 (C-4), 155.4

(C-7a). Anal. Calcd for $C_{21}H_{22}N_6O_2$: C, 64.60; H, 5.68; N, 21.52. Found: C, 64.46; H, 5.81; N, 21.27.

N^3-(4-Methylphenyl)-N^4-phenethyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*6,20*}

Light yellow solid; yield 37%; m.p. 229-231 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30 (3H, s, CH_3), 2.97 (2H, t, ^3J = 7.8 Hz, $NHCH_2C\underline{H_2}Ph$), 3.48 (2H, dt, ^3J = 6.0 Hz, ^3J = 8.6 Hz, $NHC\underline{H_2}CH_2Ph$), 6.43 (1H, t, ^3J = 5.3 Hz, $N\underline{H}CH_2CH_2Ph$), 7.15-7.35 (7H, m, $NHCH_2CH_2\underline{Ph}$, H-2″ and H-6″), 7.53 (2H, d, ^3J = 8.4 Hz, H-3″ and H-5″), 8.14 (1H, s, H-6), 8.65 (1H, s, NH), 12.25 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 34.9 ($NHCH_2\underline{C}H_2Ph$), 44.7 ($NH\underline{C}H_2CH_2Ph$), 90.1 (C-3a), 122.8 (2C), 125.9, 128.2 (2C), 128.6 (2C), 128.8 (2C), 132.7, 136.1, 140.1, 147.6 (C-3), 154.5 (C-6), 155.2 (C-4), 155.3 (C-7a). Anal. Calcd for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.40. Found: C, 69.64; H, 5.97; N, 24.25.

N^3-(4-Ethylphenyl)-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*7,7*}

Yellow solid; yield 58%; m.p. 263-265 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (3H, t, ^3J = 7.6 Hz, $CH_2C\underline{H_3}$), 2.30 (3H, s, CH_3), 2.55 (2H, q, ^3J = 6.4 Hz, CH_2), 7.11 (2H, d, ^3J = 8.5 Hz, H-3′ and H-5′), 7.18 (2H, d, ^3J = 8.2 Hz, H-3″ and H-5″), 7.44 (2H, d, ^3J = 8.5 Hz, H-2′ and H-6′), 7.51 (2H, d, ^3J = 8.4 Hz, H-2″ and H-6″), 8.24 (1H, s, H-6), 8.53 (1H, s, NH), 8.78 (1H, s, NH), 12.74 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.8 ($CH_2\underline{C}H_3$), 20.4 (CH_3), 27.4 (CH_2), 91.8 (C-3a), 116.8 (2C), 122.6 (2C), 127.9 (2C), 128.9 (2C), 132.9, 135.2, 136.0, 140.6, 143.2 (C-3), 154.3 (C-6), 154.9 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.40. Found: C, 69.63; H, 6.01; N, 24.21.

N^3-(4-Isopropylphenyl)-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*8,7*}

Yellow solid; yield 27%; m.p. 244-246 °C (MeCN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (6H, d, ^{3}J = 6.9 Hz, (2 x CH_3), 2.30 (3H, s, CH_3), 2.83 (1H, m, ^{3}J = 6.9 Hz, CH), 7.14 (2H, d, ^{3}J = 8.6 Hz, H-3′ and H-5′), 7.18 (2H, d, ^{3}J = 8.8 Hz, H-3″ and H-5″), 7.43 (2H, d, ^{3}J = 8.6 Hz, H-2′ and H-6′), 7.49 (2H, d, ^{3}J = 8.4 Hz, H-2″ and H-6″), 8.23 (1H, s, H-6), 8.54 (1H, s, NH), 8.74 (1H, s, NH), 12.75 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 24.0 (2 x CH_3), 32.6 (CH), 91.8 (C-3a), 116.7 (2C), 122.6 (2C), 126.4 (2C), 128.9 (2C), 132.9, 136.0, 139.9, 140.6, 143.2 (C-3), 154.2 (C-6), 154.8 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{21}H_{22}N_6$: C, 70.37; H, 6.19; N, 23.45. Found: C, 70.13; H, 5.96; N, 23.17.

N^3-(4-Isopropylphenyl)-N^4-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*8,10*}

White solid; yield 15%; m.p. 183-185 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (6H, d, ^{3}J = 6.9 Hz, 2 x CH_3), 2.83 (1H, m, ^{3}J = 6.9 Hz, CH), 3.77 (3H, s, OCH_3), 6.71 (1H, ddd, ^{4}J = 0.8 Hz, ^{4}J = 2.5 Hz, ^{3}J = 8.1 Hz, H-4″), 7.10-7.20 (3H, m, H-3′, H-5′ and H-6″), 7.27 (1H, dd, ^{3}J = 8.1 Hz, ^{3}J = 8.1 Hz, H-5″), 7.34 (1H, dd, ^{4}J = 2.2 Hz, ^{4}J = 2.2 Hz, H-2″), 7.41 (2H, d, ^{3}J = 8.6 Hz, H-2′ and H-6′), 8.29 (1H, s, H-6), 8.57 (1H, s, NH), 8.74 (1H, s, NH), 12.80 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.0 (2 x CH_3), 32.6, 55.0 (OCH_3), 92.2 (C-3a), 108.2, 108.9, 114.4, 116.7 (2C), 126.4 (2C), 129.2, 139.8, 139.9, 140.7, 143.1 (C-3), 154.1 (C-6), 154.9 (C-4), 155.4 (C-7a), 159.4. Anal. Calcd for $C_{21}H_{22}N_6O$: C, 67.36; H, 5.92; N, 22.44. Found: C, 67.11; H, 6.18; N, 22.13.

N^4-(4-Chlorophenyl)-N^3-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*9,4*}

Yellow solid; yield 71%; m.p. 229-231 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.87 (3H, s, OCH_3), 6.80-6.92 (2H, m, H-3′ and H-4′), 6.99-7.05 (1H, m, H-5′), 7.42 (2H, d, ^{3}J = 8.8 Hz, H-3″ and H-5″), 7.63-7.68 (1H, m, H-6′), 7.70 (2H, d, ^{3}J = 8.9 Hz, H-2″ and H-6″), 7.91 (1H, s, NH), 8.34 (1H, s, H-6), 9.17 (1H, s, NH), 12.93 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.6

(OCH_3), 93.5 (C-3a), 110.9, 117.1, 120.5, 120.6, 122.7 (2C), 126.8 (2C), 128.4, 132.0, 138.1, 143.4 (C-3), 148.2, 154.3 (C-6), 155.0 (C-4), 155.3 (C-7a). Anal. Calcd for $C_{18}H_{15}ClN_6O$: C, 58.94; H, 4.12; N, 22.91. Found: 58.67; H, 4.35; N, 22.64.

N^3-(2-Methoxyphenyl)-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*9,7*}

White solid; yield 39%; m.p. 215-217 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 6.80-6.91 (2H, m, H-3′ and H-4′), 6.98-7.03 (1H, m, H-5′), 7.17 (2H, d, ^3J = 8.2 Hz, H-3″ and H-5″), 7.50 (2H, d, ^3J = 8.5 Hz, H-2″ and H-6″), 7.56-7.61 (1H, m, H-6′), 7.86 (1H, s, NH), 8.29 (1H, s, H-6), 8.88 (1H, s, NH), 12.84 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 55.6 (OCH_3), 93.4 (C-3a), 110.9, 117.0, 120.5, 121.4 (3C), 129.0 (2C), 132.3, 132.4, 136.4, 143.3 (C-3), 148.2, 154.6 (C-6), 155.0 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6O$: C, 65.88; H, 5.24; N, 24.26. Found: C, 65.69; H, 5.40; N, 24.02.

N^4-(4-Chlorophenyl)-N^3-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*10,4*}

Brown solid; yield 28%; m.p. 269-271 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.73 (3H, s, OCH_3), 6.90 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 7.44 (2H, d, ^3J = 8.8 Hz, H-3″ and H-5″), 7.51 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 7.75 (2H, d, ^3J = 8.9 Hz, H-2″ and H-6″), 8.28 (1H, s, H-6), 8.46 (1H, s, NH), 9.00 (1H, s, NH), 12.72 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 91.6 (C-3a), 114.0 (2C), 118.6 (2C), 123.9 (2C), 127.3 (2C), 128.3, 135.9, 137.8, 143.7 (C-3), 153.3, 154.0 (C-6), 154.9 (C-4), 155.3 (C-7a). Anal. Calcd for $C_{18}H_{15}ClN_6O$: C, 58.94; H, 4.12; N, 22.91. Found: C, 58.73; H, 4.38; N, 22.60.

N^4-(4-Bromophenyl)-N^3-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*10,5*}

Yellow solid; yield 21%; m.p. 268-270 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.72 (3H, s, OCH_3), 6.89 (2H, d, ^{3}J = 9.1 Hz, H-3′ and H-5′), 7.50 (2H, d, ^{3}J = 9.0 Hz, H-2′ and H-6′), 7.56 (2H, d, ^{3}J = 9.0 Hz, H-2″ and H-6″), 7.70 (2H, d, ^{3}J = 8.9 Hz, H-3″ and H-5″), 8.28 (1H, s, H-6), 8.47 (1H, s, NH), 9.00 (1H, s, NH), 12.72 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 91.7 (C-3a), 113.9 (2C), 115.3, 118.6 (2C), 124.2 (2C), 131.2 (2C), 135.9, 138.2, 143.7 (C-3), 153.2, 153.9 (C-6), 154.9 (C-4), 155.3 (C-7a). Anal. Calcd for $C_{18}H_{15}BrN_6O$: C, 52.57; H, 3.68; N, 20.44. Found: C, 52.34; H, 3.90; N, 20.18.

N^3-(4-Methoxyphenyl)-N^4-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine

5{*10,6*}

Yellow solid; yield 32%; m.p. 203-205 °C (MeOH). ^{1}H NMR (300 M Hz, DMSO-d_6): δ 2.33 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 6.89 (2H, d, ^{3}J = 9.1 Hz, H-3′ and H-5′), 6.96 (1H, d, ^{3}J = 7.5 Hz, H-4″), 7.26 (1H, dd, ^{3}J = 7.8 Hz, ^{3}J = 7.8 Hz, H-5″), 7.41-7.53 (4H, m, H-2′, H-6′, H-2″ and H-6″), 8.26 (1H, s, H-6), 8.44 (1H, s, NH), 8.80 (1H, s, NH), 12.68 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0 (CH_3), 55.1 (OCH_3), 91.6 (C-3a), 114.0 (2C), 118.5 (2C), 119.8, 123.0, 124.5, 128.3, 136.1, 137.7, 138.6, 143.7 (C-3), 153.3, 154.3 (C-6), 154.9 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6O$: C, 65.88; H, 5.24; N, 24.26. Found: C, 65.65; H, 5.43; N, 24.00.

N^3-(4-Methoxyphenyl)-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine

5{*10,7*}

Light green solid; yield 62%; m.p. 255-257 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (3H, s, CH_3), 3.72 (3H, s, CH_3), 6.89 (2H, d, ^{3}J = 9.1 Hz, H-3′ and H-5′), 7.19 (2H, d, ^{3}J = 8.2 Hz, H-3″ and H-5″), 7.49 (2H, d, ^{3}J = 9.1 Hz, H-2′ and H-6′), 7.52 (2H, d, ^{3}J = 8.4 Hz, H-2″ and H-6″), 8.22 (1H, s, H-6), 8.41 (1H, s, NH), 8.82 (1H, s, NH), 12.64 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 55.1 (CH_3), 91.4 (C-3a), 114.0 (2C), 118.5 (2C), 122.8 (2C), 128.9 (2C),

132.9, 136.0, 136.1, 143.7 (C-3), 153.2, 154.4 (C-6), 154.9 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6O$: C, 65.88; H, 5.24; N, 24.26. Found: C, 65.70; H, 5.36; N, 24.11.

N^3-(4-Methoxyphenyl)-N^4-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*10,9*}

Yellow solid; yield 16%; m.p. 256-258 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.69 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 6.86 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 6.98 (1H, ddd, ^4J = 1.4 Hz, ^3J = 7.6 Hz, ^3J = 7.6 Hz, H-5″), 7.02-7.17 (2H, m, H-3″ and H-4″), 7.22 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 8.18 (1H, dd, ^4J = 1.5 Hz, ^3J = 7.9 Hz, H-6″), 8.27 (1H, s, H-6), 8.37 (1H, s, NH), 8.43 (1H, s, NH), 12.85 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 55.6 (OCH_3), 93.3 (C-3a), 111.1, 114.2 (2C), 117.2 (2C), 120.3, 123.2, 124.6, 127.3, 137.2, 143.3 (C-3), 150.4, 153.1, 154.4 (C-6), 154.8 (C-4), 155.7 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6O_2$: C, 62.97; H, 5.01; N, 23.19. Found: C, 62.74; H, 5.26; N, 22.95.

N^3-(4-Methoxyphenyl)-N^4-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*10,10*}

Brown solid; yield 55%; m.p. 205-207 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.72 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 6.72 (1H, ddd, ^4J = 1.4 Hz, ^4J = 2.4 Hz, ^3J = 7.7 Hz, H-4″), 6.89 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 7.20-7.35 (3H, m, H-2″, H-5″ and H-6″), 7.46 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 8.27 (1H, s, H-6), 8.46 (1H, s, NH), 8.83 (1H, s, NH), 12.71 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 55.2 (OCH_3), 91.9 (C-3a), 108.3, 109.0, 114.1, 114.7 (2C), 118.6 (2C), 129.3, 136.1, 139.9, 143.8 (C-3), 153.4, 154.3 (C-6), 155.0 (C-4), 155.5 (C-7a), 159.4. Anal. Calcd for $C_{19}H_{18}N_6O_2$: C, 62.97; H, 5.01; N, 23.19. Found: C, 62.78; H, 5.18; N, 22.99.

N^3,N^4-Bis(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*10,11*}

Yellow solid; yield 26%; m.p. 238-240 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.72 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 6.89 (2H, d, ^{3}J = 9.1 Hz, H-3′ and H-5′), 6.97 (2H, d, ^{3}J = 9.0 Hz, H-3″ and H-5″), 7.51 (2H, d, ^{3}J = 9.0 Hz, H-2′ and H-6′), 7.51 (2H, d, ^{3}J = 9.0 Hz, H-2″ and H-6″), 8.17 (1H, s, NH), 8.37 (1H, s, H-6), 8.86 (1H, s, NH), 12.60 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 55.1 (OCH_3), 91.0 (C-3a), 113.7 (2C), 113.9 (2C), 118.5 (2C), 125.0 (2C), 131.3, 136.0, 143.7 (C-3), 153.2, 154.6 (C-6), 154.8 (C-4), 155.5, 156.0 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6O_2$: C, 62.97; H, 5.01; N, 23.19. Found: C, 62.88; H, 5.12; N, 23.04.

N^4-Benzyl-N^3-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*10,14*}

White solid; yield 77%; m.p. 237-239 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.72 (3H, s, OCH_3), 4.82 (2H, d, ^{3}J = 5.7 Hz, CH_2), 6.87 (2H, d, ^{3}J = 9.0 Hz, H-3′ and H-5′), 7.20-7.37 (5H, m, H-2″, H-3″, H-4″, H-5″ and H-6″), 7.52 (2H, d, ^{3}J = 9.0 Hz, H-2′ and H-6′), 7.96 (1H, t, ^{3}J = 5.7 Hz, NH), 8.16 (1H, s, H-6), 8.20 (1H, s, NH), 12.48 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2), 55.1 (OCH_3), 90.5 (C-3a), 113.9 (2C), 118.5 (2C), 126.7, 127.0 (2C), 128.2 (2C), 136.1, 139.5, 144.0 (C-3), 153.1, 154.6 (C-6), 155.8 (C-4), 156.1 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6O$: C, 65.88; H, 5.24; N, 24.26. Found: C, 65.65; H, 5.42; N, 23.98.

N^4-(4-Chlorobenzyl)-N^3-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*10,16*}

White solid; yield 68%; m.p. 274-276 °C (BuOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.71 (3H, s, OCH_3), 4.78 (2H, d, ^{3}J = 5.8 Hz, CH_2), 6.87 (2H, d, ^{3}J = 9.1 Hz, H-3′ and H-5′), 7.37 (4H, s, H-2″, H-3″, H-5″ and H-6″), 7.50 (2H, d, ^{3}J = 9.1 Hz, H-2′ and H-6′), 7.99 (1H, t, ^{3}J = 5.8 Hz, NH), 8.13 (1H, s, H-6), 8.17 (1H, s, NH), 12.48 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.5 (CH_2), 55.1 (OCH_3), 90.5 (C-3a), 113.8 (2C), 118.4 (2C), 128.1 (2C), 128.9 (2C), 131.1, 136.0,

138.6, 143.9 (C-3), 153.1, 154.5 (C-6), 155.7 (C-4), 155.9 (C-7a). Anal. Calcd for $C_{19}H_{17}ClN_6O$: C, 59.92; H, 4.50; N, 22.07. Found: C, 59.67; H, 4.72; N, 21.81.

N^4-(4-Fluorophenyl)-N^3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*11,2*}

Yellow solid; yield 31%; m.p. 249-251 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.96 (2H, dd, ^4J = 1.0 Hz, ^3J = 8.6 Hz, H-2‴ and H-6‴), 7.02 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 7.07 (1H, t, ^3J = 7.3 Hz, H-4‴), 7.24 (2H, dd, $^3J_{HH}$ = 8.9 Hz, $^3J_{HF}$ = 8.9 Hz, H-3″ and H-5″), 7.35 (2H, dd, ^3J = 7.5 Hz, ^3J = 8.5 Hz, H-3‴ and H-5‴), 7.63 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 7.71 (2H, dd, $^4J_{HF}$ = 5.0 Hz, $^3J_{HH}$ = 9.0 Hz, H-2″ and H-6″), 8.27 (1H, s, H-6), 8.68 (1H, s, NH), 9.03 (1H, s, NH), 12.82 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 91.6 (C-3a), 114.6 (d, $^2J_{CF}$ = 22.3 Hz, C-3″ and C-5″), 117.1 (2C), 118.2 (2C), 120.1 (2C), 122.3, 124.3 (d, $^3J_{CF}$ = 8.1 Hz, C-2″ and C-6″), 129.8 (2C), 134.4 (d, $^4J_{CF}$ = 2.5 Hz, C-1″), 139.0, 143.2 (C-3), 148.9, 154.3 (C-6), 154.9 (C-4), 155.5 (C-7a), 158.1, 158.1 (d, $^1J_{CF}$ = 240.7 Hz, C-4″). Anal. Calcd for $C_{23}H_{17}FN_6O$: C, 66.98; H, 4.15; N, 20.38. Found: C, 66.77; H, 4.28; N, 20.10.

N^4-(4-Chlorophenyl)-N^3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*11,4*}

Yellow solid; yield 20%; m.p. 247-249 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.95 (2H, dd, ^4J = 1.0 Hz, ^3J = 9.0 Hz, H-2‴ and H-6‴), 7.02 (2H, d, ^3J = 8.9 Hz, H-3′ and H-5′), 7.06 (1H, t, ^3J = 7.9 Hz, H-4‴), 7.35 (2H, dd, ^3J = 7.9 Hz, ^3J = 7.9 Hz, H-3‴ and H-5‴), 7.45 (2H, d, ^3J = 8.9 Hz, H-3″ and H-5″), 7.61 (2H, d, ^3J = 8.9 Hz, H-2″ and H-6″), 7.78 (2H, d, ^3J = 8.8 Hz, H-2′ and H-6′), 8.32 (1H, s, H-6), 8.72 (1H, s, NH), 9.05 (1H, s, NH), 12.87 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 92.0 (C-3a), 117.1 (2C), 118.2 (2C), 120.1 (2C), 122.3, 123.8 (2C), 127.3 (2C), 128.3, 129.8 (2C), 137.8, 139.1, 143.1 (C-3), 148.9, 154.0 (C-6), 154.9 (C-4), 155.4 (C-7a),

158.1. Anal. Calcd for $C_{23}H_{17}ClN_6O$: C, 64.41; H, 4.00; N, 19.60. Found: C, 64.24; H, 4.19; N, 19.34.

N^4-(4-Bromophenyl)-N^3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*11,5*}

Yellow solid; yield 34%; m.p. 258-260 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.94 (2H, dd, ^4J = 1.0 Hz, ^3J = 8.6 Hz, H-2‴ and H-6‴), 7.00 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 7.06 (1H, t, ^3J = 7.4 Hz, H-4‴), 7.34 (2H, dd, ^3J = 7.5 Hz, ^3J = 8.5 Hz, H-3‴ and H-5‴), 7.57 (2H, d, ^3J = 8.9 Hz, H-2″ and H-6″), 7.58 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 7.72 (2H, d, ^3J = 8.9 Hz, H-3″ and H-5″), 8.32 (1H, s, H-6), 8.72 (1H, s, NH), 9.04 (1H, s, NH), 12.88 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 92.0 (C-3a), 115.3 (2C), 117.1 (2C), 118.1 (2C), 120.1, 122.3, 124.1 (2C), 129.7 (2C), 131.2 (2C), 138.2, 139.0, 143.1 (C-3), 148.9, 154.0 (C-6), 154.9 (C-4), 155.4 (C-7a), 158.1. Anal. Calcd for $C_{23}H_{17}BrN_6O$: C, 58.36; H, 3.62; N, 17.76. Found: C, 58.18; H, 3.75; N, 17.52.

N^4-(4-Methylphenyl)-N^3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*11,7*}

Yellow solid; yield 43%; m.p. 247-249 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (3H, s, CH_3), 6.95 (2H, dd, ^4J = 1.0 Hz, ^3J = 8.6 Hz, H-2‴ and H-6‴), 7.01 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 7.06 (1H, t, ^3J = 7.4 Hz, H-4‴), 7.20 (2H, d, ^3J = 8.3 Hz, H-3″ and H-5″), 7.35 (2H, dd, ^3J = 7.5 Hz, ^3J = 8.5 Hz, H-3‴ and H-5‴), 7.53-7.61 (4H, m, H-2′, H-2″, H-6′ and H-6″), 8.25 (1H, s, H-6), 8.68 (1H, s, NH), 8.88 (1H, s, NH), 12.79 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 91.7 (C-3a), 117.1 (2C), 118.1 (2C), 120.1 (2C), 122.3, 122.8 (2C), 128.9 (2C), 129.7 (2C), 133.0, 136.0, 139.1, 143.1 (C-3), 148.8, 154.3 (C-6), 154.9 (C-4), 155.5 (C-7a), 158.1. Anal. Calcd for $C_{24}H_{20}N_6O$: C, 70.57; H, 4.94; N, 20.58. Found: C, 70.42; H, 5.13; N, 20.34.

N^4-(2-Methoxyphenyl)-N^3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine

5{*11,9*}

Yellow solid; yield 43%; m.p. 243-245 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.72 (3H, s, OCH_3), 6.87 (2H, dd, ^4J = 1.0 Hz, ^3J = 8.7 Hz, H-2‴ and H-6‴), 6.94-7.00 (2H, m, H-3″ and H-5″), 7.01-7.18 (4H, m, H-3′, H-5′, H-4″ and H-4‴), 7.23-7.34 (4H, m, H-2′, H-6′, H-3‴ and H-5‴), 8.29 (1H, dd, ^4J = 1.4 Hz, ^3J = 7.9 Hz, H-6″), 8.32 (1H, s, H-6), 8.40 (1H, s, NH), 8.64 (1H, s, NH), 12.99 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.7 (OCH_3), 93.7 (C-3a), 111.0, 116.8, 116.9 (2C), 120.3 (2C), 120.6 (2C), 122.2, 122.6, 124.4, 127.3 (2C), 129.7, 140.4, 142.6 (C-3), 148.6, 150.0, 154.2 (C-6), 154.9 (C-4), 155.8 (C-7a), 158.2. Anal. Calcd for $C_{24}H_{20}N_6O_2$: C, 67.91; H, 4.75; N, 19.80. Found: C, 67.74; H, 4.97; N, 19.58.

N^4-(3-Methoxyphenyl)-N^3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine

5{*11,10*}

Yellow solid; yield 65%; m.p. 199-201 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (3H, s, OCH_3), 6.73 (1H, ddd, ^3J = 7.1 Hz, ^4J = 2.4 Hz, ^4J = 2.2 Hz, H-4″), 6.94 (2H, dd, ^4J = 1.1 Hz, ^3J = 8.7 Hz, H-2‴ and H-6‴), 7.00 (2H, d, ^3J = 9.0 Hz, H-3′ and H-5′), 7.06 (1H, t, ^3J = 7.4 Hz, H-4‴), 7.27-7.37 (5H, m, H-2″, H-5″, H-6″, H-3‴ and H-5‴), 7.55 (2H, d, ^3J = 9.0 Hz, H-2′ and H-6′), 8.30 (1H, s, H-6), 8.69 (1H, s, NH), 8.84 (1H, s, NH), 12.82 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.0 (OCH_3), 92.0 (C-3a), 108.2, 108.9, 114.6, 117.1 (2C), 118.0 (2C), 120.1 (2C), 122.3, 129.2, 129.7 (2C), 139.1, 139.8, 143.0 (C-3), 148.8, 154.1 (C-6), 154.9 (C-4), 155.4 (C-7a), 158.0, 159.4. Anal. Calcd for $C_{24}H_{20}N_6O_2$: C, 67.91; H, 4.75; N, 19.80. Found: C, 67.78; H, 4.92; N, 19.62.

N^4-(4-Methoxyphenyl)-N^3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine

5{*11,11*}

Light green solid; yield 47%; m.p. 251-253 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (3H, s, OCH_3), 6.94-7.09 (7H, m, H-3′, H-5′, H-3″, H-5″, H-2‴, H-4‴ and H-6‴), 7.35 (2H, dd, ^{3}J = 7.9 Hz, ^{3}J = 7.9 Hz, H-3‴ and H-5‴), 7.54 (2H, d, ^{3}J = 8.9 Hz, H-2″ and H-6″), 7.61 (2H, d, ^{3}J = 8.9 Hz, H-2′ and H-6′), 8.20 (1H, s, H-6), 8.62 (1H, s, NH), 8.90 (1H, s, NH), 12.74 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.2 (OCH_3), 91.3 (C-3a), 113.7 (2C), 117.1 (2C), 118.1 (2C), 120.1 (2C), 122.3, 124.9 (2C), 129.7 (2C), 131.3, 139.1, 143.1 (C-3), 148.8, 154.6 (C-6), 154.8 (C-4), 155.6 (C-7a), 156.0, 158.1. Anal. Calcd for $C_{24}H_{20}N_6O_2$: C, 67.91; H, 4.75; N, 19.80. Found: C, 67.69; H, 5.02; N, 19.47.

N^4-Benzyl-N^3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5** {*11,14*}

White solid; yield 68%; m.p. 221-223 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.85 (2H, d, ^{3}J = 5.7 Hz, CH_2), 6.96 (2H, dd, ^{4}J = 1.0 Hz, ^{3}J = 8.7 Hz, H-2‴ and H-6‴), 7.01 (2H, d, ^{3}J = 9.0 Hz, H-3′ and H-5′), 7.06 (1H, t, ^{3}J = 7.4 Hz, H-4‴), 7.20-7.42 (7H, m, H-2″, H-3″, H-4″, H-5″, H-6″, H-3‴ and H-5‴), 7.63 (2H, d, ^{3}J = 9.0 Hz, H-2′ and H-6′), 8.03 (1H, t, ^{3}J = 5.8 Hz, NH), 8.20 (1H, s, H-6), 8.46 (1H, s, NH), 12.63 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.2 (CH_2), 90.8 (C-3a), 117.2 (2C), 118.1 (2C), 120.0 (2C), 122.3, 126.7, 127.1 (2C), 128.3 (2C), 129.7 (2C), 139.1, 139.5, 143.4, 148.8, 154.6 (C-6), 155.9 (C-4), 156.1 (C-7a), 158.1. Anal. Calcd for $C_{24}H_{20}N_6O$: C, 70.57; H, 4.94; N, 20.58. Found: C, 70.36; H, 5.22; N, 20.27.

N^4-(4-Chlorobenzyl)-N^3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*11,10*}

White solid; yield 65%; m.p. 220-222 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.81 (2H, d, ^{3}J = 5.8 Hz, CH_2), 6.96 (2H, dd, ^{4}J = 1.0 Hz, ^{3}J = 8.6 Hz, H-2‴ and H-6‴), 7.01 (2H, d, ^{3}J = 8.9 Hz, H-3′ and H-5′), 7.06 (1H, t, ^{3}J = 7.4 Hz, H-4‴), 7.35 (2H, dd, ^{3}J = 7.5 Hz, ^{3}J = 8.5 Hz, H-3‴ and H-5‴), 7.39 (4H, s, H-2″, H-3″, H-5″ and H-6″), 7.62 (2H, d, ^{3}J = 9.0 Hz, H-2′ and H-6′), 8.05

(1H, t, ^{3}J = 5.8 Hz, NH), 8.18 (1H, s, H-6), 8.43 (1H, s, NH), 12.63 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.6 (CH_2), 90.9 (C-3a), 117.2 (2C), 118.1 (2C), 120.0 (2C), 122.3, 128.2 (2C), 128.9 (2C), 129.8 (2C), 131.2, 138.6, 139.1, 143.4 (C-3), 148.8, 154.6 (C-6), 155.8 (C-4), 156.0 (C-7a), 158.1. Anal. Calcd for $C_{24}H_{19}ClN_6O$: C, 65.08; H, 4.32; N, 18.98. Found: C, 64.88; H, 4.56; N, 18.65.

N^3-(2,5-Dimethoxyphenyl)-N^4-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*12,1*}

Yellow solid; yield 38%; m.p. 179-181 °C (Et_2O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.65 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.41 (1H, dd, ^{4}J = 3.0 Hz, ^{3}J = 8.8 Hz, H-4′), 6.91 (1H, d, ^{3}J = 8.8 Hz, H-3′), 7.09 (1H, t, ^{3}J = 7.4 Hz, H-4″), 7.31-7.40 (3H, m, H-6′, H-3″and H-5″), 7.63 (2H, d, ^{3}J = 7.6 Hz, H-2″ and H-6″), 7.95 (1H, s, NH), 8.31 (1H, s, H-6), 9.06 (1H, s, NH), 12.94 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 56.3 (OCH_3), 93.6 (C-3a), 103.5, 103.7, 111.6, 121.1 (2C), 123.2, 128.6 (2C), 133.1, 139.1, 142.3, 143.0 (C-3), 153.5, 154.5 (C-6), 154.9 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{19}H_{18}N_6O_2$: C, 62.97; H, 5.01; N, 23.19. Found: C, 62.81; H, 5.16; N, 22.98.

N^4-(4-Fluorophenyl)-N^3-(2,5-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*12,2*}

Light brown solid; yield 36%; m.p. 215-217 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.67 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.42 (1H, dd, ^{4}J = 2.9 Hz, ^{3}J = 8.8 Hz, H-4′), 6.92 (1H, d, ^{3}J = 8.0 Hz, H-3′), 7.22 (2H, dd, $^{3}J_{HH}$ = 8.8 Hz, $^{3}J_{HF}$ = 8.8 Hz, H-3″ and H-5″), 7.38 (1H, s, H-6′), 7.65 (2H, dd, $^{4}J_{HF}$ = 4.9 Hz, $^{3}J_{HH}$ = 8.2 Hz, H-2″ and H-6″), 7.93 (1H, s, NH), 8.31 (1H, s, H-6), 9.15 (1H, s, NH), 12.94 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.2 (OCH_3), 56.3 (OCH_3), 93.3 (C-3a), 103.7, 104.0, 111.5, 114.7 (d, $^{2}J_{CF}$ = 22.3 Hz, C-3″ and C-5″), 122.9 (d, $^{3}J_{CF}$ = 7.9 Hz, C-2″ and C-6″), 132.9, 135.4, 142.4, 143.1 (C-3), 153.5, 154.6 (C-6), 154.9 (C-4), 155.4 (C-7a),

157.8 (d, $^{1}J_{CF}$ = 240.1 Hz, C-4″). Anal. Calcd for $C_{19}H_{17}FN_6O_2$: C, 59.99; H, 4.50; N, 22.09. Found: C, 59.76; H, 4.68; N, 21.82.

N^4-(4-Chlorophenyl)-N^3-(2,5-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*12,4*}

Light brown solid; yield 24%; m.p. 225-227 °C (MeCN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.65 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.41 (1H, dd, ^{4}J = 2.9 Hz, ^{3}J = 8.8 Hz, H-4′), 6.91 (1H, d, ^{3}J = 8.8 Hz, H-3′), 7.37 (1H, d, ^{4}J = 2.8 Hz, H-6′), 7.42 (2H, d, ^{3}J = 8.8 Hz, H-3″ and H-5″), 7.69 (2H, d, ^{3}J = 8.8 Hz, H-2″ and H-6″), 7.94 (1H, s, NH), 8.34 (1H, s, H-6), 9.24 (1H, s, NH), 12.98 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 56.3 (OCH_3), 93.6 (C-3a), 103.6, 103.9, 111.5, 122.6 (2C), 126.8, 128.5 (2C), 132.9, 138.2, 142.3, 143.0 (C-3), 153.5, 154.3 (C-6), 154.9 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{19}H_{17}ClN_6O_2$: C, 57.51; H, 4.32; N, 21.18. Found: C, 57.35; H, 4.54; N, 20.97.

N^4-(4-Bromophenyl)-N^3-(2,5-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*12,5*}

White solid; yield 29%; m.p. 208-210 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.65 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.41 (1H, dd, ^{4}J = 2.9 Hz, ^{3}J = 8.7 Hz, H-4′), 6.91 (1H, d, ^{3}J = 8.9 Hz, H-3′), 7.37 (1H, d, ^{4}J = 2.9 Hz, H-6′), 7.54 (2H, d, ^{3}J = 8.8 Hz, H-2″ and H-6″), 7.64 (2H, d, ^{3}J = 8.9 Hz, H-3″ and H-5″), 7.94 (1H, s, NH), 8.34 (1H, s, H-6), 9.23 (1H, s, NH), 12.97 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 56.3 (OCH_3), 93.6 (C-3a), 103.6, 103.9, 111.5, 114.7, 122.9 (2C), 131.4 (2C), 132.9, 138.6, 142.3, 143.0 (C-3), 153.5, 154.2 (C-6), 154.9 (C-4), 155.3 (C-7a). Anal. Calcd for $C_{19}H_{17}BrN_6O_2$: C, 51.71; H, 3.88; N, 19.04. Found: C, 51.58; H, 4.02; N, 18.79.

N^3-(2,5-Dimethoxyphenyl)-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*12,7*}

White solid; yield 30%; m.p. 216-218 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (3H, s, CH_3), 3.65 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.41 (1H, dd, ^4J = 3.0 Hz, ^3J = 8.8 Hz, H-4′), 6.91 (1H, d, ^3J = 8.8 Hz, H-3′), 7.17 (2H, d, ^3J = 8.3 Hz, H-3″ and H-5″), 7.31 (1H, d, ^4J = 2.9 Hz, H-6′), 7.50 (2H, d, ^3J = 8.4 Hz, H-2″ and H-6″), 7.92 (1H, s, NH), 8.28 (1H, s, H-6), 8.96 (1H, s, NH), 12.91 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 55.1 (OCH_3), 56.2 (OCH_3), 93.4 (C-3a), 103.5, 103.8, 111.6, 121.3 (2C), 129.0 (2C), 132.3, 133.1, 136.5, 142.3, 143.0 (C-3), 153.5, 154.6 (C-6), 154.9 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{20}H_{20}N_6O_2$: C, 63.82; H, 5.36; N, 22.33. Found: C, 63.67; H, 5.54; N, 22.06.

N^3-(2,5-Dimethoxyphenyl)-N^4-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*12,11*}

Yellow solid; yield 30%; m.p. 195-197 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.65 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.41 (1H, dd, ^4J = 3.0 Hz, ^3J = 8.8 Hz, H-4′), 6.91 (1H, d, ^3J = 8.8 Hz, H-3′), 6.95 (2H, d, ^3J = 9.0 Hz, H-3″ and H-5″), 7.33 (1H, d, ^4J = 3.0 Hz, H-6′), 7.50 (2H, d, ^3J = 9.0 Hz, H-2″ and H-6″), 7.87 (1H, s, NH), 8.24 (1H, s, H-6), 8.94 (1H, s, NH), 12.86 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 55.1 (OCH_3), 56.2 (OCH_3), 93.1 (C-3a), 103.6, 104.0, 111.5, 113.8 (2C), 123.4 (2C), 131.9, 133.1, 142.4, 143.0 (C-3), 153.5, 154.8 (C-6), 154.9 (C-4), 155.5 (C-7a), 155.6. Anal. Calcd for $C_{20}H_{20}N_6O_3$: C, 61.22; H, 5.14; N, 21.42. Found: C, 61.06; H, 5.31; N, 21.23.

N^3-(2,5-Dimethoxyphenyl)-N^4-(4-trifluoromethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*12,12*}

Yellow solid; yield 9%; m.p. 169-171 °C (Et_2O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.66 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.42 (1H, dd, ^4J = 2.9 Hz, ^3J = 8.8 Hz, H-4′), 6.92 (1H, d, ^3J = 8.8 Hz, H-3′), 7.35-7.41 (3H, m, H-6′, H-3″ and H-5″), 7.75 (2H, d, ^4J = 9.0 Hz, H-2″ and H-6″), 7.96 (1H, s, NH), 8.34 (1H, s, H-6), 9.32 (1H, s, NH), 12.98 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 56.3 (OCH_3), 93.5 (C-3a), 103.6, 103.9, 111.5, 121.4 (2C), 122.5 (2C), 132.8, 138.4, 142.3, 143.0 (C-3), 143.5, 153.5, 154.4 (C-6), 154.9 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{20}H_{17}F_3N_6O_3$: C, 53.81; H, 3.84; N, 18.83. Found: C, 53.67; H, 4.01; N, 18.58.

N^3-(2,5-Dimethoxyphenyl)-N^4-(3,5-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*12,13*}

White solid; yield 50%; m.p. 185-187 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (6H, s, 2 x CH_3), 3.64 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.41 (1H, dd, ^4J = 3.0 Hz, ^3J = 8.8 Hz, H-4′), 6.74 (1H, s, H-4″), 6.91 (1H, d, ^3J = 8.8 Hz, H-3′), 7.21-7.27 (3H, m, H-6′, H-2″ and H-6″), 7.91 (1H, s, NH), 8.31 (1H, s, H-6), 8.85 (1H, s, NH), 12.93 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0 (2 x CH_3), 55.1 (OCH_3), 56.2 (OCH_3), 93.7 (C-3a), 103.5, 103.7, 111.6, 118.8 (2C), 124.9, 133.2, 137.6 (2C), 138.9, 142.3, 143.0 (C-3), 153.5, 154.5 (C-6), 154.9 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{21}H_{22}N_6O_2$: C, 64.60; H, 5.68; N, 21.52. Found: C, 64.43; H, 5.84; N, 21.29.

N^4-Benzyl-N^3-(2,5-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*12,14*}

White solid; yield 32%; m.p. 157-159 °C (Et_2O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.64 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.74 (2H, d, ^3J = 5.7 Hz, CH_2), 6.40 (1H, dd, ^4J = 3.0 Hz, ^3J = 8.8 Hz, H-4′), 6.88 (1H, d, ^3J = 8.8 Hz, H-3′), 7.19 (1H, d, ^4J = 2.9 Hz, H-6′), 7.20-7.38 (5H, m, Ph), 7.72 (1H, s NH), 7.74 (1H, t, ^3J = 5.8 Hz, NH), 8.18 (1H, s, H-6), 12.69 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.4 (CH_2), 55.1 (OCH_3), 56.1 (OCH_3), 92.5 (C-3a), 103.6, 104.3, 111.5, 126.7, 127.1 (2C), 128.2 (2C), 133.2, 139.3, 142.5, 143.3 (C-3), 153.4, 154.6 (C-6), 155.8 (C-4),

156.4 (C-7a). Anal. Calcd for $C_{20}H_{20}N_6O_2$: C, 63.82; H, 5.36; N, 22.33. Found: C, 63.69; H, 5.48; N, 22.12.

N^4-(4-Chlorobenzyl)-N^3-(2,5-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*12,16*}

Yellow solid; yield 37%; m.p. 188-190 °C (Et_2O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.64 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.72 (2H, d, ^3J = 5.8 Hz, CH_2), 6.41 (1H, dd, ^4J = 3.1 Hz, ^3J = 8.9 Hz, H-4′), 6.89 (1H, d, ^3J = 8.8 Hz, H-3′), 7.19 (1H, d, ^4J = 3.0 Hz, H-6′), 7.37 (4H, s, H-2″, H-3″, H-5″ and H-6″), 7.70 (1H, s, NH), 7.80 (1H, t, ^3J = 5.8 Hz, NH), 8.17 (1H, s, H-6), 12.70 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.7 (CH_2), 55.1 (OCH_3), 56.1 (OCH_3), 92.5 (C-3a), 103.7, 104.4, 111.5, 128.1 (2C), 129.0 (2C), 131.2, 133.2, 138.5, 142.5, 143.3 (C-3), 153.4, 154.6 (C-6), 155.7 (C-4), 156.3 (C-7a). Anal. Calcd for $C_{20}H_{19}ClN_6O_2$: C, 58.47; H, 4.66; N, 20.46. Found: C, 58.34; H, 4.80; N, 20.29.

N^3-(2,5-Dimethoxyphenyl)-N^4-(4-methylbenzyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*12,17*}

Light pink solid; yield 49%; m.p. 191-193 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (3H, s, CH_3), 3.64 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.68 (2H, d, ^3J = 5.7 Hz, CH_2), 6.40 (1H, dd, ^4J = 3.0 Hz, ^3J = 8.9 Hz, H-4′), 6.89 (1H, d, ^3J = 8.8 Hz, H-3′), 7.12 (2H, d, ^3J = 7.9 Hz, H-3″ and H-5″), 7.17 (1H, d, ^4J = 3.0 Hz, H-6′), 7.23 (2H, d, ^3J = 7.9 Hz, H-2″ and H-6″), 7.68 (1H, t, ^3J = 5.9 Hz, NH), 7.71 (1H, s, NH), 8.17 (1H, s, H-6), 12.67 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.6 (CH_3), 43.1 (CH_2), 55.1 (OCH_3), 56.1 (OCH_3), 92.5 (C-3a), 103.7, 104.3, 111.5, 127.1 (2C), 128.7 (2C), 133.2, 135.7, 136.2, 142.5, 143.3 (C-3), 153.4, 154.6 (C-6), 155.8 (C-4), 156.3 (C-7a). Anal. Calcd for $C_{21}H_{22}N_6O_2$: C, 64.60; H, 5.68; N, 21.52. Found: C, 64.48; H, 5.80; N, 21.37.

N^3-(4-Fluorobenzyl)-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*13,7*}

Yellow solid; yield 38%; m.p. 214-216 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30 (3H, s, CH_3), 4.47 (2H, d, ^3J = 5.9 Hz, CH_2), 6.84 (1H, t, ^3J = 5.9 Hz, NH), 7.15 (2H, dd, $^3J_{HH}$ = 9.0 Hz, $^3J_{HF}$ = 9.0 Hz, H-3′ and H-5′), 7.17 (2H, d, ^3J = 8.2 Hz, H-3″ and H-5″), 7.47 (2H, dd, $^4J_{HF}$ = 5.7 Hz, $^3J_{HH}$ = 8.7 Hz, H-2′ and H-6′), 7.52 (2H, d, ^3J = 8.4 Hz, H-2″ and H-6″), 8.14 (1H, s, H-6), 8.75 (1H, s, NH), 12.76 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 45.6 (CH_2), 90.1 (C-3a), 114.7 (d, $^2J_{CF}$ = 21.1 Hz, C-3′ and C-5′), 122.9 (2C), 128.8 (2C), 129.4 (d, $^3J_{CF}$ = 8.2 Hz, C-2′ and C-6′), 132.7, 136.1, 136.4 (d, $^4J_{CF}$ = 3.4 Hz, C-1′), 147.4 (C-3), 154.5 (C-6), 155.3 (C-4), 155.4 (C-7a), 161.0 (d, $^1J_{CF}$ = 241.6 Hz, C-4′). Anal. Calcd for $C_{19}H_{17}FN_6$: C, 65.50; H, 4.92; N, 24.12. Found: C, 65.32; H, 5.16; N, 23.89.

N^3-(3-Methylbenzyl)-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*14,7*}

Yellow solid; yield 31%; m.p. 216-218 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30 (3H, s, CH_3), 4.45 (2H, d, ^3J = 5.6 Hz, CH_2), 6.81 (1H, t, ^3J = 5.6 Hz, NH), 7.00-7.08 (1H, m, H-4′), 7.17 (2H, d, ^3J = 8.2 Hz, H-3″ and H-5″), 7.19-7.25 (3H, m, H-2′, H-5′ and H-6′), 7.52 (2H, d, ^3J = 8.4 Hz, H-2″ and H-6″), 8.14 (1H, s, H-6), 8.78 (1H, s, NH), 12.23 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 21.0 (CH_3), 46.4 (CH_2), 90.1 (C-3a), 122.9 (2C), 124.7, 127.2, 128.0, 128.2, 128.8 (2C), 132.7, 136.1, 137.1, 140.1, 147.6 (C-3), 154.5 (C-6), 155.2 (C-4), 155.4 (C-7a). Anal. Calcd for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.40. Found: C, 69.58; H, 6.03; N, 24.18.

N^4-(4-Methylphenyl)-N^3-pyrrolidino-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*15,7*}

Light yellow solid; yield 35%; m.p. 240-242 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.88-1.95 (4H, m, CH_2CH_2), 2.28 (3H, s, CH_3), 3.36-3.41 (4H, m, CH_2CH_2), 7.14 (2H, d, ^3J = 8.2 Hz, H-3″ and H-5″), 7.61 (2H, d, ^3J = 8.4 Hz, H-2″ and H-6″), 8.22 (1H, s, H-6), 8.40 (1H, s, NH), 12.59 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 24.6 (CH_2CH_2), 50.8 (CH_2CH_2),

92.5 (C-3a), 121.3 (2C), 128.8 (2C), 132.1, 136.6, 150.4 (C-3), 154.5 (C-6), 155.1 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{16}H_{18}N_6$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.12; H, 6.33; N, 28.29.

N^4-(3-Methoxyphenyl)-N^3-pyrrolidino-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*15,10*}

White solid; yield 27%; m.p. 218-220 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.88-1.94 (4H, m, CH_2CH_2), 3.36-3.42 (4H, m, CH_2CH_2), 6.65 (1H, ddd, ^4J = 0.9 Hz, ^4J = 2.5 Hz, ^3J = 8.1 Hz, H-4″), 7.23 (1H, dd, ^3J = 8.1 Hz, ^3J = 8.1 Hz, H-5″), 7.31 (1H, ddd, ^4J = 1.0 Hz, ^4J = 1.9 Hz, ^3J = 8.1 Hz, H-6″), 7.45 (1H, dd, ^4J = 2.2 Hz, ^4J = 2.2 Hz, H-2″), 8.28 (1H, s, H-6), 8.54 (1H, s, NH), 12.64 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.6 (CH_2CH_2), 50.7 (CH_2CH_2), 55.0 (OCH_3), 92.7 (C-3a), 106.9, 108.1, 113.3, 129.1, 140.3, 150.3 (C-3), 154.3 (C-6), 155.0 (C-4), 155.5 (C-7a), 159.4. Anal. Calcd for $C_{16}H_{18}N_6O$: C, 61.92; H, 5.85; N, 27.08. Found: C, 61.76; H, 6.00; N, 26.87.

N^4-(4-Chlorophenyl)-N^3-morpholino-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*16,4*}

White solid; yield 18%; m.p. 258-260 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.11-3.17 (4H, m, CH_2NCH_2), 3.77-3.83 (4H, m, CH_2OCH_2), 7.42 (2H, d, ^3J = 8.9 Hz, H-3″ and H-5″), 7.80 (2H, d, ^3J = 8.9 Hz, H-2″ and H-6″), 8.36 (1H, s, H-6), 8.47 (1H, s, NH), 13.01 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 51.3 (CH_2NCH_2), 65.5 (CH_2OCH_2), 93.3 (C-3a), 122.4 (2C), 126.8 (2C), 128.4, 137.8, 151.5 (C-3), 154.1 (C-6), 155.3 (C-4), 155.5 (C-7a). Anal. Calcd for $C_{15}H_{15}ClN_6O$: C, 54.47; H, 4.57; N, 25.41. Found: C, 54.30; H, 4.69; N, 25.23.

N^4-(4-Methylphenyl)-N^3-morpholino-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*16,7*}

White solid; yield 63%; m.p. 258-260 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30 (3H, s, CH_3), 3.11-3.16 (4H, m, CH_2NCH_2), 3.35 (1H, s, CH), 3.79-3.84 (4H, m, CH_2OCH_2), 7.18 (2H, d, ^3J = 8.5 Hz, H-3′ and H-5′), 7.65 (2H, d, ^3J = 8.3 Hz, H-2′ and H-6′), 8.18 (1H, s, H-6), 8.33 (1H, s, NH), 12.95 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 51.5 (CH_2NCH_2),

65.7 (CH_2OCH_2), 93.1 (C-3a), 120.1 (2C), 129.0 (2C), 132.4, 136.2, 151.6 (C-3), 154.3 (C-6), 155.2 (C-4), 155.7 (C-7a). Anal. Calcd for $C_{16}H_{18}N_6O$: C, 61.92; H, 5.85; N, 27.08. Found: C, 61.84; H, 5.93; N, 26.92.

N^4-(2-Methoxyphenyl)-N^3-morpholino-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*16,9*}

Light yellow solid; yield 30%; m.p. 249-251 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.11-3.18 (4H, m, CH_2NCH_2), 3.84-3.91 (4H, m, CH_2OCH_2), 3.99 (3H, s, OCH_3), 7.01 (1H, ddd, ^4J= 1.6 Hz, ^3J= 7.6 Hz, ^3J= 7.6 Hz, H-5″), 7.06 (1H, dd, ^4J= 1.8 Hz, ^3J= 8.0 Hz, H-3″), 7.12 (1H, ddd, ^4J= 1.6 Hz, ^3J= 7.2 Hz, ^3J= 7.8 Hz, H-4″), 8.42 (1H, s, H-6), 8.44 (1H, s, NH), 8.79 (1H, dd, ^4J= 1.7 Hz, ^3J= 7.8 Hz, H-6″), 13.10 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 52.0 (OCH_3), 55.9 (CH_2NCH_2), 66.1 (CH_2OCH_2), 93.7 (C-3a), 110.6, 119.7, 120.5, 123.0, 127.8, 147.7 (C-3), 151.6, 153.7 (C-6), 154.8 (C-4), 155.9 (C-7a). Anal. Calcd for $C_{16}H_{18}N_6O_2$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.72; H, 5.69; N, 25.57.

N^4-(3-Methoxyphenyl)-N^3-morpholino-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*16,10*}

Yellow solid; yield 55%; m.p. 252-254 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.10-3.20 (4H, m, CH_2NCH_2), 3.78 (3H, s, OCH_3), 3.78-3.85 (4H, m, CH_2OCH_2), 6.65-6.75 (1H, m, H-4″), 7.20-7.55 (3H, m, H-2″, H-5″ and H-6″), 8.30 (1H, s, H-6), 8.38 (1H, s, NH), 12.99 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 51.4 (OCH_3), 55.0 (CH_2NCH_2), 65.6 (CH_2OCH_2), 93.3 (C-3a), 106.6, 108.4, 112.9, 129.4, 139.9, 151.5 (C-3), 154.2 (C-6), 155.2 (C-4), 155.6 (C-7a), 159.5. Anal. Calcd for $C_{16}H_{18}N_6O_2$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.75; H, 5.72; N, 25.52.

N^4-(4-Methylphenyl)-N^3-(N-methylpiperazino)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*17,7*}

White solid; yield 31%; m.p. 228-230 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.26 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.48-2.57 (4H, m, CH_2NCH_2), 3.12-3.17 (4H, m, CH_2NCH_2), 7.19 (2H,

d, ^{3}J = 8.1 Hz, H-3′ and H-5′), 7.65 (2H, d, ^{3}J = 8.4 Hz, H-2′ and H-6′), 8.05 (1H, s, NH), 8.33 (1H, s, H-6), 12.90 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 45.7 (CH_3), 51.0 (CH_2NCH_2), 54.2 (CH_2NCH_2), 93.1 (C-3a), 120.4 (2C), 129.1 (2C), 132.3, 136.1, 151.7 (C-3), 154.2 (C-6), 155.1 (C-4), 155.7 (C-7a). Anal. Calcd for $C_{17}H_{21}N_7$: C, 63.14; H, 6.55; N, 30.32. Found: C, 62.93; H, 6.72; N, 30.06.

N^4-(4-Fluorophenyl)-N^3-indolino-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*18,2*}

Light brown solid; yield 46%; m.p. 273-275 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.15 (2H, t, ^{3}J = 9.2 Hz, H-3′), 4.01 (2H, t, ^{3}J = 8.3 Hz, H-2′), 6.66 (1H, d, ^{3}J = 7.8 Hz, H-7′), 6.78 (1H, t, ^{3}J = 7.4 Hz, H-5′), 7.00 (1H, t, ^{3}J = 7.7 Hz, H-6′), 7.14 (2H, dd, $^{3}J_{HF}$ = 8.9 Hz, $^{3}J_{HH}$ = 8.9 Hz, H-3″ and H-5″), 7.22 (1H, d, ^{3}J = 7.2 Hz, H-4′), 7.51 (2H, dd, $^{4}J_{HF}$ = 5.0 Hz, $^{3}J_{HH}$ = 9.1 Hz, H-2″ and H-6″), 8.24 (1H, s, NH), 8.35 (1H, s, H-6), 13.27 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.0 (H-3′), 53.1 (H-2′), 94.9 (C-3a), 108.9, 114.9 (d, $^{2}J_{CF}$ = 22.4 Hz, C-3″ and C-5″), 119.6, 124.2 (d, $^{3}J_{CF}$ = 8.1 Hz, C-2″ and C-6″), 124.7, 126.8 (2C), 130.8 (2C), 134.7 (d, $^{4}J_{CF}$ = 2.4 Hz, C-1″), 144.1, 148.1 (C-3), 154.3 (C-6), 155.2 (C-4), 155.6 (C-7a), 158.5 (d, $^{1}J_{CF}$ = 240.6 Hz, C-4″). Anal. Calcd for $C_{19}H_{15}FN_6$: C, 65.89; H, 4.37; N, 24.26. Found: C, 65.65; H, 4.53; N, 23.98.

N^4-(4-Chlorophenyl)-N^3-indolino-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*18,4*}

Brown solid; yield 36%; m.p. 270-272 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.15 (2H, t, ^{3}J = 8.2 Hz, H-3′), 4.01 (2H, t, ^{3}J = 8.3 Hz, H-2′), 6.64 (1H, d, ^{3}J = 8.3 Hz, H-7′), 6.77 (1H, t, ^{3}J = 7.0 Hz, H-5′), 6.98 (1H, t, ^{3}J = 7.3 Hz, H-6′), 7.22 (1H, d, ^{3}J = 7.2 Hz, H-4′), 7.34 (2H, d, ^{3}J = 8.9 Hz, H-3″ and H-5″), 7.55 (2H, d, ^{3}J = 8.9 Hz, H-2″ and H-6″), 8.30 (1H, s, NH), 8.39 (1H, s, H-6), 13.30 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.0 (H-3′), 53.1 (H-2′), 95.1 (C-3a), 108.8, 119.6, 123.2 (2C), 124.7, 126.8, 127.2 (2C), 128.2, 130.8, 137.5, 144.0, 148.0 (C-3), 154.0

(C-6), 155.2 (C-4), 155.6 (C-7a). Anal. Calcd for $C_{19}H_{15}ClN_6$: C, 62.90; H, 4.17; N, 23.16. Found: C, 62.74; H, 4.36; N, 22.93.

N^4-(4-Bromophenyl)-N^3-indolino-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*18,5*}

Light brown solid; yield 53%; m.p. 286-288 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.14 (2H, t, ^3J = 8.2 Hz, H-3′), 4.01 (2H, t, ^3J = 8.3 Hz, H-2′), 6.64 (1H, d, ^3J = 7.8 Hz, H-7′), 6.77 (1H, t, ^3J = 7.0 Hz, H-5′), 6.98 (1H, t, ^3J = 7.3 Hz, H-6′), 7.22 (1H, d, ^3J = 7.1 Hz, H-4′), 7.46 (2H, d, ^3J = 9.2 Hz, H-2″ and H-6″), 7.50 (2H, d, ^3J = 9.1 Hz, H-3″ and H-5″), 8.32 (1H, s, NH), 8.40 (1H, s, H-6), 13.31 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.0 (C-3′), 53.0 (C-2′), 95.1 (C-3a), 108.8, 115.3, 119.6, 123.5 (2C), 124.7, 126.8, 130.8 (2C), 131.1, 137.9, 143.9, 147.9 (C-3), 153.9 (C-6), 155.2 (C-4), 155.6 (C-7a). Anal. Calcd for $C_{19}H_{15}BrN_6$: C, 56.03; H, 3.71; N, 20.64. Found: C, 55.86; H, 3.89; N, 20.35.

N^3-Indolino-N^4-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*18,7*}

White solid; yield 67%; m.p. 276-278 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (3H, s, CH_3), 3.16 (2H, t, ^3J = 8.2 Hz, H-3′), 4.02 (2H, t, ^3J = 8.3 Hz, H-2′), 6.63 (1H, d, ^3J = 7.8 Hz, H-7′), 6.79 (1H, t, ^3J = 7.0 Hz, H-5′), 7.00 (1H, t, ^3J = 7.3 Hz, H-6′), 7.10 (2H, d, ^3J = 8.3 Hz, H-3″ and H-5″), 7.23 (1H, d, ^3J = 7.1 Hz, H-4′), 7.37 (2H, d, ^3J = 8.4 Hz, H-2″ and H-6″), 7.96 (1H, s, NH), 8.36 (1H, s, H-6), 13.26 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 28.0 (H-3′), 53.1 (H-2′), 95.0 (C-3a), 108.7, 119.7, 121.8 (2C), 124.8, 126.9, 128.8 (2C), 130.8, 132.8, 135.8, 144.0, 148.1 (C-3), 154.2 (C-6), 155.2 (C-4), 155.8 (C-7a). Anal. Calcd for $C_{20}H_{18}N_6$: C, 70.16; H, 5.30; N, 24.54. Found: C, 69.98; H, 5.43; N, 24.32.

N^3-Indolino-N^4-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*18,11*}

Light brown solid; yield 68%; m.p. 259-261 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.15 (2H, t, ^3J = 8.3 Hz, H-3′), 3.73 (3H, s, OCH_3), 4.01 (2H, t, ^3J = 8.2 Hz, H-2′), 6.64 (1H, d, ^3J = 7.8

Hz, H-7′), 6.78 (1H, t, ^3J = 7.3 Hz, H-5′), 6.88 (2H, d, ^3J = 8.9 Hz, H-3″ and H-5″), 7.02 (1H, t, ^3J = 7.6 Hz, H-6′), 7.22 (1H, d, ^3J = 7.2 Hz, H-4′), 7.37 (2H, d, ^3J = 8.9 Hz, H-2″ and H-6″), 8.00 (1H, s, NH), 8.31 (1H, s, H-6), 13.22 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.0 (H-3′), 53.1 (H-2′), 55.1 (OCH_3), 94.8 (C-3a), 108.7, 113.6 (2C), 119.6, 124.1 (2C), 124.8, 126.8, 130.8, 131.2, 144.1, 148.2 (C-3), 154.4 (C-6), 155.2 (C-4), 155.8 (C-7a), 155.9. Anal. Calcd for $C_{20}H_{18}N_6O$: C, 67.02; H, 5.06; N, 23.45. Found: C, 66.89; H, 5.23; N, 23.18.

N^4-Benzyl-N^3-indolino-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*18,14*}

White solid; yield 77%; m.p. 238-240 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.13 (2H, t, ^3J = 8.2 Hz, H-3′), 3.95 (2H, t, ^3J = 8.2 Hz, H-2′), 4.72 (2H, d, ^3J = 6.1 Hz, CH_2), 6.56 (1H, d, ^3J = 7.8 Hz, H-7′), 6.75 (1H, t, ^3J = 7.0 Hz, H-5′), 6.96 (1H, t, ^3J = 7.3 Hz, H-6′), 7.11 (1H, t, ^3J = 6.1 Hz, H-6), 7.16-7.31 (6H, m, Ph and H-4′), 8.23 (1H, s, H-6), 13.07 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.1 (H-3′), 43.2 (CH_2), 53.3 (H-2′), 94.6 (C-3a), 109.1, 119.5, 124.6, 126.5, 126.8, 127.0 (2C), 128.1 (2C), 130.6, 139.5, 144.5, 148.7 (C-3), 154.9 (C-6), 156.0 (C-4), 156.1 (C-7a). Anal. Calcd for $C_{20}H_{18}N_6$: C, 70.16; H, 5.30; N, 24.54. Found: C, 70.04; H, 5.41; N, 24.38.

N^4-(4-Chlorobenzyl)-N^3-indolino-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **5**{*18,16*}

White solid; yield 80%; m.p. 253-255 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.13 (2H, t, ^3J = 8.1 Hz, H-3′), 3.95 (2H, t, ^3J = 8.2 Hz, H-2′), 4.69 (2H, d, ^3J = 6.1 Hz, CH_2), 6.55 (1H, d, ^3J = 7.8 Hz, H-7′), 6.76 (1H, t, ^3J = 7.3 Hz, H-5′), 6.98 (1H, t, ^3J = 7.5 Hz, H-6′), 7.17-7.24 (2H, m, H-4′ and NH), 7.31 (2H, d, ^3J = 8.8 Hz, H-2″ and H-6″), 7.35 (2H, d, ^3J = 8.8 Hz, H-3″ and H-5″), 8.22 (1H, s, H-6), 13.08 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.1 (H-3′), 42.6 (CH_2), 53.2 (H-2′), 94.6 (C-3a), 109.1, 119.5, 124.6, 126.8, 128.0 (2C), 128.9 (2C), 130.6, 131.0, 138.6, 144.5, 148.7 (C-3), 154.9 (C-6), 155.9 (C-4), 156.0 (C-7a). Anal. Calcd for $C_{20}H_{17}ClN_6$: C, 63.74; H, 4.55; N, 22.30. Found: C, 63.58; H, 4.29; N, 22.04.

General method for the synthesis of 6-alkyl-*N*^{4}-(4-methylphenyl)-*N*^{3}-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-3,4-diamines (7)

The substituted pyrazole (199 mg, 1 mmol), trimethyl orthoesters (3 mmol), and *p*-toluidine (321 mg, 3 mmol) was added to toluene (2 mL) in a 10 mL seamless pressure vial. The reaction mixture was irradiated in a Discover SP (CEM) microwave reactor operating at maximal microwave power of 150 W and pressure of 435 psi at 200 °C for 55 minutes. After cooling, the precipitated product was isolated by vacuum filtration and recrystallised using an appropriate solvent.

6-Methyl-N^4-(4-methylphenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **7**{*1,7,1*}

White solid; yield 47%; m.p. 285-287 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30 (3H, s, CH_3), 2.42 (3H, s, CH_3), 6.85 (1H, t, ^3J = 7.3 Hz, H-4′), 7.18 (2H, d, ^3J = 8.3 Hz, H-3″ and H-5″), 7.26 (2H, t, ^3J = 7.9 Hz, H-3′ and H-5′), 7.50 (2H, d, ^3J = 7.8 Hz, H-2′ and H-6′), 7.57 (2H, d, ^3J = 8.4 Hz, H-2″ and H-6″), 8.61 (1H, s, NH), 8.69 (1H, s, NH), 12.60 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (CH_3), 25.7 (CH_3), 90.2 (C-3a), 116.3 (2C), 119.6, 122.1 (2C), 128.7 (2C), 128.9 (2C), 132.5, 136.3, 142.6, 143.0 (C-3), 153.8 (C-4), 156.0 (C-7a), 164.4 (C-6). Anal. Calcd for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 68.92; H, 5.63; N, 25.29.

6-Ethyl-N^4-(4-methylphenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **7**{*1,7,2*}

Yellow solid; yield 31%; m.p. 277-279 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (3H, t, ^3J = 7.6 Hz, $CH_2C\underline{H}_3$), 2.30 (3H, s, CH_3), 2.71 (2H, q, ^3J = 7.6 Hz, $C\underline{H}_2CH_3$), 6.85 (1H, t, ^3J = 7.3 Hz, H-4′), 7.18 (2H, d, ^3J = 8.3 Hz, H-3″ and H-5″), 7.26 (2H, t, ^3J = 7.9 Hz, H-3′ and H-5′), 7.50 (2H, d, ^3J = 7.7 Hz, H-2′ and H-6′), 7.61 (2H, d, ^3J = 8.4 Hz, H-2″ and H-6″), 8.63 (1H, s, NH), 8.69 (1H, s, NH), 12.64 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.3 ($CH_2\underline{C}H_3$), 20.4 (CH_3), 31.9 ($\underline{C}H_2CH_3$), 90.4 (C-3a), 116.3 (2C), 119.6, 121.8 (2C), 128.7 (2C), 128.8 (2C), 132.3,

136.4, 142.6, 143.0 (C-3), 153.8 (C-4), 156.1 (C-7a), 168.5 (C-6). Anal. Calcd for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.40. Found: C, 69.58; H, 5.98; N, 24.23.

N^4-(4-Methylphenyl)-N^3-phenyl-6-propyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **7**{*1,7,3*}

Light yellow solid; yield 22%; m.p. 205-207 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.93 (3H, t, ^3J = 7.4 Hz, $CH_2CH_2C\underline{H_3}$), 1.77 (2H, m, ^3J = 7.4 Hz, $CH_2C\underline{H_2}CH_3$), 2.30 (3H, s, CH_3), 2.66 (2H, t, ^3J = 7.4 Hz, $C\underline{H_2}CH_2CH_3$), 6.85 (1H, t, ^3J = 7.3 Hz, H-4′), 7.17 (2H, d, ^3J = 8.2 Hz, H-3″ and H-5″), 7.26 (2H, t, ^3J = 7.9 Hz, H-3′ and H-5′), 7.50 (2H, d, ^3J = 7.8 Hz, H-2′ and H-6′), 7.59 (2H, d, ^3J = 8.6 Hz, H-2″ and H-6″), 8.62 (1H, s, NH), 8.69 (1H, s, NH), 12.63 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.7 ($CH_2CH_2\underline{C}H_3$), 20.4 ($CH_2\underline{C}H_2CH_3$ and CH_3), 20.8 ($\underline{C}H_2CH_2CH_3$), 90.4 (C-3a), 116.3 (2C), 119.6, 121.8 (2C), 128.7 (2C), 128.8 (2C), 132.3, 136.4, 142.6, 143.0 (C-3), 153.8 (C-4), 156.0 (C-7a), 167.5 (C-6). Anal. Calcd for $C_{21}H_{22}N_6$: C, 70.37; H, 6.19; N, 23.45. Found: C, 70.24; H, 6.36; N, 23.27.

6-Butyl-N^4-(4-methylphenyl)-N^3-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,4-diamine **7**{*1,7,4*}

Light yellow solid; yield 33%; m.p. 188-190 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.91 (3H, t, ^3J = 7.3 Hz, $CH_2CH_2CH_2C\underline{H_3}$), 1.35 (2H, m, ^3J = 7.4 Hz, $CH_2CH_2C\underline{H_2}CH_3$), 1.74 (2H, m, ^3J = 7.5 Hz, $CH_2C\underline{H_2}CH_2CH_3$), 2.30 (3H, s, CH_3), 2.68 (2H, t, ^3J = 7.4 Hz, $C\underline{H_2}CH_2CH_2CH_3$), 6.85 (1H, t, ^3J = 7.3 Hz, H-4′), 7.17 (2H, d, ^3J = 8.3 Hz, H-3″ and H-5″), 7.26 (2H, t, ^3J = 7.9 Hz, H-3′ and H-5′), 7.50 (2H, d, ^3J = 7.7 Hz, H-2′ and H-6′), 7.59 (2H, d, ^3J = 8.4 Hz, H-2″ and H-6″), 8.62 (1H, s, NH), 8.69 (1H, s, NH), 12.62 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.8 ($CH_2CH_2CH_2C\underline{H_3}$), 20.4 ($CH_2CH_2C\underline{H_2}CH_3$), 21.8 ($CH_3$), 29.7 ($CH_2C\underline{H_2}CH_2CH_3$), 38.2 ($C\underline{H_2}CH_2CH_2CH_3$), 90.4 (C-3a), 116.3 (2C), 119.6, 121.8 (2C), 128.7 (2C), 128.8 (2C), 132.3, 136.4, 142.6, 143.0 (C-3), 153.8 (C-4), 156.0 (C-7a), 167.7 (C-6). Anal. Calcd for $C_{22}H_{24}N_6$: C, C, 70.94; H, 6.49; N, 22.56. Found: C, 70.78; H, 6.64; N, 22.35.

X-ray crystallographic analysis

Crystals were obtained for **5**{*1*,*18*}, **5**{*2*,*3*}, **5**{*4*,*10*} and **5**{*7*,*7*}, with those of **5**{*2*,*3*} and **5**{*4*,*10*} as 1:1 methanol solvates -perhaps more details of the crystallisation conditions can be added here??? Crystal data are given in ESI† Table 3. X-ray intensity data were measured at T = 100 K on Rigaku/Oxford Diffraction XtaLAB Synergy diffractometer (Dualflex, AtlasS2) fitted with CuKα radiation (λ = 1.54178 Å). Data reduction and Gaussian absorption correction were accomplished with CrysAlisPro.[x1] The structures were solved by direct-methods[x2] and refined (anisotropic displacement parameters and C-bound H atoms in the riding model approximation) on F^2.[x3] The N-bound H atoms were refined with the N–H bond lengths constrained to 0.88 ± 0.01 Å, and with U_{iso}(H) = 1.2U_{eq}(N). A weighting scheme of the form $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$) was introduced towards the end of the refinement in each case. Molecular structure diagrams were generated with ORTEP for Windows[x4] with 70% displacement ellipsoids, and the packing diagrams were drawn with DIAMOND.[x5] Additional data analysis was made with PLATON.[x6]

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MTS cell viability assessment assay

The 114 synthesised compounds were tested against the chronic myelogenous leukaemia cell line (K562), acute T cell leukemia (Jurkat T), and non-cancerous fibroblast cell (MRC-5) by the MTS colorimetric assay. The three cell lines were grown in RPMI supplemented with 10% fetal bovine serum (FBS) and 1% pen-strep antibiotic. For the cytotoxic assay, 15 to 20 x 10^3 cells per mL were seeded in 96-well plates and the plates were incubated overnight in a humided air atmosphere at 37 C in 5% CO_2 incubator. The cells were then treated with compounds at different concentrations. After 72 h of incubation, the mixture of PMS and MTS in a ratio of 1: 10 was added to wells to make up a final concentration of 0.2 mg/mL MTS in each well, followed by 2 h of incubation. The absorbance values were measured at 490 nm using the Molecular Devices SpectraMax iD3 multi-mode microplate reader. The percentage of cell viability was calculated using the formula: ($OD_{treated}/OD_{untreated}$ x 100%) taking into account of vehicle control untreated cells. Growth inhibitory values (GI_{50}) were obtained using GraphPad Prism 7 (GraphPad Software, San Diego, USA) by nonlinear regression analysis. The three chemotherapeutic drugs were used as positive controls: 6-mercaptopurine, methotrexate, and cytarabine. Three independent experiments were carried out and the data was expressed as meeand and mean standard error (SEM).

Conflicts of interest

There are no conflicts to declare.

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