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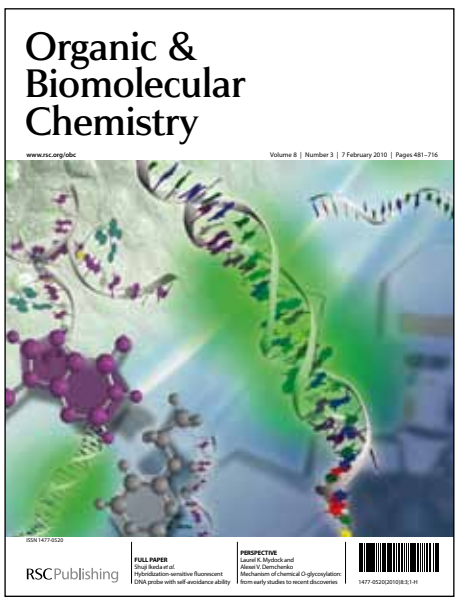

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DOI: 10.1039/C3OB41146J

ARTICLE TYPE

Synthesis of novel pyrazole-based heterocycles via a copper(II)-catalysed domino annulation

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Pyrazole-based β-aminonitriles and β-amino-carbaldehydes as bifunctional building blocks are introduced in a facile copper(II)-catalysed one-pot domino generation of multiple *N*-containing heterobi- and tricycles. This streamlined synthetic approach permits easy access to novel pyrazole-fused imidazo- and pyrimido[1,2-*c*]pyrimidinones and to pyrazolo[3,4-*d*]pyrimidinone species with isolated yields up to 90%. The present study also reveals a unique amine-isocyanate coupling promotion via copper(II)-based catalytic activation.

Introduction

Domino transformations, as multi-step one-pot processes, are effective tools in organic synthesis, allowing the formation of several new bonds in a simple and elegant one-pot synthetic operation, thereby providing access to various types of molecular entities.[1] In order to design and achieve efficient tandem processes, polifunctional building blocks, such as β-aminonitriles are needed to be employed.[1,2]

The benefits of bifuncional β-aminonitriles containing pyrazole ring can be exploited in their use as valuable synthons in the construction of multiple *N*-containing heterocycles, such as tacrine analogues through the Friedländer reaction, or pyrazolo[3,4-*d*]pyrimidines via a Dimroth rearrangement.[3,4] (Figure 1).[2] Moreover, concerning the medicinal chemistry aspects, pyrazole scaffolds (*e.g.* Celebrex®) are of great pharmaceutical interest due to their extensively studied biological and medicinal properties, including selective COX-2 inhibition and antiviral activities.[10,11]

The common feature of these transformations is the amine-electrophile coupling step, which depends on the correlated chemical character of the reactants and determines the reaction outcome. Reactivity profiles and parameters of several aromatic *N*-nucleophiles in different chemical processes have already been determined.[5-9] It is to be noted, that we are not aware of previous quantitative investigations on the nucleophilic behaviour of amino-substituted pyrazole scaffolds reacted with isocyanates as electrophile agents.

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

In case of relatively weak aromatic nucleophiles (*e.g.* 5-aminopyrazoles), the catalytic activation of the electrophilic coupling partners may be needed to improve the efficiency.

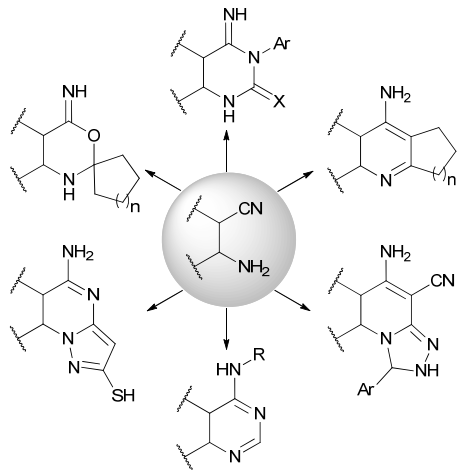

Figure. **1** Applicability of β-aminonitrile building blocks.

In the present article, we report a facile Lewis acid-catalysed domino transformation of substituted 5-amino-1*H*-pyrazole-4-carbonitriles and carbaldehydes with chloroalkyl isocyanates to give novel pyrazolo[3,4-*d*]pyrimidine unit-based heterobi- and tricycles. The study also points out the synthetic potential of bifunctional building blocks to readily construct *N*,*N*-multiheterocycles through rapid domino processes.

Results and Discussion

Initial experiments were performed with 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitrile (**1a**) and 2-chloroethyl isocyanate (**2a**) in order to adjust the reaction parameters. Starting material **1a** was synthetized on the basis of literature data (see Supporting Information).[12] Preliminary trials indicated that neither the formation of the intermediate urea adduct **3a** nor that of the cyclic product **4a** could be detected, even after either conventional or

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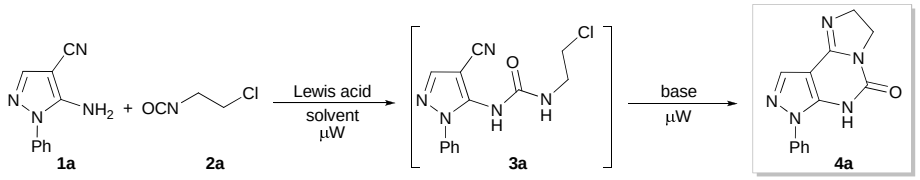
microwave heating, demonstrating the extremely low nucleophilic character of the examined amino function (Table 1, entries 1-4).

Various Lewis acids were therefore tested in catalytic quantities to promote the amine-isocyanate coupling (Table 1, entries 5-15). Rapid microwave-aided optimization revealed that the reaction was improved dramatically by copper(II) salts, which led to the exclusive formation of urea adduct **3a**. Among the catalysts tested, $Cu(OAc)_2$ was found to be the best, though $CuCl_2$ and $Cu(C_5HF_6O_2)_2$ also exhibited noteworthy catalytic efficiency (Table 1, entries 10-12). The dependence of the coupling conversion on the quantity of $Cu(OAc)_2$ applied was examined in the range 5-40 mol% under microwave conditions. Treatment of 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitrile (**1a**) with isocyanate **2a** in the presence of 10 mol% $Cu(OAc)_2$ for 5 min furnished the best result and led to adduct **3a** in an isolated yield of 90% (Table 1, entry 15). Reactions were monitored at different temperatures in the range 25-100 °C; quantitative conversions were observed at 80 °C with a 10 mol% catalyst load.

Various basic additives were next examined in order to trigger the domino ring-closure process (**4a**, Table 1, entries 20-30). Following completion of our study of copper-catalysed isocyanate-amine coupling, the subsequent experiments were focused on the one-pot sequence, and it was therefore not considered necessary to isolate the urea intermediates. The use of 1.2 equivalents of Cs_2CO_3 in a one-pot fashion was found to be the most effective way to obtain pyrazole-fused imidazo[1,2-*c*]pyrimidinone **4a** in a good yield (82%, Table 1, entry 30).

Table 1 Microwave-aided optimization of the model reaction.



Intermediate **3a**					Product **4a**				
Entry	Solvent	Catalyst	Base	Yield [%][a]	Entry	Solvent	Catalyst	Base	Yield [%][f]
1	DMF	–	–	0[b]	16	DMF	–	TEA	17[g]
2	Toluene	–	–	0[c]	17	DMF	–	DABCO	18[g]
3	MeCN	–	–	0[c]	18	MeCN	–	TEA	18[g]
4	DMF	–	–	0[c]	19	MeCN	–	DABCO	16[g]
5	DMF	AgOTf	–	0[d]	20	MeCN	$Cu(OAc)_2$	DABCO	33[h]
6	DMF	$In(OTf)_3$	–	0[d]	21	DMF	$Cu(OAc)_2$	DBU	trace[h]
7	DMF	Me_2SnCl_2	–	0[d]	22	DMF	$Cu(OAc)_2$	*t*BuOK	trace[h]
8	DMF	$InCl_3$	–	0[d]	23	DMF	$Cu(OAc)_2$	K_3PO_4	trace[h]
9	DMF	$FeCl_3$*$6H_2O$	–	0[d]	24	DMF	$Cu(OAc)_2$	TEA	10[h]
10	DMF	$CuCl_2$	–	70[d]	25	DMF	$Cu(OAc)_2$	DIPEA	13[h]
11	DMF	$Cu(C_5HF_6O_2)_2$	–	66[d]	26	DMF	$Cu(OAc)_2$	DABCO	45[h]
12	DMF	$Cu(OAc)_2$	–	81[d]	27	DMF	$Cu(OAc)_2$	NaOAc	trace[h]
13	MeCN	$Cu(OAc)_2$	–	81[d]	28	DMF	$Cu(OAc)_2$	K_2CO_3	trace[h]
14	DMF/H_2O	$Cu(OAc)_2$		0[d]	29	DMF	$Cu(OAc)_2$	NaOMe	40[h]
15	**DMF**	**$Cu(OAc)_2$**	–	**90[e]**	**30**	**DMF**	**$Cu(OAc)_2$**	**Cs_2CO_3**	**82[h]**

[a] Isolated yield of **3a** after flash chromatography.

[b] Reaction conditions: **1a** (1 mmol), **2a** (3 equiv.), DMF (1.5 mL), 150 °C, 1 day.

[c] Reaction conditions: **1a** (1 mmol), **2a** (3 equiv.), solvent (1.5 mL), μW: 300 W, 150 °C, 30 min.

[d] Reaction conditions: **1a** (1 mmol), **2a** (1.5 equiv.), catalyst (20 mol%), solvent (1.5 mL), μW: 150 W, 80 °C, 5 min.

[e] Optimized reaction conditions: **1a** (1 mmol), **2a** (1.5 equiv.), $Cu(OAc)_2$ (10 mol%), 4Å MS powder (100 mg), dry DMF (1.5 mL), μW: 150 W, 80 °C, 5 min.

[f] Isolated yield of **4a** after flash chromatography.

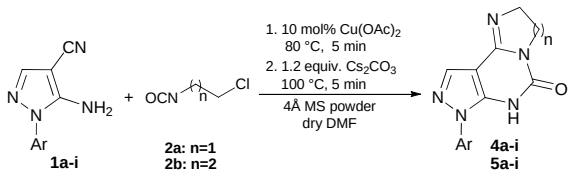
[g] Reaction conditions: **1a** (1 mmol), **2a** (3 equiv.), solvent (1.5 mL), base (3 equiv.), μW: 250 W, 125 °C, 20 min.

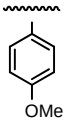
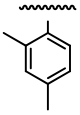
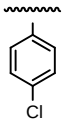
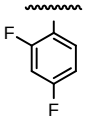
[h] Reaction conditions: **1a** (1 mmol), **2a** (1.5 equiv.), $Cu(OAc)_2$ (10 mol%), 4Å MS powder (100 mg), solvent (1.5 mL), μW_1: 150 W, 80 °C, 5 min; then base (1.2 equiv.), μW_2: 150 W, 100 °C, 5 min.

A comparative study of microwave versus conventional heating surprisingly revealed similar efficiencies in terms of reaction time, applied temperature and yield. In both cases, the amine-isocyanate coupling was completed in 5 min at 80 °C, with full conversion. Subsequent Cs_2CO_3-induced domino annulation was achieved in an additional 5 min at 100 °C, affording **4a** with an overall yield of 82%.

Interestingly, the use of tertiary amines without $Cu(OAc)_2$ in the reaction between **1a** and **2a** yielded tricyclic target compound **4a** in low yields (22-26%, Table 1, entries 16-19). The reaction might proceed via a tertiary amine-isocyanate activated complex,[13] but the open-chain intermediate **3a** could not be detected in the reaction mixture.[14]

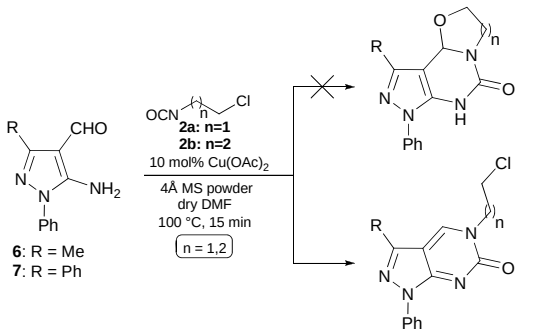
Table 2 Synthesis of tricyclic products **4a-i** and **5a-i**.



Entry	Product	Ar	Yield [%][a,b]
1	**4a**		82
2	**5a**		85
3	**4b**		82
4	**5b**		81
5	**4c**		79
6	**5c**		80
7	**4d**		84
8	**5d**		77
9	**4e**		86
10	**5e**		85
11	**4f**		83
12	**5f**		80
13	**4g**		79
14	**5g**		80
15	**4h**		90
16	**5h**		85
17	**4i**		82
18	**5i**		80

[a] Isolated yields of **4a-i** and **5a-i** after flash chromatography.
[b] Reaction conditions: **1a-i** (1 mmol), **2a** or **2b** (1.5 equiv.), $Cu(OAc)_2$ (10 mol%), 4Å MS powder (100 mg), dry DMF (1.5 mL), 80 °C, 5 min; then Cs_2CO_3 (1.2 equiv.), 100 °C, 5 min.

The well-established protocol was then adopted to synthetize a series of pyrazole-based tricyclic analogues (Table 2). β-Aminonitriles **1a-i** possessing electron-donating and/or electron-withdrawing groups were successfully reacted with chloroalkyl isocyanates **2a** and **2b** in the presence of 10 mol% $Cu(OAc)_2$ under thermal conditions (80 °C, 5 min, dry DMF). To induce the domino ring-closure, subsequent Cs_2CO_3 addition and a further 5 min at 100 °C afforded pyrazole-fused imidazo- and pyrimido[1,2-*c*]pyrimidinones **4a-i** and **5a-i**, in yields of 77-90% (Table 2, entries 1-18). The substitution pattern of the starting materials **1a-i** did not have an appreciable effect on the reaction outcome.

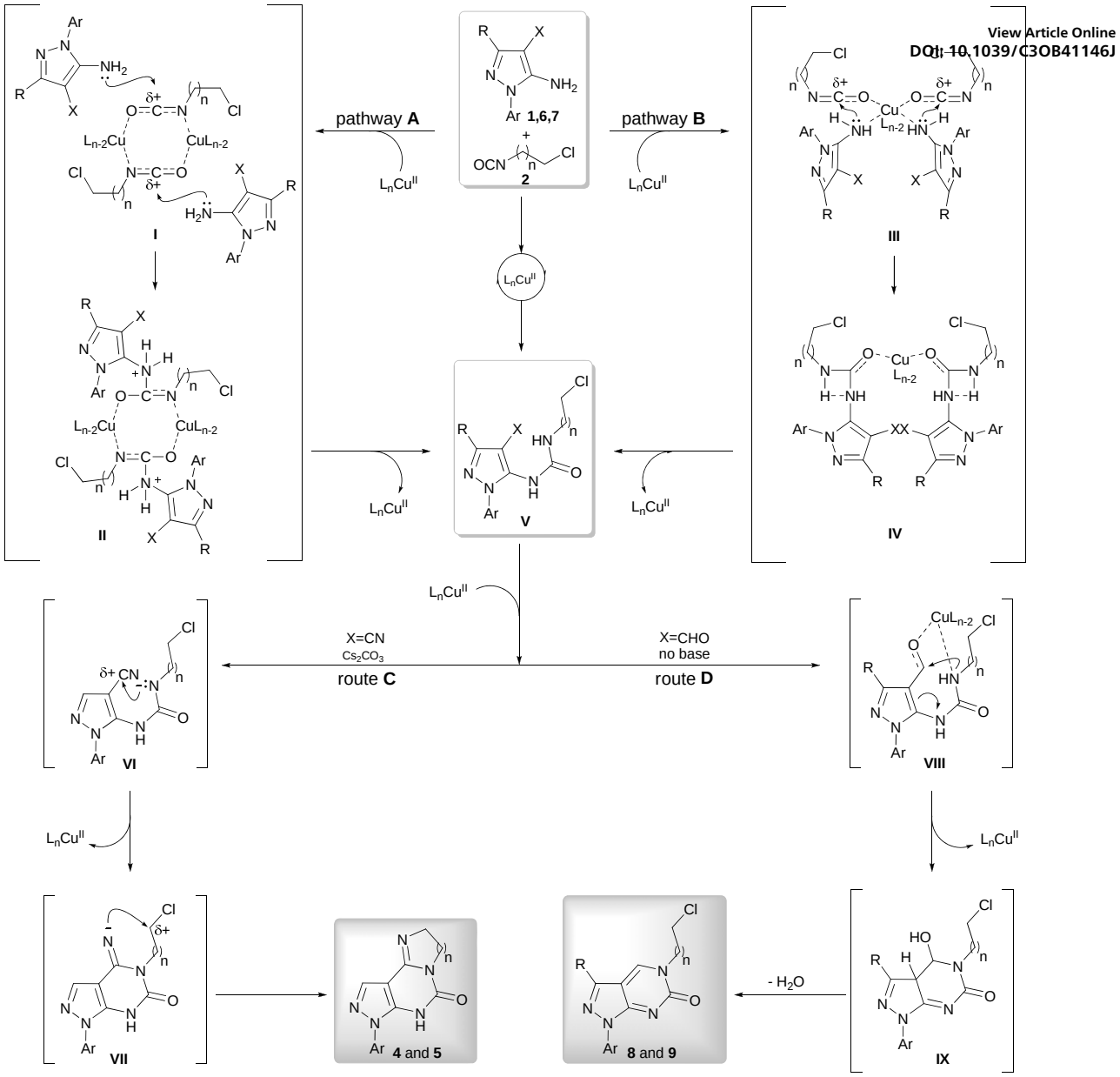


Scheme 1 Transformation of β-aminocarbaldehydes.

Experiments were then performed to reveal whether β-aminocarbaldehydes as bifunctional building blocks can be subjected to a copper(II)-catalysed domino transformation with chloroalkyl isocyanates. Starting materials **6** and **7** were synthetized via a Vilsmeier-Haack reaction – aza-functionalization – chemoselective reduction strategy based on reported data.[15] With the previously described two-step, one-pot concept, reactions between β-aminocarbaldehydes **6** and **7** and chloroalkyl isocyanates **2a** and **2b** were also investigated. Interestingly, a copper(II)-induced single cyclisation process was observed both under microwave conditions and on conventional heating, furnishing pyrazolo[3,4-*d*]pyrimidin-6(5*H*)-ones **8a**, **8b**, **9a** and **9b** exclusively, instead of the anticipated tricycle (Scheme 1). It should be mentioned that the presence of Cs_2CO_3 led to complex reaction mixtures, whereas in the absence of the copper(II)-salt no reaction occurred. This transformation can be regarded as an easy and elegant access route to pyrazolo[3,4-*d*]pyrimidin-6(5*H*)-one frameworks.[16]

Possible catalytic cycles of the copper-catalyzed amine-isocyanate coupling and the following domino processes are depicted in Scheme 2. Considerable interest has been demonstrated in copper-mediated transformations due to their wide-ranging applicability, including C-N, C-O and C-C bond formation reactions.[17] Theoretical and experimental studies on intermediate copper(II)-isocyanate complexes in a copper(II)-catalysed urethane formation were earlier described, and such intermediates might explain the specific activator effect on the above-mentioned coupling process.[18,19]

In pathway **A**, copper(II) is introduced as a dinuclear core in complex **I,** leading to cyclic conjugation and a reduced electron density on the isocyanate carbon.[20] The attack by the 5-aminopyrazole derivative on the activated NCO carbon provides access to the amino-imidate-copper transition state **II**. An intramolecular *N*→*N* H-shift, followed by the release of copper, leads to urea adduct **V**.



Scheme 2 Possible catalytic cycles for copper-catalysed domino annulations.

Pathway **B** shows an alternative route, incorporating the amine and the isocyanate in a single copper-centred complex (**III**).[21] The 'cage-like' shape provides the requisite proximity between the amine and the coordinated isocyanate. The attack by the amino group on the activated carbon (**IV**), the subsequent *N*→*N* H-shift and the degradation of the copper complex generates urea intermediate **V**.

Intermediate **V** undergoes deprotonation, which induces an intramolecular nucleophilic attack on the nitrile carbon atom (route **C**). The base-induced first ring-closure gives reactive amino-imidate species **VII**, which undergo a further annulation via an intramolecular S_N2 reaction, affording target compounds **4** or **5**.

As regards β-aminocarbaldehydes **6** and **7**, a copper salt-generated electron shift leads to activation of the formyl group, thereby improving the reactivity (**VIII**) and initiating the spontaneous ring-closure reaction in the absence of base (route **D**). Subsequent tautomeric equilibrium, followed by water elimination, provides pyrazolo[3,4-*d*]pyrimidin-6(5*H*)-one **8** or **9** and inhibits the *in situ* formation of the third ring, as displayed in Scheme 1.

Conclusions

In conclusion, we have described here an efficient copper(II)-catalysed two-step one-pot domino process for the rapid synthesis of novel *N*,*N*-multiheterocycles. The copper(II)-acetate-promoted amine-isocyanate coupling and Cs_2CO_3-induced one-pot domino

ring-closure process afforded 18 novel pyrazole-fused imidazo- and pyrimido[1,2-*c*]pyrimidinone scaffolds, with isolated yields of up to 90%. Copper(II)-acetate was also introduced as catalyst in the reactions of β-aminocarbaldehydes and chloroalkyl isocyanates, furnishing pyrazolo[3,4-*d*]pyrimidin-6(5*H*)-ones via a cyclocondensation procedure.

Experimental Section

General procedure for the synthesis of products 4a-i and 5a-i

To a mixture of 4-amino-1-aryl-1*H*-pyrazole-4-carbonitrile **1a-i** (1 mmol), chloroalkyl isocyanate **2a** or **2b** (1.5 mmol) and 4Å molecular sieve powder (100 mg) in 1.5 mL of dry DMF, anhydrous $Cu(OAc)_2$ (18 mg, 10 mol%) was added. The reaction vessel was placed in a preheated oil bath at 80 °C, and the contents were stirred for 5 min, monitored by TLC (eluent: *n*-hexane/EtOAc (1:1)). The resulting dark mixture was cooled down to room temperature. Cs_2CO_3 (423 mg, 1.2 mmol) was added, the reaction vessel was placed in a preheated oil bath at 100 °C and the mixture was stirred for an additional 5 min, monitored by TLC (eluent: *n*-hexane/EtOAc (1:2)). The suspension was then poured into ice and extracted with EtOAc (2×30 mL). The combined organic phases were extracted with brine (2×30 mL), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The crude product **4a-i** or **5a-i** was purified by flash chromatography, using *n*-hexane/EtOAc (1:1) as eluent.

Note: In the event of microwave irradiation, the following settings were applied: a standard 10 mL microwave vial; 1. μW $power_1$ (150 W), T_1 (80 °C), t_1 (5 min), ramping time (15 s); 2. μW $power_2$ (150 W), T_2 (100 °C), t_2 (5 min), ramping time (20 s).

1-(2-chloroethyl)-3-(4-cyano-1-phenyl-1H-pyrazol-5-yl)-urea (3a). White powder, (260 mg, 90%), mp 142-144 °C, $C_{13}H_{12}ClN_5O$; Elemental analysis: Calcd.: C, 53.89; H, 4.17; Cl, 12.24; N, 24.17; O, 5.52; Found: C, 53.92; H, 4.15; Cl, 12.27; N, 24.15; O, 5.50; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.35 (bs, 2H), 3.56 (bs, 2H), 6.94 (s, 1H), 7.29-7.76 (broad s, 4H), 8.17 (s, 1H), 8.91 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 41.5, 43.9, 88.4, 113.2, 124.4, 128.7, 129.4, 137.4, 142.1, 142.2, 153.8; MS (ES, pos. mode) m/z = 290.1 $[M + H]^+$.

7-phenyl-6,7-dihydro-2H-imidazo[1,2-c]pyrazolo[4,3-e]-pyrimidin-5(3H)-one (4a). White crystalline, (207 mg, 82%), mp 185-187 °C, $C_{13}H_{11}N_5O$; Elemental analysis: Calcd.: C, 61.65; H, 4.38; N, 27.65; O, 6.32; Found: C, 61.63; H, 4.36; N, 27.68; O, 6.34; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.39 (t, J = 7.5 Hz, 2H), 3.68 (t, J = 7.5 Hz, 2H), 7.31 (s, 1H), 7.45-7.57 (m, 5H), 8.28 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ; 37.9, 46.1, 88.8, 112.6, 124.0, 128.9, 129.5, 137.7, 142.5, 143.1, 157.9; MS (ES, pos. mode) m/z = 254.1 $[M + H]^+$.

8-phenyl-3,4,7,8-tetrahydropyrazolo[4,3-e]pyrimido[1,2-c]pyrimidin-6(2H)-one (5a). Pale-brown powder, (227 mg, 85%), mp 179-180 °C, $C_{14}H_{13}N_5O$; Elemental analysis: Calcd.: C, 62.91; H, 4.90; N, 26.20; O, 5.99; Found: C, 62.93; H, 4.93; N, 26.17; O, 5.97; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.78 (s, 2H), 3.16 (s, 2H), 3.44 (s, 2H), 7.10 (s, 1H), 7.42-7.66 (m, 5H), 8.25 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 21.5, 48.1, 90.0, 112.7, 123.8, 128.9, 129.4, 137.5, 142.1, 146.4, 152.6; MS (ES, pos. mode) m/z = 268.1 $[M + H]^+$.

7-(4-methoxyphenyl)-6,7-dihydro-2H-imidazo[1,2-c]pyrazolo[4,3-e]pyrimidin-5(3H)-one (4b). White crystalline, (232 mg, 82%), mp 197-199 °C, $C_{14}H_{13}N_5O_2$; Elemental analysis: Calcd.: C, 59.36; H, 4.63; N, 24.72; O, 11.30; Found: C, 59.34; H, 4.66; N, 24.70; O, 11.32; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.55 (t, J = 8.4 Hz, 2H), 3.70 (t, J = 8.4 Hz, 2H), 3.86 (s, 3H), 5.34 (s, 1H), 6.99 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.90 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 37.9, 46.1, 55.5, 88.5, 112.7, 114.5, 125.7, 130.5, 142.1, 143.0, 158.0, 159.4; MS (ES, pos. mode) m/z = 284.1 $[M + H]^+$.

8-(4-methoxyphenyl)-3,4,7,8-tetrahydropyrazolo[4,3-e]-pyrimido[1,2-c]pyrimidin-6(2H)-one (5b). Pale-brown powder, (240 mg, 81%), mp 189-190 °C, $C_{15}H_{15}N_5O_2$; Elemental analysis: Calcd.: C, 60.60; H, 5.09; N, 23.56; O, 10.76; Found: C, 60.62; H, 5.06; N, 23.59; O, 10.74; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.76 (bs, 2H), 3.15 (bs, 2H), 3.40 (bs, 2H), 7.04-7.12 (m, 3H), 7.38 (d, J = 8.6 Hz, 2H),8.20 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 21.5, 39.5 (*C*H_2, overlapped with DMSO signal), 48.0, 55.5, 89.6, 112.8, 114.5, 125.4, 130.4, 141.7, 146.2, 152.7, 159.4; MS (ES, pos. mode) m/z = 298.1 $[M + H]^+$.

7-(2-ethylphenyl)-6,7-dihydro-2H-imidazo[1,2-c]pyrazolo-[4,3-e]pyrimidin-5(3H)-one (4c). White powder, (222 mg, 79%), mp 162-164 °C, $C_{15}H_{15}N_5O$; Elemental analysis: Calcd.: C, 64.04; H, 5.37; N, 24.90; O, 5.69; Found: C, 64.01; H, 5.40; N, 24.87; O, 5.71; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.03 (t, J = 7.5 Hz, 3H), 2.34 (q, J = 7.4 Hz, 2H), 3.26 (t, J = 7.8 Hz, 2H), 3.45 (t, J = 7.4 Hz, 2H), 7.24 (s, 1H), 7.38-7.39 (m, 2H), 7.43-7.54 (m, 2H); 8.25 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 14.3, 23.2, 37.8, 45.9, 87.5, 112.9, 126.8, 127.3, 129.6, 130.4, 135.9, 140.9, 142.2, 144.2, 157.6; MS (ES, pos. mode) m/z = 282.1 $[M + H]^+$.

***8-(2-ethylphenyl)-3,4,7,8-tetrahydropyrazolo[4,3-e]pyr-imido[1,2-c]pyrimidin-6(2H)-one (5c)*.** White powder, (236 mg, 80%), mp 127-128 °C, $C_{16}H_{17}N_5O$; Elemental analysis: Calcd.: C, 65.07; H, 5.80; N, 23.71; O, 5.42; Found: C, 65.09; H, 5.82; N, 23.68; O, 5.39; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.06 (t, J = 6.9 Hz, 3H), 1.65 (bs, 2H), 2.37 (d, J = 7.1 Hz, 2H), 3.06 (bs, 2H), 3.35 (bs, 2H), 6.99 (s, 1H), 7.22-7.40 (m, 2H), 7.40-7.56 (m, 2H); 8.23 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 14.4, 21.5, 23.1, 39.5 (*C*H_2, overlapped with DMSO signal), 48.0, 89.0, 112.9, 126.4, 126.8, 129.5, 130.2, 135.6, 141.1, 141.7, 147.4, 152.4; MS (ES, pos. mode) m/z = 296.1 $[M + H]^+$.

7-(2,4-dimethylphenyl)-6,7-dihydro-2H-imidazo[1,2-c]-pyrazolo[4,3-e]pyrimidin-5(3H)-one (4d). White powder, (236 mg, 84%), mp 203-205 °C, $C_{15}H_{15}N_5O$; Elemental analysis: Calcd.: C, 64.04; H, 5.37; N, 24.90; O, 5.69; Found: C, 64.02; H, 5.39; N, 24.88; O, 5.71;^{1}H NMR (500 MHz, DMSO-d_6): δ 1.99 (s, 3H), 2.33 (s, 3H), 3.21-3.37 (m, 2H), 3.44-3.60 (m, 2H), 7.09-7.34 (m, 4H), 8.23 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 16.8, 20.7, 37.8, 45.8, 87.3, 112.9, 126.8, 127.3, 131.6, 134.1, 134.9, 139.7, 142.3, 144.0, 157.6; MS (ES, pos. mode) m/z = 282.1 $[M + H]^+$.

8-(2,4-dimethylphenyl)-3,4,7,8-tetrahydropyrazolo[4,3-e]-pyrimido[1,2-c]pyrimidin-6(2H)-one (5d). White powder, (227 mg, 77%), mp 165-166 °C, $C_{16}H_{17}N_5O$; Elemental analysis: Calcd.: C, 65.07; H, 5.80; N, 23.71; O, 5.42; Found: C, 65.04; H, 5.84; N, 23.67; O, 5.45; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.61-1.77 (m, 2H), 2.02 (s, 3H), 2.32 (s, 3H), 3.01-3.14 (m, 2H), 3.33-

3.47 (m, 2H), 6.95 (s, 1H), 7.07-7.26 (m, 3H), 8.21 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 17.0, 20.7, 21.5, 39.5 (*C*H_2, overlapped with DMSO signal), 48.0, 88.7, 113.0, 126.5, 126.9, 131.7, 133.8, 135.1, 139.5, 141.7, 147.3, 152.4; MS (ES, pos. mode) *m/z* = 296.1 $[M + H]^+$.

7-(4-chlorophenyl)-6,7-dihydro-2H-imidazo[1,2-c]pyrazolo-[4,3-e]pyrimidin-5(3H)-one (4e). Light yellow powder, (247 mg, 86%), mp 202-204 °C, $C_{13}H_{10}ClN_5O$; Elemental analysis: Calcd.: C, 54.27; H, 3.50; Cl, 12.32; N, 24.34; O, 5.56; Found: C, 54.29; H, 3.48; Cl, 12.34; N, 24.32; O, 5.58; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.42 (t, *J* = 8.0 Hz, 2H), 3.76 (t, *J* = 7.6 Hz, 2H), 7.34 (s, 1H), 7.54-7.63 (m, 4H), 8.29 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 37.9, 46.0, 88.5, 112.5, 125.7, 129.5, 133.3, 136.7, 142.7, 143.3, 157.6; MS (ES, pos. mode) *m/z* = 288.0 $[M + H]^+$.

8-(4-chlorophenyl)-3,4,7,8-tetrahydropyrazolo[4,3-e]pyr-imido[1,2-c]pyrimidin-6(2H)-one (5e). Pale-yellow powder, (256 mg, 85%), mp 216-218 °C, $C_{14}H_{12}ClN_5O$; Elemental analysis: Calcd.: C, 55.73; H, 4.01; Cl, 11.75; N, 23.21; O, 5.30; Found: C, 55.70; H, 4.04; Cl, 11.73; N, 23.23; O, 5.32; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.79-1.88 (m, 2H), 3.14-3.21 (m, 2H), 3.48-3.57 (m, 2H), 7.12 (s, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 8.27 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 21.5, 48.1, 89.9, 112.6, 125.5, 129.5, 133.3, 136.5, 142.3, 146.6, 152.4; MS (ES, pos. mode) *m/z* = 302.1 $[M + H]^+$.

7-(3-chlorophenyl)-6,7-dihydro-2H-imidazo[1,2-c]pyrazolo-[4,3-e]pyrimidin-5(3H)-one (4f). White powder, (238 mg, 83%), mp 188-189 °C, $C_{13}H_{10}ClN_5O$; Elemental analysis: Calcd.: C, 54.27; H, 3.50; Cl, 12.32; N, 24.34; O, 5.56; Found: C, 54.29; H, 3.48; Cl, 12.34; N, 24.33; O, 5.57; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.43 (t, *J* = 7.6 Hz, 2H), 3.80 (t, *J* = 7.3 Hz, 2H), 7.37 (s, 1H), 7.46-7.71 (m, 4H), 8.31 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 38.0, 46.0, 88.5, 112.5, 122.6, 123.8, 128.8, 131.1, 133.5, 139.0, 142.9, 143.4, 157.6; MS (ES, pos. mode) *m/z* = 288.1 $[M + H]^+$.

8-(3-chlorophenyl)-3,4,7,8-tetrahydropyrazolo[4,3-e]pyr-imido[1,2-c]pyrimidin-6(2H)-one (5f). White powder, (241 mg, 80%), mp 196-198 °C, $C_{14}H_{12}ClN_5O$; Elemental analysis: Calcd.: C, 55.73; H, 4.01; Cl, 11.75; N, 23.21; O, 5.30; Found: C, 55.71; H, 4.03; Cl, 11.78; N, 23.19; O, 5.31; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.84 (bs, 2H), 3.19 (bs, 2H), 3.56 (bs, 2H), 7.16 (s, 1H), 7.47 (d, *J* = 7.0 Hz, 1H), 7.52-7.61 (m, 3H), 8.29 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 21.5, 39.5 (*C*H_2, overlapped with DMSO signal), 48.0, 90.0, 112.5, 122.4, 123.6, 128.8, 131.1, 133.5, 138.7, 142.4, 146.7, 152.4; MS (ES, pos. mode) *m/z* = 302.1 $[M + H]^+$.

7-(2,4-difluorophenyl)-6,7-dihydro-2H-imidazo[1,2-c]pyrazolo-[4,3-e]pyrimidin-5(3H)-one (4g). White powder, (228 mg, 79%), mp 183-184 °C, $C_{13}H_9F_2N_5O$; Elemental analysis: Calcd.: C, 53.98; H, 3.14; F, 13.14; N, 24.21; O, 5.53; Found: C, 53.96; H, 3.16; F, 13.12; N, 24.23; O, 5.51; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.37 (t, *J* = 7.6 Hz, 2H), 3.75 (t, *J* = 8.0 Hz, 2H), 7.21-7.35 (m, 2H), 7.51-7.60 (m, 1H), 7.62-7.71 (m, 1H), 8.30 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 37.9, 45.7, 86.9, 105.2, 105.4, 105.6, 112.3, 112.5, 112.6, 122.4, 122.5, 129.8, 129.9, 143.2, 144.8, 155.5, 155.7, 156.9, 157.6, 157.7, 161.4, 161.5, 163.4, 163.5; MS (ES, pos. mode) *m/z* = 290.1 $[M + H]^+$.

8-(2,4-difluorophenyl)-3,4,7,8-tetrahydropyrazolo[4,3-e]pyr-imido[1,2-c]pyrimidin-6(2H)-one (5g). White powder, (242 mg, 80%), mp 133-134 °C, $C_{14}H_{11}F_2N_5O$; Elemental analysis: Calcd.: C, 55.45; H, 3.66; F, 12.53; N, 23.09; O, 5.28; Found: C, 55.43; H, 3.64; F, 12.55; N, 23.10; O, 5.29; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.81 (bs, 2H), 3.12 (bs, 2H), 3.58 (bs, 2H), 7.02 (s, 1H), 7.23-7.30 (m, 1H), 7.50-7.64 (m, 2H), 8.29 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 21.6, 39.5 (*C*H_2, overlapped with DMSO signal) 48.0, 88.6, 105.2, 105.4, 105.6, 112.2, 112.3, 112.6, 122.1, 122.2, 129.9, 130.0, 142.7, 148.2, 151.8, 155.5, 155.6, 157.5, 157.6, 161.4, 161.5, 163.4, 163.5; MS (ES, pos. mode) *m/z* = 304.1 $[M + H]^+$.

7-(3-fluorophenyl)-6,7-dihydro-2H-imidazo[1,2-c]pyrazolo-[4,3-e]pyrimidin-5(3H)-one (4h). White powder, (244 mg, 90%), mp 178-179 °C, $C_{13}H_{10}FN_5O$; Elemental analysis: Calcd.: C, 57.56; H, 3.72; F, 7.00; N, 25.82; O, 5.90; Found: C, 57.58; H, 3.70; F, 7.02; N, 25.80; O, 5.90; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.43 (t, *J* = 7.9 Hz, 2H), 3.79 (t, *J* = 7.9 Hz, 2H), 7.29-7.47 (m, 4H), 7.54-7.63 (m, 1H), 8.31 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 38.0, 46.0, 88.6, 111.2, 111.4, 112.5, 115.7, 115.8, 120.0, 131.2, 131.3, 139.1, 139.2, 142.8, 143.4, 157.6, 161.0, 162.9; MS (ES, pos. mode) *m/z* = 272.1 $[M + H]^+$.

8-(3-fluorophenyl)-3,4,7,8-tetrahydropyrazolo[4,3-e]pyr-imido[1,2-c]pyrimidin-6(2H)-one (5h). Pale-yellow powder, (242 mg, 85%), mp 195-196 °C, $C_{14}H_{12}FN_5O$; Elemental analysis: Calcd.: C, 58.94; H, 4.24; F, 6.66; N, 24.55; O, 5.61; Found: C, 58.92; H, 4.26; F, 6.66; N, 24.53; O, 5.63; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.84 (bs, 2H), 3.18 (bs, 2H), 3.54 (bs, 2H), 7.15 (s, 1H), 7.30-7.41 (m, 3H), 7.55-7.64 (m, 1H), 8.28 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 21.5, 39.5 (*C*H_2, overlapped with DMSO signal), 48.1, 90.0, 111.1, 111.3, 112.5, 115.7, 115.9, 119.8, 131.2, 131.3, 138.8, 138.9, 142.4, 146.7, 152.5, 160.9, 162.9; MS (ES, pos. mode) *m/z* = 286.1 $[M + H]^+$.

7-(2-chlorophenyl)-6,7-dihydro-2H-imidazo[1,2-c]pyrazolo-[4,3-e]pyrimidin-5(3H)-one (4i). Pale-yellow powder, (232 mg, 82%), mp 227-229 °C, $C_{13}H_{10}ClN_5O$; Elemental analysis: Calcd.: C, 54.27; H, 3.50; Cl, 12.32; N, 24.34; O, 5.56; Found: C, 54.25; H, 3.52; Cl, 12.30; N, 24.36; O, 5.54; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.32 (CH_2, overlapped with DMSO signal, 2H), 3.61 (t, *J* = 8.0 Hz, 2H), 7.27 (s, 1H), 7.48-7.55 (m, 1H), 7.55-7.61 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 8.28 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 37.8, 45.5, 86.8, 112.7, 128.3, 129.8, 130.2, 130.4, 131.8, 135.2, 142.9, 144.6, 156.9; MS (ES, pos. mode) *m/z* = 288.1 $[M + H]^+$.

8-(2-chlorophenyl)-3,4,7,8-tetrahydropyrazolo[4,3-e]pyr-imido[1,2-c]pyrimidin-6(2H)-one (5i). White crystalline, (241 mg, 80%), mp 197-198 °C, $C_{14}H_{12}ClN_5O$; Elemental analysis: Calcd.: C, 55.73; H, 4.01; Cl, 11.75; N, 23.21; O, 5.30; Found: C, 55.73; H, 4.03; Cl, 11.73; N, 23.23; O, 5.32; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.72 (bs, 2H), 3.08 (bs, 2H), 3.49 (bs, 2H), 6.99 (s, 1H), 7.46-7.53 (m, 2H), 7.54-7.61 (m, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 8.28 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 21.6, 39.5 (*C*H_2, overlapped with DMSO signal), 47.9, 88.5, 112.7, 128.1, 129.7, 130.2, 130.4, 131.7, 134.9, 142.4, 147.9, 152.0; MS (ES, pos. mode) *m/z* = 302.1 $[M + H]^+$.

General procedure for the synthesis of products 8a, 8b, 9a and 9b

To a mixture of β-aminocarbaldehyde **5** or **6** (1 mmol), chloroalkyl isocyanate **2a** or **2b** (1.5 mmol) and 4Å molecular sieve powder (100 mg) in 1.5 mL of dry DMF, anhydrous $Cu(OAc)_2$ (18 mg, 10 mol%) was added. The reaction vessel was placed in a preheated oil bath at 100 °C and the contents were stirred for 15 min, monitored by TLC (eluent: *n*-hexane/EtOAc (2:3)). The suspension was then poured into ice and extracted with EtOAc (2×30 mL). The combined organic phases were extracted with brine (2×30 mL), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The crude product **8a**, **8b**, **9a** or **9b** was purified by flash chromatography using *n*-hexane/EtOAc (2:3) as eluent.

Note: In the event of microwave irradiation, the following settings were applied: a standard 10 mL microwave vial; μW power (150 W), T (100 °C), t (15 min), ramping time (20 s).

5-(2-chloroethyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-6(5H)-one (8a). White crystalline, (233 mg, 81%), mp 193-194 °C, $C_{14}H_{13}ClN_4O$; Elemental analysis: Calcd.: C, 58.24; H, 4.54; Cl, 12.28; N, 19.40; O, 5.54; Found: C, 58.22; H, 4.55; Cl, 12.26; N, 19.42; O, 5.55; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.43 (s, 3H), 4.01 (t, *J* = 5.6 Hz, 2H), 4.31 (t, *J* = 5.6 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 2H), 9.10 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 12.2, 41.9, 53.2, 106.0, 119.7, 125.6, 129.0, 138.2, 146.3, 148.8, 153.6, 157.7; MS (ES, pos. mode) *m/z* = 289.1 $[M + H]^+$.

5-(3-chloropropyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]-pyrimidin-6(5H)-one (8b). Pale-yellow powder, (229 mg, 76%), mp 171-172 °C, $C_{15}H_{15}ClN_4O$; Elemental analysis: Calcd.: C, 59.51; H, 4.99; Cl, 11.71; N, 18.51; O, 5.28; Found: C, 59.52; H, 4.98; Cl, 11.72; N, 18.50; O, 5.28; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.15-2.24 (m, 2H), 2.41 (s, 3H), 3.71 (t, *J* = 6.4 Hz, 2H), 4.09 (t, *J* = 6.9 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 8.10 (d, *J* = 7.9 Hz, 2H), 9.12 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 12.2, 31.2, 42.5, 49.7, 106.1, 119.5, 125.4, 129.0, 138.4, 146.2, 148.3, 153.8, 157.6; MS (ES, pos. mode) *m/z* = 303.1 $[M + H]^+$.

5-(2-chloroethyl)-1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidin-6(5H)-one (9a). White crystalline, (273 mg, 78%), mp 178-179 °C, $C_{19}H_{15}ClN_4O$; Elemental analysis: Calcd.: C, 65.05; H, 4.31; Cl, 10.11; N, 15.97; O, 4.56; Found: C, 65.03; H, 4.33; Cl, 10.10; N, 15.999; O, 4.55; ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.02 (t, *J* = 6.1 Hz, 2H), 4.42 (t, *J* = 5.8 Hz, 2H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.49-7.61 (m, 5H), 8.01 (d, *J* = 6.9 Hz, 2H), 8.18 (d, *J* = 8.1 Hz, 2H), 9.50 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 41.7, 52.8, 103.6, 120.4, 126.1, 127.0, 129.1, 129.2, 130.1, 130.2, 138.1, 146.4, 149.8, 153.3, 158.2; MS (ES, pos. mode) *m/z* = 351.1 $[M + H]^+$.

5-(3-chloropropyl)-1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidin-6(5H)-one (9b). Yellow powder, (273 mg, 75%), mp 187-188 °C, $C_{20}H_{17}ClN_4O$; Elemental analysis: Calcd.: C, 65.84; H, 4.70; Cl, 9.72; N, 15.36; O, 4.39; Found: C, 65.82; H, 4.72; Cl, 9.70; N, 15.37; O, 4.38; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.19-2.30 (m, 2H), 3.74 (t, *J* = 6.3 Hz, 2H), 4.19 (t, *J* = 7.0 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.48-7.61 (m, 5H), 8.02 (d, *J* = 6.8 Hz, 2H), 8.19 (d, *J* = 7.7 Hz, 2H), 9.42 (s, 1H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 31.2, 42.6, 50.0, 103.7, 120.2, 126.0, 127.1, 129.1, 129.9, 130.4, 138.2, 146.3, 149.4, 153.5, 158.2; MS (ES, pos. mode) *m/z* = 364.1 $[M + H]^+$.

View Article Online
DOI: 10.1039/C3OB41146J

Acknowledgements

This work was supported by the grants from the National Innovation Agency (NIH): GOP-1.3.1-11/b-2011-0002 and TÉT_10-1-2011-0376 for AVIDIN Ltd.

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