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Regioselective synthesis of 1- and 4-substituted 7-oxopyrazolo[1,5-*a*]pyrimidine-3-carboxamides

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ABSTRACT

The synthesis of 7-substituted pyrazolo[1,5-*a*]pyrimidine-3-carboxamides was studied. First, methyl 7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**5**) was prepared in three steps from methyl 5-amino-1*H*-pyrazole-4-carboxylate (**3**). Treatment of **5** with $POCl_3$ gave the highly reactive 7-chloro derivative **10**, which was reacted with amines, benzyl alcohol, and phenylboronic acid in the presence of Pd-catalyst to give the corresponding 7-substituted derivatives **11**. Hydrolysis of the esters **5** and **11** followed by amidation gave the corresponding carboxamides **16a**–**h** and **15**. Regioselectivity of N-alkylation of 7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid derivatives **5** and **16** was tunable by the carboxy function. Alkylation of the secondary amides **16a**–**f** furnished the 1-alkyl derivatives **17a**–**f**, whereas the ester **5** and the tertiary amides **16g**,**h** gave the 4-alkyl derivatives **14a**–**d** and **16m**,**n**, selectively.

1. Introduction

Annelated heterocycles are important scaffolds for the preparation of compound libraries for medicinal and pharmaceutical applications.[1] Among 5–6-fused systems, pyrazolo[1,5-*a*]pyrimidine is an important heterocycle, due to biological activity of many of its derivatives.[2] For example, a literature search shows more than 100,000 known pyrazolo[1,5-*a*]pyrimidine derivatives with almost 5000 references and with preparation, biological study, and uses as the predominant substance roles. For 2014 alone, over one hundred references can be found for ~15,000 pyrazolo[1,5-*a*]pyrimidines. Examples of bioactive pyrazolo[1,5-*a*]pyrimidines include hepatitis C virus inhibitors,[3] antagonists of serotonin 5-HT6 receptors,[4] kinase inhibitors,[5] PET tumour imaging agents,[6] and inhibitors of amyloid β-peptide 1–42 aggregation.[7] Sedative agents zaleplon and indiplon and the anxyolytic agent ocinaplon are approved drugs containing a pyrazolo[1,5-*a*]pyrimidine core (Fig. 1).

Pyrazolo[1,5-*a*]pyrimidines are commonly available by cyclocondensation of a 3-aminopyrazole derivative with a 1,3-dicarbonyl compound[2,8] or its synthetic equivalent, such as a β-alkoxy-[9] or β-amino enone.[10] Due to this ease of access, a plethora of known pyrazolo[1,5-*a*]pyrimidine derivatives (see above) is not surprising.

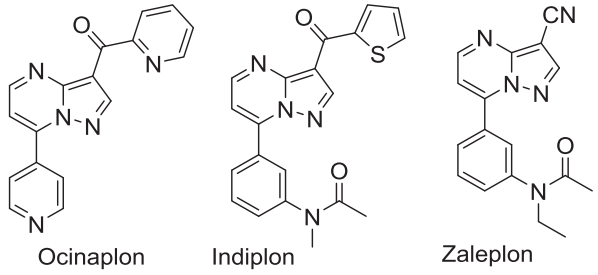

Fig. 1. Approved drugs containing a pyrazolo[1,5-*a*]pyrimidine.

Nevertheless, a more detailed literature search also reveals that 7-alkoxy-, and 7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxamides are much less known, while their 5,6-unsubstituted analogues are, to the best of our knowledge, unknown. In continuation of our long-term study on utilization of enaminones as reagents and/or key-intermediates in heterocyclic[11] and combinatorial syntheses,[12] we recently focused our attention on the synthesis and transformations of derivatives of pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. Within this context, we recently reported a parallel synthesis of 24 novel 7-(pyridin-2-yl)- and 7-pyrazinyl substituted pyrazolo[1,5-*a*]pyridine-3-carboxamides from 3-(dimethylamino)-1-(heteroaryl)prop-2-en-1-ones.[12a] In extension, we tried to develop another synthetic approach utilizing a pyrazolo[1,5-*a*]

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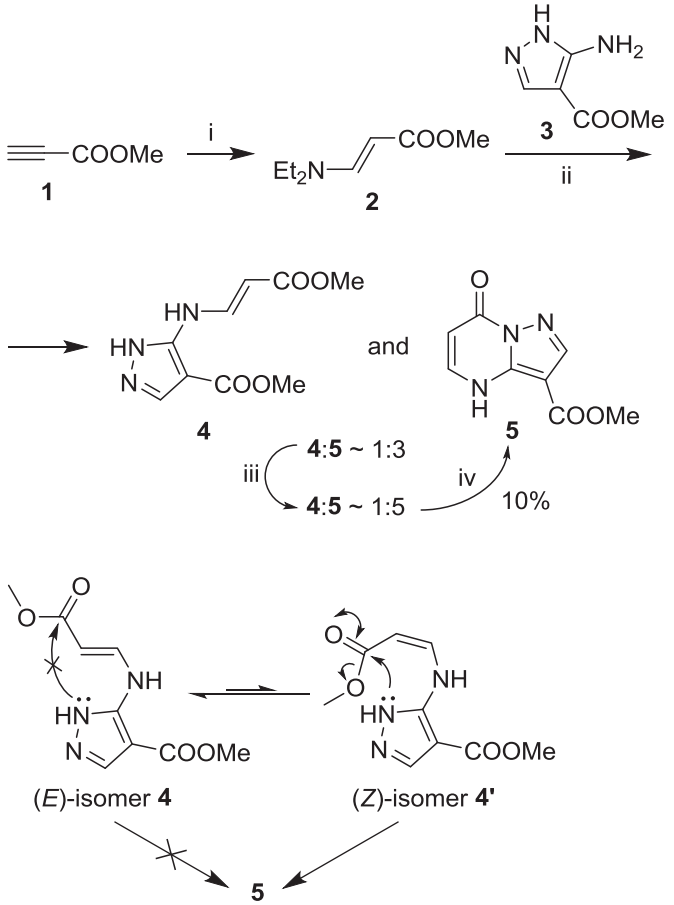
pyrimidine central building block for a late-stage derivatisation at different positions. Herein we report the results, the synthesis of methyl 7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**5**) as the central building block and its transformations into differently substituted pyrazolo[1,5-*a*]pyrimidine-3-carboxamides.

2. Results and discussion

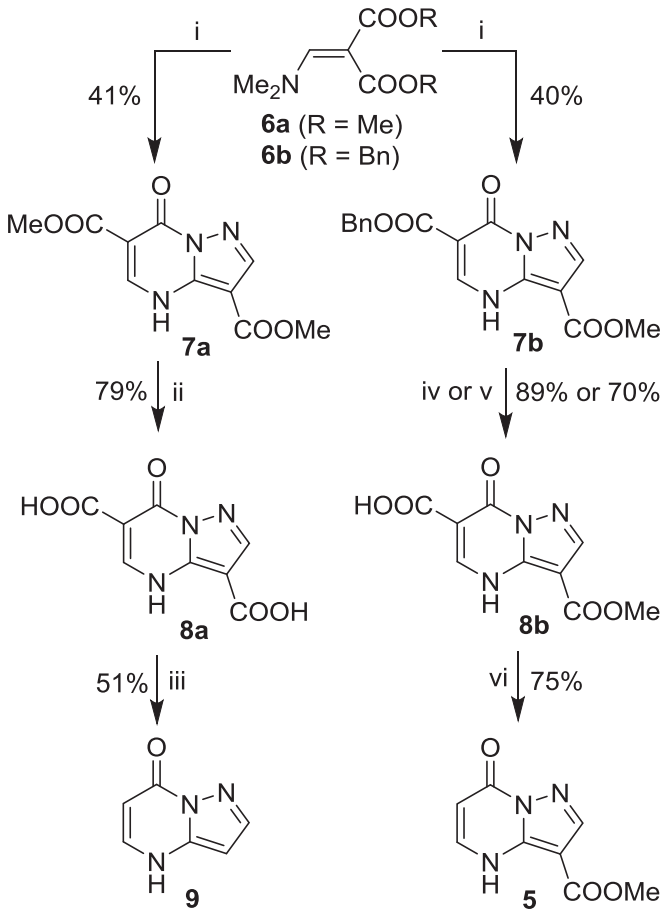
2.1. Synthesis of target compounds

The initial idea was to prepare the central intermediate **5** in two steps from methyl propiolate (**1**) via 1,4-addition of diethylamine to give the enaminone **2**[13] followed by cyclisation with methyl 5-amino-1*H*-pyrazole-4-carboxylate (**3**) in refluxing acetic acid. Although numerous enaminones cyclize smoothly with α-amino azoles and azines under these conditions,[11] the reaction of enaminone **2** with 3-aminopyrazole **3** under the above conditions gave a 1:3 mixture of the intermediate **4** and the product **5** in ~50% yield. Crystallization of a mixture of **4** and **5** from ethanol provided the desired central intermediate **5** in only 10% yield. Unfortunately, crystallization of a mixture of **4** and **5** from ethanol was not reproducible. At best, improvement of the product ratio of **4**:**5** to ~1:10 was achieved. Neither did prolonged heating in acetic acid, nor prolonged microwave-assisted heating at 180 °C did not affect the product ratio. It is noteworthy that attempts to obtain **5** from **3** and ethyl 2,2-diethoxyacetate following the literature procedure for the synthesis of the ethyl analogue of **5**[14] were not successful, either. When the neat mixture of **4** and **5** was heated at 250 °C for 3 h, the product ratio of **4**:**5** improved to ~ 1:5. Our difficulty to prepare pure compound **5** in reasonable yield and purity may be due to an *E*/*Z*-equilibrium between the isomers of substitution intermediates **4** and **4′**. Probably, this equilibrium is strongly shifted towards the thermodynamically more stable (*E*)-isomer **4**, which cannot easily cyclize (Scheme 1).



Scheme 1. Reaction conditions: (i) Et_2NH, CH_2Cl_2, 0 °C (Ref. 13); (ii) AcOH, reflux; (iii) 250 °C (neat), 3 h; (iv) crystallization from EtOH.

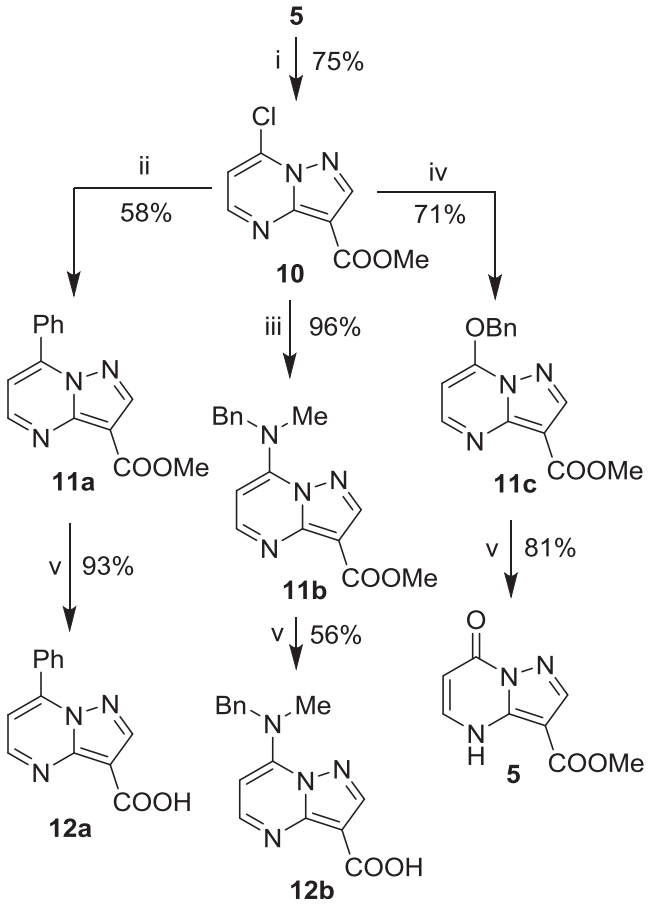
If the above explanation was correct, then cyclisation of **3** with dimethyl (dimethylamino)methylidenemalonate (**6a**) should take place easily,[15] since one of the ester groups is always in position to undergo cyclisation. Indeed, treatment of **3** with **6a** in refluxing acetic acid produced the cyclisation product **7a** in 41% yield. Variation of solvent, temperature, and reaction time did not improve the yield of **7a**. Hydrolysis of **7a** with 1–2 equivalents of aqueous KOH in methanol under various conditions produced mixtures of regioisomeric (semi)hydrolysed products, whereas the reaction with excess $LiOH \cdot H_2O$ gave the diacid **8a**, which decarboxylated at 250 °C for 4 h to give 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine (**9**)[10a,16] in 51% yield. To obtain the desired central intermediate **5**, the carboxy groups in the diester **7** had to be orthogonally protected. The dibenzyl ester **6b** was cyclized into the 6-benzyl 3-methyl 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate (**7b**). Though hydrogenolytic debenzylation of **7b** gave the mono-acid **8b** in 89% yield, this method was suitable only for a small scale preparation of **10** (<3 mmol), due to extremely low solubility of **7b** and **8b** in most organic solvents including DMF. On the other hand, acidolytic debenzylation of **7b** with HBr/AcOH proceeded smoothly to give **8b** in 70% yield. Finally, decarboxylation of **8b** with Cu/quinoline at 180 °C furnished **5** in 75% yield (Scheme 2).



Scheme 2. Reaction conditions: (i) Compound **3**, AcOH, reflux; (ii) $LiOH \cdot H_2O$, MeOH, reflux; (iii) 250 °C (neat), 4 h; (iv) H_2 (3 bar), Pd–C, DMF, rt; (v) 33% HBr/AcOH, 60 °C; (vi) quinoline, Cu (cat.), 180 °C.

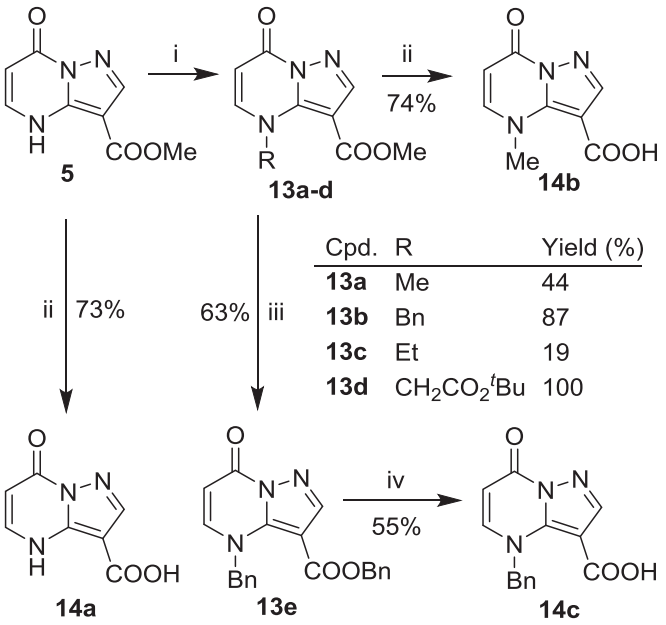
Once access to the central intermediate **5** was gained, we studied the substitution of the oxo group. Treatment of **5** with the

standard chlorination reagents $POCl_3$ or $POCl_3/PCl_5$ did not give the desired chloride **10**, even upon prolonged heating under reflux. On the other hand, chlorination in the presence of *N*,*N*-dimethylaniline or Et_3N at 100 °C did give **10**, however, the yields were not reproducible. The best yield was obtained by treating **5** with $POCl_3$ in the presence of 2 equiv of Et_3N under reflux for 3 h (75% yield). The chloride **10** was highly reactive and hydrolysed back into **5** within two weeks unless stored under anhydrous conditions. Thus, **10** had to be used for further transformations immediately upon isolation. Suzuki–Miyaura cross-coupling of **10** with phenylboronic acid in the presence of a Pd-catalyst gave the 7-phenyl derivative **11a**, whereas nucleophilic substitution with benzyl(methyl)amine produced the corresponding amino derivative **11b**. Attempted substitution with sodium benzylate in benzyl alcohol was not successful and gave the hydroxy compound **5**. However, reaction of **10** with excess benzyl alcohol in dichloromethane in the presence of 1 equiv of aq NaOH and a phase-transfer catalyst afforded the 7-benzyloxy derivative **11c** in 71% yield. Finally, the esters **11a**–**c** were hydrolysed with aq NaOH in methanol at 50 °C. The hydrolysis of **11a**,**b** with NaOH produced the desired carboxylic acids **12a**,**b**, whereas reaction of **11c** somewhat unexpectedly proceeded preferentially at position C(7) to give the central intermediate **5** (Scheme 3).



Scheme 3. Reaction conditions: (i) $POCl_3$, Et_3N, reflux, 3 h; (ii) $PhB(OH)_2$, $Pd(PPh_3)_4$-$[PdCl(allyl)]_2$, Cs_2CO_3, DMF, 95 °C; (iii) Bn(Me)NH, MeCN, rt; (iv) BnOH, CH_2Cl_2, 2 M NaOH, $Bu_4N^+Br^-$ (cat.), rt; (v) 2 M NaOH, MeOH, 50 °C.

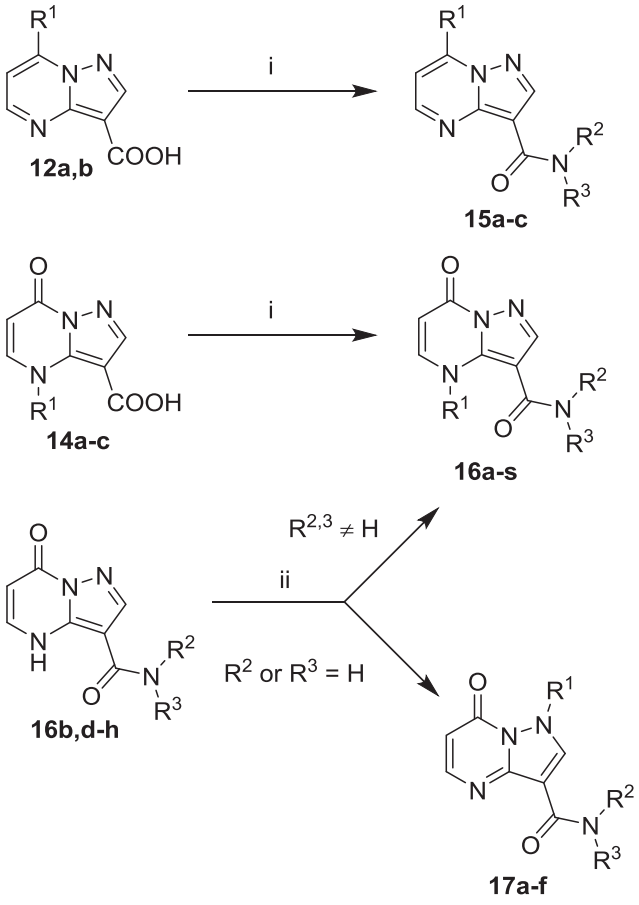
N-Alkylation of the central intermediate **5** with primary alkyl halides in DMF in the presence of potassium carbonate took place regioselectively at position 4 to afford the 4-alkyl-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylates **13a**–**d** in 19–100% yields. Hydrolysis of the central intermediate **5** and the *N*-methyl derivative **13a** gave the corresponding acids **14a** and **14b** in good yields. Quite surprisingly, the same treatment of the *N*-benzyl analogue **13b** gave a non-separable mixture of products with **14c** as the minor component. Therefore, the acid **14c** was prepared in two steps via transesterification of **13b** into the benzyl ester **13e**, followed by regioselective hydrogenolytic *O*-debenzylation. It is noteworthy that mild reaction conditions and a short reaction time were essential, otherwise both benzyl groups were removed (Scheme 4).



Scheme 4. Reaction conditions: (i) R–X, K_2CO_3, DMF, rt; (ii) $LiOH{\cdot}H_2O$, H_2O, rt; (iii) BnOH, DBU (1 equiv), 150 °C; (iv) H_2 (balloon), Pd–C, rt, 15 min.

Carboxylic acids **12a**,**b** and **14a**–**c** were amidated using bis-(pentafluorophenyl) carbonate (BPC) as the activating reagent. As usual, these amidations proceeded smoothly to provide the corresponding carboxamides **15a**–**c** and **16a**–**q** in good yields. Finally, the alkylation of different secondary and tertiary carboxamides **16b**,**d**–**h** was performed with alkyl halides in the presence of a base. To our surprise, the regioselectivity of N-alkylation was dependent on the carboxamide moiety. Thus, alkylation of the secondary amides **16b**,**d**–**f** (R^2 or R^3=H) led to the 1-alkyl regioisomers **17a**–**f**, whereas alkylation of the tertiary carboxamides **16g** and **16h** furnished the 4-alkyl derivatives **16m** and **16n**. In other words, the regioselectivity of N-alkylation of 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine derivatives with purely hydrogen bond accepting groups at position 3 (COOMe, $CONR_2$) were alkylated at position N(4), whereas compounds with hydrogen bond donor/acceptor groups (CONHR) were alkylated at position N(1) (Scheme 5, Table 1).

A plausible rationale for *N*(4)-selective alkylation of the ester **5** (cf. Scheme 4) and the tertiary amides **16g**,**h** is the (4)N–H···O=C hydrogen bond-promoted tautomerization of the 4-NH tautomer **16** into the 1-NH tautomer **16′**, which could form a dimeric associate in solution. Attack of the electrophile would then take place at the sterically more accessible and more nucleophilic sp^2 nitrogen atom *N*(4) to give the 4-alkyl regioisomers **16m**,**n**. Accordingly, the 1-NH tautomers of the secondary amides **16′b**–**f** could also undergo (4)N···H–N–C=O promoted tautomerization into the lactim **16″** with sterically accessible and nucleophilic sp^2 nitrogen atom *N*(1). Consequently, attack of the electrophile would then take place at position 1 to furnish the 1-alkyl regioisomers **17** (Scheme 6).

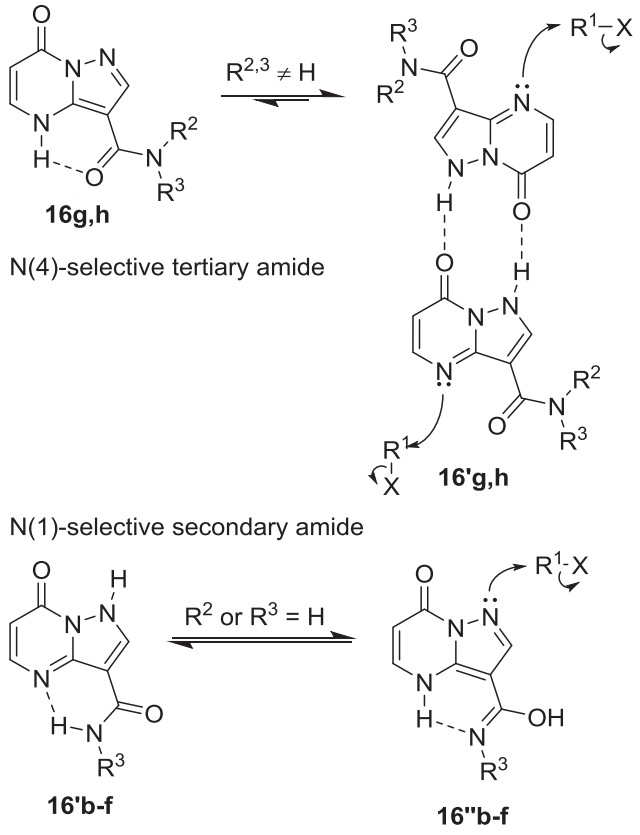


Scheme 5. Reaction conditions: (i) BPC, Et_3N, MeCN, rt, then R^2R^3NH, Et_3N, rt, reflux; (ii) R^1–X, K_2CO_3, DMF, rt.

Table 1
Experimental data for carboxamides **15a**–**c**, **16a**–**q**, and **17a**–**f**

Cpd.	R^1	NR^2R^3	Yield (%)
15a	Ph	$NH(CH_2)_2OMe$	100
15b	N(Bn)Me	$NH(CH_2)_2OMe$	66
15c	N(Bn)Me	$NH(CH_2)_3NMe_2$	79
16a	H	NH_2	92
16b	H	$NH(CH_2)_2OMe$	81
16c	H	$NH(CH_2)_3NMe_2$	94
16d	H	$NHCH_2Ph$	86
16e	H	$NHCH_2C_6H_4$–4-Me	90
16f	H	$NHCH_2C_6H_3$–3,5-Cl_2	53
16g	H	NMe_2	84
16h	H	Pyrrolidin-1-yl	91
16i	Me	NH-*cy*-C_3H_5	60
16j	Me	$NHCH_2Ph$	83
16k	Me	$NH(CH_2)_3OH$	94
16l	Me	2-Picolylamino	73
16m	Me	NMe_2	83[a], 93[b]
16n	Me	Pyrrolidin-1-yl	79[a], 96[b]
16o	Me	Morpholin-4-yl	94[a]
16p	Bn	NH-*cy*-C_3H_5	90
16q	Bn	$NHCH_2Ph$	76
16r	Bn	$NH(CH_2)_3NMe_2$	93
16s	Bn	$N(Me)CH_2Ph$	82
17a	Me	$NH(CH_2)_2OMe$	39
17b	Bn	$NH(CH_2)_2OMe$	64
17c	Bn	$NHCH_2Ph$	75
17d	Bn	$NHCH_2C_6H_3$–3,5-Cl_2	86
17e	3-MeO–Bn	$NHCH_2Ph$	72
17f	3-MeO–Bn	$NHCH_2C_6H_4$–4-Me	91

[a] From **14** by amidation.
[b] From **16** by alkylation.



Scheme 6. A plausible rationale for regioselective N-alkylation of carboxamides **16**.

2.2. Structure determination

The structures of all novel compounds **5**, **7**, **8**, **10**–**17** were determined by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, MS, HRMS) and by elemental analyses for C, H, and N. Compounds **5**, **7a**,**b**, **8a**,**b**, **10**, **11a**–**c**, **12a**, **13a**,**b**,**e**, **14a**–**c**, **16j**,**p**,**q**, and **17a**–**f** were obtained in analytically pure form, whereas the identities of compounds **12b**, **13c**,**d**, **15a**,**b**, and **16a**–**i**,**k**–**o**,**r**,**s** were confirmed by ^{13}C NMR and HRMS. ^{13}C NMR spectrum of compound **16g** could not be recorded due to its low solubility in DMSO-d_6.

The regiochemistry of *N*(1)-(**17a**–**f**) and *N*(1)-alkylated compounds **13a**–**e**, **14b**,**c**, and **16i**–**s** was primarily determined by NMR (HMBC technique). Thus, a strong correlation through three bonds between *C*(5) and *CH*$_2$R and between C(5)–*H* and *C*H$_2$R in HMBC spectra of compounds **13b** and **13d** strongly supported attachment of the alkyl group at position N(4). On the other hand, strong correlation between C(2)–*H* and *C*H$_2$R HMBC spectra of the 1-alkyl regioisomers **17a** and **17b** were in agreement with the proposed structures. The regiochemistry of the rest of compounds was determined on the basis of correlation of vicinal coupling constants, $^3J_{5H-6H}\sim$7.7 Hz for the 4-alkylated compounds **13**, **14**, and **16** and $^3J_{5H-6H}\sim$6.3 Hz for the 1-alkyl analogues **17** (Fig. 2, Table 2).

Finally, the structures of compounds **13b**, **16o**, **17a**, and **17b** were unambiguously determined by X-ray diffraction (Figs. 3–6).

3. Conclusion

A new synthetic method for the late-stage derivatisation of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid scaffold was developed. First, methyl 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**5**) was prepared as the central intermediate in three steps starting from dibenzyl malonate and methyl 3-amino-1*H*-pyrazole-4-carboxylate (**3**) as starting materials. Chlorination of

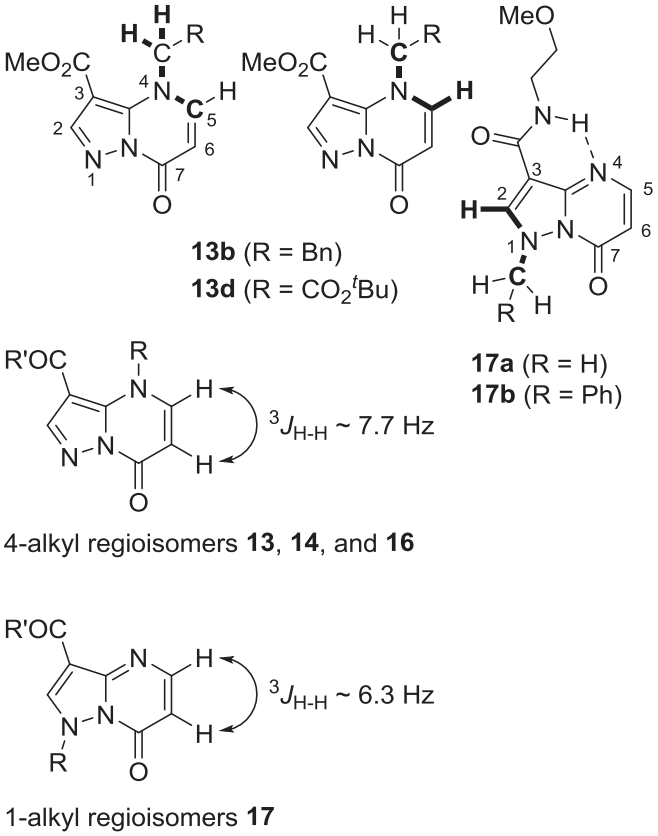


Fig. 2. Structure determination by ^{1}H NMR and HMBC NMR.

Table 2
Selected ^{1}H NMR data for compounds **13a**–**e**, **14b**,**c**, **16i**–**s**, and **17a**–**f**

Cpd.	$^{3}J_{5H-6H}$ (Hz)	δ (ppm)		
		6-H	5-H	2-H
13a	7.8	6.00	7.96	8.27
13b	8.0	6.07	7.43	8.32
13c	7.8	6.06	8.06	8.31
13d	7.8	6.10	7.94	8.28
13e	7.8	6.14	8.15	8.33
14b	7.7	5.98	7.94	8.23
14c	7.7	6.10	8.12	8.25
16i	7.7	5.89	7.91	8.10
16j	7.7	5.90	7.92	8.22
16k	7.7	5.89	7.91	8.13
16l	7.7	5.91	7.92	8.27
16m	7.7	5.92	7.49	7.90
16n	7.6	5.86	7.91	8.16
16o	7.7	5.97	7.35	7.86
16p	7.7	6.02	8.21	8.05
16q	7.8	6.04	8.20	8.19
16r	7.7	6.00	7.49	7.96
16s	7.7	6.03	7.71/8.11[a]	8.19
17a	6.3	5.95	8.00	8.80
17b	6.3	6.01	8.02	9.19
17c	6.3	6.01	8.00	9.22
17d	6.3	6.09	7.94	8.37
17e	6.3	6.07	7.92	8.41
17f	6.3	6.06	7.91	8.37

[a] Mixture of rotamers.

5 gave the chloro derivative **10**, which was a reactive intermediate suitable for introduction of the amino, alkoxy, and aryl function at position 7. Alkylation of **5** took place selectively at position N(1). Hydrolysis of the ester group followed by amidation gave the title

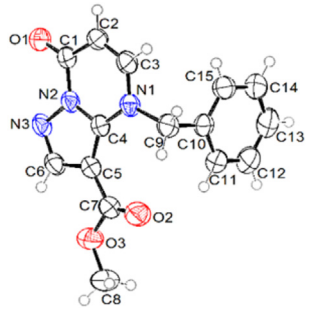


Fig. 3. The molecular structure of **13b**, showing the atom labelling. The displacement ellipsoids are drawn with 50% probability and the hydrogen atoms are shown as small spheres of arbitrary radii.

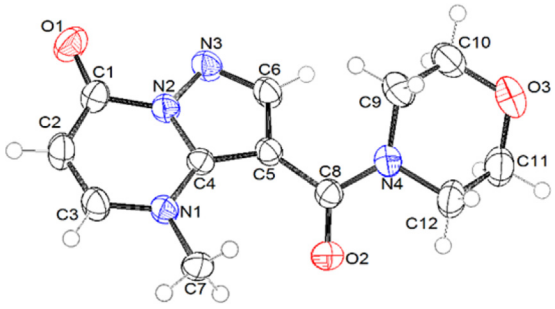


Fig. 4. The molecular structure of **16o**, showing the atom labelling. The displacement ellipsoids are drawn with 50% probability and the hydrogen atoms are shown as small spheres of arbitrary radii.

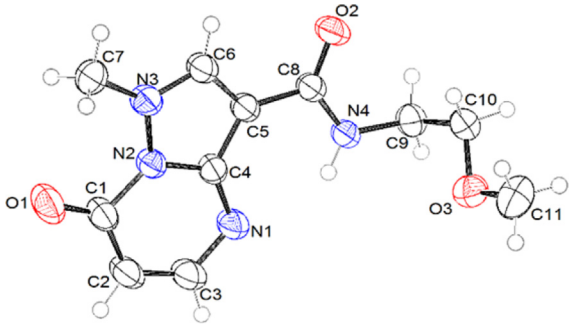


Fig. 5. The molecular structure of **17a**, showing the atom labelling. The displacement ellipsoids are drawn with 50% probability and the hydrogen atoms are shown as small spheres of arbitrary radii.

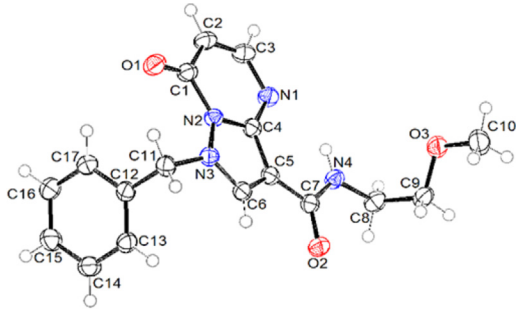


Fig. 6. The molecular structure of **17b**, showing the atom labelling. The displacement ellipsoids are drawn with 50% probability and the hydrogen atoms are shown as small spheres of arbitrary radii.

carboxamides in good yields. Regioselectivity of N-alkylation of various 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine derivatives was tunable by the type of carbonyl function at position 3. Thus, the alkylation was directed to position N(4) by hydrogen bond acceptors (COOMe, $CONR_2$), whereas alkylation was directed to position N(1) by hydrogen bond donors (CONHR). In summary, the presented synthetic method is simple and allows the late-stage decoration of the heterocyclic scaffold. Therefore, it should be suitable for the preparation of combinatorial libraries of 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamides, which might be interesting for various biological and pharmaceutical applications.

4. Experimental

4.1. General

Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting point system. The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C and on a Bruker Avance III UltraShield 500 plus at 500 MHz for ^{1}H and 126 MHz for ^{13}C, using $CDCl_3$, and DMSO-d_6 with Me_4Si as the internal standard, as solvents. Mass spectra were recorded on a Q-Tof Premier spectrometer and on a Agilent 6224 Accurate Mass TOF LC/MS spectrometer, IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyzer 2400 II. Flash column chromatography (FC) was performed on silica gel (Fluka, Silica gel 60, particle size 35–70 μm).

Methyl propiolate (**1**), dibenzyl malonate (TCI Europe), and BPC (ABCR) are commercially available. Methyl 5-amino-1*H*-pyrazole-4-carboxylate (**3**) was prepared following the literature procedure.[17]

4.2. Synthesis of methyl 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (5) from methyl propiolate (1)

Diethylamine (2.8 mL, 27 mmol) was added to a cold solution of **1** (1.8 mL, 20 mmol) in dichloromethane (60 mL) at 0 °C and the so formed solution was stirred at 0 °C for 5 h and the volatile components were evaporated in vacuo (30 °C, 20 mbar). The crude enamino ester **2**, which was obtained as yellow oil, was dissolved in acetic acid (45 mL), aminopyrazole **3** (2.8 g, 20 mmol) was added and the mixture was heated under reflux for 24 h. Volatile components were evaporated in vacuo (40 °C, 7 mbar) and the residue was triturated with warm water (60 °C, 50 mL). The precipitate was collected by filtration and washed with ethanol (15 mL) to give a 1:3 mixture of **4** and **5** (~2 g). Subsequent crystallization from ethanol afforded the *title compound* **5** 0.40 g (10%) as a pale yellow solid; mp 280–287 °C; [Found: C, 49.67; H, 3.40; N, 21.64. $C_8H_7N_3O_3$ requires: C, 49.74; H, 3.65; N, 21.75%]; ν_{max} (ATR) 3068, 2963, 1699, 1624, 1575, 1504, 1468, 1433, 1411, 1391, 1249, 1209, 1150, 1123, 1069, 1017, 944, 904, 876, 800, 772, 719, 631 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.83 (3H, s, OMe), 5.95 (1H, d, J=7.5 Hz, 6-H), 7.85 (1H, d, J=7.5 Hz, 5-H), 8.25 (1H, s, 2-H), 12.24 (1H, br s, 4-H); δ_C (126 MHz, DMSO-d_6) 51.5, 96.7, 99.1, 140.6, 142.9, 143.5, 155.8; HRMS (ESI): MH$^+$, found 194.0557. $C_8H_8N_3O_3$ requires 194.0566.

4.3. Synthesis of dialkyl 7-hydroxypyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylates 7a and 7b

A mixture of dialkyl malonate (10 mmol), anhyd toluene (25 mL), and *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) (1.6 mL, 12 mmol) was heated under reflux for 2 h, cooled, and volatile components were evaporated in vacuo. The crude enamino ester **6** was dissolved in acetic acid (30 mL), aminopyrazole **3** (1.4 g, 10 mmol) was added and the mixture was heated under reflux for 5 h. The reaction mixture was cooled to rt and the precipitate was collected by filtration and washed with ethanol (2×10 mL) to give the *title compound* **7**. The following compounds were prepared in this manner.

*4.3.1. Dimethyl 7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3,6-dicarboxylate (**7a**).* Prepared from dimethyl malonate via enaminone **6a**. Yield: 1.04 g (41%) of pale yellow solid; mp 270–275 °C; [Found: C, 47.61; H, 3.39; N, 16.67. $C_{10}H_9N_3O_5$ requires: C, 47.81; H, 3.61; N, 16.73%]; ν_{max} (ATR) 3157, 3113, 3060, 2964, 1743, 1708, 1622, 1581, 1507, 1438, 1322, 1237, 1124, 1025, 958, 799, 769, 747, 631 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.79 and 3.84 (6H, 2s, 2×OMe), 8.27 (1H, s, 2-H), 8.39 (1H, s, 5-H); δ_C (126 MHz, DMSO-d_6) 51.5, 51.8, 98.4, 101.7, 134.4, 143.3, 146.4, 152.6, 161.8, 163.6; HRMS (ESI): MH$^+$, found 252.062. $C_{10}H_{10}N_3O_5$ requires 252.0620.

*4.3.2. 6-Benzyl-3-methyl 7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3,6-dicarboxylate (**7b**).* Prepared from dibenzyl malonate via enaminone **6b**. Yield: 1.30 g (40%) of white solid; mp 240–247 °C; [Found: C, 57.95; H, 3.79; N, 12.65. $C_{16}H_{13}N_3O_5 \cdot ¼H_2O$ requires: C, 57.92; H, 4.10; N, 12.66%]; ν_{max} (ATR) 3194, 3116, 3065, 2959, 2946, 1744, 1685, 1642, 1598, 1506, 1455, 1437, 1356, 1282, 1248, 1199, 1180, 1122, 1035, 975, 778, 748, 696, 631 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.85 (3H, s, OMe), 5.32 (2H, s, CH_2Ph), 7.35 (1H, t, J=7.3 Hz, *p*-Ph), 7.41 (2H, t, J=7.5 Hz, *m*-Ph), 7.48 (2H, d, J=7.1 Hz, *o*-Ph), 8.30 (1H, s, 2-H), 8.41 (1H, s, 5-H), 12.86 (1H, s, N*H*); δ_C (126 MHz, DMSO-d_6) 51.6, 65.8, 98.4, 101.8, 127.8, 128.0, 128.5, 136.2, 142.2, 143.3, 146.1, 152.4, 161.8, 162.9. HRMS (ESI): MH$^+$, found 328.0926. $C_{16}H_{14}N_3O_5$ requires 328.0933.

4.4. 7-Oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylic acid (8a)

Dimethyl ester **7a** (251 mg, 1 mmol) was added to a solution of $LiOH \cdot H_2O$ (251 mg, 6 mmol) in 50% aq MeOH (10 mL) and the mixture was stirred under reflux for 1.5 h. Methanol was evaporated in vacuo (35 °C, 50 mbar) and the aqueous residue was acidified with 1 M aq HCl to pH ~ 3. The precipitate was collected by filtration and washed with ether (2×5 mL) to give the *title compound* **8a** (177 mg, 79%) as a pale yellow solid; mp 280–285 °C; [Found: C, 41.88; H, 2.33; N, 18.22. $C_8H_5N_3O_5 \cdot {}^1/_3\ H_2O$ requires: C, 41.94; H, 2.49; N, 18.34%]; ν_{max} (ATR) 3089, 2940, 2742, 1742, 1707, 1627, 1583, 1500, 1462, 1435, 1376, 1346, 1285, 1256, 1200, 1145, 1117, 1026, 912, 862, 822, 791, 775, 714, 663, 626 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 8.09 (1H, s, 2-H), 8.48 (1H, s, 5-H), 2×COOH exchanged; δ_C (126 MHz, DMSO-d_6) 99.7, 100.9, 143.5, 144.1, 146.9, 155.2, 163.1, 164.5, HRMS (ESI): MH$^+$, found 224.0302. $C_8H_6N_3O_5$ requires 224.0307.

4.5. 3-(Methoxycarbonyl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (8b)

Method A. A mixture of benzyl methyl ester **7b** (1.635 g, 5 mmol), 10% Pd–C (164 mg), and DMF (70 mL) was hydrogenated at rt under 3 bar of hydrogen for 1 h. The catalyst was removed by filtration through a sintered glass funnel and washed with the DMF (2×10 mL). The combined filtrate was evaporated in vacuo to remove most of DMF and the residue was diluted with dichloromethane (50 mL) and stirred at rt for 12 h. The precipitate was collected by filtration and washed with dichloromethane (2×5 mL) to give the *title compound* **8b** as a white solid.

Method B. A mixture of benzyl methyl ester **7b** (1.635 g, 5 mmol) and 33% HBr–AcOH (30 mL) was stirred at 60 °C for 2 h and cooled to rt. The precipitate was collected by filtration and washed with

ethanol (5 mL) and ether (2×5 mL) to give the *title compound* **8b** as a white solid.

Yield: 1.118 g (89%, Method A) and 830 mg (70%, Method B) of white solid; mp 271–275 °C; [Found: C, 45.81; H, 3.07; N, 17.48. $C_9H_7N_3O_5$ requires: C, 45.58; H, 2.97; N, 17.72%]; ν_{max} (ATR) 3089, 2934, 2885, 2741, 1742, 1707, 1627, 1582, 1500, 1461, 1435, 1376, 1346, 1256, 1200, 1117, 1026, 942, 912, 862, 822, 791, 775, 714, 663, 626 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 8.32 (1H, s, 2-H), 8.42 (1H, s, 5-H), COOH exchanged; δ_C (126 MHz, DMSO-d_6) 51.5, 98.5, 101.8, 142.7, 143.6, 146.2, 154.3, 161.8, 164.2; HRMS (ESI): MH^+, found 238.0926. $C_9H_8N_3O_5$ requires 238.0933.

4.6. Thermal decarboxylation of the dicarboxylic acid 8a. Synthesis of 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine (9)

Compound **8a** (167 mg, 0.75 mmol) was heated at 250 °C for 4 h to give a 1:2 mixture of **8a** and **9**. Subsequent crystallization of this mixture from aqueous EtOH gave the *title compound* **9** (52 mg, 51%) as a white solid; mp 333–338 °C, lit.[10a] mp 335–338 °C, lit.[16] mp 338–340 °C; δ_H (500 MHz, DMSO-d_6) 5.69 (1H, d, J=7.0 Hz, 6-H), 6.18 (1H, d, J=2.0 Hz, 3-H), 7.81–7.93 (2H, m, 2-H, 5-H), 12.36 (1H, br s, 4-*H*); HRMS (ESI): MH^+, found 136.0503. $C_6H_6N_3O$ requires 136.0511.

4.7. Decarboxylation of carboxylic acid 8b. Synthesis of methyl 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (5)

A mixture of **8b** (2.37 g, 10 mmol), quinoline (20 mL), and Cu powder (200 mg) was stirred at 180 °C for 45 min and cooled to rt. The precipitate was collected by filtration and washed with quinoline (2×25 mL) and ether (2×50 mL) to give the *title compound* **5** (1.45 g, 75%) as a white solid. Physical, analytical and spectral data were identical to the data of **5** obtained from methyl propiolate (**1**) (see Section 4.2).

4.8. Methyl 7-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (10)

A mixture of **8b** (193 mg, 1 mmol), $POCl_3$ (4 mL), and Et_3N (300 μL, 2 mmol) was stirred under reflux for 3 h (*Caution: addition of Et_3N to $POCl_3$ is exothermic*!). Volatile components were evaporated in vacuo and the residue was triturated with crushed ice/water (20 mL). The precipitate was collected by filtration, washed with cold water (0 °C, 5 mL), and then suspended in dichloromethane (10 mL). The undissolved residue was removed by filtration and the filtrate was dried over anhyd sodium sulfate, filtered, and the filtrate was evaporated in vacuo to give the *title compound* **10** (159 mg, 75%) as white crystals; mp 203–208 °C; [Found: C, 45.26; H, 2.54; N, 19.69. $C_8H_6ClN_3O_2$ requires: C, 45.41; H, 2.86; N, 19.86%]; ν_{max} (ATR) 3061, 3003, 2952, 2848, 1715, 1608, 1542, 1507, 1466, 1437, 1382, 1272, 1247, 1206, 1156, 1090, 958, 919, 906, 859, 830, 798, 777, 654, 637 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.99 (3H, s, OMe), 7.18 (1H, d, J=4.6 Hz, 6-H), 8.69 (1H, d, J=4.6 Hz, 5-H), 8.70 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 52.0, 104.6, 109.9, 140.5, 148.2, 148.9, 151.7, 162.5; HRMS (ESI): MH^+, found 212.0219. $C_8H_7ClN_3O_2$ requires 212.0227.

4.9. Methyl 7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (11a)

A mixture of **10** (100 mg, 0.5 mmol), phenylboronic acid (163 mg, 0.5 mmol), cesium carbonate (175 mg, 0.5 mmol), $Pd(PPh_3)_4$ (6 mg, 0.005 mmol), $[PdCl(allyl)]_2$ (2 mg, 0.005 mmol), and DMF (4 mL) was stirred at 95 °C for 24 h. Volatile components were evaporated in vacuo and the residue was purified by FC (EtOAc). Fractions containing the product were combined and evaporated in vacuo to afford the *title compound* **11a** (75 mg, 58%) as a white solid; mp 150–154 °C; [Found: C, 65.92; H, 4.21; N, 16.33. $C_{14}H_{11}N_3O_2 \cdot 1/10H_2O$ requires: C, 65.93; H, 4.43; N, 16.47%]; ν_{max} (ATR) 3089, 3063, 3028, 2995, 2951, 1807, 1690, 1609, 1543, 1494, 1483, 1443, 1371, 1345, 1335, 1298, 1263, 1234, 1200, 1172, 1125, 1054, 1000, 958, 905, 858, 805, 858, 805, 780, 763, 681, 654, 632, 612 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.18 (3H, s, NMe), 3.96 (3H, s, OMe), 5.29 (2H, s, NC*H*$_2$Ph), 6.16 (1H, s, J=5.4 Hz, 6-H), 7.20–7.26 (2H, m, 2H of Ph), 7.28–7.39 (3H, m, 3H of Ph), 8.43 (1H, d, J=5.4 Hz, 5-H), 8.50 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 39.5, 51.1, 101.6, 109.9, 128.5, 129.7, 129.9, 131.4, 146.9, 147.0, 148.2, 153.1, 162.2; HRMS (ESI): MH^+, found 254.0924. $C_{14}H_{12}N_3O_2$ requires 254.0930.

4.10. Methyl 7-(benzyl(methyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylate (11b)

A mixture of **10** (211 mg, 1 mmol), benzyl(methyl)amine (0.5 mL, 4 mmol), and MeOH (4 mL) was stirred under reflux for 1 h. Volatile components were evaporated in vacuo and the residue was purified by FC (EtOAc). Fractions containing the product were combined and evaporated in vacuo to afford the *title compound* **11b** (310 mg, 96%) as a white solid; mp 140–142 °C; [Found: C, 64.99; H, 5.20; N, 18.83. $C_{16}H_{16}N_4O_2$ requires: C, 64.85; H, 5.44; N, 18.91%]; ν_{max} (ATR) 3110, 3001, 2951, 2902, 1684, 1597, 1558, 1533, 1498, 1464, 1439, 1404, 1387, 1364, 1326, 1302, 1282, 1249, 1221, 1200, 1187, 1167, 1134, 1090, 1077, 1009, 957, 894, 800, 791, 777, 759, 713, 628 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.00 (3H, s, OMe), 7.10 (1H, d, J=4.0 Hz, 6-H), 7.51–7.67 (3H, m, *m*, *p*-Ph), 8.01 (2H, dd, J=8.0, 2.0 Hz, *o*-Ph), 8.65 (1H, s, 2-H), 8.85 (1H, d, J=4.0 Hz, 5-H); δ_C (126 MHz, DMSO-d_6) 39.2, 51.7, 56.6, 93.9, 101.1, 127.8, 128.0, 128.9, 136.3, 146.4, 150.6, 150.7, 152.4, 163.7 HRMS (ESI): MH^+, found 297.1351. $C_{16}H_{17}N_4O_2$ requires 297.1352.

4.11. Methyl 7-(benzyloxy)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (11c)

Tetrabutylammonium bromide (4 mg, 12.5 μmol, 5 mol %) and BnOH (258 μL, 2.5 mmol) were added to a solution of chloro compound **10** (52 mg, 0.25 mmol) in dichloromethane (1 mL) and the mixture was stirred for 5 min. Then, 2 M aq NaOH (125 μL, 0.25 mmol) was added and the mixture was stirred at rt for 12 h. Water (10 mL) was added and the product was extracted with dichloromethane (2×5 mL). The combined organic phases were dried over anhyd sodium sulfate, filtered, the filtrate was evaporated in vacuo, and the residue was purified by FC (EtOAc). Fractions containing the product were combined and evaporated in vacuo to give the *title compound* **11c** (50 mg, 71%) as a white solid; mp 175–176 °C; [Found: C, 63.34; H, 4.42; N, 14.96. $C_{15}H_{13}N_3O_3$ requires: C, 63.60; H, 4.63; N, 14.83%]; ν_{max} (ATR) 3108, 3071, 2950, 1687, 1615, 1551, 1537, 1491, 1435, 1368, 1344, 1312, 1281, 1235, 1222, 1205, 1188, 1169, 1127, 1093, 1010, 948, 909, 858, 827, 800, 776, 757, 741, 697, 656, 639 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.98 (3H, s, OMe), 5.54 (2H, s, OC*H*$_2$Ph), 6.44 (1H, d, J=5.2 Hz, 6-H), 7.35–7.60 (5H, m, Ph), 8.65 (1H, s, 2-H), 8.64 (1H, d, J=5.2 Hz, 5-H); δ_C (126 MHz, DMSO-d_6) 51.8, 72.9, 77.1, 90.2, 102.8, 127.9, 129.2, 129.5, 133.0, 148.1, 149.8, 154.0, 155.5, 163.2; HRMS (ESI): MH^+, found 284.1033. $C_{15}H_{14}N_3O_3$ requires 284.1035.

4.12. Hydrolysis of the esters 11a and 11b. Synthesis of 7-substituted pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acids 12a and 12b

A mixture of the ester **11** (1 mmol), MeOH (3 mL), and 2 M aq NaOH (2 mL, 4 mmol) was added and the mixture was stirred at 50 °C for 1 h. Methanol was evaporated in vacuo (40 °C, 50 mbar),

water (5 mL) was added to the aqueous residue, and the solution was acidified with 37% aq HCl. The precipitate was collected by filtration to give the *title compound* **12**. The following compounds were prepared in this manner:

*4.12.1. 7-Phenylpyrazolo[1,5-a]pyrimidine-3-carboxylic acid (**12a**).* Prepared from **11a** (252 mg, 1 mmol), acidification to pH ~1. Yield: 232 mg (93%) of white solid; mp 224–226 °C; [Found: C, 65.04; H, 3.59; N, 17.51. $C_{13}H_9N_3O_2$ requires: C, 65.27; H, 3.79; N, 17.56%]; ν_{max} (ATR) 3471, 3311, 3210, 3097, 3070, 2528, 1951, 1657, 1610, 1576, 1541, 1496, 1448, 1365, 1342, 1316, 1270, 1229, 1204, 1184, 1170, 1132, 1084, 1057, 997, 973, 903, 860, 833, 788, 774, 756, 699, 690, 650, 633, 624 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.46 (1H, d, J=4.4 Hz, 6-H), 7.67–7.59 (3H, m, *m*, *p*-Ph), 8.09 (2H, dd, J=7.9, 1.6 Hz, *o*-Ph), 8.63 (1H, s, 2-H), 8.86 (1H, d, J=4.4 Hz, 5-H), 12.45 (1H, br s, COO*H*); δ_C (126 MHz, DMSO-d_6) 102.6, 109.6, 128.5, 129.7, 130.0, 131.3, 146.8, 147.1, 148.2, 152.6, 163.1; HRMS (ESI): MH^+, found 240.0770. $C_{13}H_{10}N_3O_2$ requires 240.0773.

*4.12.2. 7-(Benzyl(methyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (**12b**).* Prepared from **11b** (296 mg, 1 mmol), acidification to pH ~5. Yield: 158 mg (56%) of white solid; mp 60–64 °C; ν_{max} (ATR) 3637, 3398, 3025, 1648, 1598, 1551, 1495, 1451, 1430, 1404, 1369, 1333, 1278, 1229, 1202, 1182, 1093, 1073, 1011, 963, 892, 796, 762, 739, 695, 654, 630 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.40 (3H, s, OMe), 5.46 (2H, s, NC*H*$_2$Ph), 6.66 (1H, d, J=6.6 Hz, 6-H), 7.26–7.45 (5H, m, Ph), 8.30 (1H, d, J=6.6 Hz, 5-H), 8.57 (1H, s, 2-H), COOH exchanged; δ_C (126 MHz, DMSO-d_6) 39.5, 55.3, 93.8, 102.9, 127.4, 127.5, 128.6, 137.0, 145.9, 149.9, 149.9, 151.5, 164.2; HRMS (ESI): MH^+, found 283.1191. $C_{15}H_{15}N_4O_2$ requires 283.1195.

4.13. N-alkylation of 5. Synthesis of methyl 4-alkyl-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylates 13a–d

A mixture of **5** (193 mg, 1 mmol), K_2CO_3 (414 mg, 3 mmol), and anhyd DMF (5 mL) was stirred at rt for 30 min. Then, alkyl halide (3–5 mmol) was added and stirring at rt was continued for 72 h. Volatile components were evaporated in vacuo and the residue was chromatographed (FC) over silica gel (EtOAc). The combined eluate was evaporated in vacuo to afford the *title compound* **13**. The following compounds were prepared in this manner:

*4.13.1. Methyl 4-methyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxylate (**13a**).* Prepared from **5** and MeI (312 μL, 5 mmol). Yield: 54 mg (26%) of white solid; mp 204–210 °C; [Found: C, 52.44; H, 4.03; N, 19.94. $C_9H_9N_3O_3$ requires: C, 52.17; H, 4.38; N, 20.28%]; ν_{max} (ATR) 3449, 3067, 2951, 1726, 1697, 1561, 1491, 1385, 1433, 1234, 1191, 1173, 1147, 1077, 1010, 802 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.79 and 4.03 (6H, 2s, 1:1, 2×Me), 6.00 (1H, d, J=7.7 Hz, 6-H), 7.96 (1H, d, J=7.8 Hz, 5-H), 8.27 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 42.8, 51.8, 98.4, 98.9, 143.2, 144.9, 146.4, 155.0, 161.7; HRMS (ESI): MH^+, found 208.0717. $C_9H_9N_3O_3$ requires 208.0645.

*4.13.2. Methyl 4-benzyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxylate (**13b**).* Prepared from **5** and BnBr (355 μL, 3 mmol). Yield: 246 mg (87%) of white solid; mp 168–174 °C; [Found: C, 63.58; H, 4.41; N, 14.57. $C_{15}H_{13}N_3O_3$ requires: C, 63.60; H, 4.63; N, 14.83%]; ν_{max} (ATR) 3062, 3032, 2958, 1708, 1680, 1612, 1559, 1486, 1456, 1435, 1421, 1356, 1238, 1184, 1164, 1108, 1078, 1029, 806, 755, 706 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.84 (3H, s, OMe), 5.94 (2H, s, C*H*$_2$Ph), 6.07 (1H, d, J=8.0 Hz, 6-H), 7.32–7.40 (5H, m, Ph), 7.43 (1H, d, J=8.0 Hz, 5-H), 8.32 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 52.0, 56.3, 98.4, 100.0, 126.8, 128.0, 128.8, 136.3, 142.7, 145.1, 145.8, 155.0, 161.9; HRMS (ESI): MH^+, found 284.1021. $C_{15}H_{14}N_3O_3$ requires 283.1030.

*4.13.3. Methyl 4-ethyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxylate (**13c**).* Prepared from **5** and EtI (400 μL, 3 mmol). Yield: 44 mg (20%) of white solid; mp 150–151 °C; ν_{max} (ATR) 3049, 2920, 2850, 1720, 1694, 1561, 1490, 1474, 1233, 1217, 1188, 1173, 1143, 1094, 1081, 799, 767 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.29 (3H, t, J=7.0 Hz, C*H*$_3$CH$_2$), 3.81 (3H, s, OMe), 4.63 (2H, q, J=7.1 Hz, C*H*$_2$CH$_3$), 6.06 (1H, d, J=7.8 Hz, 6-H), 8.06 (1H, d, J=7.8 Hz, 5-H), 8.31 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 15.2, 49.8, 51.8, 97.7, 99.6, 142.3, 145.2, 155.0, 161.7; HRMS (ESI): MH^+, found 221.0874. $C_{10}H_{12}N_3O_3$ requires 221.0873.

*4.13.4. Methyl 4-(2-tert-butoxy-2-oxoethyl)-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxylate (**13d**).* Prepared from **5** and *tert*-butyl bromoacetate (443 μL, 3 mmol). Yield: 306 mg (100%) of white solid; mp 216–217 °C; ν_{max} (ATR) 3105, 2986, 2951, 1744, 1712, 1691, 1559, 1362, 1235, 1149, 1115, 936, 855 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.40 (9H, s, *t*-Bu), 3.76 (3H, s, OMe), 5.34 (2H, s, CH_2), 6.10 (1H, d, J=7.8 Hz, 6-H), 7.96 (1H, d, J=7.8 Hz, 5-H), 8.28 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 27.6, 21.2, 55.9, 82.1, 98.5, 99.4, 143.1, 145.0, 146.3, 154.8, 161.8, 162.3, 166.8; HRMS (ESI): MH^+, found 308.1240. $C_{14}H_{18}N_3O_5$ requires 307.1241.

4.14. Benzyl 4-benzyl-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (13e)

A mixture of **13b** (1.192 g, 4.21 mmol), BnOH (40 mL), and DBU (0.5 mL, 3.34 mmol) was stirred at 130 °C for 24 h. Volatile components were evaporated in vacuo and the residue was purified by FC (EtOAc). Fractions containing the product were combined and evaporated in vacuo. The residue was triturated with Et_2O (10 mL) and the precipitate was collected by filtration to give **13e**. Yield: 953 mg (63%) of light brown solid; mp 130–132 °C; [Found: C, 70.40; H, 4.92; N, 11.70. $C_{21}H_{17}N_3O_3$ requires: C, 70.18; H, 4.77; N, 11.69%]; ν_{max} (ATR) 3034, 3014, 1692, 1607, 1566, 1487, 1454, 1400, 1367, 1336, 1233, 1171, 1106, 1077, 1026, 984, 959, 899, 877, 802, 783, 769, 737, 694, 639, 613 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 5.26 (2H, s, COO–C*H*$_2$–Ph), 5.91 (2H, s, N–C*H*$_2$–Ph), 6.14 (1H, d, J=7.8 Hz, 2-H), 7.10–7.41 (10H, m, 2× Ph), 8.15 (1H, d, J=7.8 Hz, 1-H), 8.33 (1H, s, 3-H); δ_C (126 MHz, DMSO-d_6) 56.2, 65.9, 98.3, 100.1, 126.7, 127.9, 128.0, 128.5, 128.8, 136.0, 136.1, 142.8, 145.1, 145.8, 154.9, 161.2; HRMS (ESI): MH^+, found 360.1341. $C_{21}H_{18}N_3O_3$ requires 360.1343.

4.15. Hydrolysis of the esters 5 and 13a. Synthesis of 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylic acids 14a and 14b

$LiOH \cdot H_2O$ (252 mg, 6 mmol) was added to a stirred suspension of the ester **5** or **13a** (1 mmol) in water (8 mL) the mixture was stirred at rt for 1 h. The so formed solution was acidified with 1 M aq HCl (~6 mL) to pH ~4. The precipitate was collected by filtration to give the *title compound* **14**. The following compounds were prepared in this manner:

*4.15.1. 7-Oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxylic acid (**14a**).* Prepared from **5** (193 mg, 1 mmol). Yield: 131 mg (73%) of white solid; mp 255–257 °C; [Found: C, 43.16; H, 3.18; N, 21.21. $C_7H_5N_3O_3 \cdot 7/8H_2O$ requires: C, 43.14; H, 3.49; N, 21.56%]; ν_{max} (ATR) 3106, 3074, 2969, 2868, 2585, 1681, 1616, 1582, 1501, 1467, 1421, 1301, 1267, 1195, 1137, 1070, 1007, 924, 883, 797, 780, 746 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 5.91 (1H, d, J=7.5 Hz, 6-H), 7.79 (1H, d, J=7.5 Hz, 5-H), 8.18 (1H, s, 2-H), OH and NH exchanged; δ_C

(126 MHz, DMSO-d_6) 97.7, 98.9, 140.5, 143.2, 143.4, 155.9, 163.4; HRMS (ESI): $[M-H]^-$, found 179.0257. $C_7H_6N_3O_3$ requires 179.0258.

*4.15.2. 4-Methyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxylic acid (**14b**).* Prepared from **13a** (207 mg, 1 mmol). Yield: 106 mg (55%) of white solid; mp 220–223 °C; [Found: 49.29; H, 3.51; N, 21.34. $C_8H_7N_3O_3 \cdot 1/10H_2O$ requires: C, 49.29; H, 3.72; N, 21.55%]; ν_{max} (ATR) 3000, 2919, 1711, 1651, 1564, 1492, 1455, 1426, 1365, 1334, 1240, 1216, 1182, 1149, 1088, 972, 911, 826, 801, 771, 744, 684, 647, 635 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.06 (3H, s, Me), 5.98 (1H, d, J=7.7 Hz, 6-H), 7.94 (1H, d, J=7.7 Hz, 5-H), 8.23 (1H, s, 2-H), 12.74 (1H, br s, CO_2H); δ_C (126 MHz, DMSO-d_6) 42.8, 98.6, 99.5, 143.0, 145.4, 146.3, 155.13, 162.8; HRMS (ESI): MH^+, found 194.0560. $C_8H_8N_3O_3$ requires 194.0560.

4.16. 4-Benzyl-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (14c)

A mixture of **13e** (0.5391 g, 1.5 mmol), MeOH (25 mL), and 10% Pd–C (25 mg) was hydrogenated (via balloon) at rt and the reaction progress was monitored by TLC in 15 min intervals. Upon completion of reaction (~45 min), the catalyst was removed by filtration through a glass-sintered funnel and the filtrate was evaporated in vacuo to give the *title compound* **14c**. Yield: 223 mg (55%) of white solid; mp 209–213 °C; [Found: C, 62.26; H, 3.89; N, 15.52. $C_{14}H_{11}N_3O_3$ requires: C, 62.45; H, 4.12; N, 15.61%]; ν_{max} (ATR) 3084, 3012, 2887, 2822, 2756, 2710, 2592, 2568, 2527, 2471, 1710, 1646, 1596, 1543, 1482, 1457, 1416, 1338, 1323, 1259, 1213, 1160, 1118, 1009, 965, 901, 823, 767, 739, 708, 695, 656, 634, 617 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 6.01 (2H, s, CH_2Ph), 6.10 (1H, d, J=7.7 Hz, 2-H), 7.10–7.41 (5H, m, Ph), 8.12 (1H, d, J=7.7 Hz, 1-H), 8.25 (1H, s, 3-H), 12.89 (1H, br s, COOH); δ_C (126 MHz, DMSO-d_6) 56.1, 99.6, 99.7, 126.8, 127.9, 128.7, 136.5, 142.5, 146.0, 155.0, 163.1; HRMS (ESI): MH^+, found 270.0874. $C_{14}H_{12}N_3O_3$ requires 270.0873.

4.17. Amidation of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acids 12a,b and 14a–c. General procedure for the synthesis of carboxamides 15a–c and 16a–q

A mixture of carboxylic acid **12** or **14** (0.5 mmol), anh. DMF (5 mL), and Et_3N (70 μL, 0.5 mmol) was stirred at room temperature for 5 min. Then, BPC (197 mg, 0.5 mmol) was added and the mixture was stirred at rt for 1 h (activation of carboxylic acid). Next, amine (0.5 mmol) and Et_3N (70 μL, 0.5 mmol) were added and stirring at rt was continued for 24 h. Volatile components were evaporated in vacuo (2 mbar, 50 °C), dichloromethane (5 mL) was added, and the mixture was evaporated in vacuo (first at 2 mbar/50 °C, then at 0.01 mbar/80 °C) to give **15** or **16**. The crude product was purified by FC (silica gel, first EtOAc/hexanes to elute the non-polar impurities, then EtOAc/MeOH, $CHCl_3$/MeOH, or $CHCl_3$/MeOH/Et_3N to elute the product). Fractions containing the product were combined, and evaporated in vacuo to give the purified carboxamide **15** or **16**. The following compounds were prepared in this manner:

*4.17.1. N-(2-Methoxyethyl)-7-phenylpyrazolo[1,5-a]pyrimidine-3-carboxamide (**15a**).* Prepared from **12a** (120 mg, 0.5 mmol) and 2-methoxyethylamine (45 μL, 0.5 mmol), FC: 67% EtOAc/hexanes, then 90% EtOAc/MeOH. Yield: 149 mg (100%) of white solid; mp 110 °C (decomp.); ν_{max} (ATR) 3354, 3088, 3059, 2981, 2928, 2834, 2814, 1935, 1799, 1740, 1649, 1606, 1544, 1516, 1492, 1445, 1403, 1374, 1340, 1324, 1272, 1258, 1197, 1186, 1174, 1158, 1105, 1081, 1052, 1029, 1013, 996, 952, 902, 860, 821, 768, 709, 689, 651, 632, 618 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.31 (3H, s, OMe), 3.50 (2H, t, J=5.3 Hz, OCH_2), 3.56 (2H, q, J=5.3 Hz, CH_2NH), 7.48 (d, J=4.5 Hz, 6-H), 7.61–7.68 (3H, m, *o*,*p*-Ph), 8.09–8.16 (2H, m, *m*-Ph), 8.21 (1H, t, J=5.7 Hz, N*H*CH_2), 8.62 (1H, s, 2-H). δ_C (126 MHz, DMSO-d_6) 38.2, 58.1, 71.0, 105.1, 109.2, 128.6, 129.7, 129.9, 131.6, 145.6, 146.5, 147.2, 152.0, 161.2; HRMS (ESI): MH^+, found 297.1332 $C_{16}H_{17}N_4O_2$ requires 297.1352.

*4.17.2. 7-(Benzyl(methyl)amino)-N-(2-methoxyethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**15b**).* Prepared from **12b** (141 mg, 0.5 mmol) and 2-methoxyethylamine (45 μL, 0.5 mmol), FC: first EtOAc, then 90% EtOAc/MeOH. Yield: 112 mg (66%) of white solid; mp 97–100 °C; ν_{max} (ATR) 3357, 3315, 3026, 2996, 2977, 2929, 2892, 2864, 2830, 2650, 2570, 1646, 1598, 1558, 1535, 1510, 1453, 1439, 1415, 1384, 1352, 1327, 1302, 1257, 1232, 1192, 1180, 1154, 1117, 1095, 1077, 1058, 1002, 978, 893, 872, 831, 814, 789, 770, 748, 706, 696, 672, 633, 605 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.22 (3H, s, NMe), 3.44 (3H, s, OMe), 3.64 (2H, t, J=5.3 Hz, CH_2NH), 3.74 (2H, q, J=5.5 Hz, OCH_2), 5.33 (2H, s, NCH_2), 6.11 (1H, d, J=5.4 Hz, 6-H), 7.22–7.39 (5H, m, Ph), 8.27 (1H, d, J=5.4 Hz, 5-H), 8.57 (1H, s, 2-H), 8.75 (1H, br t, J=5.6 Hz, CON*H*); δ_C (126 MHz, DMSO-d_6) 38.9, 39.1, 56.4, 58.8, 71.5, 92.8, 103.2, 127.7, 127.8, 128.8, 136.1, 144.7, 149.3, 150.3, 150.7, 163.7; HRMS (ESI): MH^+, found 340.1768. $C_{18}H_{22}N_5O_2$ requires 340.1773.

*4.17.3. 7-(Benzyl(methyl)amino)-N-(3-(dimethylamino)propyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**15c**).* Prepared from **12b** (141 mg, 0.5 mmol) and 3-(dimethylamino)propylamine (64 μL, 0.5 mmol), FC: first EtOAc, then 75% $CHCl_3$/MeOH containing 3% Et_3N. Yield: 145 mg (79%) of brownish oil; ν_{max} (ATR) 3307, 3031, 2944, 1641, 1601, 1546, 1494, 1453, 1410, 1365, 1325, 1295, 1234, 1180, 1151, 1107, 1076, 1002, 978, 908, 895, 832, 776, 729, 707, 696, 629, 612 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.94–2.13 (2H, m, $CH_2CH_2CH_2$), 2.63 (6H, s, Me_2N), 2.86–3.02 (2H, m, Me_2NCH_2), 3.22 (3H, s, NMe), 3.58 (2H, q, J=6.4 Hz, CH_2NH), 5.35 (2H, s, CH_2Ph), 6.10 (1H, d, J=5.4 Hz 6-H), 7.15–7.49 (5H, m, Ph), 8.20 (1H, d, J=5.4 Hz, 5-H), 8.51 (1H, br t, J=6.4 Hz, N*H*CH_2), 8.52 (1H, s, 2-H); δ_C (75 MHz, DMSO-d_6) 26.7, 36.6, 39.5, 41.2, 44.0, 56.6, 56.9, 93.1, 103.7, 128.0, 128.2, 129.2, 136.6, 145.1, 149.6, 150.8, 150.9, 163.9; HRMS (ESI): MH^+, found 367.2242. $C_{20}H_{27}N_6O$ requires 367.2248.

*4.17.4. 7-Oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16a**).* Prepared from **14a** (90 mg, 0.5 mmol) and excess NH_3 (gentle bubbling for 15 min into the reaction mixture after activation of **14a** with BPC; addition of Et_3N was omitted). The precipitate was collected by filtration to give the *title compound* **16a** (82 mg, 92%) as a grey–white solid; mp 305–318 °C; ν_{max} (ATR) 3328, 3190, 2996, 2890, 1659, 1637, 1581, 1542, 1522, 1459, 1408, 1350, 1310, 1236, 1213, 1162, 1132, 1005, 886, 874, 810, 774, 724, 686, 625 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 5.55 (1H, d, J=5.9 Hz, 6-H), 6.88 (1H, s, NH), 7.14 (1H, br s, NH), 7.79 (1H, d, J=5.9 Hz, 5-H), 7.96 (1H, br s, NH), 7.97 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 95.2, 101.2, 141.8, 150.1, 150.5, 157.9, 164.6; HRMS (ESI): MH^+, found 179.0563. $C_7H_7N_4O_2$ requires 179.0564.

*4.17.5. N-(2-Methoxyethyl)-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16b**).* Prepared from **14a** (90 mg, 0.5 mmol) and 2-methoxyethylamine (45 μL, 0.5 mmol); FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 96 mg (81%) of grey–white solid; mp 229–234 °C; ν_{max} (ATR) 3315, 3201, 3069, 2925, 1684, 1614, 1556, 1533, 1489, 1454, 1397, 1361, 1292, 1241, 1211, 1163, 1149, 1117, 1092, 1062, 1032 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.27 (3H, s, OMe), 3.41–3.47 (4H, m, CH_2CH_2), 5.80 (1H, d, J=6.9 Hz, 6-H), 7.79 (1H, d, J=7.1 Hz, 5-H), 8.34 (1H, s, 2-H), 8.48 (1H, t, J=5.1 Hz, N*H*CH_2); δ_C (126 MHz, DMSO-d_6) 38.1, 58.0, 70.9, 97.5, 100.2, 141.0, 143.9, 156.6, 162.1, 168.6; HRMS (ESI): MH^+, found 237.0983. $C_{10}H_{13}N_4O_4$ requires 237.0982.

*4.17.6. N-(3-(Dimethylamino)propyl)-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16c**).* Prepared from **14a** (90 mg, 0.5 mmol) and 3-(dimethylamino)propylamine (64 μL, 0.5 mmol), FC: first EtOAc, then 75% $CHCl_3$/MeOH containing 3% Et_3N to elute

the product. Yield: 125 mg (94%) of brownish semi-solid; ν_{max} (ATR) 3291, 3023, 2944, 2702, 2657, 2485, 1624, 1524, 1344, 1227, 1151, 998, 794, 619 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.99–2.08 (2H, m, $CH_2CH_2CH_2$), 2.71 (6H, s, NMe_2), 3.08 (2H, br t, J=7.4 Hz, OCH_2), 3.48 (2H, br q, J=6.2 Hz, CH_2NH), 5.80 (1H, br d, J=5.7 Hz, 6-H), 7.91 (1H, br d, J=5.7 Hz, 5-H), 8.15 (1H, br s, 2-H), 8.48 (1H, br t, J=6.0 Hz, $NHCH_2$), 9.91 (1H, br s, NH); δ_C (126 MHz, DMSO-d_6) 26.5, 35.9, 43.8, 56.4, 95.6, 102.0, 142.6, 149.8, 151.5, 159.6, 164.6; HRMS (ESI): MH^+, found 264.1456. $C_{12}H_{18}N_5O_2$ requires 264.1455.

*4.17.7. N-Benzyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16d**).* Prepared from **14a** (90 mg, 0.5 mmol) and benzylamine (56 μL, 0.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 116 mg (86%) of white solid; mp 277–290 °C; ν_{max} (ATR) 3277, 1696, 1619, 1604, 1592, 1566, 1493, 1454, 1412, 1362, 1299, 1244, 1192, 1151, 1071, 1048, 1018, 950, 907, 875, 800, 788, 770, 737, 720, 696, 636, 611 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.50 (2H, d, J=6.0 Hz, CH_2NH), 5.82 (1H, d, J=7.2 Hz, 6-H), 7.21–7.27 (1H, m, *p*-Ph), 7.29–7.42 (4H, m, *o*,*m*-Ph), 7.78 (1H, d, J=7.2 Hz, 5H), 8.38 (1H, s, 2-H), 8.93 (1H, t, J=6.0 Hz, $NHCH_2$), 12.02 (1H, br s, NH); δ_C (126 MHz, DMSO-d_6) 41.9, 97.8, 100.0, 126.8, 127.4, 128.4, 139.7, 140.8, 141.7, 143.9, 156.3, 162.0; HRMS (ESI): MH^+, found 269.1034. $C_{14}H_{13}N_4O_2$ requires 269.1033.

*4.17.8. N-(4-Methylbenzyl)-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16e**).* Prepared from **14a** (90 mg, 0.5 mmol) and 4-methylbenzylamine (65 μL, 0.5 mmol), FC: first 67% EtOAc/hexanes, then 90% $CHCl_3$/MeOH. Yield: 128 mg (90%) of white solid; mp 255–270 °C; ν_{max} (ATR) 3288, 3071, 1689, 1616, 1534, 1515, 1491, 1454, 1411, 1358, 1281, 1235, 1212, 1148, 1075, 1059, 979, 910, 883, 795, 739, 723, 677, 626, 607 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.26 (3H, s, Me), 4.45 (2H, d, J=5.9 Hz, CH_2NH), 5.80 (1H, d, J=7.1 Hz, 6-H), 7.12 and 7.22 (4H, 2d, 1:1, J=7.7 Hz, C_6H_4), 7.79 (1H, d, J=7.1 Hz, 5-H), 8.35 (1H, s, 2-H), 8.88 (1H, t, J=6.2 Hz, $NHCH_2$), 11.53 (1H, br s, OH); δ_C (126 MHz, DMSO-d_6) 20.7, 41.6, 97.4, 100.3, 127.4, 128.9, 135.9, 136.7, 141.0, 142.9, 144.7, 156.5, 162.1; HRMS (ESI): MH^+, found 283.1190. $C_{15}H_{15}N_4O_2$ requires 283.1190.

*4.17.9. N-(3,5-Dichlorobenzyl)-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16f**).* Prepared from **14a** (90 mg, 0.5 mmol) and 3,5-dichlorobenzylamine (70 μL, 0.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 89 mg (53%) of white solid; mp 240–260 °C; ν_{max} (ATR) 3277, 1702, 1618, 1587, 1570, 1489, 1455, 1431, 1411, 1347, 1290, 1209, 1192, 1101, 1068, 1046, 1021, 956, 903, 855, 801, 784, 769, 738, 719, 695, 637 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.48 (2H, d, J=5.8 Hz, CH_2NH), 5.83 (1H, d, J=7.2 Hz, 6-H), 7.38 (1H, d, J=2.0 Hz, *p*-C_6H_3), 7.47 (1H, t, J=1.9 Hz, *o*-C_6H_3), 7.78 (1H, d, J=7.2 Hz, 5-H), 8.40 (1H, s, 2-H), 9.09 (1H, br t, J=5.8 Hz, $NHCH_2$), 12.01 (s, 1H); δ_C (126 MHz, DMSO-d_6) 41.1, 97.9, 99.8, 126.2, 126.4, 133.9, 140.9, 141.6, 144.0, 144.3, 156.3, 162.2; HRMS (ESI): MH^+, found 337.0258. $C_{14}H_{11}Cl_2N_4O_2$ requires 337.0254.

*4.17.10. N,N-Dimethyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16g**).* Prepared from **14a** (90 mg, 0.5 mmol) and dimethylamine (5.6 M in EtOH, 300 μL, 1.68 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 87 mg (84%) of grey–white solid; mp >300 °C (decomp.); ν_{max} (ATR) 3269, 3141, 3054, 2923, 1673, 1583, 1514, 1400, 1342, 1279, 1184, 1056, 1010, 902, 836, 764, 680, 608 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.08 (br *s*, 3H, NMe_2), 3.21 (6H, br s, NMe_2), 5.87 (1H, d, J=7.4 Hz, 6-H), 7.79 (1H, d, J=7.4 Hz, 5-H), 8.28 (*s*, 1H, 2-H), 12.10 (br *s*, 1H, NH); HRMS (ESI): MH^+, found 207.0876. $C_9H_{11}N_4O_2$ requires 207.0877.

*4.17.11. 3-(Pyrrolidine-1-carbonyl)pyrazolo[1,5-a]pyrimidin-7(4H)-one (**16h**).* Prepared from **14a** (90 mg, 0.5 mmol) and pyrrolidine (43 μL, 0.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 106 mg (91%) of beige solid; mp >300 °C (decomp.); ν_{max} (ATR) 3284, 3140, 3056, 2974, 2875, 1681, 1662, 1619, 1583, 1505, 1452, 1434, 1349, 1325, 1243, 1179, 1161, 1149, 1064, 1021, 898, 810 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.76–1.86 (4H, m, 2× CH_2), 3.00–3.10 (2H, m, CH_2N), 3.44 and 3.73 (2H, 2 br s, 1:1, CH_2N), 5.61 (1H, d, J=7.5 Hz, 6-H), 7.76 (1H, d, J=7.5 Hz, 5-H), 8.31 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 23.8, 44.5, 103.9, 113.4, 141.3, 142.7, 156.9, 160.7, 171.7; HRMS (ESI): MH^+, found 233.1029. $C_{11}H_{13}N_4O_2$ requires 233.1033.

*4.17.12. N-Cyclopropyl-4-methyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16i**).* Prepared from **14b** (97 mg, 0.5 mmol) and cyclopropylamine (36 μL, 0.5 mmol), FC: FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 70 mg (60%) of white solid; mp 286–290 °C; ν_{max} (ATR) 3302, 3045, 3011, 2948, 1703, 1678, 1630, 1584, 1525, 1489, 1451, 1412, 1366, 1336, 1286, 1219, 1165, 1143, 1102, 1025, 997, 944, 882, 853, 825, 796, 770, 695, 676, 640, 622 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.53–0.57 and 0.67–0.71 (4H, 2m, 1:1, CH_2CH_2), 2.79 (1H, octet, J=4.0 Hz, $CHNH$), 3.90 (3H, s, Me), 5.89 (1H, d, J=7.6 Hz, 6-H), 7.91 (1H, d, J=7.6 Hz, 5-H), 8.10 (1H, s, 2-H), 8.46 (1H, br d, J=4.1 Hz, NH); δ_C (126 MHz, DMSO-d_6) 5.7, 22.8, 41.7, 97.3, 103.0, 141.0, 142.8, 145.8, 155.3, 162.4; HRMS (ESI): MH^+, found 233.1031. $C_{11}H_{12}N_4O_2$ requires 233.1033.

*4.17.13. N-Benzyl-4-methyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16j**).* Prepared from **14b** (97 mg, 0.5 mmol) and benzylamine (56 μL, 0.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 118 mg (83%) of white solid; mp 197–199 °C; [Found: C, 64.09; H, 4.94; N, 19.68. $C_{15}H_{14}N_4O_2$ requires: C, 63.82; H, 5.00; N, 19.85%]; ν_{max} (ATR) 3270, 3046, 1704, 1676, 1620, 1578, 1538, 1484, 1452, 1413, 1390, 1367, 1350, 1334, 1308, 1234, 1145, 1110, 1082, 1062, 1035, 1018, 991, 969, 876, 860, 797, 780, 732, 690, 664, 626 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.90 (3H, s, Me), 4.45 (2H, d, J=5.9 Hz, CH_2Ph), 5.90 (1H, d, J=7.6 Hz, 6-H), 7.37–7.23 (5H, m, Ph), 7.92 (1H, d, J=7.7 Hz, 5-H), 8.22 (1H, s, 2-H), 9.01 (1H, br t, J=6.0 Hz, NH); δ_C (126 MHz, DMSO-d_6) 41.8, 42.5, 97.4, 102.9, 126.8, 127.1, 128.3, 139.4, 141.3, 142.8, 145.8, 155.3, 161.4; HRMS (ESI): MH^+, found 283.1186. $C_{15}H_{15}N_4O_2$ requires 283.1190.

*4.17.14. N-(3-Hydroxypropyl)-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16k**).* Prepared from **14b** (97 mg, 0.5 mmol) and 3-hydroxypropylamine (38 μL, 0.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 118 mg (94%) of white solid; mp 228–232 °C; ν_{max} (ATR) 3404, 3269, 3090, 3055, 2926, 2898, 2873, 1682, 1657, 1633, 1579, 1555, 1484, 1449, 1391, 1373, 1316, 1286, 1230, 1205, 1155, 1112, 1063, 995, 941, 877, 832, 794, 737, 725, 694, 667, 642, 625 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.67 (2H, br quintet, J=6.6 Hz, $CH_2CH_2CH_2$), 3.27 (2H, br q, J=6.7 Hz, OCH_2), 3.47 (2H, br q, J=6.0 Hz, CH_2NH), 3.89 (3H, s, Me), 4.48 (1H, t, J=5.1 Hz, OH), 5.89 (1H, d, J=7.7 Hz, 6-H), 7.91 (1H, d, J=7.7 Hz, 5-H), 8.13 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 32.3, 36.4, 41.6, 58.5, 97.2, 103.2, 141.0, 142.7, 145.7, 155.3, 161.3; HRMS (ESI): MH^+, found 251.1142. $C_{11}H_{15}N_4O_3$ requires 251.1139.

*4.17.15. 4-Methyl-7-oxo-N-(pyridin-2-ylmethyl)-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16l**).* Prepared from **14b** (97 mg, 0.5 mmol) and 2-picolylamine (50 μL, 0.5 mmol), FC: first EtOAc, then 75% $CHCl_3$/MeOH containing 3% Et_3N. Yield: 103 mg (73%) of white solid; mp 167–170 °C; ν_{max} (ATR) 3258, 3050, 2960, 2925, 1705, 1677, 1629, 1577, 1541, 1478, 1435, 1365, 1350, 1293, 1268, 1225, 1147, 1114, 1095, 1072, 1051, 1018, 993, 958, 875, 797, 754, 723, 664, 624 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.90 (3H, s, Me), 4.54 (2H, d, J=6.0 Hz, CH_2NH), 5.91 (1H, d, J=7.7 Hz, 6-H), 7.28 (1H, dd, J=7.0, 5.0 Hz, 5′-H), 7.38 (1H, d, J=7.8 Hz, 3′-H), 7.78 (1H, td, J=7.7, 1.8 Hz, 4′-H), 7.92 (1H, d, J=7.7 Hz, 5-H), 8.27 (1H, s, 2-H), 8.52 (1H, d, J=4.4 Hz, 6′-H), 9.08 (1H, br t, J=5.9 Hz, NH); δ_C (126 MHz, DMSO-d_6) 41.9, 44.6, 97.4, 102.9, 120.8, 122.1, 136.7, 141.3,

142.8, 145.8, 148.8, 155.3, 158.5, 161.6; HRMS (ESI): MH^+, found 284.1143. $C_{14}H_{13}N_5O_2$ requires 284.1142.

*4.17.16. N,N,4-Trimethyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16m**).* Prepared from **14b** (97 mg, 0.5 mmol) and dimethylamine (5.6 M in EtOH, 300 μL, 1.68 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 91 mg (83%) of grey-white solid; mp 231–235 °C; ν_{max} (ATR) 3060, 2921, 1682, 1584, 1510, 1480, 1441, 1412, 1400, 1344, 1257, 1214, 1154, 1134, 1076, 992, 887, 808, 751, 678, 656, 635, 613 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.14 and 3.19 (6H, 2s, 1:1, NMe_2), 3.83 (3H, s, 4-Me), 5.92 (1H, d, J=7.7 Hz, 6-H), 7.49 (1H, d, J=7.7 Hz, 5-H), 7.90 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 35.3, 39.8, 41.4, 98.4, 101.3, 141.0, 141.8, 143.9, 155.9, 163.2; HRMS (ESI): MH^+, found 221.1035. $C_{10}H_{13}N_4O_2$ requires 221.1033.

*4.17.17. 4-Methyl-3-(pyrrolidine-1-carbonyl)pyrazolo[1,5-a]pyrimidin-7(4H)-one (**16n**).* Prepared from **14b** (97 mg, 0.5 mmol) and pyrrolidine (43 μL, 0.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 98 mg (79%) of grey-white solid; mp 205–208 °C; ν_{max} (ATR) 3106, 3061, 3034, 2953, 2872, 1686, 1587, 1497, 1435, 1405, 1340, 1321, 1266, 1256, 1210, 1164, 1144, 1102, 1038, 973, 913, 888, 843, 806, 754, 732, 706, 657, 638, 618 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.87 (4H, br octet, J=6.6 Hz, CH_2CH_2), 3.44–3.51 (4H, m, 2× CH_2N), 3.73 (3H, s, 4-Me), 5.86 (1H, d, J=7.6 Hz, 6-H), 7.91 (1H, d, J=7.6 Hz, 5-H), 8.16 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 24.1, 25.6, 40.6, 45.6, 48.6, 96.9, 102.7, 140.4, 141.5, 145.3, 155.4, 160.9; HRMS (ESI): MH^+, found 247.119. $C_{12}H_{14}N_4O_2$ requires 247.119.

*4.17.18. 4-Methyl-3-(morpholine-4-carbonyl)pyrazolo[1,5-a]pyrimidin-7(4H)-one (**16o**).* Prepared from **14b** (97 mg, 0.5 mmol) and morpholine (43 μL, 0.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 123 mg (94%) of grey-white solid; mp 189–191 °C; ν_{max} (ATR) 3075, 2956, 2925, 2860, 1690, 1622, 1561, 1451, 1428, 1411, 1359, 1347, 1303, 1265, 1242, 1194, 1176, 1153, 1100, 1065, 1031, 980, 910, 874, 828, 794, 752, 699, 678, 651, 624 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.75 (8H, br s, 4× CH_2), 3.83 (3H, s, 4-Me), 5.97 (1H, d, J=7.7 Hz, 6-H), 7.35 (1H, d, J=7.7 Hz, 5-H), 7.86 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 41.7, 66.9, 76.8, 77.1, 99.1, 100.6, 141.8, 143.6, 155.8, 162.2; HRMS (ESI): MH^+, found 263.1138. $C_{12}H_{14}N_4O_3$ requires 263.1139.

*4.17.19. 4-Benzyl-N-cyclopropyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16p**).* Prepared from **14b** (97 mg, 0.5 mmol) and cyclopropylamine (36 μL, 0.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH=10:1. Yield: 138 mg (90%) of grey–white solid; mp 288–291 °C; [Found: C, 66.26; H, 5.04; N, 18.01. $C_{17}H_{16}N_4O_2$ requires: C, 66.22; H, 5.23; N, 18.17%]; ν_{max} (ATR) 3075, 2956, 2925, 2860, 1690, 1622, 1561, 1451, 1428, 1411, 1359, 1347, 1303, 1265, 1242, 1194, 1176, 1153, 1100, 1065, 1031, 980, 910, 874, 828, 794, 752, 699, 678, 651, 624 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 0.45 (2H, td, J=4.2, 6.1 Hz, CH_2CH_2), 0.68 (2H, br dt, J=5.0, 7.0 Hz, CH_2), 2.73 (1H, br octet, J=3.9 Hz, CHNH), 5.80 (2H, s, CH_2Ph), 6.02 (1H, d, J=7.7 Hz, 6-H), 7.11–7.34 (5H, m, Ph), 8.05 (1H, s, 2-H), 8.21 (1H, d, J=7.7 Hz, 5-H), 8.38 (1H,br d, J=3.9 Hz, NH), δ_C (126 MHz, DMSO-d_6) 5.6, 22.8, 55.6, 98.1, 103.2, 127.0, 128.0, 128.7, 136.1, 140.2, 143.0, 145.5, 155.2, 162.7; HRMS (ESI): MH^+, found 309.1348. $C_{17}H_{16}N_4O_2$ requires 309.1346.

*4.17.20. N,4-Dibenzyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16q**).* Prepared from **14b** (97 mg, 0.5 mmol) and benzylamine (56 μL, 0.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 137 mg (76%) of grey–white solid; mp 242–246 °C; [Found: C, 69.60; H, 4.83; N, 15.19. $C_{21}H_{18}N_4O_2 \cdot 1/5H_2O$ requires: C, 69.68; H, 5.12; N, 15.48%]; ν_{max} (ATR) 3075, 2956, 2925, 2860, 1690, 1622, 1561, 1451, 1428, 1411, 1359, 1347, 1303, 1265, 1242, 1194, 1176, 1153, 1100, 1065, 1031, 980, 910, 874, 828, 794, 752, 699, 678, 651, 624 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.41 (2H, d, J=5.9 Hz, CH_2NH), 5.85 (2H, s, CH_2N), 6.04 (1H, d, J=7.7 Hz, 6-H), 7.04–7.34 (10H, m, 2× Ph), 8.19 (1H, s, 2-H), 8.20 (1H, d, J=7.7 Hz, 5-H), 8.95 (1H, br t, J=5.9 Hz, NH); δ_C (126 MHz, DMSO-d_6) 42.5, 55.6, 98.3, 102.9, 126.8, 126.9, 127.3, 127.8, 128.3, 128.7, 136.1, 139.2, 140.6, 143.1, 145.6, 155.2, 161.5; HRMS (ESI): MH^+, found 359.1502. $C_{21}H_{19}N_4O_2$ requires 359.1503.

*4.17.21. 4-Benzyl-N-(3-(dimethylamino)propyl)-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16r**).* Prepared from **14b** (97 mg, 0.5 mmol) and 3-(dimethylamino)propylamine (64 μL, 0.5 mmol), FC: first EtOAc, then 70% $CHCl_3$/MeOH. Yield: 164 mg (93%) of white solid; mp 202–205 °C; ν_{max} (ATR) 3306, 3062, 2942, 2859, 2814, 2760, 1710, 1685, 1630, 1607, 1575, 1538, 1495, 1481, 1446, 1420, 1385, 1359, 1334, 1292, 1262, 1232, 1216, 1185, 1154, 1140, 1103, 1076, 1043, 1024, 1002, 980, 954, 887, 842, 807, 769, 739, 730, 691, 665, 641, 717 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 1.65–1.72 (2H, m, CH_2CH_2CH_2), 2.21 (6H, s, NMe_2), 2.44 (2H, t, J=5.9 Hz, OCH_2), 3.43 (2H, q, J=5.7 Hz, NHCH_2), 5.81 (2H, s, CH_2Ph), 6.00 (1H, d, J=7.7 Hz, 6-H), 7.12–7.16 and 7.28–7.33 (5H, 2m, 2:3, Ph), 7.49 (1H, d, J=7.7 Hz, 5-H), 7.96 (1H, s, 2-H), 8.39 (1H, t, J=4.9 Hz, NH); δ_C (126 MHz, DMSO-d_6) 24.8, 40.6, 45.2, 57.4, 59.1, 99.3, 104.2, 127.4, 128.5, 129.1, 135.3, 140.9, 142.7, 143.7, 156.1, 162.0; HRMS (ESI): MH^+, found 354.1925. $C_{19}H_{24}N_5O_2$ requires 354.1925.

*4.17.22. N,4-Dibenzyl-N-methyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16s**).* Prepared from **14b** (97 mg, 0.5 mmol) and 3-(dimethylamino)propylamine (64 μL, 0.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 164 mg (93%) of grey–white solid; mp 196–200 °C; ν_{max} (ATR) 3098, 2965, 1698, 1613, 1588, 1496, 1472, 1445, 1425, 1406, 1370, 1355, 1336, 1318, 1294, 1260, 1235, 1220, 1183, 1166, 1146, 1086, 1036, 1028, 1001, 964, 931, 895, 801, 756, 737, 729, 711, 692, 660, 641, 609 cm^{-1}; δ_H (500 MHz, DMSO-d_6) mixture of rotamers 2.42 and 2.70 (3H, 2br s, 2:1, NMe), 3.78 and 4.49 (2H, 2br s, 1:2, NCH_2Ph), 5.51 (2H, br s, N(4)-CH_2Ph), 6.03 (1H, d, J=7.7 Hz, 6-H), 6.95–7.44 (10H, m, 2× Ph), 7.71 and 8.11 (1H, 2s, 1:2, 2-H), 8.19 (d, J=7.7 Hz, 5-H); δ_H (500 MHz, $CDCl_3$) mixture of rotamers 2.42 and 2.86 (3H, 2br s, 1:1, NMe), 3.80 and 4.52 (2H, 2br s, 1:1, NCH_2Ph), 5.47 (2H, br s, N(4)-CH_2Ph), 6.03 (1H, d, J=7.7 Hz, 6-H), 6.93–7.10 and 7.19–7.40 (10H, 2m, 3:7, 2× Ph), 7.54 (1H, d, J=7.7 Hz, 5-H), 7.61 and 7.78 (1H, 2s, 1:1, 2-H); δ_C (126 MHz, $CDCl_3$) mixture of rotamers 33.5 and 36.9 (NMe), 51.0 and 54.8 (NCH_2Ph), 57.0 and 57.1 (N(4)–CH_2Ph), 99.0 and 99.1 (6-C), 102.2 and 102.3 (3-C), 126.2, 126.7, 127.8, 127.8, 128.5, 128.6, 128.7, 128.9, 129.0, and 129.1 (*o*,*m*,*p*-C of 2× Ph), 134.6, 134.9, 136.0, and 136.3 (*i*-C of 2× Ph), 140.4 and 140.4 (3a-C), 141.1 and 142.0 (2-C), 143.7 and 143.8 (5-C), 156.0 and 156.1 (7-C), 163.8 and 164.5 (C(3)–*C*=O); HRMS (ESI): MH^+, found 373.1660. $C_{22}H_{21}N_4O_2$ requires 373.1559.

4.18. N-alkylation of carboxamides 16b,d–h. Regioselective synthesis of 4-alkyl- (16m,n) and 1-alkyl 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxamides 17a–f

Alkyl halide (2.5 mmol) was added to a stirred mixture of carboxamide **16b**,**d**–**h** (0.5 mmol), anhyd DMF (5 mL), and anhyd K_2CO_3 (345 mg, 2.5 mmol) and the mixture was stirred at rt for 24 h. Volatile components were evaporated in vacuo and the residue was purified by FC (silica gel, first EtOAc/hexanes to elute the non-polar impurities, then EtOAc or $CHCl_3$/MeOH to elute the product). Fractions containing the product were combined and volatile components evaporated in vacuo to give the *title compound* **16** or **17**. The following compounds were prepared in this manner:

*4.18.1. N,N,4-Trimethyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**16m**).* Prepared from **16g** (103 mg, 0.5 mmol) and MeI (156 μL, 2.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 102 mg (93%) of grey–white solid. Physical, analytical and spectral data were identical to the data of **16m** obtained by amidation of **14b** (see Section 4.17.16).

*4.18.2. 4-Methyl-3-(pyrrolidine-1-carbonyl)pyrazolo[1,5-a]pyrimidin-7(4H)-one (**16n**).* Prepared from **16h** (116 mg, 0.5 mmol) and MeI (156 μL, 2.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 118 mg (96%) of grey–white solid. Physical, analytical and spectral data were identical to the data of **16n** obtained by amidation of **14b** (see Section 4.17.17).

*4.18.3. N-(2-Methoxyethyl)-1-methyl-7-oxo-1,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**17a**).* Prepared from **16b** (118 mg, 0.5 mmol) and MeI (156 μL, 2.5 mmol), FC: first EtOAc, then 90% $CHCl_3$/MeOH. Yield: 49 mg (39%) of grey–white solid; mp 160–161 °C; [Found: C, 52.88; H, 5.56; N, 22.39. $C_{11}H_{14}N_4O_3$ requires: C, 52.79; H, 5.64; N, 22.39%]; ν_{max} (ATR) 3301, 3052, 2920, 1686, 1644, 1574, 1553, 1512, 1473, 1445, 1310, 1276, 1118, 1087, 1025, 944, 867, 791, 771, 695 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.28 (3H, s, OMe), 3.45 (2H, br t, J=5.4 Hz, OCH_2), 3.51 (2H, br q, J=5.4 Hz, NCH_2), 4.35 (3H, s, NMe), 5.95 (1H, d, J=6.3 Hz, 6-H), 8.00 (1H, d, J=6.3 Hz, 5-H), 8.54 (1H, br t, J=5.4 Hz, NH), 8.80 (1H, s, 2-H), δ_C (126 MHz, DMSO-d_6) 38.1, 40.8, 58.1, 70.8, 101.5, 103.9, 141.2, 149.6, 153.1, 156.4, 159.9; HRMS (ESI): MH^+, found 251.1141. $C_{11}H_{15}N_4O_3$ requires 251.1139.

*4.18.4. 1-Benzyl-N-(2-methoxyethyl)-7-oxo-1,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**17b**).* Prepared from **16b** (118 mg, 0.5 mmol) and BnBr (303 μL, 2.5 mmol), FC: EtOAc. Yield: 104 mg (64%) of grey–white solid; mp 138–140 °C; [Found: C, 62.76; H, 5.35; N, 17.12. $C_{17}H_{18}N_4O_3$ requires: C, 62.57; H, 5.56; N, 17.17%]; ν_{max} (ATR) 3290, 3056, 2990, 1683, 1645, 1580, 1552, 1510, 1495, 1441, 1426, 1320, 1265, 1200, 1175, 1119, 1094, 1026, 966, 769 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.27 (3H, s, OMe), 3.43–3.47 and 3.48–3.53 (4H, 2m, 1:1, CH_2CH_2), 6.01 (1H, d, J=6.3 Hz, 6-H), 6.04 (2H, s, NCH_2Ph), 7.21–7.24 and 7.26–7.35 (5H, 2m, 2:3, Ph), 8.02 (1H, d, J=6.3 Hz, 5-H), 8.55 (1H, t, J=5.7 Hz, NH), 9.19 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 38.2, 55.5, 58.1, 70.7, 102.5, 105.7, 127.6, 128.4, 128.8, 135.1, 141.8, 150.3, 153.2, 156.2, 159.6; HRMS (ESI): MH^+, found 327.1435. $C_{17}H_{19}N_4O_3$ requires 327.1452.

*4.18.5. N,1-Dibenzyl-7-oxo-1,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**17c**).* Prepared from **16d** (134 mg, 0.5 mmol) and BnBr (303 μL, 2.5 mmol), FC: first 33% EtOAc/hexanes, then EtOAc. Yield: 129 mg (75%) of white solid; mp 180–183 °C; [Found: C, 68.95; H, 4.96; N, 14.81. $C_{21}H_{18}N_4O_2$ requires: C, 70.38; H, 5.06; N, 15.63%]; ν_{max} (ATR) 3276, 3060, 2924, 1693, 1644, 1577, 1555, 1508, 1451, 1421, 1357, 1327, 1263, 1202, 1179, 1099, 1079, 1051, 1026, 939, 897, 837, 825, 788, 773, 722, 710, 692, 638, 627, 604 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.57 (2H, d, J=6.1 Hz, CH_2NH), 6.01 (1H, d, J=6.3 Hz, 6-H), 6.05 (2H, s, CH_2N), 7.21–7.36 (10H, m, 2× Ph), 8.00 (1H, d, J=6.3 Hz, 5-H), 8.85 (1H, br t, J=6.1 Hz, $NHCH_2$), 9.22 (1H, s, 2-H); δ_C (126 MHz, DMSO-d_6) 43.1, 57.0, 103.5, 106.7, 127.4, 127.6, 128.66, 128.72, 129.29, 129.30, 133.4, 138.4, 140.0, 150.7, 153.1, 157.3, 160.4; HRMS (ESI): MH^+, found 359.1503. $C_{21}H_{19}N_4O_2$ requires 359.1503.

*4.18.6. 1-Benzyl-N-(3,5-dichlorobenzyl)-7-oxo-1,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**17d**).* Prepared from **16f** (169 mg, 0.5 mmol) and BnBr (303 μL, 2.5 mmol), FC: first 33% EtOAc/hexanes, then EtOAc. Yield: 185 mg (86%) of white solid; mp 181–183 °C; [Found: C, 59.09; H, 3.70; N, 12.70. $C_{21}H_{16}Cl_2N_4O_2$ requires: C, 59.03; H, 3.77; N, 13.11%]; ν_{max} (ATR) 3297, 3062, 1687, 1655, 1576, 1557, 1507, 1437, 1418, 1314, 1261, 1200, 1173, 1101, 1010, 929, 867, 847, 804, 775, 733, 708, 700, 670, 621 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 4.59 (2H, d, J=6.2 Hz, CH_2NH), 6.05 (2H, s, CH_2N), 6.09 (1H, d, J=6.3 Hz, 6-H), 7.21–7.25 (3H, m, 3H of Arl), 7.30–7.37 (5H, m, 5H of Arl), 7.94 (1H, d, J=6.3 Hz, 5-H), 8.37 (1H, s, 2-H), 9.01 (1H, t, J=6.2 Hz, $NHCH_2$); δ_C (126 MHz, DMSO-d_6) 42.1, 57.2, 103.7, 106.3, 126.0, 127.6, 128.8, 129.42, 129.45, 133.2, 135.2, 139.8, 142.1, 150.7, 153.1, 157.3, 160.6; HRMS (ESI): MH^+, found 427.0723. $C_{21}H_{17}Cl_2N_4O_2$ requires 427.0722.

*4.18.7. N-Benzyl-1-(3-methoxybenzyl)-7-oxo-1,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**17e**).* Prepared from **16d** (134 mg, 0.5 mmol) and 3-methoxybenzyl bromide (356 μL, 2.5 mmol), FC: first 33% EtOAc/hexanes, then EtOAc. Yield: 140 mg (72%) of white solid; mp 148–150 °C; [Found: C, 67.88; H, 4.86; N, 14.04. $C_{22}H_{20}N_4O_3$ requires: C, 68.03; H, 5.19; N, 14.42%]; ν_{max} (ATR) 3269, 3058, 1677, 1654, 1573, 1512, 1440, 1322, 1297, 1258, 1172, 1048, 931, 774, 740, 698, 658, 630 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 3.76 (3H, s, OMe), 4.66 (2H, d, J=5.8 Hz, CH_2NH), 5.99 (2H, s, CH_2N), 6.07 (1H, d, J=6.3 Hz, 6-H), 6.84–6.87 (3H, m, 3H of Arl), 7.22–7.28 (2H, m, 2H of Arl), 7.30–7.37 (4H, m, 4H of Arl), 7.92 (1H, d, J=6.3 Hz, 5-H), 8.41 (1H, s, 2-H), 8.94 (1H, br t, J=5.8 Hz, $NHCH_2$); δ_C (126 MHz, DMSO-d_6) 43.1, 55.4, 56.9, 103.5, 106.7, 114.3, 114.7, 120.7, 127.4, 127.6, 128.7, 130.4, 134.7, 138.4, 140.0, 150.7, 153.1, 157.4, 160.2, 160.4; HRMS (ESI): MH^+, found 389.1585. $C_{22}H_{21}N_4O_3$ requires 389.1608.

*4.18.8. 1-(3-Methoxybenzyl)-N-(4-methylbenzyl)-7-oxo-1,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**17f**).* Prepared from **16e** (141 mg, 0.5 mmol) and 3-methoxybenzyl bromide (356 μL, 2.5 mmol), FC: first 33% EtOAc/hexanes, then 67% EtOAc/hexanes. Yield: 183 mg (91%) of white solid; mp 162–164 °C; [Found: C, 68.92; H, 5.65; N, 13.71. $C_{23}H_{22}N_4O_3$ requires: C, 68.64; H, 5.51; N, 13.92%]; ν_{max} (ATR) 3269, 3056, 1673, 1650, 1575, 1556, 1510, 1490, 1439, 1420, 1375, 1344, 1325, 1299, 1257, 1176, 1157, 1088, 1059, 996, 936, 899, 816, 800, 774, 755, 739, 709, 693, 649, 629 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 2.32 (3H, s, Me), 3.76 (3H, s, OMe), 4.61 (2H, d, J=5.9 Hz, CH_2NH), 5.99 (2H, s, NCH_2), 6.06 (1H, d, J=6.3 Hz, 6-H), 6.83–6.88 (3H, m, 3H of Arl), 7.13 (2H, d, J=7.7 Hz, 2H of Arl), 7.22–7.27 (3H, m, 3H of Arl), 7.91 (1H, d, J=6.3 Hz, 5-H), 8.37 (1H, s, 2-H), 8.88 (1H, t, J=5.9 Hz, $NHCH_2$); δ_C (126 MHz, DMSO-d_6) 21.2, 42.9, 55.4, 57.0, 103.5, 106.8, 114.3, 114.7, 120.7, 127.7, 129.4, 130.4, 134.7, 135.4, 137.1, 139.9, 150.7, 153.2, 157.4, 160.2, 160.3; HRMS (ESI): MH^+, found 403.1753. $C_{23}H_{23}N_4O_3$ requires 403.1765.

4.19. X-ray structure analysis for compounds 13b, 16o, 17a and 17b

Single crystal diffraction data for compounds **13b**, **16o**, **17a** and **17b** have been collected on an Agilent SuperNova dual source diffractometer with an Atlas detector with Cu Ka radiation (1.54184 Å). For **13b**, **16o** and **17a** data were collected at room temperature and for **17b** at 150(1) K, respectively. The diffraction data were processed using CrysAlis PRO software.[18]

All structures were solved by direct methods, using SIR97.[19] A full-matrix least-squares refinement on F^2 was employed with anisotropic displacement parameters for all non-hydrogen atoms. H atoms were placed at calculated positions and treated as riding. SHELXL97 software[20] was used for structure refinement and interpretation. Drawings of the structures were produced using ORTEP-3.[21] Structural and other crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1007397–CCDC 1007400, for **13b**, **16o**, **17a** and **17b**, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/

retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.09.020. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Dolle, R. E. Solid-phase Synthesis of Heterocyclic Systems (Heterocycles Containing One Heteroatom) In*Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.. Handbook of Combinatorial Chemistry. Drugs, Catalysts, Materials*; Wiley-VCH GmbH: Weinheim, Germany, 2002; Vol. 2, pp 643–684; (b) Pernerstorfer, J. Molecular Design and Combinatorial Compound In*Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.. Handbook of combinatorial chemistry. Drugs, catalysts, materials*; Wiley-VCH GmbH: Weinheim, Germany, 2002; Vol. 2, pp 725–742; (c) Dolle, R. E.; Le Bourdonnec, B.; Worm, K.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2009**, *12*, 765–806; (d) Patrick, G. L. *Introduction to Medicinal Chemistry*, 4th ed.; Oxford University: Oxford, UK, 2009.
2. (a) Regan, A. C. In *Pyrazolo[1,5-c]pyrimidine (73) in Comprehensive heterocyclic chemistry III*, Katritzky, A. R.; Ramsden, C. A., Scriven E. F. V., Taylor, R. J. K., Eds.; Elsevier Science Ltd.: Oxford, UK, 2008; Vol. 11, Cossy, J., Ed.; pp 577–577; and references cited therein; (b) Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeie, G. E. H. *Adv. Heterocycl. Chem.* **1987**, *41*, 319–376.
3. Hwang, J. Y.; Windisch, M. P.; Jo, S.; Kim, H. C.; Kim, S.; Kim, H.; Lee, M. E.; Park, D.-S.; Park, E.; Ahn, S.; Cechetto, J.; Kim, J.; Liuzzi, M.; No, Z.; Lee, J. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7297–7301.
4. Ivashchenko, A. V.; Golovina, E. S.; Kadieva, M. G.; Kysil, V. M.; Mitkin, O. D.; Okun, I. M. *Pharm. Chem. J.* **2012**, *46*, 406–410.
5. (a) Hanan, E. J.; van Abbema, A.; Barrett, K.; Blair, W. S.; Blaney, J.; Chang, C.; Eigenbrot, C.; Flynn, S.; Gibbons, P.; Hurley, C. A.; Kenny, J. R.; Kulagowski, J.; Lee, L.; Magnuson, S. R.; Morris, C.; Murray, J.; Pastor, R. M.; Rawson, T.; Siu, M.; Ultsch, M.; Zhou, A.; Sampath, D.; Lyssikatos, J. P. *J. Med. Chem.* **2012**, *55*, 10090–10107; (b) Asano, T.; Yamazaki, H.; Kasahara, C.; Kubota, H.; Kontani, T.; Harayama, Y.; Ohno, K.; Mizuhara, H.; Yokomoto, M.; Misumi, K.; Kinoshita, T.; Ohta, M.; Takeuchi, M. *J. Med. Chem.* **2012**, *55*, 7772–7785; (c) Kosugi, T.; Mitchell, D. R.; Fujino, A.; Imai, M.; Kambe, M.; Kobayashi, S.; Makino, H.; Matsueda, Y.; Oue, Y.; Komatsu, K.; Imaizumi, K.; Sakai, Y.; Sugiura, S.; Takenouchi, O.; Unoki, G.; Yamakoshi, Y.; Cunliffe, V.; Frearson, J.; Gordon, R.; Harris, C. J.; Kalloo-Hosein, H.; Le, J.; Patel, G.; Simpson, D. J.; Sherborne, B.; Thomas, P. S.; Suzuki, N.; Takimoto-Kamimura, M. *J. Med. Chem.* **2012**, *55*, 6700–6715.
6. Xu, J.; Liu, H.; Li, G.; He, Y.; Ding, R.; Wang, X.; Feng, M.; Zhang, S.; Chen, Y.; Li, S.; Zhao, M.; Li, Y.; Qi, C. *Z. Naturforsch.* **2012**, *67B*, 827–834.
7. Lopez, L. C.; Dos-Reis, S.; Espargaro, A.; Carrodeguas, J. A.; Maddelein, M.-L.; Ventura, S.; Sancho, J. *J. Med. Chem.* **2012**, *55*, 9521–9530.
8. Hajos, G.; Riedl, Z.. In Aza Analogues of Pyrazolo[1,5-*a*]pyridines Containing Additional Nitrogen Atoms in the Sixmembered Ring in Science of Synthesis, Houben–Weyl: Methods of Molecular Transformations, Neier, R., Ed.; Thieme: Stuttgart, Germany, Vol. 12, pp 667–678.
9. (a) Bruni, F.; Selleri, S.; Costanzo, A.; Guerrini, G.; Casilli, M. L.; Giusti, L. *J. Heterocycl. Chem.* **1995**, *32*, 291–298; (b) Gregg, B. T.; Tymoshenko, D. O.; Razzano, D. A.; Johnson, M. R. *J. Comb. Chem.* **2007**, *9*, 507–512.
10. (a) Japelj, B.; Rečnik, S.; Čebašek, P.; Stanovnik, B.; Svete, J. *J. Heterocycl. Chem.* **2005**, *42*, 1167–1173; (b) Čebašek, P.; Bevk, D.; Pirc, S.; Stanovnik, B.; Svete, J. *J. Comb. Chem.* **2006**, *8*, 95–102.
11. (a) Svete, J.; Stanovnik, B. *Chem. Rev.* **2004**, *104*, 2433–2480; (b) Svete, J. *Monatsh. Chem.* **2004**, *125*, 629–647.
12. (a) Ahmetaj, S.; Velikanje, N.; Grošelj, U.; Šterbal, I.; Prek, B.; Golobič, A.; Kočar, D.; Dahmann, G.; Stanovnik, B.; Svete, J. *Mol. Divers.* **2013**, *17*, 731–743; (b) Baškovč, J.; Dahmann, G.; Golobič, A.; Grošelj, U.; Kočar, D.; Stanovnik, B.; Svete, J. *ACS Comb. Sci.* **2012**, *14*, 513–519; (c) Perdih, P.; Baškovč, J.; Dahmann, G.; Grošelj, U.; Kočar, D.; Novak, A.; Stanovnik, B.; Svete, J. *Synthesis* **2011**, *17*, 2822–2832 and references cited therein.
13. (a) Irlapati, N. R.; Baldwin, J. E.; Adlington, R. M.; Pritchard, G. J.; Cowley, A. *Org. Lett.* **2013**, *5*, 2351–2354; (b) Irlapati, N. R.; Baldwin, J. E.; Adlington, R. M.; Pritchard, G. J.; Cowley, A. *Tetrahedron* **2006**, *62*, 4603–4614; (c) Pirc, S.; Bevk, D.; Golobič, A.; Stanovnik, B.; Svete, J. *Helv. Chim. Acta* **2006**, *89*, 30–44.
14. (a) Cheng, W.; Gu, Z.; Tang, J.; Jia, H. CN 102603752, *Chem. Abstr.* **2012**, *157*, 261872; (b) Tung, R.; Harbeson, S. WO2008005471; *Chem. Abstr.* **2008**, *148*, 144785; (c) Sorbera, L. A.; Castaner, J.; Martin, L. *Drugs Future* **2003**, *28*, 739–746.
15. Kušar, M.; Svete, J.; Stanovnik, B. *J. Heterocycl. Chem.* **1996**, *33*, 1041–1046.
16. Reimlinger, H.; Pieren, M. A.; Merényi, R. *Chem. Ber.* **1970**, *103*, 3252–3265.
17. Nitz, T. J.; Salzwedel, K., Finnegan, C.; Wild, C.; Brunton, S.; Flanagan, S.; Montalbetti, C.; Coulter, T. S.; Kimber, M.; Magaraci, F.; Johnston D. WO 2008134035, *Chem. Abstr.* **2008**, *149*, 534234.
18. Agilent Technologies. *CrysAlis PRO. Version 1.171.35.11*; Agilent Technologies: Yarnton, Oxfordshire, England, 2011.
19. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
20. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.
21. Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565–565.