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A multicomponent reaction of 2-aminoimidazoles: microwave-assisted synthesis of novel 5-aza-7-deaza-adenines†‡

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An efficient and highly selective multicomponent synthesis of 4-aminoimidazo[1,2-*a*][1,3,5]triazines, which are 5-aza-7-deaza-isosteres of adenine, was developed. The reaction of 2-aminoimidazoles, triethyl orthoformate and cyanamide under microwave irradiation proceeded regioselectively to provide a library of novel 5-aza-7-deaza-adenines in good yields and purity. The developed method was demonstrated to be scalable and highly reproducible in three different monomode microwave reactors. A rearrangement was proposed to explain the high selectivity of the reaction.

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Introduction

Purine is a heterocyclic scaffold of primary importance in nature. Purine bases adenine and guanine encode half of the genetic information in DNA molecules.² Being the most ubiquitous nitrogen-containing heterocycle in nature, purine serves as a scaffold for molecules involved in the functioning of thousands of proteins in the human body.³ Thus, purines have become a privileged scaffold in drug discovery and development, inspiring also research in the area of structurally related heterocyclic systems *i.e.* purine isosteres. Among 1,3,5-triazine based purine isosteres, 5-azapurines (1,2,4-triazolo[1,5-*a*][1,3,5]triazines)⁴ and 5-aza-9-deazapurines (pyrazolo[1,5-*a*][1,3,5]triazines)⁵ have been widely investigated and considerable success has been achieved in the development of new bioactive compounds based on these scaffolds.⁶ Due to limited methods for their preparation, biological activity of imidazo-fused 1,3,5-triazines has been less explored. However, the 5-aza-7-deaza-isostere of the purine system (imidazo[1,2-*a*][1,3,5]triazine) has been employed as a scaffold for the construction of inhibitors of therapeutically valuable enzymes: activated Cdc42-

associated tyrosine kinase 1,⁷ focal adhesion kinase,⁸ and dipeptidyl peptidase IV.⁹ Some 5-aza-7-deazapurines were claimed to be agonists of opioid μ -receptors,¹⁰ ligands of adenosine receptors,¹¹ and potential antiviral agents.¹²

The search for bioactive molecules among aza-/deaza-isosteres of adenine has been an efficient research strategy in medicinal chemistry. For example, the 8-aza-7-deaza-adenine analogue **1** (Chart 1) was developed as an isosteric modification of *erythro*-9-(2-hydroxy-3-nonyl)adenine (EHNA), the earliest selective inhibitor of phosphodiesterase 2 (PDE2).¹³ Compound **1** was found to be much more potent inhibitor of PDE2, inhibiting this enzyme with K_i value of 0.053 nM (compared with $K_i = 7$ nM for EHNA).¹⁴ Another 8-aza-7-deaza-adenine based drug ibrutinib (**2**) has been recently approved for

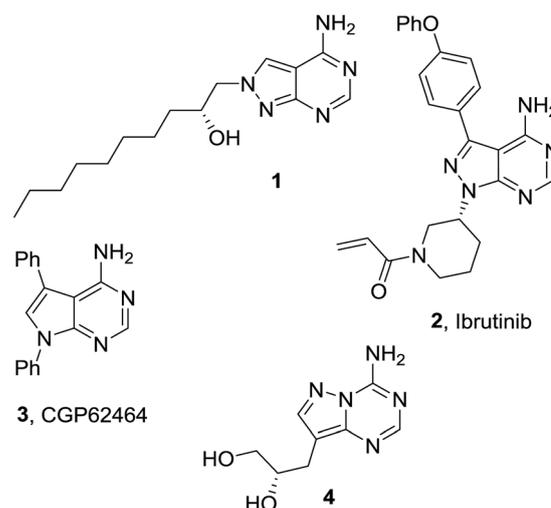


Chart 1 Biologically active aza-/deaza-isosteres of adenine.

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the treatment of mantle cell lymphoma and chronic lymphocytic leukemia.¹⁵ 7-Deaza-adenine derivative CGP62464 (**3**) was found to be a potent inhibitor of Src family kinases.¹⁶ An antiviral agent inhibiting *S*-adenosyl homocysteinase was developed on the 5-aza-9-deaza-adenine scaffold (compound **4**).¹⁷

The discovery of bioactive aza/deaza isosteres of adenine has encouraged us to develop new and effective methods for the synthesis of compounds within this general framework. As part of our ongoing research program on practical approaches for preparation of 1,3,5-triazine based purine-like compounds, in this contribution we report a new method for the synthesis of 4-aminoimidazo[1,2-*a*][1,3,5]triazines (**6**), which are 5-aza-7-deaza-isosteres of adenine.

The annulation of imidazole onto the 1,3,5-triazine ring was the first and has been the most common approach reported to date for the synthesis of imidazo[1,2-*a*][1,3,5]triazines.^{18–20} We decided to investigate the less explored annulation of the 1,3,5-triazine ring onto substituted 2-aminoimidazoles. Our group has previously achieved successful annulation of 1,3,5-triazine ring onto aminoazoles *via* 5-aminopyrazoles and 5-aminotriazoles *via* their three-component, microwave-assisted reaction with orthoformates and cyanamide.²¹ Herein we extend this methodology to a similar heterocyclic system preparing hitherto unknown 5-aza-7-deaza-adenines *via* our multicomponent, microwave-assisted reaction using 2-aminoimidazoles. These substrates are different from those previously used by their significantly greater basicity. Moreover, regioselectivity of the ring closure could be a potential challenge for non-symmetrically substituted 2-aminoimidazoles due to the similarity of their reactive endocyclic nitrogen atoms.

Results and discussion

Synthesis

The optimisation of conditions for the multicomponent reaction was performed with 2-amino-4-phenylimidazole (**5a**) as a model substrate (1 mmol in 2 mL of solvent) using the Discover SP (CEM) microwave synthesizer (Table 1). Initially, we attempted a one-pot, three-component reaction of **5a** with triethyl orthoformate and cyanamide in methanol under microwave irradiation at 150 °C for 25 min (Entry 1). To our satisfaction, the product **6a** was obtained in high purity after simple filtration, but the yield was rather low (26%). The analysis of the filtrate revealed the presence of a substantial quantity of unreacted **5a** together with the product. In the screening of solvents for this reaction, we found that the yield of isolated product could be improved to 61% when the reaction was carried out in ethyl acetate (Entry 6). Continuing optimisation of the reaction conditions by altering the time of reaction, we found that shortening the reaction time to 20 min gave further improvement in the yield (Entry 7). Varying reagent ratio revealed that **6a** could be obtained in a better yield using the 1 : 2.5 : 2.5 ratio of **5a**, triethyl orthoformate and cyanamide, respectively (Entry 10). The further increase of this ratio to 1 : 3 : 3 as well as changes of the reaction temperature did not improve the outcome of reaction. It should be noted that increase

of the reaction temperature to 160 °C resulted in the substantial loss of the product purity. For comparison purposes, we also performed the reaction using conventional heating under reflux in ethyl acetate. The reflux of the reagents in the optimised ratio for 24 h enabled us to isolate the desired product **6a** in 13% yield.

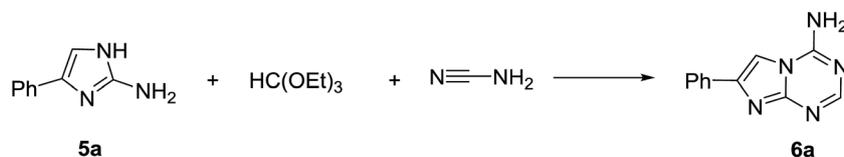
The developed method was validated using three different models of microwave synthesizers: Discover SP (CEM), Monowave 450 (Anton Paar), and Initiator+ (Biotage). The three-component reaction of **5a**, triethyl orthoformate and cyanamide under optimised conditions was conducted with all three systems in triplicates. Similar results were obtained for all three reactors: 83%, 80%, and 75% for Discover SP, Monowave 450, and Initiator+, respectively. We also attempted to scale up our microwave-assisted reaction by a factor of ten. To our satisfaction, conducting the reaction with 10 mmol of **5a** under identical conditions gave an even better yield (92%).

To test the scope of our developed method for the synthesis of 5-aza-7-deaza-adenines, we prepared a series of substituted 2-aminoimidazoles (**5**) using the method developed by Van der Eiken's group²² and then used them as substrates in our multicomponent reaction with triethyl orthoformate and cyanamide. The reaction of different **5** proceeded with the formation of the desired products **6**. Various aromatic substituents with electron-withdrawing and electron-donating groups in different positions were tolerated on **5** in the reaction (Table 2).

In principle, the formation of the aminotriazine ring in the three-component reaction of 2-aminoimidazoles **5** with triethyl orthoformate and cyanamide may proceed in four different ways (Scheme 1). Two regioisomeric pairs of isosteres of adenine (compounds **6** and **7**) and isoadenine (compounds **8** and **9**) could be theoretically obtained. However, only one product was isolated from the multicomponent reaction. The same product was obtained in the independent two-step synthesis using the general method reported earlier.²³ Treatment of **5a** with *N,N*-dimethylformamide dimethylacetal produced formamidine **11**, which was found to exist in DMSO solution in the equilibrium with its tautomer **11'** (Scheme 2). The formamidine **11** further reacted with cyanamide in the presence of sodium methoxide affording the triazine ring formation. This approach excluded formation of **8** and **9**, but the triazine ring closure might happen at any of the two imidazole nitrogen atoms resulting in **6** or **7**. The unambiguous structure assignment for the products was done using X-ray crystallography of **6i** (Fig. 1).

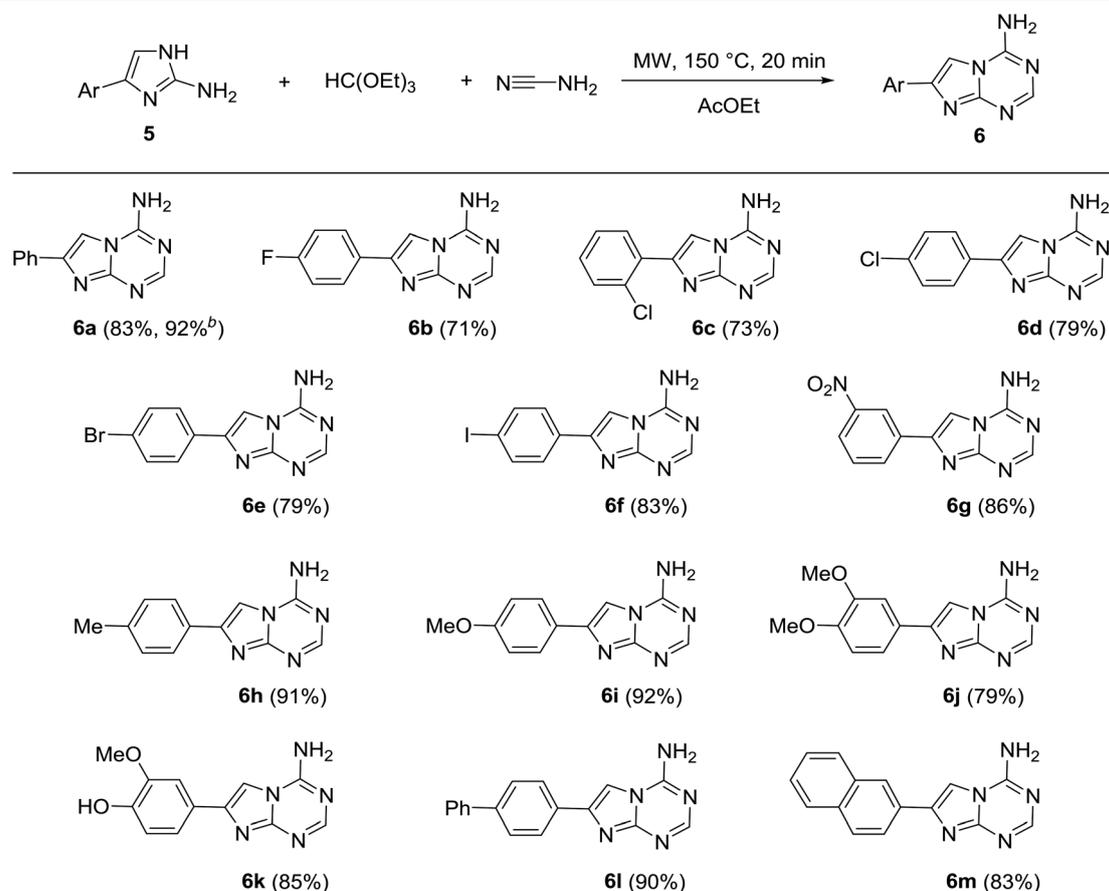
It was confirmed that our multicomponent reaction exclusively produced 4-amino-7-arylimidazo[1,2-*a*][1,3,5]triazines (**6**). Their regioisomers **7** are probably less stable due to steric hindrance between the amino group and the aryl; even if formed, they immediately rearrange at the reaction conditions to **6** (Scheme 1). The proposed rearrangement pathway involves formation of intermediate **10** resembling to the mechanism suggested for the amino-1,3,5-triazine ring rearrangement in a similar heterocyclic system.²⁴ The reaction was found to be highly chemo- and regioselective. Compounds **6** were produced exclusively for all aminoimidazoles **5** involved in the reaction and no traces of other isomers were detected.



Table 1 Optimization of conditions for the synthesis of 8-phenyl-5-aza-7-deaza-adenine (**6a**)^a

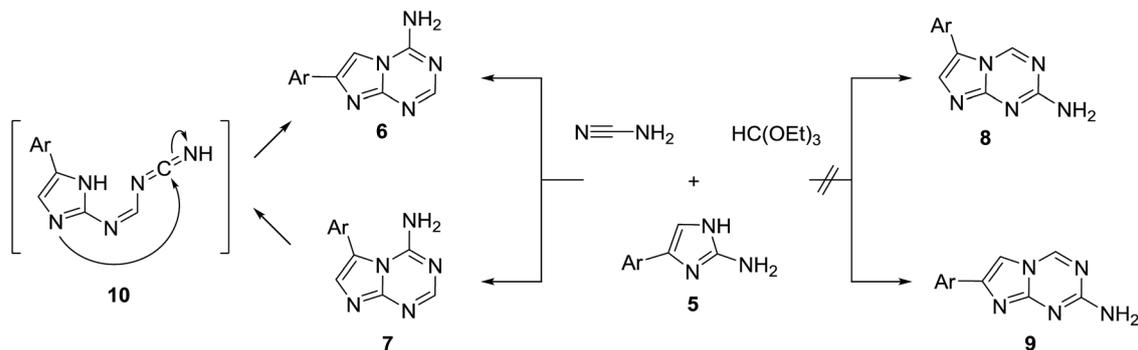
Entry	Solvent	Ratio of 5a : HC(OEt) ₃ : NCNH ₂	Temperature (°C)	Time (min)	Isolated yield (%)
1	MeOH	1 : 1.8 : 1.2	150	25	26
2	PhMe	1 : 1.8 : 1.2	150	25	57
3	MeCN	1 : 1.8 : 1.2	150	25	51
4	EtOH	1 : 1.8 : 1.2	150	25	19
5	THF	1 : 1.8 : 1.2	150	25	36
6	AcOEt	1 : 1.8 : 1.2	150	25	61
7	AcOEt	1 : 1.8 : 1.2	150	20	68
8	AcOEt	1 : 1.8 : 1.2	150	15	66
9	AcOEt	1 : 2 : 2	150	20	74
10	AcOEt	1 : 2.5 : 2.5	150	20	83
11	AcOEt	1 : 3 : 3	150	20	56
12	AcOEt	1 : 2.5 : 2.5	140	20	76

^a The reaction was performed using a Discover SP CEM microwave synthesizer with 1 mmol of **5a** in 2 mL of the solvent.

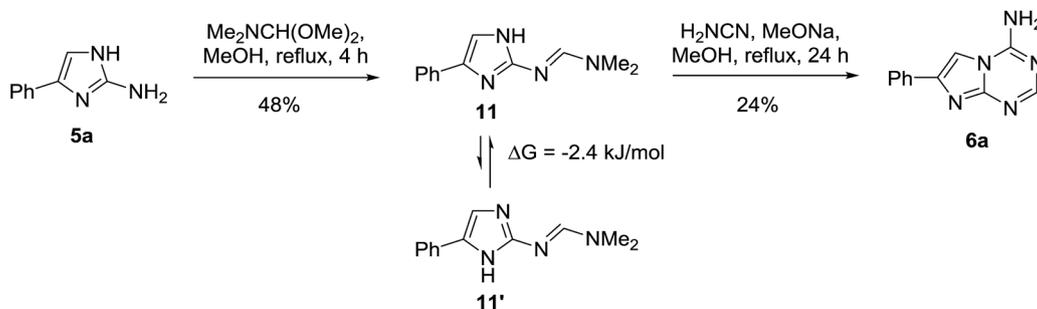
Table 2 One pot, multicomponent synthesis of 7-aryl substituted 4-aminoimidazo[1,2-a][1,3,5]triazines (**6**)^a

^a Microwave-assisted step performed on a 1 mmol scale in EtOAc (2 mL) using a Discover SP CEM microwave synthesiser. ^b Microwave-assisted step performed on a 10 mmol scale in EtOAc (20 mL) using a Discover SP CEM microwave synthesiser.





Scheme 1 Possible annulations of the 1,3,5-triazine ring onto 2-amino-1*H*-imidazoles.



Scheme 2 Step-wise synthesis of 6a.

X-ray crystallography

The molecular structure of **6i** is shown in Fig. 1a and comprises two planar fragments with the r.m.s. deviation of the nine atoms of the fused ring system being 0.015 Å. The maximum

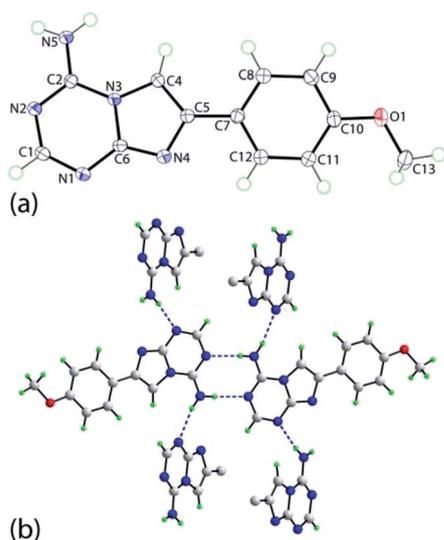


Fig. 1 (a) Molecular structure of **6i** showing atom labelling scheme and 70% anisotropic displacement parameters, and (b) a view of the N–H⋯N hydrogen bonding (blue dashed lines) leading to double-chains (see ESI Fig. S1†). The outer four molecules are represented by only the ispo-C atom of the methoxyphenyl groups for reasons of clarity.

deviation from the least-squares plane is 0.022(1) Å for the N3 atom, and the amino-N5 atom lies 0.046(1) Å out of the plane in the opposite direction to N3. A twist in the molecule is indicated by the dihedral angle of 14.20(3)° between the imidazo[1,2-*a*] [1,3,5]triazine and phenyl planes. Finally, the methoxy group is twisted out of the plane of the ring to which it is connected with the C13–O1–C10–C9 being 172.03(8)°.

The crystal of **6i** comprises double-layers of hydrogen bonded molecules with a fragment of the array illustrated in Fig. 1b. Thus, centrosymmetric eight-membered {⋯HNCN}₂ supramolecular synthons are formed between the amine-N–H and endocyclic nitrogen atoms of triazine residues with the remaining amine-N–H atom being connected to the second available triazine-N atom of a different molecule. The double-layers are formed parallel to [0 0 1] and are connected into a three-dimensional architecture *via* methyl-C–H⋯O(methoxy) and methyl-C–H⋯N(imidazo) non-conventional hydrogen bonding. The geometric details for the mentioned intermolecular contacts are given in the ESI Table S1† and a view of the unit cell contents is given in the ESI Fig. S1.†

Conclusions

In summary, we have successfully developed a new, microwave-assisted, multicomponent reaction for the synthesis of 5-aza-7-deaza-adenines (**6**). The catalyst-free reaction was found to proceed with high selectivity and produce the desired product in good yields and purity. A rearrangement was suggested to explain regioselectivity of the ring closure.



Experimental section

General information

Melting points (uncorrected) were determined on a StuartTM SMP40 automatic melting point apparatus. ¹H and ¹³C NMR spectra were recorded on a Bruker Fourier 300 spectrometer (300 MHz) using DMSO-*d*₆ as a solvent and TMS as an internal reference. Microwave-assisted reactions were carried out in the closed vessel focused single mode using a Discover SP microwave synthesizer (CEM, USA) monitoring reaction temperature by equipped IR sensor. For the method validation, the model reaction was also carried out using Monowave 450 (Anton Paar, Austria) and Initiator+ (Biotage, Sweden) reactors.

General method for the microwave-assisted synthesis of 5-aza-7-deaza-adenines (4-aminoimidazo[1,2-*a*][1,3,5]triazines, 6)

The mixture of a 2-amino-1*H*-imidazole (5, 1 mmol), cyanamide (105 mg, 2.5 mmol) and triethyl orthoformate (0.4 mL, 2.5 mmol) in ethyl acetate (2 mL) were irradiated in a 10 mL seamless pressure vial using microwave system operating at maximal microwave power up to 150 W at 150 °C for 20 min. After cooling, the precipitate was filtered, washed with ethyl acetate and recrystallised from DMF.

4-Amino-7-phenylimidazo[1,2-*a*][1,3,5]triazine (6a). Brown solid, yield 83%, mp 313–315 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.37 (1H, t, ³*J* = 7.3 Hz, H-4'), 7.48 (2H, t, ³*J* = 7.5 Hz, H-3' and H-5'), 7.88 (2H, d, ³*J* = 7.1 Hz, H-2' and H-6'), 8.15 (1H, s, H-2), 8.23 (1H, s, H-6), 8.50 (2H, brs, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 102.1 (C-6), 125.3 (C-2' and C-6'), 128.1 (C-4'), 128.8 (C-3' and C-5'), 133.1 (C-1'), 143.5 (C-7), 149.6 (C-8a), 151.3 (C-4), 155.5 (C-2). Anal. calcd for C₁₁H₉N₅: C, 62.55; H, 4.29; N, 33.16. Found: C, 62.35; H, 4.37; N, 33.02.

4-Amino-7-(4-fluorophenyl)imidazo[1,2-*a*][1,3,5]triazine (6b). Brown solid, yield 71%, mp 314–316 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.32 (2H, dd, ³*J* = 9.0 Hz, ³*J*_{HF} = 9.0 Hz, H-3' and H-5'), 7.90 (2H, dd, ³*J* = 8.9 Hz, ⁴*J*_{HF} = 5.5 Hz, H-2' and H-6'), 8.14 (1H, s, H-2), 8.18 (1H, s, H-6), 8.47 (2H, brs, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 101.9 (C-6), 115.7 (d, ²*J*_{CF} = 21.7 Hz, C-3' and C-5'), 127.3 (d, ³*J*_{CF} = 8.3 Hz, C-2' and C-6'), 129.6 (d, ⁴*J*_{CF} = 3.0 Hz, C-1'), 142.6 (C-7), 149.6 (C-8a), 151.3 (C-4), 155.5 (C-2), 162.0 (d, ¹*J*_{CF} = 244.8 Hz, C-4'). Anal. calcd for C₁₁H₈FN₅: C, 57.64; H, 3.52; N, 30.55. Found: C, 57.55; H, 3.60; N, 30.28.

4-Amino-7-(2-chlorophenyl)imidazo[1,2-*a*][1,3,5]triazine (6c). Yellow solid, yield 73%, mp 312–314 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.38 (1H, ddd, ⁴*J* = 1.8 Hz, ³*J* = 7.6 Hz, ³*J* = 7.6 Hz, H-4'), 7.47 (1H, ddd, ⁴*J* = 1.4 Hz, ³*J* = 7.6 Hz, ³*J* = 7.6 Hz, H-5'), 7.57 (1H, dd, ⁴*J* = 1.3 Hz, ³*J* = 7.9 Hz, H-3'), 7.95 (1H, s, H-2), 8.25 (1H, dd, ⁴*J* = 1.8 Hz, ³*J* = 7.9 Hz, H-6'), 8.55 (1H, s, H-6), 8.60 (2H, brs, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 106.3 (C-6), 127.3 (C-6'), 129.1 (C-5'), 130.3 (C-3'), 130.5 (C-4'), 130.6 (C-2'), 131.2 (C-1'), 140.0 (C-7), 148.6 (C-8a), 151.5 (C-4), 155.9 (C-2). Anal. calcd for C₁₁H₈ClN₅: C, 53.78; H, 3.28; N, 28.51. Found: C, 53.59; H, 3.40; N, 28.45.

4-Amino-7-(4-chlorophenyl)imidazo[1,2-*a*][1,3,5]triazine (6d). Brown solid, yield 79%, mp 339–340 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.54 (2H, d, ³*J* = 8.6 Hz, H-3' and H-5'),

7.87 (2H, d, ³*J* = 8.6 Hz, H-2' and H-6'), 8.15 (1H, s, H-2), 8.24 (1H, s, H-6), 8.52 (2H, brs, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 102.5 (C-6), 127.0 (C-2' and C-6'), 128.9 (C-3' and C-5'), 132.0 (C-1'), 132.5 (C-4'), 142.3 (C-7), 149.7 (C-8a), 151.3 (C-4), 155.7 (C-2). Anal. calcd for C₁₁H₈ClN₅: C, 53.78; H, 3.28; N, 28.51. Found: C, 53.63; H, 3.36; N, 28.31.

4-Amino-7-(4-bromophenyl)imidazo[1,2-*a*][1,3,5]triazine (6e). Brown solid, yield 79%, mp 341–342 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.68 (2H, d, ³*J* = 8.6 Hz, H-3' and H-5'), 7.81 (2H, d, ³*J* = 8.6 Hz, H-2' and H-6'), 8.14 (1H, s, H-2), 8.25 (1H, s, H-6), 8.51 (2H, brs, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 102.6 (C-6), 121.1 (C-4'), 127.3 (C-2' and C-6'), 131.8 (C-3' and C-5'), 132.3 (C-1'), 142.3 (C-7), 149.7 (C-8a), 151.3 (C-4), 155.7 (C-2). Anal. calcd for C₁₁H₈BrN₅: C, 45.54; H, 2.78; N, 24.14. Found: C, 45.42; H, 2.88; N, 23.98.

4-Amino-7-(4-iodophenyl)imidazo[1,2-*a*][1,3,5]triazine (6f). Brown solid, yield 83%, mp 331–332 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.66 (2H, d, ³*J* = 8.5 Hz, H-3' and H-5'), 7.85 (2H, d, ³*J* = 8.5 Hz, H-2' and H-6'), 8.14 (1H, s, H-2), 8.25 (1H, s, H-6), 8.49 (2H, brs, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 94.1 (C-4'), 102.5 (C-6), 127.3 (C-2' and C-6'), 132.7 (C-1'), 137.6 (C-3' and C-5'), 142.5 (C-7), 149.6 (C-8a), 151.3 (C-4), 155.6 (C-2). Anal. calcd for C₁₁H₈IN₅: C, 39.19; H, 2.39; N, 20.77. Found: C, 39.03; H, 2.44; N, 20.59.

4-Amino-7-(3-nitrophenyl)imidazo[1,2-*a*][1,3,5]triazine (6g). Brown solid, yield 86%, mp 296–298 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.79 (1H, t, ³*J* = 8.0 Hz, H-5'), 8.18 (1H, s, H-2), 8.21 (1H, ddd, ⁴*J* = 0.9 Hz, ⁴*J* = 2.3 Hz, ³*J* = 8.2 Hz, H-6'), 8.27 (1H, ddd, ⁴*J* = 1.0 Hz, ⁴*J* = 1.6 Hz, ³*J* = 7.6 Hz, H-4'), 8.44 (1H, s, H-6), 8.55 (2H, brs, NH₂), 8.64 (1H, dd, ⁴*J* = 1.6 Hz, ⁴*J* = 2.3 Hz, H-2'). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 103.7 (C-6), 119.5 (C-2'), 122.6 (C-4'), 130.6 (C-5'), 131.3 (C-6'), 134.8 (C-1'), 141.1 (C-7), 148.3 (C-3'), 149.9 (C-8a), 151.5 (C-4), 156.0 (C-2). Anal. calcd for C₁₁H₈N₆O₂: C, 51.56; H, 3.15; N, 32.80. Found: C, 51.46; H, 3.27; N, 32.71.

4-Amino-7-(4-methylphenyl)imidazo[1,2-*a*][1,3,5]triazine (6h). Brown solid, yield 91%, mp > 380 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 2.35 (3H, s, Me), 7.28 (2H, d, ³*J* = 7.9 Hz, H-3' and H-5'), 7.76 (2H, d, ³*J* = 8.1 Hz, H-2' and H-6'), 8.13 (1H, s, H-2), 8.17 (1H, s, H-6), 8.47 (2H, brs, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 20.8 (Me), 101.6 (C-6), 125.3 (C-2' and C-6'), 129.3 (C-3' and C-5'), 130.3 (C-1'), 137.5 (C-4'), 143.6 (C-7), 149.5 (C-8a), 151.2 (C-4), 155.3 (C-2). Anal. calcd for C₁₂H₁₁N₅: C, 63.99; H, 4.92; N, 31.09. Found: C, 63.85; H, 5.06; N, 30.87.

4-Amino-7-(4-methoxyphenyl)imidazo[1,2-*a*][1,3,5]triazine (6i). Brown solid, yield 92%, mp > 380 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 3.81 (3H, s, OMe), 7.05 (2H, d, ³*J* = 8.9 Hz, H-3' and H-5'), 7.80 (2H, d, ³*J* = 8.9 Hz, H-2' and H-6'), 8.10 (1H, s, H-6), 8.12 (1H, s, H-2), 8.43 (2H, brs, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 55.1 (OMe), 100.8 (C-6), 114.2 (C-3' and C-5'), 125.6 (C-1'), 126.7 (C-2' and C-6'), 143.6 (C-7), 149.5 (C-8a), 151.2 (C-4), 155.2 (C-2), 159.3 (C-4'). Anal. calcd for C₁₂H₁₁N₅O: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.66; H, 4.67; N, 28.91.

4-Amino-7-(3,4-dimethoxyphenyl)imidazo[1,2-*a*][1,3,5]triazine (6j). Brown solid, yield 79%, mp 252–254 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 3.80 (3H, s, OMe), 3.85 (3H, s, OMe), 7.06 (1H, d, ³*J* = 8.4 Hz, H-5'), 7.39–7.45 (2H, m, H-2' and H-6'), 8.11



(2H, s, H-6 and H-2), 8.40 (2H, brs, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 55.3 (OMe), 55.5 (OMe), 101.1 (C-6), 108.9 (C-2'), 112.0 (C-5'), 117.8 (C-6'), 125.9 (C-1'), 143.7 (C-7), 148.9 (C-3' and C-4'), (C-8a), 151.1 (C-4), 155.2 (C-2). Anal. calcd for C₁₃H₁₃N₅O₂: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.41; H, 4.60; N, 25.59.

4-Amino-7-(4-hydroxy-3-methoxyphenyl)-imidazo[1,2-*a*][1,3,5]triazine (6k). Grey solid, yield 85%, mp 273–275 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 3.87 (3H, s, OMe), 6.87 (1H, d, ³*J* = 8.2 Hz, H-5'), 7.29 (1H, dd, ⁴*J* = 1.9 Hz, ³*J* = 8.2 Hz, H-6'), 7.44 (1H, d, ⁴*J* = 1.9 Hz, H-2'), 8.07 (1H, s, H-6), 8.11 (1H, s, H-2), 8.39 (2H, brs, NH₂), 9.21 (1H, s, OH). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 55.4 (OMe), 100.6 (C-6), 109.4 (C-2'), 115.8 (C-5'), 118.2 (C-6'), 124.5 (C-1'), 144.1 (C-7), 146.9 (C-3'), 147.7 (C-4'), 149.4 (C-8a), 151.1 (C-4), 155.1 (C-2). Anal. calcd for C₁₂H₁₁N₅O₂: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.88; H, 4.54; N, 27.06.

4-Amino-7-(biphenyl-4-yl)imidazo[1,2-*a*][1,3,5]triazine (6l). Brown solid, yield 90%, mp > 380 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.38 (1H, t, ³*J* = 7.3 Hz, H-4''), 7.49 (2H, t, ³*J* = 7.5 Hz, H-3'' and H-5''), 7.74 (2H, d, ³*J* = 7.1 Hz, H-2'' and H-6''), 7.80 (2H, d, ³*J* = 8.5 Hz, H-3' and H-5'), 7.96 (2H, d, ³*J* = 8.5 Hz, H-2' and H-6'), 8.15 (1H, s, H-2), 8.27 (1H, s, H-6), 8.49 (2H, brs, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 102.2 (C-6), 125.9 (C-2' and C-6'), 126.4 (C-2'' and C-6''), 127.0 (C-3' and C-5'), 127.5 (C-4''), 128.9 (C-3'' and C-5''), 132.2 (C-1'), 139.5 (C-1''), 139.7 (C-4'), 143.1 (C-7), 149.7 (C-8a), 151.3 (C-4), 155.5 (C-2). Anal. calcd for C₁₇H₁₃N₅: C, 71.06; H, 4.56; N, 24.37. Found: C, 70.94; H, 4.62; N, 24.28.

4-Amino-7-(naphthalene-2-yl)imidazo[1,2-*a*][1,3,5]triazine (6m). Brown solid, yield 83%, mp 317–319 °C (DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.51–7.58 (2H, m, H-6' and H-7'), 7.91–8.05 (4H, m, H-3', H-4', H-5' and H-8'), 8.16 (1H, s, H-2), 8.36 (1H, s, H-6), 8.46 (1H, s, H-1'), 8.50 (2H, brs, NH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 102.7, 123.4, 124.1, 126.2, 126.5, 127.6, 128.1, 128.4, 130.5, 132.7, 133.1, 143.4, 149.8, 151.3, 155.6. Anal. calcd for C₁₅H₁₁N₅: C, 68.95; H, 4.24; N, 26.80. Found: C, 68.79; H, 4.41; N, 26.63.

Step-wise approach for the synthesis of 4-amino-7-phenylimidazo[1,2-*a*][1,3,5]triazine (6a)

***N,N*-Dimethyl-*N*-[3(5)-phenylimidazo-5(3)yl]formamidine (11).** A mixture of 2-amino-1*H*-imidazole 5a (320 mg, 2 mmol) with *N,N*-dimethylformamide dimethyl acetal (0.4 mL, 3 mmol) in methanol (5 mL) was heated under reflux for 4 h. Upon completion of the reaction, the solvent was removed under vacuum and the residue was triturated with diethyl ether. The precipitate was filtered and recrystallised from toluene to give pure formamidine 11. Brown solid, yield 58%, mp 133–135 °C (toluene). ¹H NMR (300 MHz, DMSO-*d*₆): δ 2.94 (3H, s, NMe), 3.07 (3H, s, NMe), 7.10 (2H, t, ³*J* = 7.3 Hz, H-4'), 7.19 (1H, brs, CH), 7.28 (2H, t, ³*J* = 7.7 Hz, H-3' and H-5'), 7.66 (2H, d, ³*J* = 7.4 Hz, H-2' and H-6'), 8.41 (1H, s, CH), 11.23 & 11.64 (1H, brs, NH). Anal. calcd for C₁₂H₁₄N₄: C, 67.27; H, 6.59; N, 26.15. Found: C, 67.16; H, 6.64; N, 26.08.

4-Amino-7-phenylimidazo[1,2-*a*][1,3,5]triazine (6a). To the sodium methoxide solution prepared by dissolving sodium (60 mg, 2.5 mmol) in methanol (5 mL), formamidine 11

(215 mg, 1 mmol) and cyanamide (105 mg, 2.5 mmol) were added. The reaction mixture was heated under reflux for 24 h, cooled and the precipitate was filtered to obtain a compound, which was identical to 6a prepared using the multicomponent reaction. Yield 24%.

X-Ray crystallographic analysis

The crystals for X-ray diffraction study were grown from the very dilute MeOH solution. Intensity data for 6i were measured at *T* = 100(2) K on a SuperNova Dual AtlasS2 diffractometer fitted with Mo K α radiation so that θ_{\max} was 33.0°. Data reduction, including absorption correction, was accomplished with CrysalisPro.²⁵ Of the 29 046 measured reflections, 3968 were unique ($R_{\text{int}} = 0.017$) and of these, 3510 data satisfied the $I \geq 2\sigma(I)$ criterion. The structure was solved by direct-methods²⁶ and refined (anisotropic displacement parameters, C-bound H atoms in the riding model approximation, N-bound H atoms with N–H = 0.88 ± 0.01 Å and a weighting scheme $w = 1/[\sigma^2(F_o^2) + 0.067P^2 + 0.331P]$ where $P = (F_o^2 + 2F_c^2)/3$) on F^2 .²⁷ Owing to poor agreement, the (–3 3 6) reflection was omitted from the final cycles of refinement. Based on the refinement of 170 parameters, the final values of *R* and *wR* (all data) were 0.040 and 0.114, respectively. The molecular structure diagram was generated with ORTEP for Windows²⁸ and the packing diagram with DIAMOND.²⁹

Crystal data for 4-amino-7-(4-methoxyphenyl)imidazo[1,2-*a*][1,3,5]triazine (6i). *M* = 241.26, monoclinic, *P*2₁/*c*, $\alpha = 6.97780(10)$, $b = 12.4862(2)$, $c = 12.6501(2)$ Å, $\beta = 93.808(2)^\circ$, $V = 1099.72(3)$ Å³, $Z = 4$, $D_x = 1.457$ g cm^{–3}, $F(000) = 504$, $\mu = 0.100$ mm^{–1}. CCDC deposition number: 1578001.†

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 F. P. L. Lim, K. K. Kow, E. H. Yeo, S. C. Chow and A. V. Dolzhenko, *Heterocycles*, 2016, **92**, 1121–1131.
- 2 G. Burnstock and A. Verkhatsky, *Acta Physiol.*, 2009, **195**, 415–447.
- 3 (a) J. M. Murray and D. E. Bussiere, *Methods Mol. Biol.*, 2009, **575**, 47–92; (b) C. Volonté and N. D'Ambrosi, *FEBS J.*, 2009, **276**, 318–329; (c) T. A. J. Haystead, *Curr. Top. Med. Chem.*, 2006, **6**, 1117–1127.
- 4 A. V. Dolzhenko, A. V. Dolzhenko and W.-K. Chui, *Heterocycles*, 2006, **68**, 1723–1759.
- 5 A. V. Dolzhenko, A. V. Dolzhenko and W.-K. Chui, *Heterocycles*, 2008, **75**, 1575–1622.



- 6 F. P. L. Lim and A. V. Dolzhenko, *Eur. J. Med. Chem.*, 2014, **85**, 371–390.
- 7 X. Jiao, D. J. Kopecky, J. Liu, J. Liu, J. C. Jaen, M. G. Cardozo, R. Sharma, N. Walker, H. Wesche, S. Li, E. Farrelly, S.-H. Xiao, Z. Wang and F. Kayser, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 6212–6217.
- 8 P. Dao, N. Smith, C. Tomkiewicz-Raulet, E. Yen-Pon, M. Camacho-Artacho, D. Lietha, J.-P. Herbeuval, X. Coumoul, C. Garbay and H. Chen, *J. Med. Chem.*, 2015, **58**, 237–251.
- 9 J. Feng, S. L. Gwaltney, J. A. Stafford, M. B. Wallace and Z. Zhang, *US Pat.*, 20060135767, 2006.
- 10 (a) D. Matosiuk and S. Fidecka, *PL Pat.*, 186228, 2003; (b) D. Matosiuk, S. Fidecka, L. Antkiewicz-Michaluk, J. Lipkowski, I. Dybala and A. E. Koziol, *Eur. J. Med. Chem.*, 2002, **37**, 761–772; (c) M. Rzadkowska, E. Szacon, D. Matosiuk, E. Kedzierska and S. Fidecka, *Acta Pol. Pharm.*, 2012, **69**, 1270–1275; (d) M. Rzadkowska, E. Szacon, D. Matosiuk, E. Kedzierska and S. Fidecka, *PL Pat.*, 211865, 2012.
- 11 (a) F. Da Settimo, G. Primofiore, S. Taliani, C. La Motta, E. Novellino, G. Greco, A. Lavecchia, B. Cosimelli, M. Iadanza, K.-N. Klotz, D. Tuscano, M. L. Trincavelli and C. Martini, *Drug Dev. Res.*, 2004, **63**, 1–7; (b) E. Novellino, E. Abignente, B. Cosimelli, G. Greco, M. Iadanza, S. Laneri, A. Lavecchia, M. G. Rimoli, F. Da Settimo, G. Primofiore, D. Tuscano, L. Trincavelli and C. Martini, *J. Med. Chem.*, 2002, **45**, 5030–5036.
- 12 (a) J. O. Ojwang, *US Pat.*, 20060035848, 2006; (b) G. Gosselin, P. La Colla, F. Seela, R. Storer, D. Dukhan and F. Leroy, *WO Pat.*, 2006000922, 2006; (c) P. La Colla, G. Gosselin, F. Seela, D. Dukhan, and F. Leroy, *WO Pat.*, 2004096197, 2004; (d) J. O. Ojwang, S. Ali, D. F. Smee, J. D. Morrey, C. D. Shimasaki and R. W. Sidwell, *Antiviral Res.*, 2005, **68**, 49–55; (e) D. Dukhan, F. Leroy, J. Peyronnet, E. Bosc, D. Chaves, M. Durka, R. Storer, P. La Colla, F. Seela and G. Gosselin, *Nucleosides, Nucleotides Nucleic Acids*, 2005, **24**, 671–674.
- 13 (a) M. Bessodes, G. Bastian, E. Abushanab, R. P. Panzica, S. F. Berman, E. J. Marcaccio Jr, S.-F. Chen, J. D. Stoeckler and R. E. Parks Jr, *Biochem. Pharmacol.*, 1982, **31**, 879–882; (b) P.-F. Méry, C. Pavoine, F. Pecker and R. Fischmeister, in *Phosphodiesterase Inhibitors*, ed. C. S. Dent and K. F. Rabe, Academic Press, San Diego, 1996, pp. 81–88.
- 14 F. Da Settimo, G. Primofiore, C. La Motta, S. Taliani, F. Simorini, A. M. Marini, L. Mugnaini, A. Lavecchia, E. Novellino, D. Tuscano and C. Martini, *J. Med. Chem.*, 2005, **48**, 5162–5174.
- 15 F. Cameron and M. Sanford, *Drugs*, 2014, **74**, 263–271.
- 16 M. Missbach, E. Altmann, L. Widler, M. Susa, E. Buchdunger, H. Mett, T. Meyer and J. Green, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 945–949.
- 17 G. V. Ullas, C. K. Chu, M. K. Ahn and Y. Kosugi, *J. Org. Chem.*, 1988, **53**, 2413–2418.
- 18 F. C. Schaefer, *J. Am. Chem. Soc.*, 1955, **77**, 5922–5928.
- 19 J. Kobe, B. Stanovnik and M. Tisler, *Chem. Commun.*, 1968, 1456.
- 20 (a) S.-H. Kim, D. G. Bartholomew, L. B. Allen, R. K. Robins, G. R. Revankar and P. Dea, *J. Med. Chem.*, 1978, **21**, 883–889; (b) T. Hanami, H. Oda, A. Nakamura, H. Urata, M. Itoh and Y. Hayashizaki, *Tetrahedron Lett.*, 2007, **48**, 3801–3803; (c) P. Cui, T. L. Macdonald, M. Chen and J. L. Nadler, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3401–3405; (d) P. Dao, C. Garbay and H. Chen, *Tetrahedron*, 2013, **69**, 3867–3871.
- 21 (a) F. P. L. Lim, G. Luna and A. V. Dolzhenko, *Tetrahedron Lett.*, 2014, **55**, 5159–5163; (b) F. P. L. Lim, G. Luna and A. V. Dolzhenko, *Tetrahedron Lett.*, 2015, **56**, 521–524; (c) F. P. L. Lim, G. Luna and A. V. Dolzhenko, *Tetrahedron Lett.*, 2015, **56**, 7016–7019; (d) A. V. Dolzhenko, S. A. Kalinina and D. V. Kalinin, *RSC Adv.*, 2013, **3**, 15850–15855; (e) S. A. Kalinina, D. V. Kalinin and A. V. Dolzhenko, *Tetrahedron Lett.*, 2013, **54**, 5537–5540.
- 22 (a) D. S. Ermolatev, E. P. Svidritsky, E. V. Babaev and E. Van der Eycken, *Tetrahedron Lett.*, 2009, **50**, 5218–5220; (b) D. S. Ermolat'ev and E. V. Van der Eycken, *J. Org. Chem.*, 2008, **73**, 6691–6697; (c) D. S. Ermolat'ev, B. Savaliya, A. Shah and E. Van der Eycken, *Mol. Diversity*, 2011, **15**, 491–496.
- 23 D. V. Kalinin, S. A. Kalinina and A. V. Dolzhenko, *Heterocycles*, 2013, **87**, 147–154.
- 24 Y. S. Agasimundin, F. T. Oakes and N. J. Leonard, *J. Org. Chem.*, 1984, **50**, 2474–2480.
- 25 Rigaku Oxford Diffraction, *CrysAlis PRO*, Agilent Technologies Inc., Santa Clara, CA, USA, 2015.
- 26 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112–122.
- 27 L. J. Farrugia, *J. Appl. Crystallogr.*, 2012, **45**, 849–854.
- 28 G. M. Sheldrick, *Acta Crystallogr., Sect. C: Struct. Chem.*, 2015, **71**, 3–8.
- 29 K. Brandenburg, *DIAMOND*, Crystal Impact GbR, Bonn, Germany, 2006.

