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Access to azolopyrimidine-6,7-diamines as a valuable "building-blocks" to develop new fused heteroaromatic systems

Denis A. Gazizov [a, *], Victor V. Fedotov [b], Konstantin A. Chistyakov [a], Evgeny B. Gorbunov [a], Gennady L. Rusinov [a, b], Valery N. Charushin [a, b]

[a] Postovsky Institute of Organic Synthesis of Ural Branch of Russian Academy of Sciences, Sofia Kovalevskoy St. 22/20, Ekaterinburg, 620108, Russia
[b] Ural Federal University, Department of Organic and Biomolecular Chemistry, Mira St. 19, Ekaterinburg, 620002, Russia

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ABSTRACT

A simple and convenient approach for the synthesis of new azolopyrimidine-6,7-diamines has been developed by the method of reductive cleavage of azo-group in series 6-[2-(4-methylphenyl)diazenyl] azolo[1,5-*a*]pyrimidine-7-amines, which was obtained by the interaction of aminoazoles with [2-(4-methylphenyl)hydrazinylidene]-3-oxo-propionitrile. The proposed approach allows to use a wide range of aminoazoles as a starting reagent and it also distinguishes itself by the simplicity of isolation and purification of products. The synthetic potential of presented diamines was demonstrated by the reaction of obtaining azolo[*a*]annulated pteridines.

1. Introduction

The chemistry of azoloannulated pyrimidines has lately been developed rapidly [1], the interest to this system is caused by the wide range of the possible usage of the structures containing the present fragment. For example, various azolo[1,5-*a*]pyrimidines exhibit antiviral [2], antiinflammatory [3], antibacterial [4], antifungal [5], antiparasitic [6], and antitumour [7] activities. Besides the biological application, [1,2,4]triazolo- and pyrazolo[1,5-*a*]pyrimidine scaffolds are established as promising acceptor systems for the construction of luminescent molecules [8], including those with mechanochromic properties [9].

Polycyclic structures, containing the azolo[1,5-*a*]pyrimidine fragment, also demonstrate the promising potential for the creation of biologically active compounds [10]. However, approaches to their preparation are presented in the literature by isolated examples of the synthesis of azolopurines and azolopteridines [10a,11], which emphasizes the urgency of developing a convenient and universal method of obtaining these structures.

It is known that the annulation of the imidazole ring to the diaminopyrimidines is one of the classic methods of the formation of the purines [12], it is also important that the same diamines can be used for the annulation of other rings; this fact confirms their universality as the "building-blocks" for the formation of the polycyclic systems [13].

As a part of this approach, in our previous work, we developed the method for the synthesis of the series of 2-*R*-triazolo[1,5-*a*]-pyrimidine-6,7-diamines (Scheme 1, a) and demonstrated the possibility of their cyclization to various triazolo-purines and -pteridines [11d]. In spite of the efficiency of the proposed method for some aminotriazoles, the nitration stage imposed significant restrictions for the substituent in the azole ring and the azole system as a whole.

Analyzing the literature we found two ways to obtain pyrazolo [1,5-*a*]pyrimidine-6,7-diamines (Scheme 1, **b**).[10b,11a] While the first approach turned out too labour-consuming, the second approach excited our curiosity by the convenience amino-group introduction, using the ordinary stage of the reductive cleavage of the azo-group in 6-(aryldiazenyl)-2-methylpyrazolo[1,5-*a*]pyrimidine-7-amines, obtained by the interaction of 3-oxo-2-(2-arylhydrazinylidene)butanenitrile with 2-alkyl and -aryl substituted 5-amino-1*H*-pyrazoles (Scheme 1, **b (2)**). In this case, the azo-group acts as the nitro-group synthetic equivalent that permits to avoid applying nitration, and using unstable compounds such as nitroacetonitrile, nitroacetaldehyde, metazonic acid, and their derivatives.

Inspired by this example, we continued our work and decided to develop a common method of obtaining various azolo[1,5-*a*]pyrimidine-6,7-diamines, that is based on using 1,3-*bis*-electrophile

* Corresponding author.
E-mail address: gazizov@ios.uran.ru (D.A. Gazizov).

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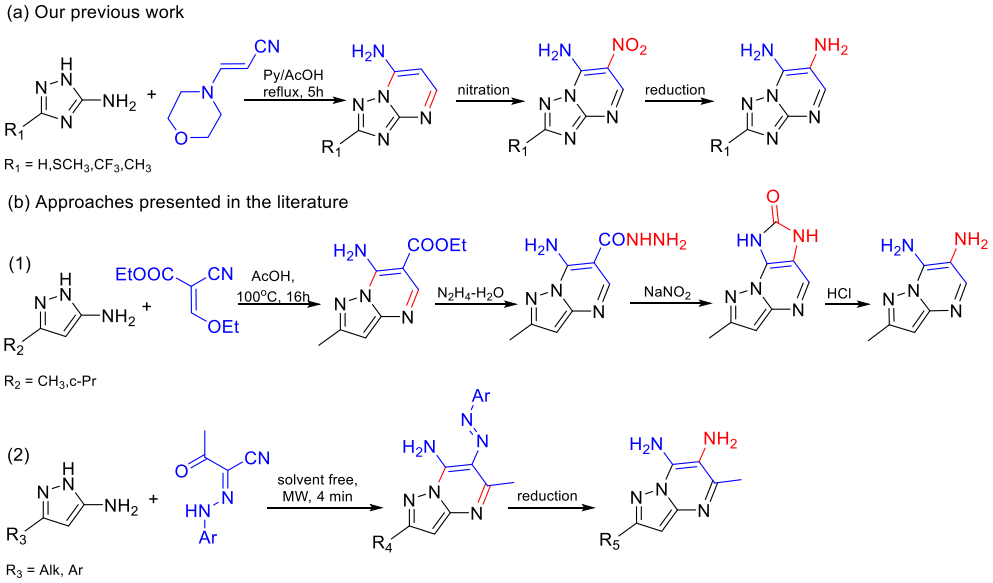


Scheme 1. Literary approaches to azolopyrimidine-6,7-diamines.

which contains azo- and cyano-groups.

2. Results and discussion

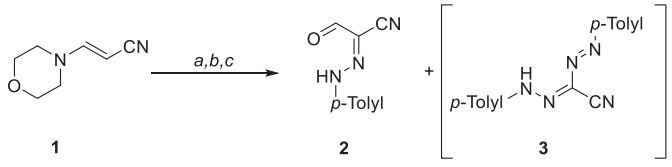
We have chosen 3-(morpholin-4-yl)acrylonitrile (**1**), which was used by us before, as a readily available started reagent for obtaining the aforementioned 1,3-*bis*-electrophile. Its interaction with *p*-toluene diazonium chloride, by the methods presented in the literature, led to the formation of the desired 2-[2-(4-methylphenyl)-hydrazinylidene]-3-oxo-propionitrile (**2**) with the yield of 56% and 2-[2-(4-methylphenyl)diazenyl]-2-[2-(4-methylphenyl)-hydrazinylidene]-acetonitrile (**3**), as a by-product (Scheme 2, condition (a)) [14].

Obviously, that the by-product **3** is formed as a result of the Japp-Klingemann reaction (ESI, S73-74), which is promoted by excess of the base [15]. To confirm it we carried out the reaction without the base; it allowed us to obtain product **2** without the formazan formation, but its yield formed only 29% (Scheme 2, condition (b)). The reduction of the amount of the sodium acetate allowed to obtain 2-[2-(4-methylphenyl)hydrazinyliden]-3-oxo-propionitrile (**2**) with the yield of 82%. (Scheme 2, condition (c)).

The appropriate products of condensation **5** were obtained by the reaction of hydrazinylidene **2** with a number of aminoazoles in DMF at the temperature of 120°C. In all cases, except the azole **4i**, the reaction in DMF proceeds smoothly, the products of cyclization precipitate from the reaction mixture that makes their isolation easy (Scheme 3). For aminotetrazole **4i** the reaction with hydrazone **2** in acetic acid allows to obtain the appropriate tetrazolopyrimidine **5i** with a high yield.

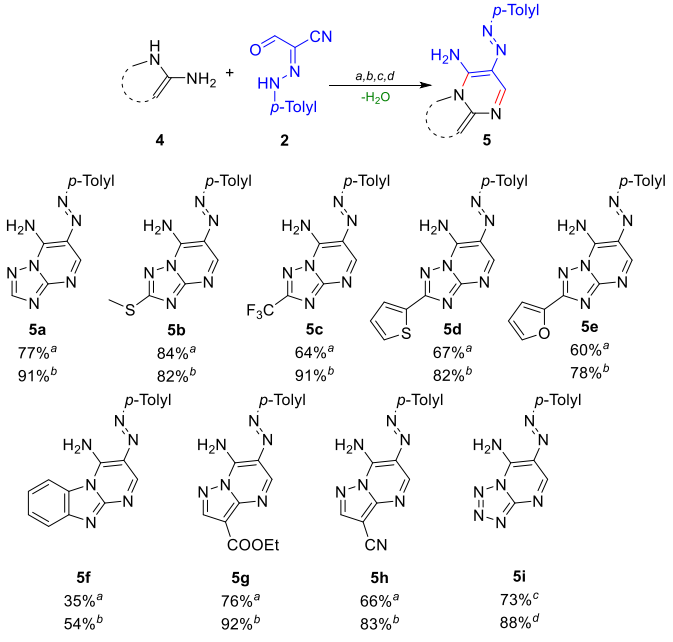
Within the scope of the optimization of the conditions and because of the precedent, shown earlier in literature, and also the world tendency to the "green" processes, we attempted to obtain the structures **5** in the solvent-free conditions. Despite all advantages of the microwave activation [11a], the difficulty of the subsequent laboratory scaling of the process made us choose conventional heating.

As a model reaction, we carried out the interaction of equimolar amounts of aminoazole **4c** and hydrazine **2** under heating to the



a: p-toluidine (1 equiv), $NaNO_2$ (1.2 equiv), HCl (3 equiv), AcONa (1.3 equiv);
b: p-toluidine (1 equiv), $NaNO_2$ (1.2 equiv), HCl (3 equiv);
c: p-toluidine (1 equiv), $NaNO_2$ (1.2 equiv), HCl (3 equiv), AcONa (0.8 equiv)

Scheme 2. Synthesis of 2-[2- (4-methylphenyl)-hydrazinylidene]-3-oxo-propionitrile.



a: DMF, 140°C, 5h
b: solvent-free, 160°C, 1h
c: 1.2 eq. **4i**, AcOH, 100°C, 5h
d: solvent-free, 140°C, 1h

Scheme 3.

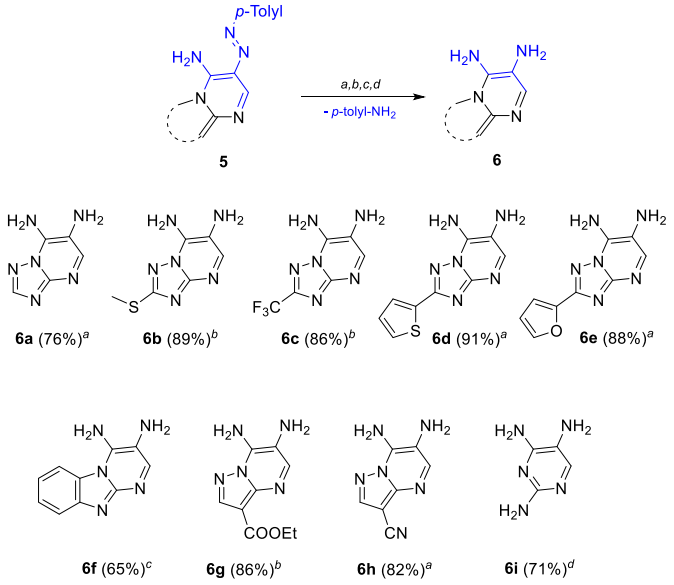
temperature of 160°C with the HPLC control. The heating of the reaction mixture was carrying out continuously (without exposure) under mechanical stirring and sampling upon reaching the necessary temperature. It was found that about 2% of the product **5c** was formed after grinding the reaction mixture in a mortar; subsequent stepwise heating ensured complete conversion of the starting compounds, which made it possible to obtain a high-purity product **5c** without purification (full data, ESI, S56-62).

By widening this approach to another aminoazoles, as the optimum conditions to carry out the reaction, we chose the temperature of 160°C and the exposure of an hour, because the carrying out of the reaction by lower temperature, even with the longer exposure, in some cases, didn't provide the full conversion of the initial compounds.

The use of the optimum conditions allowed to obtain the desired azolopyrimidines **5a-i** with a high degree of purity 92–100% (HPLC data, ESI, S63-70), which makes it possible to use them for synthesis without further purification. In the case of the unsubstituted aminotriazole **4a** by the reaction was formed the mixture of two products, supposedly [1,5-*a*] and [4,3-*a*]regioizmers in the 87/12 ratio (by HPLC and NMR data, ESI, S63, and S75). The treatment of this mixture by the 1% aqueous-alcohol solution KOH at room temperature during the night increases the part of the [1,5-*a*]isomer, leading to the 98/2 ratio (by HPLC data, ESI, S63), that allows us to make a conclusion about the proceeding of the Dimroth rearrangement. The [4,3-*a*] isomer formation is also fixed when the reaction is carried out in DMF (by NMR data, ESI, S75), but the subsequent heating leads exclusively to the [1,5-*a*] product, that points to the possibility of the rearrangement proceeding without the catalysis. We couldn't isolate [4,3-*a*] isomer in pure form because of the bad solubility of the obtained isomers mixture and the rearrangement proceeding at high temperatures, but in our previous work we had demonstrated the tendency of the unsubstituted aminotriazole to form [4,3-*a*] isomer, that conforms to our supposition [16].

The structure of the synthesized compounds was confirmed by the data of the NMR spectra and the elemental analysis. The NMR spectra for compounds **5b,f,g** are presented in $CDCl_3/CF_3COOD$ due to limited solubility in other organic solvents; HRMS spectral data are additionally presented. The azide-tetrazole tautomerism is peculiar to the compound **5i**, it is expressed by the presence of three sets of the signals in the NMR ^1H spectrum in DMSO-d_6. The use of $CDCl_3$ as a solvent allows to fix exceptionally azide form in the NMR spectrum of this compound, that is confirmed by the data of IR spectroscopy in $CHCl_3$.

The next step of our work was the hydrogenolysis of the azo-bond of compounds **5** in the presence of Pd/C in the atmosphere of hydrogen at the pressure of 3–5 bar. The reaction proceeds in mild conditions and with the high yield of the key diamines **6** (Scheme 4). It ought to mark that *p*-toluidine is educed as a single by-product and after the insignificant purification can be used for the second time for the obtaining of the hydrazone **2**. In the case of compound **6f**, the ^1H NMR spectrum contains no signals of the protons of the amino groups, which probably occurs as a result of the hydrogen-deuterium exchange process, and also the broadening of the signal of the pyrimidine proton is observed. The peak of the molecular ion is unambiguously recorded in the HRMS spectrum. For further transformations, diamine **6f** was used without additional purification. Upon the reduction of the compound **5i** in EtOH, in addition to hydrogenolysis of the azo bond, the tetrazole ring is destroyed, which leads to the formation of 1,2,4-triaminopyrimidine **6i**. We decided to appraise the influence of the solvent on the azide-tetrazole equilibrium supposing that the displacement of the equilibrium to the side of the tetrazole form would assist in the conservation of the annulated tetrazole ring. So,



a: H_2, 10% Pd/C (5 wt %), DMF, 5 bar, 50°C, 5h;
b: H_2, 10% Pd/C (5 wt %), EtOH, 5 bar, 50°C, 5h;
c: H_2, 10% Pd/C (5 wt %), DMF, 5 bar, 100°C, 10h;
d: H_2, 10% Pd/C (5 wt %), EtOH or DMF, 3 bar, rt, 6h

Scheme 4.

the band of the azido-group was fixed in the IR spectra, recorded in the solutions of benzene, $CHCl_3$, dioxane, DMF, EtOH, and in solid form, in the region of 2133–2137 cm^{-1} (ESI, S71). Nevertheless, in the case of the DMF solution, its next exposure during a day at room temperature leads to the disappearance of the absorption band of the azido-group (ESI, S71). Despite this, the attempt of the reduction of the compound **5i** in DMF with the beforehand exposure of obtained solution also leads to triamine **6i**.

To confirm the reproducibility and economic feasibility of the developed protocol, as well as the possibility of using compounds **5** without preliminary purification, gram-scale synthesis of 2-(trifluoromethyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6,7-diamine (**6c**) was carried out (Scheme 5).

In the capacity of the demonstration of the synthetic potential of the obtained diamines and as a continuation of our previous work, we carried out their reaction with glyoxal under acid catalysis to obtain new azoloannulated pteridines **7** (Scheme 6). The molecular structure of **7f** was additionally established by XRD analysis (ESI, S72).

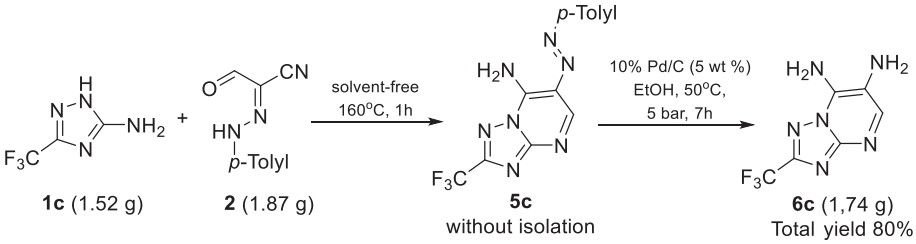
3. Conclusion

Thus, we have developed a simple and convenient method of azolo[1,5-*a*]pyrimidine-6,7-diamines synthesis. The proposed synthetic strategy provides good yields of the target diamines without the extra purification. Furthermore, high tolerance to the starting aminoazoles and the possibility of the formed toluidine for regeneration provides the practical significance and the economic effectiveness of the process. The possibility of using the obtained diamines was presented by the example of the reaction of obtaining azolo[*a*]annulated pteridines.

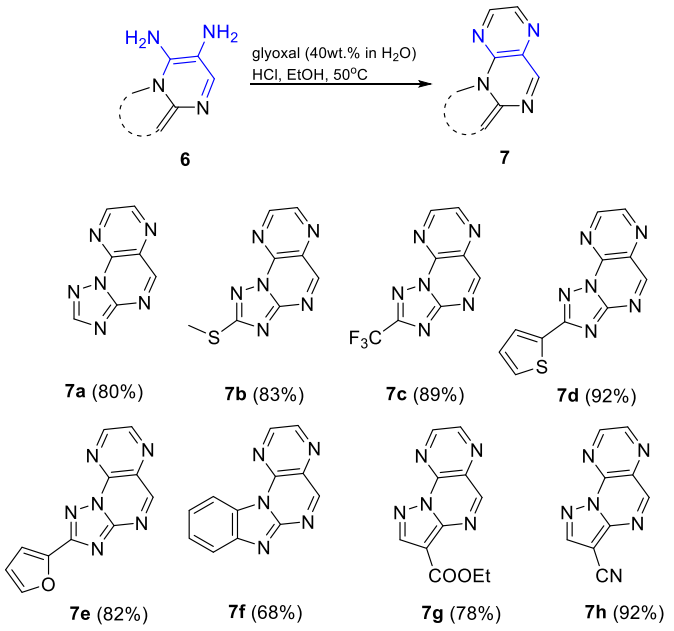
3.1. Experimental data

3.1.1. General information

^1H, ^{13}C and ^{19}F NMR spectra were acquired on a Bruker DRX-400



Scheme 5. Synthetic application of the obtained diamines.



Scheme 6.

instrument (400, 101 and 376 MHz, respectively), a Bruker DRX-500 (500, 126 and 470 MHz, respectively) or a Bruker Avance NEO 600 instrument (600 and 151 MHz, respectively), equipped with a Prodigy broadband gradient cryoprobe, using DMSO-d_6, $CDCl_3$ or $CDCl_3/CF_3COOD$ (5/1) as solvent and TMS as internal standard. The high-resolution mass spectrometry (HRMS) was performed using Bruker Daltonik MaXis Impact HD quadrupole time-of-flight mass spectrometer. Elemental analysis was performed on a PerkinElmer PE 2400 elemental analyzer. Melting points were determined in open capillaries on a Stuart SMP3 apparatus. The IR spectra were recorded on "PerkinElmer Spectrum One FT-IR" by diffuse reflection accessory (DRA) or "Thermo Nicolet 6700 FT-IR" spectrometers using the "Frustrated total internal reflection" (FTIR) method at 4000−400 cm−1. HPLC experiments were carried out in a gradient elution mode MeCN (20%)/H_2O (80%), flow rate 0.8 m/min, Kromasil 100-5C18 (250 × 4.6 mm, 5 μm), detection at 230/360 nm, injection 5 μL in DMF. All solvents and commercially available reactants/reagents were used as received. Noncommercial starting materials were prepared as described below or according to literature procedures.

3.1.2. 2-[2-(4-Methylphenyl)hydrazinylidene]-3-oxopropanenitrile (2)

A *p*-toluenediazonium salt (0.1 mol) solution was prepared by adding sodium nitrite solution (0.13 mol in 100 mL H_2O) to a chilled (−5 °C) solution of *p*-toluidine hydrochloride (0.1 mol (10.72 g) of *p*-toluidine, 0.3 mol (27 mL) 11 M HCl in 125 mL H_2O) with stirring and cooling. After 30 min exposure, the resulting *p*-toluenediazonium salt solution was added to a cold (−10 °C) solution of 3-morpholinoacrylonitrile (**1**) in EtOH (150 mL) containing sodium acetate trihydrate (0.08 mol, 10.88 g). The reaction mixture was stirred for 1 h under cooling and for another 2 h at room temperature. The solid product so formed was collected by filtration, washed with EtOH and air-dried. Yellow solid (15.3 g, 82%), m. p. (193-195 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.70 (s, 1H), 9.49 (s, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 186.5, 139.4, 135.1, 129.9, 116.5, 113.7, 110.3, 20.5. Anal. Calcd. For $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.08; H, 4.85; N, 22.53.

3.1.3. [(4-Methylphenyl)diazenyl][2-(4-methylphenyl) hydrazinylidene]acetonitrile (3)

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 7.74 (d, J = 8.0 Hz, 4H), 7.28 (d, J = 8.0 Hz, 4H), 2.42 (s, 6H). HRMS (+ESI): Calcd. For $C_{16}H_{15}N_5$ m/z 278.1400 $[M+H]^+$, found m/z 278.1405 $[M+H]^+$.

3.2. General procedure for the synthesis of compounds 5a-i

3.2.1. Method I

A mixture of the corresponding aminoazole **4a-h** (1 mmol or 1.2 mmol for **4i**) and 2-[2-(4-methylphenyl)hydrazinylidene]-3-oxopropanenitrile (**2**) (1 mmol, 187 mg) in DMF (5 mL) was stirred for 5 h at 140 °C, then the mixture was cooled. The precipitate that formed was collected by filtration, washed with a small amount of EtOH, and air-dried.

3.2.2. Method II

A mixture of the corresponding aminoazole **4a-h** (1 mmol or 1.2 mmol for **4i**) and 2-[2-(4-methylphenyl)hydrazinylidene]-3-oxopropanenitrile (**2**) (1 mmol, 187 mg) was thoroughly ground in a mortar or beaker. The resulting mixture was kept at 160 °C (140 °C for **4i**) in an oil bath with mechanical stirring for 1 h. After cooling to room temperature, the crude product can be used without further purification (except **5a,5f**). To obtain analytically pure samples, the crude product was washed with hot EtOH (**5i** washed with water), the precipitate was filtered and air-dried.

3.3. 6-(4-Methylphenyl)diazenyl][1,2,4]triazolo[1,5-a]pyrimidine-7-amine (5a)

Method I. Orange solid (195 mg, 77%), m. p. (>300 °C). **Method II.** The crude product in 1/1 (v/v) H_2O−EtOH mixture (5 mL) was treated with a solution of KOH (112 mg) in H_2O (1 mL), stirred overnight at 40 °C, then cooled to room temperature, and neutralized with 2 M HCl to pH ~7. EtOH was evaporated at reduced pressure; the precipitate was filtered off and dried under reduced pressure at 110 °C over P_2O_5. Yellow solid (230 mg, 91%), m. p. (>300 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.64 (s, 1H), 9.32 (s, 1H), 8.99 (s, 1H), 8.60 (s, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.1 Hz,

2H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.8, 155.1, 152.2, 150.1, 143.6, 140.6, 129.8, 122.2, 120.5, 21.0. Anal. Calcd. For $C_{12}H_{11}N_7$: C, 56.91; H, 4.38; N, 38.71. Found: C, 57.07; H, 4.46; N, 38.95.

3.4. 6-[(4-Methylphenyl)diazenyl]-2-(methylsulfanyl)[1,2,4]triazolo [1,5-a]pyrimidine-7-amine (5b)

Method I. Yellow crystals (250 mg, 84%), m. p. (>300 °C). **Method II.** Light brown powder (245 mg, 82%), m. p. (>300 °C). ^{1}H NMR (600 MHz, $CDCl_3$/CF_3COOD) δ 9.16 (s, 1H), 7.79 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 2.73 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$/CF_3COOD) δ 167.7, 151.3, 149.3, 147.8, 144.6, 142.8, 130.3, 123.0, 121.5, 21.6, 13.7. Anal. Calcd. For $C_{13}H_{13}N_7S$: C, 52.16; H, 4.38; N, 32.75. Found: C, 52.16; H, 4.21; N, 32.87. HRMS (+ESI): Calcd. For $C_{13}H_{14}N_7S$ m/z 300.1026 $[M+H]^+$, found m/z 300.1030 $[M+H]^+$.

3.5. 6-[(4-Methylphenyl)diazenyl]-2-(trifluoromethyl)[1,2,4] triazolo[1,5-a]pyrimidine-7-amine (5c)

Method I. Bright yellow powder (205 mg, 64%), m. p. (>300 °C). **Method II.** Brown solid (293 mg, 91%), m. p. (>300 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (br s, 1H), 9.61 (br s, 1H), 9.07 (s, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.5, 155.2 (q, J = 38.6 Hz), 152.7, 150.0, 144.5, 141.1, 129.8, 122.5, 121.5, 119.6 (q, J = 247.9 Hz), 21.0.^{19}F NMR (DMSO-d_6, 471 MHz): δ 97.93 (s). Anal. Calcd. For $C_{13}H_{10}F_3N_7$: C, 48.60; H, 3.14; N, 30.52. Found: C, 48.46; H, 3.15; N, 30.43.

3.6. 6-[(4-Methylphenyl)diazenyl]-2-(thiophen-2-yl)[1,2,4]triazolo [1,5-a]pyrimidine-7-amine (5d)

Method I. Orange crystals (224 mg, 67%), m. p. (>300 °C). **Method II.** Light brown powder (275 mg, 82%), m. p. (>300 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 9.23 (s, 1H), 8.97 (s, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.90 (d, J = 3.6 Hz, 1H), 7.81 (d, J = 5.0 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.27 (dd, J = 3.6, 5.0 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.8, 155.6, 152.8, 150.2, 143.2, 140.6, 133.2, 129.7, 129.4, 128.4, 128.3, 122.2, 120.9, 20.9. Anal. Calcd. For $C_{16}H_{13}N_7S$: C, 57.30; H, 3.91; N, 29.23. Found: C, 57.02; H, 3.72; N, 28.96.

3.7. 2-(Furan-2-yl)-6-[(4-methylphenyl)diazenyl][1,2,4]triazolo [1,5-a]pyrimidine-7-amine (5e)

Method I. Bright yellow solid (190 mg, 60%), m. p. (>300 °C). **Method II.** Light brown powder (249 mg, 78%), m. p. (>300 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 9.36 (s, 1H), 8.97 (s, 1H), 7.98 (dd, J = 0.8, 1.8 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.26 (dd, J = 0.8, 3.4 Hz, 1H), 6.75 (dd, J = 1.8, 3.4 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.4, 155.5, 152.7, 150.0, 145.7, 145.3, 143.4, 140.5, 129.7, 122.2, 120.8, 112.5, 112.2, 21.0. Anal. Calcd. For $C_{16}H_{13}N_7O$: C, 60.18; H, 4.10; N, 30.70. Found: C, 59.92; H, 3.99; N, 30.57.

3.8. 3-[(4-Methylphenyl)diazenyl]pyrimido[1,2-a]benz[4,5] imidazole-4-amine (5f)

Method I. Orange powder (136 mg, 45%), m. p. (>300 °C). **Method II.** The crude product washed with a small amount of DMF, then thoroughly washed with water and air-dried. Dark brown powder (162 mg, 54%), m. p. (>300 °C). ^{1}H NMR (400 MHz, $CDCl_3$/CF_3COOD) δ 9.27 (s, 1H), 8.39 (d, J = 8.6 Hz, 1H), 8.03–7.75 (m, 5H), 7.42 (d, J = 8.1 Hz, 2H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$/CF_3COOD) δ 155.2, 149.1, 147.3, 145.1, 144.6, 130.8, 130.3, 130.0, 126.4, 124.5, 122.9, 122.7, 114.7, 114.6, 21.0. Anal. Calcd. For $C_{17}H_{14}N_6$: C, 67.54; H, 4.67; N, 27.80. Found: C, 67.36; H, 4.71; N, 27.56. HRMS (+ESI): Calcd. For $C_{17}H_{14}N_6$ m/z 303.1353 $[M+H]^+$, found m/z 303.1358 $[M+H]^+$.

3.9. Ethyl 7-amino-6-[(4-methylphenyl)diazenyl]pyrazolo[1,5-a] pyrimidine-3-carboxylate (5g)

Method I. Yellow crystals (246 mg, 76%), m. p. (>300 °C). **Method II.** Light brown powder (297 mg, 92%), m. p. (>300 °C). ^{1}H NMR (600 MHz, $CDCl_3$/CF_3COOD) δ 9.22 (s, 1H), 8.50 (s, 1H), 7.73 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.40 (t, J = 7.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$/CF_3COOD) δ 161.0, 149.1, 148.1, 146.3, 145.2, 144.3, 138.8, 130.2, 122.8, 119.3, 101.9, 62.1, 21.5, 14.1. Anal. Calcd. For $C_{16}H_{16}N_6O_2$: C, 59.25; H, 4.97; N, 25.91. Found: C, 59.10; H, 4.81; N, 25.77. HRMS (+ESI): Calcd. For $C_{16}H_{16}N_6O_2$ m/z 325.1408 $[M+H]^+$, found m/z 325.1413 $[M+H]^+$.

3.10. 7-Amino-6-[(4-methylphenyl)diazenyl]pyrazolo[1,5-a] pyrimidine-3-carbonitrile (5h)

Method I. Light brown powder (183 mg, 66%), m. p. (>300 °C). **Method II.** Light brown powder (230 mg, 83%), m. p. (>300 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 1H), 9.41 (s, 1H), 8.92 (s, 1H), 8.79 (s, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.4, 150.2, 149.8, 147.9, 143.9, 140.7, 129.7, 122.3, 120.7, 113.4, 81.1, 20.9. Anal. Calcd. For $C_{14}H_{11}N_7$: C, 60.64; H, 4.00; N, 35.36. Found: C, 60.40; H, 3.91; N, 35.56.

3.11. 2-Azido-5-[(4-methylphenyl)diazenyl]pyrimidine-4-amine (5i)

Method I. Yellow powder (210 mg, 83%), m. p. (191-193 °C). **Method II.** Light brown powder (224 mg, 88%), m. p. (192-194 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.86 (s, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 5.87 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 161.4, 155.5, 150.2, 141.7, 129.9, 127.4, 122.2, 21.5. Anal. Calcd. For $C_{11}H_{10}N_8$: C, 51.96; H, 3.96; N, 44.07. Found: C, 51.67; H, 3.82; N, 44.01.

3.12. General procedure for the synthesis of compounds 6a-i

A mixture of corresponding 6-[(4-methylphenyl)diazenyl]-azolopyrimidine-7-amine **5a-i** (1 mmol) and 10% (by weight) Pd/C (5 wt %) in 10 mL DMF (for **5a,d,e,f,h,i**) or EtOH (for **5b,c,g**) was hydrogenated in an autoclave at 50 °C (100 °C for **5f**) and 3–5 bar pressure of hydrogen for 5–10h. The resulting solution/suspension was heated until the precipitate was completely dissolved, filtered hot from Pd/C, the solvent was removed in vacuo, the precipitate was washed off with Et_2O ($CHCl_3$ for **5f, 5i**), filtered and air-dried.

3.13. [1,2,4]Triazolo[1,5-a]pyrimidine-6,7-diamine (6a)

Light brown solid (114 mg, 76%), m. p. (>300 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.07 (s, 1H), 7.53 (s, 2H), 4.50 (s, 2H). (lit., [17], m. p. >300 °C [1],H NMR (DMSO-d_6, 400 MHz): δ 4.50 (br s, 2H), 7.52 (br s, 2H), 8.08 (s, 1H), 8.30 (s, 1H)).

3.14. 2-(Methylsulfanyl)[1,2,4]triazolo[1,5-a]pyrimidine-6,7-diamine (6b)

Beige solid (174 mg, 89%), m. p. (245–247 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.53 (s, 2H), 4.52 (s, 2H), 2.62 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.6, 151.5, 140.2, 138.3, 116.1,

13.3. Anal. Calcd. For $C_6H_8N_6S$: C, 36.72; H, 4.11; N, 42.83. Found: C, 36.60; H, 4.14; N, 42.69.

3.15. 2-(Trifluoromethyl)[1,2,4]triazolo[1,5-a]pyrimidine-6,7-diamine (6c)

Brown solid (187 mg, 86%), m. p. (226–228 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.87 (s, 2H), 4.77 (s, 2H). (lit., [17], m. p. 226–228 °C [1],H NMR (DMSO-d_6, 500 MHz): δ 4.77 (br s, 2H), 7.84 (br s, 2H), 8.16 (s, 1H)).

2-(Thiophen-2-yl)[1,2,4]triazolo [1,5-*a*]pyrimidine-6,7-diamine (6d).

Beige solid (210 mg, 91%), m. p. (284–286 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.76 (dd, J = 0.9, 3.6 Hz, 1H), 7.70 (dd, J = 0.9, 4.9 Hz, 1H), 7.53 (s, 2H), 7.21 (dd, J = 3.6 Hz, 4.9 Hz, 1H), 4.55 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.1, 151.6, 141.3, 138.6, 134.4, 128.2, 128.0, 127.0, 116.3. Anal. Calcd. For $C_9H_8N_6S$: C, 46.54; H, 3.47; N, 36.18. Found: C, 46.59; H, 3.74; N, 35.99.

3.16. 2-(Furan-2-yl)[1,2,4]triazolo[1,5-a]pyrimidine-6,7-diamine (6e)

Beige solid (178 mg, 88%), m. p. (272–274 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.88 (dd, J = 0.8, 1.8 Hz, 1H), 7.61 (s, 2H), 7.09 (dd, J = 0.8 Hz, 3.4 Hz, 1H), 6.69 (dd, J = 1.8, 3.4 Hz, 1H), 4.58 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 156.0, 151.4, 146.7, 144.3, 141.4, 138.7, 116.3, 111.9, 110.7. Anal. Calcd. For $C_9H_8N_6O$: C, 50.00; H, 3.73; N, 38.87. Found: C, 49.79; H, 3.91; N, 38.69.

3.17. Pyrimido[1,2-a]benzo[4,5]imidazole-3,4-diamine (6f)

Dark brown solid (129 mg, 65%), m. p. (>300 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (d, J = 8.3 Hz, 1H), 7.96 (br s, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.46–7.43 (m, 1H), 7.24–7.21 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 148.0, 142.1, 126.2, 125.2, 118.7, 116.1, 115.1, 114.8. HRMS (+ESI): Calcd. For $C_{10}H_9N_5$ m/z 200.0931 $[M+H]^+$, found m/z 200.0934 $[M+ H]^+$.

3.18. Ethyl 6,7-diaminopyrazolo[1,5-a]pyrimidine-3-carboxylate (6g)

White solid (190 mg, 86%), m. p. (229–231 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.06 (s, 1H), 7.53 (s, 2H), 4.61 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.4, 146.0, 143.1, 140.3, 138.5, 116.2, 98.2, 58.7, 14.6. Anal. Calcd. For $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.66. Found: C, 48.59; H, 5.28; N, 31.47.

3.19. 6,7-Diaminopyrazolo[1,5-a]pyrimidine-3-carbonitrile (6h)

Light brown solid (143 mg, 82%), m. p. (>300 °C °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.05 (s, 1H), 7.76 (s, 2H), 4.72 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 146.4, 145.2, 140.0, 139.0, 117.0, 115.1, 76.4. Anal. Calcd. For $C_7H_6N_6$: C, 48.27; H, 3.47; N, 48.25. Found: C, 48.04; H, 3.49; N, 47.99.

3.20. 2,4,5-Triaminopyrimidine (6i)

Red-brown solid (89 mg, 71%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.22 (s, 1H), 6.04 (s, 2H), 5.22 (s, 2H), 3.84 (br s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 156.9, 155.8, 139.1, 118.3. HRMS (+ESI): Calcd. For $C_4H_7N_5$ m/z 126.0774 $[M+H]^+$, found m/z 126.0773 $[M+H]^+$. (lit., [18], ^{1}H-NMR (600 MHz, (D6)DMSO): 7.23 (s, H-(C6)), 5.96 (br. s, NH2), 5.14 (br. s, NH2), 3.75 (br. s, NH2). ^{13}C NMR (150 MHz, (D6)DMSO): 157.12 (C(4)), 155.84 (C(2)), 140.12 (C(6)), 118.09 (C(5)). ESI-MS: 148 (5, $[M + Na]^+$), 126 (100, $[M + H]^+$)).

3.21. Procedure for the gram-scale synthesis of compound 6c

A mixture of the aminoazole **4c** (10 mmol, 1.521 g) and 2-[2-(4-methylphenyl)hydrazinylidene]-3-oxopropanenitrile (**2**) (10 mmol, 1.871 g) was thoroughly ground in a beaker. The resulting mixture was kept at 160 °C in an oil bath with mechanical stirring for 1 h. After cooling to room temperature, Pd/C (5 wt %) (10% by weight, 321 mg) and EtOH (120 mL) was added to the reaction mixture, the resulting mixture was transferred to an autoclave and hydrogenated at 50 °C and 5 bar pressure of hydrogen for 10h. Isolation and purification were performed similarly to the general procedure. Brown solid (1.743 g, 80%), m. p. (226–228 °C).

General procedure for the synthesis of compounds 7a-h.

A solution/suspension of the corresponding diamine **6a-h** (1 mmol) in EtOH (5 mL) was sequentially treated with HCl (36% w/w, 1 mmol, 86 μL) and glyoxal (40% w/w, 1 mmol, 115 μL). The resulting mixture was kept at 50 °C with stirring, the reaction progress was monitored by TLC in the CH_3Cl:CH_3OH (9/1, v/v) system for the disappearance of a spot of the starting diamine (Rf ~ 0.1) and forming a spot of the product (Rf ~ 0.85). Then, the reaction mixture was cooled, the formed precipitate was filtered and air-dried.

Compounds **7a,c** were obtained by the same method earlier [11d].

3.22. 2-(Methylsulfanyl)[1,2,4]triazolo[1,5-a]pteridine (7b)

Bright yellow solid (181 mg, 83%), m. p. (226–228 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 9.20 (d, J = 2.2 Hz, 1H), 9.17 (d, J = 2.2 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.7, 159.5, 155.4, 149.8, 145.2, 141.4, 130.4, 13.5. Anal. Calcd. For $C_8H_6N_6S$: C, 44.03; H, 2.77; N, 38.51. Found: C, 43.84; H, 3.10; N, 38.52.

3.23. 2-(Thiophen-2-yl)[1,2,4]triazolo[1,5-a]pteridine (7d)

Pale yellow solid (233 mg, 92%), m. p. (262–264 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (s, 1H), 9.23 (d, J = 2.2 Hz, 1H), 9.19 (d, J = 2.2 Hz, 1H), 7.96 (dd, J = 1.2, 3.6 Hz, 1H), 7.84 (dd, J = 1.2, 4.9 Hz, 1H), 7.29 (dd, J = 3.6, 4.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.9, 160.3, 155.8, 150.3, 145.9, 142.4, 133.3, 131.4, 130.1, 129.0, 128.9. Anal. Calcd. For $C_{11}H_6N_6S$: C, 51.96; H, 2.38; N, 33.05. Found: C, 51.74; H, 2.35; N, 33.03.

3.24. 2-(Furan-2-yl)[1,2,4]triazolo[1,5-a]pteridine (7e)

Pale orange solid (196 mg, 92%), m. p. (273–275 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 9.24 (d, J = 2.2 Hz, 1H), 9.20 (d, J = 2.2 Hz, 1H), 8.01 (dd, J = 0.8, 1.7 Hz, 1H), 7.34 (dd, J = 0.8, 3.4 Hz, 1H), 6.77 (dd, J = 1.7, 3.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.9, 157.2, 155.3, 149.8, 145.52, 145.47, 145.4, 142.1, 131.0, 112.4, 112.3. Anal. Calcd. For $C_{11}H_6N_6O$: C, 55.46; H, 2.54; N, 35.28. Found: C, 55.54; H, 2.40; N, 35.14.

3.25. Benzo[4,5]imidazo[1,2-a]pteridine (7f)

Brown solid (150 mg, 68%), m. p. (208–210 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ d 9.47 (s, 1H), 9.15 (d, J = 2.3 Hz, 1H), 9.04 (d, J = 2.3 Hz, 1H), 8.81–8.79 (m, 1H), 8.03–8.00 (m, 1H), 7.64–7.58 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.8, 150.4, 148.3, 145.1, 143.6, 143.3, 130.9, 128.8, 125.9, 124.7, 120.7, 116.2. Anal. Calcd. For $C_{12}H_7N_5$: C, 65.15; H, 3.19; N, 31.66. Found: C, 65.01; H, 3.08; N, 31.44.

3.26. Ethyl pyrazolo[1,5-a]pteridine-3-carboxylate (7g)

Beige solid (190 mg, 78%), m. p. (216–218 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 9.19 (d, J = 2.2 Hz, 1H), 9.17 (d, J = 2.2 Hz, 1H), 8.73 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.5, 156.7, 149.7, 146.5, 146.4, 145.5, 142.3, 130.9, 106.0, 60.1, 14.4. Anal. Calcd. For $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.79. Found: C, 54.26; H, 3.64; N, 28.75.

3.27. Pyrazolo[1,5-a]pteridine-3-carbonitrile (7h)

Dark yellow solid (181 mg, 92%), m. p. (267–269 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.55 (s, 1H), 9.23 (d, J = 2.2 Hz, 1H), 9.22 (d, J = 2.2 Hz, 1H), 8.94 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.2, 150.4, 150.2, 147.5, 146.4, 143.0, 131.9, 113.3, 86.3. Anal. Calcd. For $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.79. Found: C, 54.26; H, 3.64; N, 28.75.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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