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Regioselective synthesis of imidazo[1,2-*a*][1,3,5]triazines and 3,4-dihydroimidazo[1,2-*a*][1,3,5]triazines from [1,3,5]triazin-2,4-diamines

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ABSTRACT

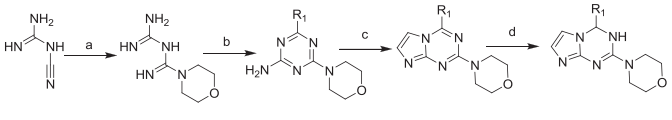
An efficient and practical procedure was developed to prepare novel imidazo[1,2-*a*][1,3,5]triazines and 3,4-dihydroimidazo[1,2-*a*][1,3,5]triazines with a good regioselectivity and high yields, starting from dicyandiamide and the corresponding arylamines. Mechanistic studies for the subsequent cyclocondensation with chloroacetaldehyde support a pathway, which begins with the displacement of the chloro atom activated by an adjacent CO group, followed by cyclization and dehydration.

1. Introduction

1,3,5-Triazine derivatives and their analogues of dihydro-1,3,5-triazines, one group of compounds known for a long period of time, have a wide array of biological activities, including anticancer,[1] anti-angiogenesis,[2] anti-HIV,[3] antimalarial,[4] antibacterial,[5] and antimicrobial activity.[6]

Fused heterocyclic 1,3,5-triazine structures have also been developed and used as important core structures in many chemotherapeutic agents due to their interesting pharmacological properties. Many such fused heterocyclic compounds, as imidazo[1,5-*a*][1,3,5]triazines, imidazo[1,2-*a*][1,3,5]triazines, pyrazolo[1,5-*a*][1,3,5]triazines, [1,2,4]triazolo[2,3-*a*][1,3,5]triazines, and benzimidazo[1,2-*a*][1,3,5]triazines, have been synthesized by several methods.[7–10] The imidazo[1,5-*a*][1,3,5]triazine derivatives have been reported as potential agents against influenza A and respiratory syncytial virus.[11] The pyrazolo[1,5-*a*][1,3,5]triazines have been used as good corticotropin-releasing factor antagonists, which makes them drug candidates for depressing and anxiety.[12] However, only a few of imidazo[1,2-*a*][1,3,5]triazine derivatives have been documented in the literature.[13]

As part of our programme investigating fused ring 1,3,5-triazine derivatives, we are particularly interested in the imidazo[1,2-*a*][1,3,5]triazines, which are very attractive heterocyclic units and could exhibit important biological properties. The current study was aimed at the synthesis of these compounds and their reduced analogues by starting from [1,3,5]triazin-2-ylamine derivatives **2** (Scheme 1), which are synthesized in two steps from the microwave-assisted reaction of cyanoguanidine with amines and further with esters.[14]



2a: $R_1 = CH_3$ **3a**: $R_1 = CH_3$ **4a**: $R_1 = CH_3$
2b: $R_1 = H$ **3b**: $R_1 = H$ **4b**: $R_1 = H$
2c: R_1 = 4-tolyl **3c**: R_1 = 4-tolyl **4c**: R_1 = 4-tolyl
2d: $R_1 = CH_2Ph$ **3d**: $R_1 = CH_2Ph$ **4d**: $R_1 = CH_2Ph$
2e: $R_1 = CH_2(2\text{-}NO_2Ph)$ **3e**: $R_1 = CH_2(2\text{-}NO_2Ph)$ **4e**: $R_1 = CH_2(2\text{-}NH_2Ph)$

Scheme 1. Reagents and conditions: (a) morpholine/dioxane/MW, 90 °C, 15 min; (b) R_1CO_2Et/MeONa/THF/MW, 70 °C, 20 min; (c) 2-chloroacetaldehyde/DMSO, 120 °C; (d) H_2/PtO_2, 20 h.

2. Results and discussion

In the initial condensation of 4-methyl-6-morpholino-1,3,5-triazin-2-amine **2a** with 4.2-fold excess of 2-chloroacetaldehyde in DMSO, surprisingly, we obtained only one isomeric product **3a**

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with high yield. In theory, it was possible from this cyclocondensation to obtain a pair of isomeric products (**3a** and **3a′**), which differ on the position of the imidazole ring (Fig. 1), because the starting compound **2a** is differently substituted in the 4 and 6 positions. NOE experiments unambiguously established the structure, because positive NOE effects were obtained between protons H9 and methyl group for **3a** and not with N–CH_2 of the morpholine ring (**3a′**). The same results were also obtained for compounds **3b**–**e**. This regioselectivity is probably due to steric hindrance of the morpholino group, which prevents the approach of 2-chloroacetaldehyde. The excellent regioselectivity is observed if this morpholino group is replaced by other secondary amines. However, the use of primary amines, such as aniline derivatives led to the other regioisomer as a minority (not published results).

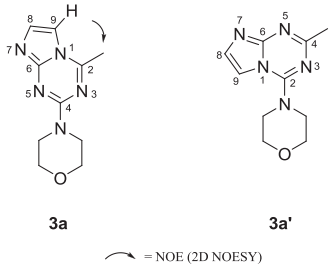
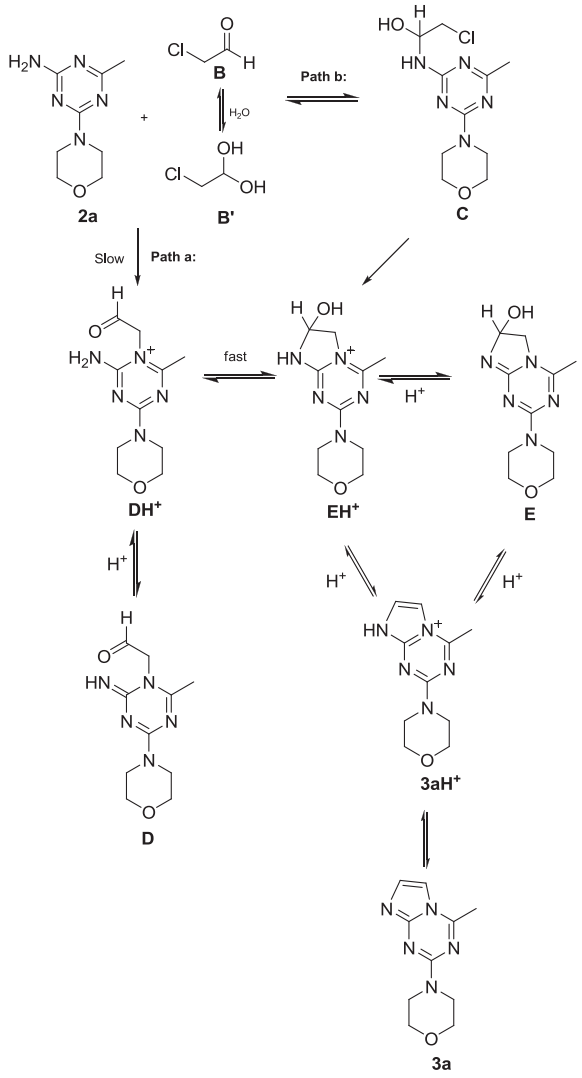


Fig. 1. NOE studies of **3a** (similar NOESY is observed for **3b**–**e**).

Naturally, it was interesting to elucidate the mechanism of this reaction. The steps for the two mechanisms to be suggested are shown in Scheme 2 for the cyclocondensation of **2a** with 2-chloroacetaldehyde as the initial step, which gives imidazo[1,2-*a*][1,3,5]triazine **3a** as the final product. We followed changes during reaction, which were monitored by ^{1}H NMR spectroscopy (DMSO-d_6) at 60 °C. Since hydrogen chloride is generated during the reaction, the various bases (**2a**, **D**, **E**, and **3a**) are in equilibrium with the protonated forms.

The changes in the ^{1}H NMR spectra, illustrated in Fig. 2 show a much greater complexity at intermediate times than at the end of the reaction, together with the disappearance of the signals due to **2a** and intermediates. The data show clearly that one intermediate **E** is formed, that is, concurrent with the formation of product **3a**. This relatively long-lived intermediate was also isolated and characterized by means of ^{1}H and 2D-NOE spectra. ^{1}H NMR (Table 1) indicates that the intermediate **EH**$^+$ has the structure shown in Scheme 2. The most characteristic data for ^{1}H NMR spectra is the presence in the region 4.0–5.7 ppm of three pairs of doublet of doublets signals. Two doublets of doublets were assigned to the intrinsically non-equivalent CH_2 protons of the five-membered ring, that shows the typical large coupling (J=12.4 Hz) of geminal protons. The third doublet of doublets, assigned also to the five-membered ring was due to vicinal proton-proton coupling between CH and two protons of CH_2. Furthermore, positive NOE effects were also obtained between the two protons H9 and CH_3 of **EH**$^+$ and not with N–CH_2 of the morpholino ring. However, the intermediates **C** and **D** were not detectable.

As shown in the 0-min spectrum, we could observe that the hydrate form of 2-chloroacetaldehyde is formed and these two compounds are in equilibrium with each other. The 1-min spectrum shows the emergence of the imidazole and methyl groups of the final product (**3aH**$^+$). These signals become deshielded by the acid liberated during the consumption of the intermediate **EH**$^+$. The two signals at 4.1 and 4.4 ppm and the third one at 5.6 ppm, assigned to protons adjacent to nitrogens of five-membered ring in structure **E**, fail to move downfield significantly during the course of the reaction. This intermediate therefore exists primarily in the



Scheme 2. Possible mechanism for the cyclocondensation of **2a** into **3a**.

protonated form **EH**$^+$ since **E** must be a stronger base than **2a**. The intensity of the signals of **2a**, **EH**$^+$ and **3a** changes in function of the reaction time. When no further changes occur, all of the signals can be assigned to product **3a** and remaining of excess of 2-chloroacetaldehyde.

The gradual downfield shift of the methyl group signal of **2a** occurs only if **2a** is in rapid equilibrium with another species having higher chemical shifts. This condition is satisfied by the formation of acid, which is possible only when **D** and/or **E** are formed in significant amount. Formation of **C** does not generate H$^+$. Therefore, the most likely species in equilibrium with **E** is **DH**$^+$, which could probably proceed via slower formation of **D** than its conversion to **EH**$^+$. However, the above data could not exclude another mechanism, which could proceed via path b.

To gain further support for the mechanism, which is favoured through path a, the methylation of **2a** by iodomethane was performed (Scheme 3). As it could be expected, this reaction produced **5** as a single product. The structure of **5** was unambiguously characterized by a combined application of ^{1}H, ^{13}C NMR, (^{1}H–^{13}C) HSQC, (^{1}H–^{13}C) HMBC, and 2D-NOE. Positive NOE effects were observed between protons of the two methyl groups.

These results suggest that the mechanism through path b in Scheme 2 is improbable. The fact that path a is favoured over path b could be explained by a lower energy of the transition state for the displacement of the chloro atom when activated by an adjacent

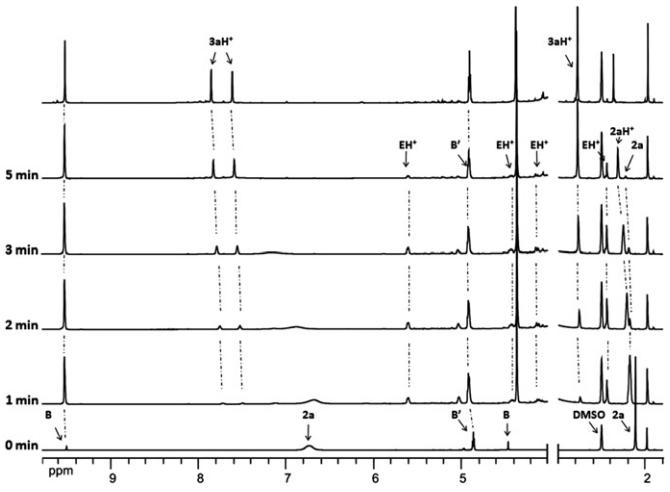
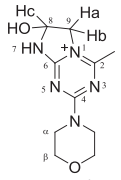
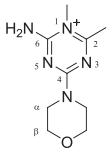


Fig. 2. Partial 500 MHz ^{1}H NMR spectra of a DMSO-d_6 solution recorded 1, 2, 3, 5 min at 60 °C after mixing 4-methyl-6-morpholino-1,3,5-triazin-2-amine **2a** with chloroacetaldehyde. The bottom scan is the sum of separately recorded spectra of the two starting materials at 27 °C. The top scan was recorded when no further changes occurred (20 min) at 60 °C. Relevant assignments are as follows: bottom scan: 2.31 (s): CH_3 protons of **2a**; 4.46 (s): CH_2 protons of **B**; 4.88 (t): CH proton of **B′** signals; 6.74 (broad peak): NH2 protons of **2a** and 9.51 (s): CHO of **B**. Signals connected by dotted lines on intermediate times (2, 3, 5 min): **2a**+**2aH**$^+$: CH_3 (s) of protonated and non-protonated species; **EH**$^+$: CH_3 (s), CH9a (dd), CH9b (dd) and CH8 (dd). Top scan: 2.78 (s): CH_3 protons of **3aH**$^+$, 7.62 (d): CH8 proton of imidazole ring, 7.86 (d): CH9 proton of imidazole ring.

Table 1
^{1}H NMR chemical shifts (δ, ppm) of compounds **EH**$^+$[a] and **5**[b]



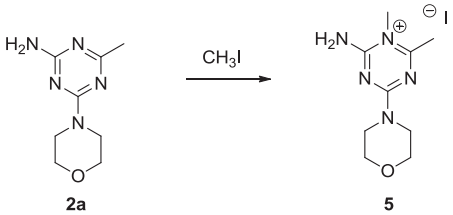
EH$^+$



5

	EH$^+$	**5**
CH_3	2.43 (s)	2.52 (s)
NCH_3		3.45 (s)
β-CH_2	3.71 (t)	3.77 (t)
α-CH_2	3.84 (t), 3.94 (t)	3.77 (t), 3.86 (t)
NH_2		8.30 (s), 8.83 (s)
Ha	4.08 (dd)	
Hb	4.37 (dd)	
Hc	5.68 (dd)	
OH	5.04 (br s)	
NH	(s)	

[a] In CD_3CN.
[b] In DMSO-d_6.



2a **5**

Scheme 3.

CO group in 2-chloroacetaldehyde. The nitrogen of the triazinic ring serves as a nucleophilic site for the first step of the mechanism and not the amine function. This is due to the delocalization of its doublet in the triazinic ring.

Initially, the reduction of the 4-(4-(2-nitrophenyl)-3,4-dihydroimidazo[1,2-*a*][1,3,5]triazin-2-yl)morpholine **3e** by hydrogenation in the presence of Pd/C or Ni using standard procedures was unsuccessful. To our surprise, when the reaction was carried out with 10% of PtO_2, not only the nitro group is reduced to an amine but also the triazine ring is reduced to dihydrotriazine ring, to form a new heterocyclic system, which, to our knowledge, has not yet been described in the literature. Similar results have been obtained for **3a**–**d**, which gave **4a**–**d** with good yields.

In conclusion, we have developed an efficient and simple approach to imidazo[1,2-*a*][1,3,5]triazines with excellent regioselectivity. A mechanism for the cyclocondensation between 4-methyl-6-morpholino-1,3,5-triazin-2-amine **2a** and 2-chloroacetaldehyde was proposed and discussed on the basis of experimental results. By means of NMR spectroscopy the structure was established of a stable intermediate product, 4,7-dimethyl-2-morpholino-6,7,8,8a-tetrahydroimidazo[1,2-*a*][1,3,5]-triazin-7-ol, whose dehydration yielded the above imidazo[1,2-*a*][1,3,5]triazines. We have also described the synthesis of the hydrogenated analogues of imidazo[1,2-*a*][1,3,5]triazines, 3,4-dihydroimidazo[1,2-*a*][1,3,5]triazines as a new heterocyclic system.

3. Experimental section

3.1. General

All commercial materials were used without further purification. Microwave irradiation was carried out with a microwave monomode reactor (IR detector for temperature). Melting points were determined on a Kofler apparatus as uncorrected values. Analytical thin-layer chromatography was performed on precoated 250 μm layer thickness silica gel 60 F_{254} plates and visualized with UV light. Column chromatography was performed using Silica gel 60 (40–63 μm). ^{1}H NMR and ^{13}C NMR spectra were measured on 250 MHz or 500 MHz spectrometer in DMSO-d_6 or $CDCl_3$ or CD_3CN with chemical shift (δ) given in parts per million (ppm) relative to TMS as internal standard and recorded at 23 °C. MS (ESI) was determined by using a Q-Tof1 spectrometer with Z-spray source. High-resolution mass spectra (HRMS) were performed on Q-TOF Micro micromass positive ESI (CV=30 V).

3.2. General method for the synthesis of compounds 2

A mixture of sodium methoxide (1.5 mmol) prepared from Na and methanol, arylbiguanide hydrochloride (1 mmol) **1**,[14] and ester (3 mmol) in dry THF (5 mL) was introduced into a round-bottomed flask equipped with a condenser and a magnetic stirring bar. The flask was placed in the microwave cavity and exposed to microwave irradiation for 20 min at 70 °C using irradiation power of 100 W. On cooling to room temperature, the mixture was evaporated under vacuum, and the residue was subjected to flash chromatography (silica gel, 5% methanol/CH_2Cl_2) to afford the desired product as a white solid.

*3.2.1. 6-Methyl-4-morpholino-1,3,5-triazin-2-amine (**2a**).* White solid, mp 192 °C (lit.,[15] 192 °C), 181.6 mg (93%). ^{1}H NMR (250 MHz, DMSO): δ 2.11 (s, 3H), 3.57 (t, J=4.8 Hz, 4H), 3.66 (t, J=4.8 Hz, 4H), 6.73 (s, 2H). ^{13}C NMR (500 MHz, DMSO): δ 176.3, 168.6, 166.5, 68.0, 45.0, 27.0. MS (ESI) m/z 196.1 $[M+H]^+$.

*3.2.2. 4-Morpholino-1,3,5-triazin-2-amine (**2b**).* White solid, mp 221 °C (lit.,[16] 215–216 °C), 177.5 mg (98%). ^{1}H NMR (250 MHz, DMSO): δ 3.6 (t, J=4.8 Hz, 4H), 3.64 (t, J=4.8 Hz, 4H), 6.87 (s, 2H), 8.04 (s, 1H). ^{13}C NMR (500 MHz, DMSO): δ 166.2, 165.7, 163.9, 65.9, 43.0. MS (ESI) m/z 182.1 $[M+H]^+$.

*3.2.3. 4-Morpholino-6-p-tolyl-1,3,5-triazin-2-amine (**2c**).* White solid, mp 167 °C (lit.,[17] 165–166 °C), 196.5 mg (72.5%). ^{1}H NMR (250 MHz, DMSO): δ 2.36 (s, 3H), 3.64 (t, J=4.7 Hz, 4H), 3.78 (t, J=4.7 Hz, 4H),

6.89 (s, 2H), 7.27 (d, *J*=8.2 Hz, 4H), 8.19 (d, *J*=8.2 Hz, 4H). ^{13}C NMR (500 MHz, DMSO): δ 169.6, 167.1, 164.9, 141.1, 134.2, 128.7, 127.8, 66.0, 43.1, 21.0. MS (ESI) *m*/*z* 272.1 $[M+H]^+$.

*3.2.4. 4-Morpholino-6-(2-benzyl)-1,3,5-triazin-2-amine (**2d**).* White solid, mp 150 °C, 271 mg (100%). ^{1}H NMR (250 MHz, DMSO): δ 2.13 (3H, s, CH_3), 3.57 (t, *J*=4.8 Hz, 4H), 3.65 (t, *J*=4.8 Hz, 4H), 3.67 (s, 2H), 6.81 (s, 2H), 7.27 (m, 5H). ^{13}C NMR (500 MHz, DMSO): δ 178.0, 168.8, 166.7, 139.9, 130.9, 130.1, 128.1, 67.8, 46.7, 45.0. MS (ESI) *m*/*z* 272.1 $[M+H]^+$.

*3.2.5. 4-Morpholino-6-(2-nitrobenzyl)-1,3,5-triazin-2-amine (**2e**).* White solid, mp 154 °C, 261.1 mg (82.6%). ^{1}H NMR (250 MHz, DMSO): δ 2.18 (3H, s), 3.53 (8H, s), 4.17 (2H, s), 6.79 (2H, s), 7.51 (2H, m), 7.66 (1H, td, *J*=7.5, 1.4 Hz), 7.98 (1H, dd, *J*=8, 1.7 Hz). ^{13}C NMR (500 MHz, DMSO): δ 174.4, 166.6, 164.3, 149.6, 133.3, 131.8, 128.0, 124.3, 65.8, 43.0, 40.5. MS (ESI) *m*/*z* 317.1 $[M+H]^+$.

3.3. General method for the synthesis of compounds 3

A solution of compound **2** (0.5 mmol) and 2-chloroacetaldehyde (50% in H_2O, 0.2 mL, 2.1 mmol) in DMSO was stirred at 120 °C for 7 h. After being cooled, the solvent was removed under reduced pressure and the residue was treated with $NaHCO_3$ saturated aqueous solution. This alkaline mixture was extracted with CH_2Cl_2 (3×20 mL). The combined extracts were dried (Na_2SO_4), reduced to a small volume and purified by flash chromatography.

*3.3.1. 4-(4-Methylimidazo[1,2-a][1,3,5]triazin-2-yl)morpholine (**3a**).* White solid, mp 196 °C, 91 mg (83.1%). ^{1}H NMR (250 MHz, DMSO): δ 2.68 (s, 3H), 3.65 (t, *J*=4.8 Hz, 4H), 3.76 (t, *J*=4.8 Hz, 4H), 7.27 (d, *J*=1.5 Hz, 1H), 7.57 (d, *J*=1.5 Hz, 1H). ^{13}C NMR (500 MHz, DMSO): δ 159.1, 158.7, 152.1, 134.4, 109.7, 67.8, 46.1, 22.3. MS (ESI) *m*/*z* 220.1 $[M+1]^+$. ESI-HRMS *m*/*z* calcd for $C_{10}H_{14}N_5O^+$ $[M+H]^+$ 220.1198, found 220.1189.

*3.3.2. 4-(Imidazo[1,2-a][1,3,5]triazin-2-yl)morpholine (**3b**).* Light-yellow solid, mp 180 °C, 85.3 mg (83.2%). ^{1}H NMR (250 MHz, DMSO): δ 3.62 (t, *J*=4.7 Hz, 4H), 3.72 (t, *J*=4.7 Hz, 4H), 7.22 (d, *J*=1.3 Hz, 1H), 7.47 (d, *J*=1.3 Hz, 2H), 9.21 (s, 1H). ^{13}C NMR (500 MHz, DMSO): δ 156.8, 149.3, 148.3, 133.1, 108.3, 65.8, 44.2. MS (ESI) *m*/*z* 206.0 $[M+1]^+$. ESI-HRMS *m*/*z* calcd for $C_9H_{12}N_5O^+$ $[M+H]^+$ 206.1042, found 206.1037.

*3.3.3. 4-(4-p-Tolylimidazo[1,2-a][1,3,5]triazin-2-yl)morpholine (**3c**).* Light-yellow solid, mp 174 °C, 119.7 mg (81.1%). ^{1}H NMR (250 MHz, DMSO): δ 2.43 (s, 3H), 3.68 (t, *J*=4.7 Hz, 4H), 3.81 (t, *J*=4.7 Hz, 4H), 7.33 (d, *J*=1.3 Hz, 1H), 7.44 (d, *J*=8.2 Hz, 1H), 7.61 (d, *J*=1.3 Hz, 2H), 7.9 (d, *J*=8.2 Hz, 2H). ^{13}C NMR (500 MHz, DMSO): δ 156.8, 155.4, 151.2, 142.6, 133.5, 129.5, 128.8, 128.7, 108.2, 65.9, 44.2, 21.1. MS (ESI) *m*/*z* 296.1 $[M+H]^+$. ESI-HRMS *m*/*z* calcd for $C_{16}H_{18}N_5O^+$ $[M+H]^+$ 296.1511, found 296.1506.

*3.3.4. 4-(4-Benzylimidazo[1,2-a][1,3,5]triazin-2-yl)morpholine (**3d**).* Light-yellow solid, mp 152 °C, 134.3 mg (91%). ^{1}H NMR (250 MHz, DMSO): δ 3.64 (t, *J*=4.7 Hz, 4H), 3.72 (t, *J*=4.7 Hz, 4H), 4.38 (s, 1H), 7.27 (d, *J*=1.9 Hz, 1H), 7.28–7.43 (m, 5H), 7.69 (d, *J*=1.9 Hz, 1H), 7.9 (d, *J*=8.2 Hz, 2H). ^{13}C NMR (500 MHz, DMSO): δ 156.1, 156.7, 150.5, 134.0, 133.0, 129.2, 128.5, 127.1, 107.5, 65.8, 44.1. MS (ESI) *m*/*z* 296.1 $[M+H]^+$. ESI-HRMS *m*/*z* calcd for $C_{16}H_{18}N_5O^+$ $[M+H]^+$ 296.1511, found 296.1503.

*3.3.5. 4-(4-(2-Nitrobenzyl)imidazo[1,2-a][1,3,5]triazin-2-yl)morpholine (**3e**).* Light-yellow solid, mp 196 °C, 129.9 mg (76.4%). ^{1}H NMR (250 MHz, DMSO): δ 3.53 (s, 8H), 4.88 (s, 2H), 7.38 (s, 1H), 7.81 (m, 2H), 7.67 (m, 2H), 8.16 (d, *J*=8 Hz, 1H). ^{13}C NMR (500 MHz, DMSO): δ 156.9, 156.1, 150.2, 148.9, 134.0, 133.7, 133.3, 129.1, 128.7, 124.8, 107.4, 65.6, 43.9, 36.9. MS (ESI) *m*/*z* 341.1 $[M+H]^+$. ESI-HRMS *m*/*z* calcd for $C_{16}H_{17}N_6O_3^+$ $[M+H]^+$ 341.1362, found 341.1355.

3.4. General method for the synthesis of compounds 4

To a solution of compound **3** (0.2 mmol) in methanol (10 mL), 10% platinum oxide (5 mg) is added under a nitrogen atmosphere. The reaction vessel is charged with hydrogen and evacuated three times until the reaction is under a hydrogen atmosphere. The reaction is stirred overnight. The reaction mixture is filtered through a pad of Celite and washed with methanol. The filtrate is concentrated to a small volume, and purified by flash chromatography.

*3.4.1. 4-(4-Methyl-3,4-dihydroimidazo[1,2-a][1,3,5]triazin-2-yl)-morpholine (**4a**).* Light-yellow solid, mp 260 °C dec, 42.5 mg (96%). ^{1}H NMR (250 MHz, DMSO): δ 1.5 (d, *J*=5.65 Hz, 3H), 3.4 (t, *J*=4.54 Hz, 4H), 3.62 (t, *J*=4.54 Hz, 4H), 5.48 (q, *J*=5.7 Hz, 1H), 6.69 (s, 1H), 6.81 (s, 1H), 7.28 (br s, 1H). ^{13}C NMR (500 MHz, DMSO): δ 153.6, 147.6, 123.3, 110.6, 65.7, 61.6, 44.9, 22.3. MS (ESI) *m*/*z* 222.1 $[M+H]^+$. ESI-HRMS *m*/*z* calcd for $C_{10}H_{16}N_5O^+$ $[M+H]^+$ 222.1355, found 222.1347.

*3.4.2. 4-(3,4-Dihydroimidazo[1,2-a][1,3,5]triazin-2-yl)morpholine (**4b**).* Light green solid, mp 228 °C, 38.5 mg (93%). ^{1}H NMR (250 MHz, DMSO): δ 3.39 (t, *J*=4.7 Hz, 4H), 3.61 (t, *J*=4.7 Hz, 4H), 5.17 (s, 2H), 6.61 (d, *J*=1.5 Hz, 1H), 6.65 (d, *J*=1.5 Hz, 1H), 7.48 (br s, 1H). ^{13}C NMR (500 MHz, DMSO): δ 153.7, 148.3, 126.0, 111.0, 65.8, 54.4, 44.9. MS (ESI) *m*/*z* 208.1 $[M+H]^+$. ESI-HRMS *m*/*z* calcd for $C_9H_{14}N_5O^+$ $[M+H]^+$ 208.1198, found 208.1187.

*3.4.3. 4-(4-p-Tolyl-3,4-dihydroimidazo[1,2-a][1,3,5]triazin-2-yl)-morpholine (**4c**).* Light- yellow, mp 216 °C, 55.3 mg (93%). ^{1}H NMR (250 MHz, DMSO): δ 2.32 (s, 3H), 3.60 (t, *J*=4.8 Hz, 4H), 3.64 (t, *J*=4.8 Hz, 4H), 6.74 (d, *J*=3.05 Hz, 1H), 6.9 (d, *J*=2.45 Hz, 1H), 7.13 (d, *J*=2.52 Hz, 1H), 7.27 (s, 4H), 8.84 (d, *J*=2.64 Hz, 1H). ^{13}C NMR (500 MHz, DMSO): δ 154.2, 146.5, 139.5, 135.4, 129.6, 126.3, 114.8, 113.1, 66.6, 65.5, 44.8, 20.7. MS (ESI) *m*/*z* 298.1 $[M+H]^+$. ESI-HRMS *m*/*z* calcd for $C_{16}H_{20}N_5O^+$ $[M+H]^+$ 298.1668, found 298.1657.

*3.4.4. 4-(4-Benzyl-3,4-dihydroimidazo[1,2-a][1,3,5]triazin-2-yl)-morpholine (**4d**).* Yellow solid, mp 203 °C, 52.9 mg (89%). ^{1}H NMR (250 MHz, DMSO): δ 2.92 (dd, *J*=4.0, 13.6 Hz, 1H), 3.0 (dd, *J*=4.0, 13.6 Hz, 1H), 3.3 (t, *J*=4.3 Hz, 4H),3.52 (t, *J*=4.37 Hz, 4H), 5.8 (t, *J*=4.3 Hz, 1H), 6.61 (s, 1H), 6.72 (s, 1H), 7.0 (dd, *J*=1.4, 7.1 Hz, 1H), 7.22 (m, 4H). ^{13}C NMR (500 MHz, DMSO): δ 154.5, 149.6, 137.0, 131.9, 129.9, 128.5, 127.2, 112.8, 67.7, 46.8, 44.9. MS (ESI) *m*/*z* 298.1 $[M+H]^+$. ESI-HRMS *m*/*z* calcd for $C_{16}H_{20}N_5O^+$ $[M+H]^+$ 298.1668, found 298.1655.

*3.4.5. 4-(4-(2-Nitrobenzyl)-3,4-dihydroimidazo[1,2-a][1,3,5]triazin-2-yl)morpholine (**4e**).* Yellow solid, mp 206 °C, 58.7 mg (94%). ^{1}H NMR (250 MHz, DMSO): δ 2.73 (dd, *J*=14, 4.7 Hz, 1H), 2.92 (dd, *J*=14, 4.7 Hz, 1H), 3.34 (t, *J*=4.3 Hz, 4H), 3.58 (t, *J*=4.3 Hz, 4H), 4.97 (br s, 2H), 5.67 (t, *J*=5.6 Hz, 1H), 6.46 (t, *J*=7.5 Hz, 1H), 6.57 (s, 1H), 6.64 (d, *J*=7.5 Hz, 1H), 6.68 (s, 1H), 6.69 (d, *J*=7.5 Hz, 1H), 6.87 (s, 1H), 6.94 (t, *J*=7.5 Hz, 1H). ^{13}C NMR (500 MHz, DMSO): δ 151.5, 146.8, 139.2, 128.0, 127.6, 124.9, 118.9, 116.2, 115.0, 111.1, 65.8, 44.9, 40.4. MS (ESI) *m*/*z* 313.2 $[M+H]^+$. ESI-HRMS *m*/*z* calcd for $C_{16}H_{21}N_6O^+$ $[M+H]^+$ 313.1777, found 313.1769.

*3.4.6. 2-Amino-1,6-dimethyl-4-morpholino-1,3,5-triazinium iodide **5**.* A mixture of compound **2** (100 mg, 0.51 mmol) and methyl iodide (1 mL, 16 mmol) and DMF (1 mL) was heated at reflux for 6 h. The mixture was cooled, the solvent removed under reduced pressure and the residue was crystallized from methanol and ether.

White solid, mp 183 °C, 99.2 mg (93%). ^{1}H NMR (250 MHz, DMSO): δ 2.52 (s, 3H), 3.45 (s, 3H), 3.66 (m, 4H), 3.77 (t, *J*=4.8 Hz,

2H), 3.86 (t, J=4.8 Hz, 2H), 8.30 (s, 1H), 8.83 (s, 1H). ^{13}C NMR (500 MHz, DMSO): δ 167.3, 158.6, 156.8, 65.8, 65.5, 44.2, 43.9, 34.4, 22.8. MS (ESI) m/z 210.1 $[M+H]^+$. ESI-HRMS m/z calcd for $C_9H_{16}N_5O^+$ $[M+H]^+$ 210.1349, found 210.1341.

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Supplementary data

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