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A Switchable Intramolecular Hydrogen Bond in Polysubstituted 5-Nitrosopyrimidines

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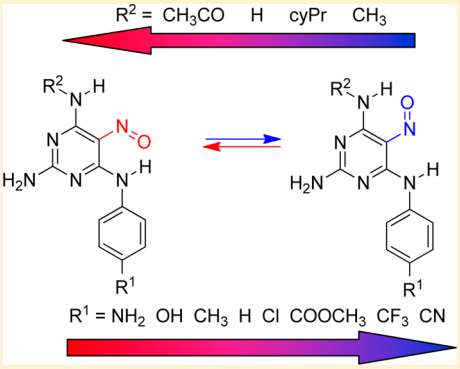
Supporting Information

ABSTRACT: The formation of strong intramolecular hydrogen bonds was observed in a series of 2-amino-5-nitrosopyrimidines with alkylamino and arylamino substituents at positions 4 and 6. Mixtures of two rotamers differing in the orientation of the nitroso group were observed in the NMR spectra of the compounds where two distinct intramolecular hydrogen bonds could be formed. The ratio of the two rotamers depends strongly on the character of the substituents at positions 4 and 6 and can be finely tuned over a broad range of conformation ratios. The experimental results were supported by DFT calculations, which also made it possible to explain the apparent contradiction in the experimental dependence of the rotamer ratio on the Hammett constants for the arylamino substituents. The UV/vis spectra of the compounds also significantly depend on the nature of the substituents; however, the orientation of the nitroso group does not have any influence on the position of the absorption bands in the spectra.



INTRODUCTION

The formation of intramolecular hydrogen bonds has a very pronounced effect on molecular structure and properties. For example, molecules mask their polarity from the environment, become more lipophilic, and might thus display a higher membrane permeability.[1] High stability of intramolecular hydrogen bonds has often been observed when a six-membered ring is formed and when the linker atoms are sp^2-hybridized (amides, heteroaromatic rings), leading to planar, conjugated systems. The high stability of these intramolecular hydrogen bonds has been termed resonance-assisted hydrogen bonding (RAHB) and can be rationalized by enhanced π-delocalization.[2] RAHB has recently been reviewed.[3−5] The high propensity to form resonance-assisted hydrogen bonds has been used in the design of new kinase inhibitors.[6] On the basis of the known bicyclic kinase inhibitor scaffold, pyrimidin-4-ylureas were suggested as bioisosteres. Molecules containing this substructure indeed turned out to be inhibitors of multiple kinases, and the binding mode was confirmed by a cocrystal structure. The literature contains a number of further examples where six-membered hydrogen-bonded pseudorings effectively mimic aromatic rings.[7−11] Nevertheless, the concept of RAHB was later criticized. It was found in a series of enols of β-diketones and β-enaminones that the RAHB effect is not the primary reason behind the strength of their intramolecular hydrogen bonds, which is simply a consequence of the structure of the σ-skeleton of the system that keeps the hydrogen-bond donor and acceptor coplanar and closer to each other.[12]

Conjugated nitrosoamines belong to the same family as the enols of β-diketones and other conjugated systems with intramolecular hydrogen bonds. Therefore, the formation of strong intramolecular hydrogen bonds may be expected, and indeed, these hydrogen bonds were found in the solid-state structures of 3-amino-2-nitrosocyclohex-2-en-1-one,[13] 5-amino-4-nitrosopyrazole,[14] and 6-amino-5-nitrosopyrimidines.[15−18]

Nitrosopyrimidine derivatives are not naturally occurring, but their interesting biological properties have been described. The cytostatic activity of 5-nitrosopyrimidines is well-known,[19,20] just like their antifungal effects.[21] They are also useful as direct precursors for the synthesis of biologically relevant heterocyclic systems, such as heteroatomic diazoles[22] and pteridines.[23,24] 5-Nitrosopyrimidines have also been shown to be able to form complexes with a variety of metal ions both in solution and in the solid state.[25−28]

In this work, a series of 32 2-amino-5-nitrosopyrimidine derivatives with a *para*-substituted phenylamino substituent at position 6 and an unsubstituted or substituted amino group (cycloalkylamino, alkylamino, acetylamino) at position 4 were prepared. A new microwave-assisted methodology for the synthesis of the derivatives has been developed. The prepared 5-nitrosopyrimidines have two competing NH groups that can form an intramolecular hydrogen bond with the nitroso group (Figure 1). The ratio of the two rotamers was determined by NMR spectroscopy, and the results were supported by DFT calculations. The effect of the substituent in the *para* position of the phenylamino group on the electronic structure was also observed by UV/vis spectroscopy.

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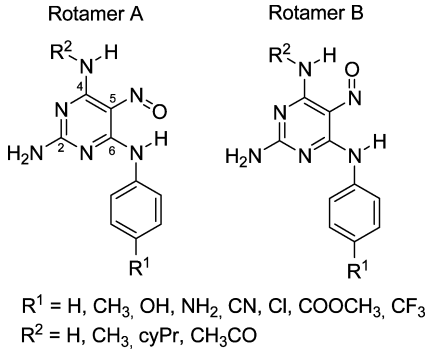


Figure 1. The two possible geometries of the nitroso group at position 5 of the studied compounds. Rotamer A (left) has the C6−C5−N−O torsion angle close to 0°, whereas rotamer B (right) has the C6−C5−N−O torsion angle close to 180°.

RESULTS AND DISCUSSION

Synthesis. A series of polysubstituted 5-nitrosopyrimidines were synthesized starting from 2-amino-4,6-dimethoxy-5-nitrosopyrimidine (**1**).[29] In the first step, compound **1** was treated with a variety of *para*-substituted anilines **2a−h** in dimethylformamide (DMF) to give the intermediates **3a−h** (Scheme 1). It is known that aminolysis of the 4- and 6-methoxy groups on the pyrimidine ring takes place because of their activation by the electron-withdrawing nitroso group at position 5.[30] Depending on the nature of the R^1 substituent in anilines **2a−h**, the aromatic nucleophilic substitution can be performed either under conventional heating or, more conveniently, in a closed vessel under microwave irradiation, especially in the case of less reactive anilines (e.g., **2a** and **2b**).

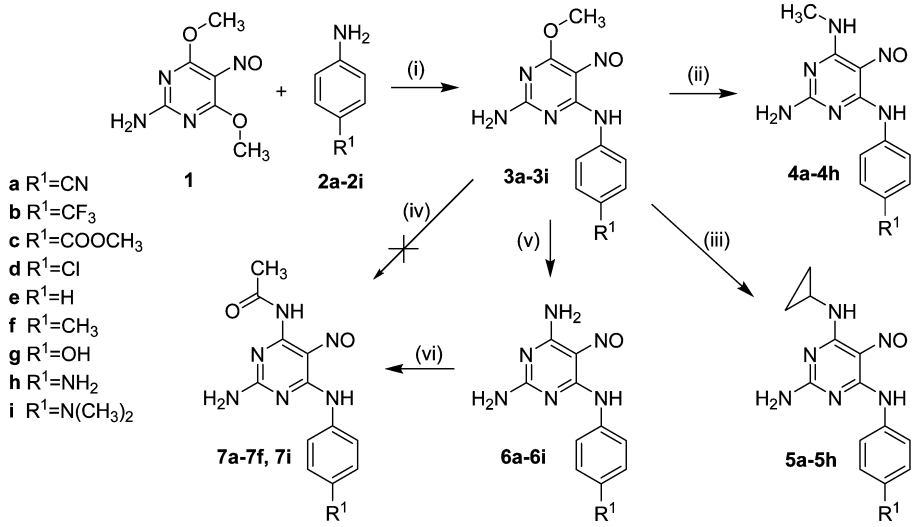
Subsequently, the remaining methoxy group of intermediates **3a−h** was replaced by a reaction with selected amines, namely, methylamine, cyclopropylamine, and ammonia (Scheme 1). Again, differences in the reactivity of various amines were observed, as reactions of compounds **3a−h** with methylamine in EtOH/DMF to obtain the products **4a−h** took place at room temperature while the analogous reactions with cyclopropylamine in DMF (to give **5a−h**) and aqueous ammonia (to give **6a−h**) required conventional heating to reach full conversion (Scheme 1). The reactivity of acetamide with the methoxy group of pyrimidines **3a−h** in the aromatic nucleophilic reaction is too low, and no desired product **7** was observed even under microwave irradiation at temperatures up to 180 °C, whereas at higher temperatures, decomposition of DMF (used as a solvent) and the subsequent formation of 4-(*N*,*N*-dimethylamino)pyrimidines were observed (UPLC-MS).[31] An alternative approach to *N*-acetyl derivatives **7a−f** involved treating compounds **6a−f** with acetic anhydride at 80 °C (Scheme 1).[32] Unfortunately, the treatment of **6g** and **6h** with acetic anhydride at 80 °C did not lead to the formation of the desired products **7g** and **7h**, respectively, as there seemed to be preferential acetylation of the *p*-hydroxy and *p*-amino groups on the aryl ring at position 6. For the subsequent NMR studies, the 4-(dimethylamino)phenylamino derivatives **6i** and **7i** were prepared instead, using the reaction of compound **1** with *N*,*N*-dimethyl-*p*-phenylenediamine (to give **3i**) followed by ammonolysis of **3i** (to give **6i**) and finally by acetylation of **6i** (to give **7i**).

In several cases, the formation of two distinct rotamers in the final products **4−7** was observed as two spots using TLC or as cleft signals in the UPLC-MS spectra.

The reactivities of the *para*-substituted anilines **2a−h** in aromatic nucleophilic substitution can be evaluated/measured in two different ways: (a) by comparing the Hammett constants and (b) by comparing their basicities using pK_b values. To compare their genuine reactivities, the anilines **2a−h** were reacted with 2-amino-4,6-dimethoxy-5-nitrosopyrimidine (**1**) in DMF under integrated conditions (160 °C, MW-assisted heating, monitoring by UPLC-MS); the data are summarized in Table 1. According to our expectations, we observed that the reaction time steadily increased in the order NH_2 < OH < CH_3 < H < Cl < $COOCH_3$ ≈ CF_3 ≈ CN.

NMR Spectroscopy. In compounds **3a−h**, the nitroso oxygen atom and the NH hydrogen atom from the aniline residue form an intramolecular hydrogen bond, whose presence

Scheme 1. Synthesis of Polysubstituted Pyrimidines[a]



[a]Conditions: (i) DMF, MW or conventional heating; (ii) 33% CH_3NH_2 in EtOH, DMF, rt; (iii) cyclopropylamine, DMF, conventional heating (70−90 °C); (iv) acetamide, DMF, MW-assisted heating (100−180 °C); (v) ammonia, conventional heating (50 °C); (vi) acetic anhydride, conventional heating (80 °C).

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Table 1. Comparison of the Reactivities and Properties of the Anilines 2a–h Depending on the Nature of the *para* Substituent R[1]

compound	R[1]	Hammett constant[33]	aniline pK_b[34]	reaction time (min)
2a	CN	0.70	1.74[35]	240
2b	CF_3	0.53	2.57	220
2c	$COOCH_3$	0.44	2.30	260
2d	Cl	0.24	3.81	80
2e	H	0	4.58	20
2f	CH_3	−0.14	5.07	25
2g	OH	−0.38	5.50	9
2h	NH_2	−0.57	6.08	3

was clearly confirmed by NMR spectroscopy. The signal of the NH hydrogen was found in the low-field region (13.5–13.7 ppm), which is a typical value for hydrogen atoms involved in strong hydrogen bonds. The signal of the NH hydrogen in similar compounds without the 5-nitroso group was found at 8–10 ppm.[36] Furthermore, we observed four-bond correlations between the NH hydrogen and carbon atom C2 in the HMBC spectra. Four-bond correlations are usually observed when the atoms in the coupling path are in a W-like arrangement (see Figure 2). The presence of the NH–C2 cross-peak and the absence of the NH–C4 cross-peak provide clear evidence of the arylamino residue conformation with the NH hydrogen heading toward the nitroso group. Similarly, the W-like arrangement can be found between the hydrogen atoms in the 2-amino group and carbon atoms C4 or C6. The two NH_2 hydrogens are not equivalent because of a slow rotation around the C2–NH_2 bond, and the two four-bond correlations are observable in the HMBC spectra (Figure 2).

Interestingly, the 6-NH hydrogen chemical shifts have an unexpected dependence on the substituent at the *para* position of the attached phenyl group. An electron-withdrawing substituent at the *para* position of an aniline derivative usually increases the chemical shift of the amino protons because of the lower electron density in the phenyl ring and the amino group, whereas electron-donating substituents have the opposite effect. For example, the NH_2 chemical shift of 4-aminobenzonitrile (**2a**) is 2 ppm higher than that of 1,4-diaminobenzene (**2h**).[37,38] In the series of compounds **3a–i**, we observed the opposite order of NH chemical shifts, as the 4-cyanophenyl derivative **3a** has a lower chemical shift than the 4-aminophenyl derivative **3h** by 0.2 ppm (Table 2). It should be noted,

Table 2. Experimental Chemical Shifts of the 6-NH Hydrogen in Compounds 3a–i (Measured in DMSO)

compound	R[1]	δ_{NH} (ppm)
3a	CN	13.45
3b	CF_3	13.47
3c	$COOCH_3$	13.53
3d	Cl	13.46
3e	H	13.51
3f	CH_3	13.52
3g	OH	13.54
3h	NH_2	13.65
3i	$N(CH_3)_2$	13.67

however, that in **3a–i** the whole molecule has a system of conjugated π electrons, and therefore, the electronic effects of the substituent at the *para* position of the aniline fragment are spread throughout the molecule. Thus, an electron-withdrawing substituent also lowers the electron density in the nitroso group, making it a poorer hydrogen-bond acceptor. Poorer hydrogen-bond acceptors may form weaker hydrogen bonds with the 6-NH group, leading to a decrease of the 6-NH chemical shift. Therefore, the effect of the *para* substituent on the 6-NH chemical shift can be divided into two contributions: (a) the influence on the NH electron density and (b) the influence on the electron density of the nitroso group. The two effects have the opposite sign and almost cancel each other out, leaving only a modest NH chemical shift dependence on the *para* substituent with the former effect (a) being slightly overridden by the latter (b).

In the case of compounds **4–7**, two intramolecular hydrogen bonds are possible, differing in the orientation of the nitroso group (Figure 1). Both of them were formed in the solutions of all the compounds studied, and two sets of signals were observed in both the ^1H and ^{13}C NMR spectra. The chemical shift of the hydrogen atom involved in the hydrogen bond was close to 14 ppm, whereas the chemical shift of the unbound

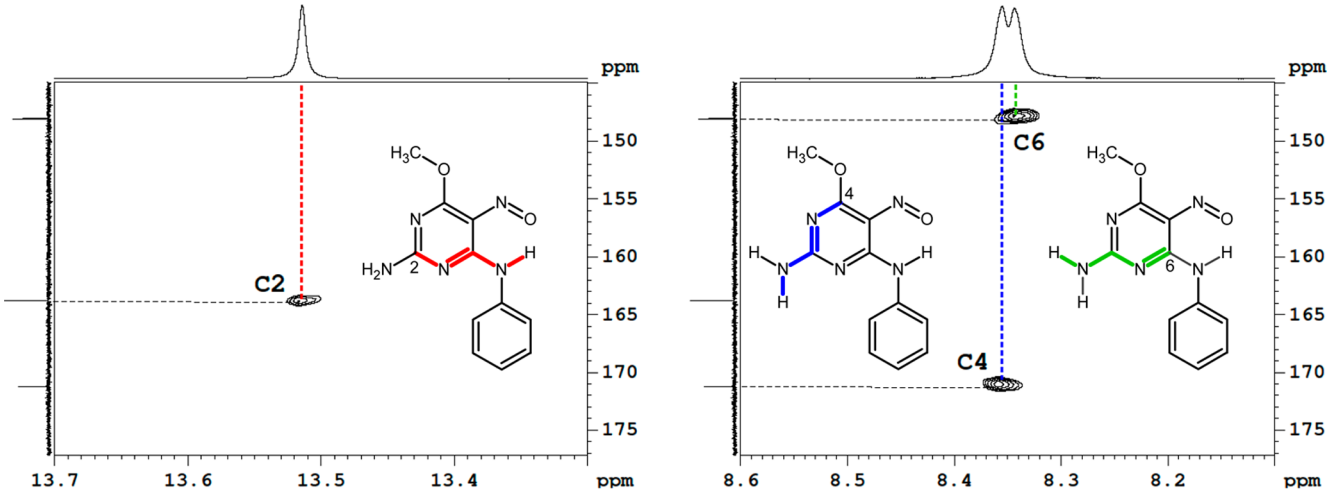

Figure 2. HMBC correlations of compound **3e** with the W-like arrangement between the aniline NH hydrogens and C2 (left) and between the amino hydrogens and C4/C6 (right).

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amino hydrogen was close to 10 ppm. Furthermore, the orientation of the nitroso group has a significant influence on the chemical shifts of the carbon atoms C4 and C6, as shown in Table 3. For example, in rotamer A of compound **5e**, where the nitroso oxygen atom is turned to the NH group at position 6, the C6 carbon atom is more shielded (148.4 ppm) than in rotamer B (161.5 ppm). The carbon chemical-shift differences between the rotamers were also confirmed by DFT calculations (see below).

Table 3. Experimental Pyrimidine Carbon Chemical Shifts of Rotamer A of Compound 5e and the Experimental and Calculated [B3LYP/6-31+G(d,p)] Chemical-Shift Differences between the Two Rotamers

		$\Delta\delta_{A-B}$ (ppm)	
atom	$\delta_{A,exptl}$ (ppm)	exptl	calcd
C2	164.5	0.1	−0.1
C4	164.2	12.1	16.2
C5	135.9	0.0	0.2
C6	148.4	−13.1	−17.2

We also measured the ^{1}H NMR spectra of compound **5e** at variable temperatures up to 140 °C [Figure S1 in the Supporting Information (SI)]. The two nonequivalent signals of the protons in the 2-amino group of both rotamers merged already at 50 °C. On the other hand, the NH signals corresponding to rotamer A did not merge with the NH signals of rotamer B over the whole temperature range into one signal set, as would be expected for a system with a fast interconversion between forms A and B. The signals of both forms became only slightly broader. The low limit of the barrier for the conformational change between the two forms was estimated from the NMR line shape analysis of the NH protons to be 21 kcal/mol. It should be noted, however, that the NH proton signal broadening is caused only partly by the rotamer interconversion and that the line broadening may be a result of other exchange processes, such as exchange of the NH protons with the traces of water present in the sample or with the 2-amino protons. The presence of these exchange processes is evidenced by a high-field shift of all of the NH proton signals (i.e., toward the water and NH_2 signals) at higher temperatures. Therefore, the estimated rotamer interconversion barrier is only a lower limit estimation, and the actual barrier may be significantly higher. An alternative approach for the determination of the exchange rate, and hence the barrier for the rotamer interconversion, relies on the determination of the coalescence temperature of the signals corresponding to the two rotamers. The coalescence temperature is defined as the temperature at which two separate peaks of the spectrum merge into one. At this temperature, an approximate equation for the exchange rate may be used: $k = \pi\Delta\nu_0/\sqrt{2}$, where $\Delta\nu_0$ is the separation of the signals (in Hz) in the slow-exchange limit. This approach could be applied only for the *meta*- and *para*-hydrogen signals of the phenyl ring because the other signals did not merge in the whole temperature range. The *meta*-hydrogens were separated by 11.2 Hz at room temperature and merged at 120 °C, whereas the *para*-hydrogens were separated by 20.0 Hz and merged at 140 °C. The free energies of activation were calculated to be 20.7 and 21.4 kcal/mol at 120 and 140 °C, respectively. It should be noted, however, that this approach also leads only to an estimation of the reaction barrier because the splitting of the signals caused by *J* coupling made the exact coalescence temperature difficult to determine.

The ratio of the two conformers depends significantly on the substituents at positions 4 and 6 of the pyrimidine ring. The observed molar ratios of the two conformers are summarized in Table 4, and a graphical representation is shown in Figure S2 in the SI. For example, for compounds **4a−h** with the methylamino group at position 4, the percentage of rotamer A ranged from 32 to 70% depending on the *para* substituent of the phenylamino group at position 6, and the percentages correlated well with the Hammett coefficients (Figure 3). Electron-withdrawing substituents decrease the concentration of the form A, whereas electron-donating substituents have the opposite effect. The ratios of the two conformers in the

Table 4. Observed Percentages of Rotamer A in the DMSO Solutions of Compounds 4−7 and the Calculated Data [B3LYP/6-31+G(d,p), vacuum]

				% A						% A	
compound	R^2	R^1	ΔG_{exptl} (kcal/mol)	exptl	calcd	compound	R^2	R^1	ΔG_{exptl} (kcal/mol)	exptl	calcd
4a	CH_3	CN	−0.45	32	42	**6a**	H	CN	−0.12	45	61
4b	CH_3	CF_3	−0.32	37	37	**6b**	H	CF_3	0.00	50	54
4c	CH_3	$COOCH_3$	−0.22	41	40	**6c**	H	$COOCH_3$	0.14	56	61
4d	CH_3	Cl	−0.14	44	46	**6d**	H	Cl	0.22	59	66
4e	CH_3	H	0.07	53	43	**6e**	H	H	0.39	66	64
4f	CH_3	CH_3	0.14	56	42	**6f**	H	CH_3	0.50	70	64
4g	CH_3	OH	0.27	61	49	**6g**	H	OH	0.68	76	70
4h	CH_3	NH_2	0.50	70	57	**6h**	H	NH_2	0.82	80	76
						6i	H	$N(CH_3)_2$	0.79	79	77
5a	cyPr	CN	−0.42	33	39	**7a**	$COCH_3$	CN	0.17	57	79
5b	cyPr	CF_3	−0.32	37	37	**7b**	$COCH_3$	CF_3	0.27	61	69
5c	cyPr	$COOCH_3$	−0.22	41	36	**7c**	$COCH_3$	$COOCH_3$	0.34	64	79
5d	cyPr	Cl	−0.17	43	44	**7d**	$COCH_3$	Cl	0.39	66	82
5e	cyPr	H	0.00	50	37	**7e**	$COCH_3$	H	0.62	74	82
5f	cyPr	CH_3	0.14	56	41	**7f**	$COCH_3$	CH_3	0.72	77	79
5g	cyPr	OH	0.27	61	46	**7g**	$COCH_3$	OH	n.a.	n.a.	84
5h	cyPr	NH_2	0.47	69	52	**7h**	$COCH_3$	NH_2	n.a.	n.a.	88
						7i	$COCH_3$	$N(CH_3)_2$	0.98	84	88

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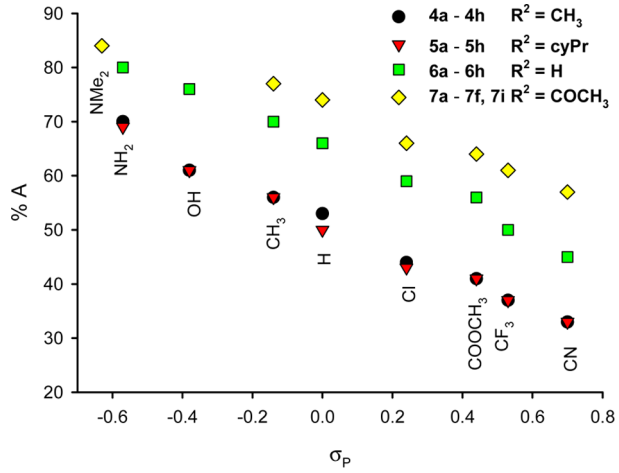

Figure 3. Dependence of the observed rotamer ratio of compounds **4**–**7** on the Hammett constant σ_p for the substituent at the *para* position of the phenylamino group (R^1).

compounds **5a**–**5h** with the cyclopropylamino group in the position 4 were almost identical to those found for the compounds **4a**–**4h**. In the 4-amino derivatives **6a**–**6h**, the A form was consistently slightly more preferred, namely by 10–15%, when compared with **4a**–**4h**, and the acetamino group in the compounds **7** promoted the formation of the conformer A by further 5–12%.

Calculations. We optimized the geometries of both rotamers of compounds **4**–**7** and determined the free energy differences and the rotamer ratios in equilibrium. The calculated rotamer ratios agree reasonably well with the experimental ones (Table 4), with the highest error being 16%. Part of the error may be ascribed to the neglect of solvation in the calculations. We also performed the geometry optimization of compounds **5e** and **5g** using a polarizable continuum solvent model, but it did not improve the calculated rotamer ratios. The specific solvation of the polar pyrimidines is probably important in the DMSO solutions. Unfortunately, these specific interactions cannot be modeled well with the implicit solvation model.[39]

Electron-donating substituents in the *para* position of the phenyl ring (R^1 in Figure 1) increase the concentration of form A, whereas electron-withdrawing substituents do the opposite. This behavior might seem surprising at first sight, as electron-donating groups increase the electron density in the aniline residue including the NH nitrogen, making the NH group less acidic and a poorer hydrogen-bond donor. The expected substituent effect was found previously for hydrogen-bonded complexes of substituted phenols with a water molecule, where the strength of the XPhOH···OH_2 complexes increased for electron-withdrawing substituents X[40] (i.e., the hydrogen-bond stability increased in the reverse order than in our compounds). In our case, however, as already discussed, the whole molecules contain systems of conjugated π-electrons, enabling the transfer of the electronic substituent effects throughout the molecule. Therefore, electron-donating substituents increase the electron density also at the nitroso oxygen atom, making it a better hydrogen-bond acceptor, as can be seen from the plots of electrostatic potentials in Figure 4 and also by comparing the calculated Mulliken charges of the oxygen atom (−0.02*e* difference between R^1 = NH_2 and R^1 = CN). The influence of the substituents on the rotamer ratio can be then explained as follows: electron-donating groups increase the electron density in both the phenyl and the pyrimidine parts of the molecule. The electrostatic potential at the aniline NH hydrogen is affected by substituent R^1 to a lower extent than that at the amino hydrogen at position 4; the corresponding differences in the Mulliken atomic charges when going from R^1 = NH_2 to R^1 = CN are −0.001*e* and −0.015*e* for the aniline and amino NH hydrogens, respectively. Electron-donating substituents thus make the 4-amino hydrogen a poorer hydrogen-bond donor, which results in the higher stability of form A.

The strength of the hydrogen bonds could be also estimated from their calculated lengths. However, in our conjugated pyrimidine derivatives, where the substituents change the properties of both the hydrogen-bond donor and acceptor, no significant changes in the bond lengths were observed. The calculated hydrogen-bond lengths are listed in the SI.

We also looked for a transition-state structure for the rotamer interconversion. The first-order saddle-point structure on the reaction coordinate for compound **5e** was localized by using the QST3 method,[41,42] and the free energy barriers to transition were calculated in vacuo and with a polarizable continuum model of solvation. The transition state is visualized in Figure 5. The free energy barrier heights calculated in vacuum (27.8 kcal/mol) and in DMSO (30.0 kcal/mol) were slightly higher than the rough estimates from the NMR experiments.

UV/Vis Spectroscopy. The UV/vis spectra of the nitrosopyrimidines in DMSO solution exhibit one weak electronic transition in the visible region (430–600 nm) and two strong transitions in the UV region (260–350 nm), which could be assigned on the basis of time-dependent density functional theory (TD-DFT) calculations (see below). The color of the solutions (green or yellow-red) arises from the weak n → π^* electronic transitions, and the UV bands are caused by π → π^*

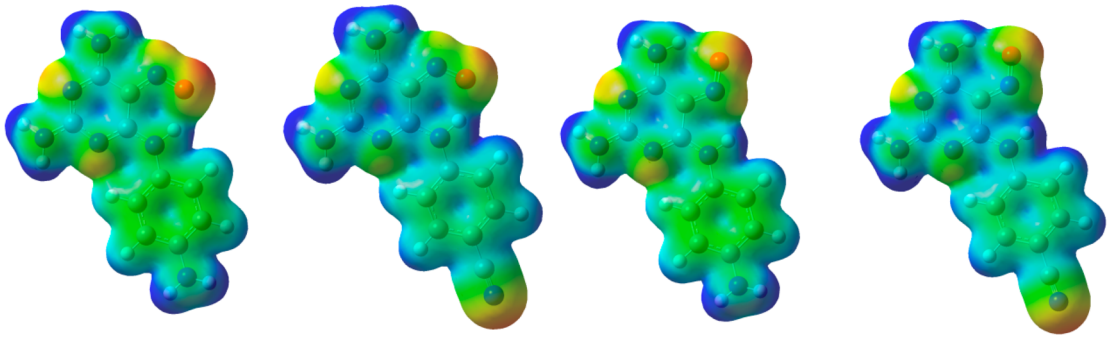

Figure 4. Electrostatic potential plots for the two rotamers of compounds **6a** and **6h**.

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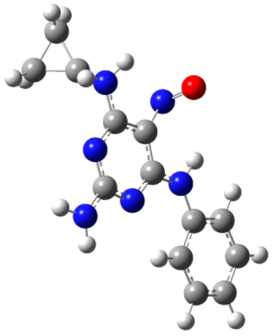

Figure 5. Transition state of compound **5e** found by QST3 calculations.

transitions. The maximum-intensity wavelengths for compounds **3a**–**i** are summarized in Table 5. The position of the maximum in the visible region (λ_{max1}) depends significantly on the *para* substituent, with a bathochromic shift for electron-withdrawing substituents and a hypsochromic shift for electron-donating substituents. The absorption bands for the amino derivative **3h** and the dimethylamino derivative **3i** are significantly broader and shifted to lower wavelengths than the bands for the other compounds in the series (see the SI). The position of the first UV maximum (λ_{max2} in Table 5) is almost independent of the nature of the substituent, whereas the position of the second UV maximum (λ_{max3}) slightly varies in the series. However, no clear Hammett-like correlation of λ_{max3} was observed. We also measured the electronic spectra of compound **3e** in a series of solvents and observed a significant solvatochromic effect, with λ_{max1} found at 608, 594, 552, and 540 nm in acetone, DMSO, ethanol, and methanol, respectively. The solutions of compound **3e** had different colors in these solvents (see Figure S4 in the SI for a photo of the solutions).

Table 5. Experimental and Calculated UV/Vis Absorption Maxima for Compounds 3a–i

compound	R^1	λ_{max3}^{exptl} (nm)	λ_{max2}^{exptl} (nm)	λ_{max1}^{exptl} (nm)	λ_{max1}^{calcd} (nm)
3a	CN	–[a]	342	596	619
3b	CF_3	–[a]	342	602	615
3c	$COOCH_3$	276	342	600	617
3d	Cl	264	338	596	609
3e	H	260	338	594	608
3f	CH_3	260	338	592	606
3g	OH	260	336	582	602
3h	NH_2	274	336	436	598
3i	$N(CH_3)_2$	–[a]	336	442	597

[a]The absorption maximum overlapped with other maxima.

The UV/vis absorption maxima of derivatives **4**–**7** are shifted by an almost constant shift with respect to the corresponding methoxy derivatives **3** (see the SI), indicating that the orientation of the nitroso group does not affect the electronic spectrum.

The TD-DFT calculations predicted the positions of the absorption maxima well (see Table 5 and the SI), making it possible to explain the observed experimental spectra. We calculated the five lowest-energy electronic transitions for compounds **3a**–**i**. Typically, one transition in the visible range with a very low oscillator strength (corresponding to a weak intensity of the peak in the experimental spectrum) and two transitions with high oscillator strengths in the UV region were found among the calculated transitions. Additional weak transitions were found in the UV region of some derivatives; however, these bands are probably overlapped by the intense bands in the experimental spectra. In the calculated transitions for the amino derivative **3h**, one of the $\pi \rightarrow \pi^*$ transitions is close to the $n \rightarrow \pi^*$ transition, which could explain the unusually broad experimental signal in the visible range. Furthermore, the lowest-energy transitions in the visible range for compounds **3a**–**g** correspond to excitation from the HOMO to the LUMO, whereas for the amino derivative **3h**, the lowest-energy transition corresponds to excitation from the HOMO−1 orbital.

■ CONCLUSIONS

We prepared a series of polysubstituted 5-nitrosopyrimidine derivatives capable of forming strong intramolecular hydrogen bonds. Mixtures of two forms with distinct hydrogen-bond patterns were found in the solutions of compounds with two hydrogen-bond donors neighboring the nitroso group. The ratio of the two forms was significantly substituent-dependent, and the concentrations of the two forms can be found in a broad range. Furthermore, the rotamer ratio can be predicted well by DFT calculations. It has been speculated previously that 5-nitrosopyrimidines with an intramolecular hydrogen bond might mimic purine derivatives.[43] Our switchable 5-nitrosopyrimidines might thus mimic two different purine derivatives depending on the orientation of the nitroso group. For example, form A of compound **6e** (Figure 6) resembles 2-amino-9-phenyladenine, which can act as a phosphatidylinositol-kinase inhibitor,[44] whereas form B of the same compound resembles 2-amino-6-phenylaminopurine, which can act as a cytokinin-receptor activator.[45] Theoretically, one compound may hence target two different metabolic pathways. Studies of the biological properties of the polysubstituted 5-nitrosopyrimidines are in progress.

■ EXPERIMENTAL SECTION

Instrumentation and Calculations. The NMR spectra were measured at room temperature on a spectrometer operating at 499.9 MHz for ^1H and at 125.7 MHz for ^{13}C in DMSO-d_6 (2 mg of the compound dissolved in 0.6 mL of the solvent). A combination of 1D and 2D experiments (COSY, HSQC, HMBC) was used for the

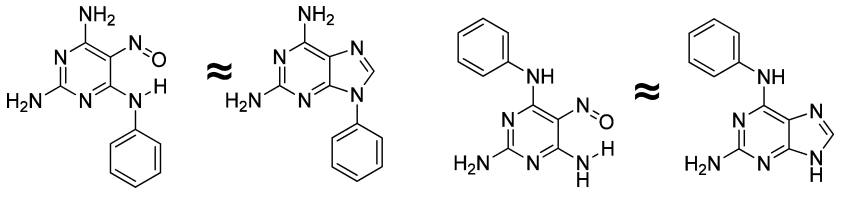

Figure 6. The two forms of 5-nitrosopyrimidine **6e** as purine mimics.

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assignment of all of the ^{1}H and ^{13}C resonances. The general numbering scheme for the assignment of the NMR signals of the polysubstituted pyrimidines is shown in Figure 7. The rotamer

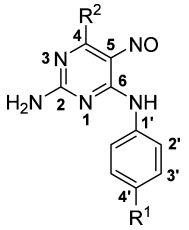

Figure 7. General numbering scheme for the assignment of the NMR signals of the polysubstituted pyrimidines.

mixtures of compounds **4**−**7** were allowed to equilibrate for 24 h prior to the NMR measurements, and we checked that the equilibrium composition did not change over 4 weeks. High-resolution electrospray mass spectrometry (HRMS) was performed using an Orbitrap spectrometer.

All of the structures were optimized at the DFT level of theory using the B3LYP functional[46,47] and a standard 6-31+G(d,p) basis set. The NMR parameters were calculated using the GIAO method. The calculations were done for the molecules in vacuum, but for comparison we also optimized the geometries of compounds **5e** and **5g** in DMSO using the PCM method.[30,31] The Gaussian 09 program package was used throughout this study.[48] The QST3 optimization method[41,42] was applied in the search for the transition state of the rotamer interconversion of compound **5e** in vacuum, that is, the structures of the reactants and products and an estimate of the transition state were used. Once the transition state had been optimized in vacuum, a single-point energy and frequency calculation was performed with the PCM method of solvation. The vibrational frequencies and free energies were calculated for all of the optimized structures, and the character of each stationary point (a minimum or a first-order saddle point) was thus confirmed. The electronic spectra were calculated using the TD-DFT method[49] with the PCM method of DMSO solvation.

All of the microwave-assisted reactions were carried out in a CEM Discover (Explorer) microwave apparatus with a 24-position system for 10 mL vessels sealed with a Teflon septum. It was operated at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W. The solutions were steadily stirred during the reaction. The temperature was measured with an IR sensor on the outer surface of the process vessel. The vials were cooled to ambient temperature with a gas jet cooling system. The pressure was measured with an inboard CEM Explorer pressure control system (0−21 bar).

Preparation of 5-Nitrosopyrimidines. *General Procedure A: Synthesis of 2-Amino-6-arylamino-4-methoxy-5-nitrosopyrimidines* ***3a*****−*****i*****.** A mixture of compound **1** and 1.1 equiv of the corresponding *para*-substituted aniline (**2a**−**i**) in DMF (3 mL per 1 mmol of **1**) was stirred and heated under conventional heating (conv.) or microwave-assisted (MW) heating until full conversion (as judged by TLC). The reaction mixture was evaporated in vacuum, and the product was isolated by silica gel column chromatography (5−8% MeOH in $CHCl_3$). In the case of compounds **3a** and **3f**, the solid residues after solvent evaporation were dissolved in acetone and methanol, respectively, and the products were filtered off, washed, and dried. Compounds **3a**−**c** and **3f** were crystallized.

*4-[(2-Amino-4-methoxy-5-nitrosopyrimidin-6-yl)amino]-benzonitrile (**3a**).* Treatment of **1** (600 mg, 3.3 mmol) and 4-aminobenzonitrile (**2a**) (429 mg, 3.6 mmol) by general procedure A (MW, 170 °C, 2 h) gave **3a** (267 mg, 30%) as green crystals (from methanol/acetone, 1:1) with mp = 245 °C. ^{1}H NMR (DMSO-d_6): δ 13.45 (1H, s, 6-NH), 8.57 and 8.53 (2H, bs, 2-NH_2), 8.06 (2H, m, H2′), 7.79 (2H, m, H3′), 4.10 (3H, s, O−CH_3). ^{13}C NMR (DMSO-d_6): δ 171.2 (C4), 163.7 (C2), 147.5 (C6), 142.1 (C1′), 138.4 (C5), 133.2 (C3′), 123.2 (C2′), 119.0 (CN), 106.6 (C4′). UV/vis (DMSO): λ_{max} = 342, 596 nm. ESI MS *m*/*z*: 293.2 $[M + Na]^+$, 271.2 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{11}N_6O_2$ $[M + H]^+$ 271.0938, found 271.0938.

*4-Methoxy-5-nitroso-N⁶-[4-(trifluoromethyl)phenyl]pyrimidine-2,6-diamine (**3b**).* Treatment of **1** (600 mg, 3.3 mmol) and 4-(trifluoromethyl)aniline (**2b**) (585 mg, 3.6 mmol) by general procedure A (MW, 170 °C, 2 h) gave **3b** (310 mg, 30%) as green crystals (from methanol) with mp = 217−219 °C. ^{1}H NMR (DMSO-d_6): δ 13.47 (1H, s, 6-NH), 8.48 (2H, bs, 2-NH_2), 8.05 (2H, m, H2′), 7.69 (2H, m, H3′), 4.11 (3H, s, O−CH_3). ^{13}C NMR (DMSO-d_6): δ 171.3 (C4), 163.8 (C2), 147.8 (C6), 141.3 (C1′, $J_{C1'-F}$ = 1.1 Hz), 138.5 (C5), 126.0 (C3′, $J_{C3'-F}$ = 3.8 Hz), 124.8 (C4′, $J_{C4'-F}$ = 32.0 Hz), 124.4 (CF_3, J_{C-F} = 271.8 Hz), 123.4 (C2′), 54.7 (O−CH_3). UV/vis (DMSO): λ_{max} = 342, 602 nm. ESI MS *m*/*z*: 336.0 $[M + Na]^+$, 314.0 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{11}F_3N_5O_2$ $[M + H]^+$ 314.0859, found 314.0859.

*Methyl 4-[(2-Amino-4-methoxy-5-nitrosopyrimidin-6-yl)amino]-benzoate (**3c**).* Treatment of **1** (600 mg, 3.3 mmol) and methyl 4-aminobenzoate (**2c**) (549 mg, 3.6 mmol) by general procedure A (MW, 170 °C, 1 h) gave **3c** (630 mg, 63%) as red crystals with mp = 230 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 13.53 (1H, s, 6-NH), 8.50 (2H, bs, 2-NH_2), 8.00 (2H, m, H2′), 7.92 (2H, m, H3′), 4.11 (3H, s, O−CH_3), 3.84 (3H, s, $COOCH_3$). ^{13}C NMR (DMSO-d_6): δ 171.2 (C4), 165.8 (C4′−CO), 163.8 (C2), 147.6 (C6), 142.1 (C1′), 138.5 (C5), 130.2 (C3′), 125.4 (C4′), 122.6 (C2′), 54.7 (O−CH_3), 52.2 ($COOCH_3$). UV/vis (DMSO): λ_{max} = 276, 342, 600 nm. ESI MS *m*/*z*: 326.1 $[M + Na]^+$, 304.1 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{14}N_5O_4$ $[M + H]^+$ 304.1040, found 304.1039.

*N⁶-(4-Chlorophenyl)-4-methoxy-5-nitrosopyrimidine-2,6-diamine (**3d**).* Treatment of **1** (400 mg, 2.2 mmol) and 4-chloroaniline (**2d**) (309 mg, 2.4 mmol) by general procedure A (MW, 160 °C, 1 h) gave **3d** (474 mg, 77%) as a green solid with mp = 219 °C. ^{1}H NMR (DMSO-d_6): δ 13.46 (1H, s, 6-NH), 8.40 (2H, bs, 2-NH_2), 7.85 (2H, m, H2′), 7.40 (2H, m, H3′), 4.09 (3H, s, O−CH_3). ^{13}C NMR (DMSO-d_6): δ 171.2 (C4), 163.7 (C2), 147.9 (C6), 138.4 (C5), 136.4 (C1′), 128.9 (C3′), 128.9 (C4′), 124.8 (C2′), 54.7 (O−CH_3). UV/vis (DMSO): λ_{max} = 264, 338, 596 nm. ESI MS *m*/*z*: 302.0 $[M + Na]^+$, 280.0 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{10}ClN_5O_2Na$ $[M + Na]^+$ 302.0410, found 302.0414.

*4-Methoxy-5-nitroso-N⁶-phenylpyrimidine-2,6-diamine (**3e**).* Treatment of **1** (900 mg, 4.9 mmol) and aniline (**2e**) (502 mg, 2.0 mmol) by general procedure A (MW, 160 °C, 20 min) gave **3e** (1.01 g, 84%) as a red solid with mp = 204−210 °C. ^{1}H NMR (DMSO-d_6): δ 13.51 (1H, s, 6-NH), 8.36 (1H, s, 2-NH^B), 8.34 (1H, s, 2-NH^A), 7.80 (2H, m, H2′), 7.37 (2H, m, H3′), 7.17 (1H, m, H4′), 4.09 (3H, s, O−CH_3). ^{13}C NMR (DMSO-d_6): δ 171.2 (C4), 163.8 (C2), 148.0 (C6), 138.4 (C5), 137.3 (C1′), 129.1 (C3′), 125.1 (C4′), 123.1 (C2′), 54.6 (O−CH_3). UV/vis (DMSO): λ_{max} = 260, 338, 594 nm. ESI MS *m*/*z*: 268.0 $[M + Na]^+$, 246.0 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{12}N_5O_2$ $[M + H]^+$ 246.0985, found 246.0985.

*4-Methoxy-5-nitroso-N⁶-(p-tolyl)pyrimidine-2,6-diamine (**3f**).* Treatment of **1** (900 mg, 4.9 mmol) and *p*-toluidine (**2f**) (577 mg, 5.4 mmol) by general procedure A (MW, 160 °C, 20 min) gave **3f** (939 mg, 74%) as red crystals (from methanol) with mp = 210 °C. ^{1}H NMR (DMSO-d_6): δ 13.52 (1H, s, 6-NH), 8.32 (1H, bs, 2-NH^B), 8.31 (1H, bs, 2-NH^A), 7.68 (2H, m, H2′), 7.17 (2H, m, H3′), 4.08 (3H, s, O−CH_3), 2.29 (3H, s, CH_3). ^{13}C NMR (DMSO- d_6): δ 171.2 (C4), 163.7 (C2), 148.0 (C6), 138.3 (C5), 134.7 (C1′), 134.4 (C4′), 129.5 (C3′), 123.1 (C2′), 54.6 (O−CH_3), 20.7 (CH_3). UV/vis (DMSO): λ_{max} = 260, 338, 592 nm. ESI MS *m*/*z*: 282.1 $[M + Na]^+$, 260.1 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{14}N_5O_2$ $[M + H]^+$ 260.1142, found 260.1141.

*4-[(2-Amino-4-methoxy-5-nitrosopyrimidin-6-yl)amino]phenol (**3g**).* Treatment of **1** (200 mg, 1.1 mmol) and 4-aminophenol (**2g**) (132 mg, 1.2 mmol) by general procedure A (conv., 70 °C, 6 h) gave **3g** (163 mg, 56%) as an orange solid with mp = 230 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 13.54 (1H, s, 6-NH), 9.49 (1H, s, 4′-OH), 8.21 (2H, bs, 2-NH_2), 7.58 (2H, m, H2′), 6.75 (2H, m, H3′), 4.07 (3H, s, O−CH_3). ^{13}C NMR (DMSO-d_6): δ 171.1 (C4), 163.7 (C2), 155.0 (C4′), 147.9 (C6), 138.2 (C5), 128.5 (C1′), 124.7 (C2′), 115.6 (C3′),

54.5 (O−CH_3). UV/vis (DMSO): λ_{max} = 260, 336, 582 nm. ESI MS *m*/*z*: 284.1 $[M + Na]^+$, 262.1 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{11}N_5O_3Na$ $[M + Na]^+$ 284.0754, found 284.0754.

*N^6-(4-Aminophenyl)-4-methoxy-5-nitrosopyrimidine-2,6-diamine (**3h**).* Treatment of **1** (1.00 g, 5.4 mmol) and benzene-1,4-diamine (**2h**) (643 mg, 5.9 mmol) by general procedure A (conv., 90 °C, 24 h) gave **3h** (1.23 g, 88%) as a red solid with mp = 220 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 13.65 (1H, s, 6-NH), 8.14 (2H, bs, 2-NH_2), 7.45 (2H, m, H2′), 6.56 (2H, m, H3′), 5.16 (2H, s, 4′-NH_2), 4.06 (3H, s, O−CH_3). ^{13}C NMR (DMSO-d_6): δ 171.0 (C4), 163.5 (C2), 147.7 (C6), 146.7 (C4′), 138.1 (C5), 125.6 (C1′), 124.3 (C2′), 114.0 (C3′), 54.5 (O−CH_3). UV/vis (DMSO): λ_{max} = 274, 336, 436 nm. ESI MS *m*/*z*: 283.1 $[M + Na]^+$, 261.1 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{12}N_6O_2Na$ $[M + Na]^+$ 283.0913, found 283.0914.

*N^6-(4-(Dimethylamino)phenyl)-4-methoxy-5-nitrosopyrimidine-2,6-diamine (**3i**).* Treatment of **1** (1.00 g, 5.4 mmol) and *N*,*N*-dimethyl-*p*-phenylenediamine (**2i**) (809 mg, 5.9 mmol) by general procedure A (conv., 80 °C, 5 h) gave **3i** (1.11 g, 71%) as a black solid with mp = 220 °C. ^{1}H NMR (DMSO-d_6): δ 13.67 (1H, s, 6-NH), 8.18 (2H, bs, 2-NH_2), 7.60 (2H, m, H2′), 6.70 (2H, m, H3′), 4.07 (3H, s, O−CH_3), 2.89 (6H, s, $N(CH_3)_2$). ^{13}C NMR (DMSO-d_6): δ 171.1 (C4), 163.6 (C2), 148.2 (C4′), 147.8 (C6), 138.2 (C5), 126.1 (C1′), 124.2 (C2′), 112.5 (C3′), 54.5 (O−CH_3), 40.3 ($N(CH_3)_2$). UV/vis (DMSO): λ_{max} = 336, 442 nm. ESI MS *m*/*z*: 311.0 $[M + Na]^+$, 289.0 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{17}N_6O_2$ $[M + H]^+$ 289.1407, found 289.1407.

*General Procedure B: Synthesis of N^4,N^6-Disubstituted 5-Nitrosopyrimidine-2,4,6-triamines **4**–**6**.* The corresponding amine (1.1 equiv) or an excess of aq. ammonia was added dropwise to the mixture of the corresponding compound **3a**–**i** (1.0 equiv) in DMF (20 mL per 1 mmol of **3**), and the reaction mixture was stirred at room temperature (rt) or under conventional heating (conv.) for 3–24 h. The solvents were evaporated, and the corresponding product **4a**–**h**, **5a**–**h**, or **6a**–**i** was obtained by silica gel column chromatography (3–20% MeOH in $CHCl_3$).

*4-[(2-Amino-4-(methylamino)-5-nitrosopyrimidin-6-yl)amino]-benzonitrile (**4a**).* Treatment of **3a** (100 mg, 0.37 mmol) with methylamine (33% ethanolic solution, 17 μL) in DMF by general procedure B (rt, 4 h) gave **4a** (40 mg, 40%) as a red solid with mp = 300 °C. ^{1}H NMR (DMSO-d_6): Rotamer A: δ 14.15 (1H, s, 6-NH), 9.02 (1H, q, J_{NH-CH_3} = 4.8 Hz, 4-NH), 8.08 (2H, m, H2′), 8.03 and 7.98 (2H, bs, 2-NH_2), 7.77 (2H, m, H3′), 2.96 (3H, d, J_{CH_3-NH} = 4.8 Hz, N−CH_3). Rotamer B: δ 11.34 (1H, q, J_{NH-CH_3} = 5.0 Hz, 4-NH), 10.64 (1H, s, 6-NH), 8.31 (2H, m, H2′), 7.95 (1H, bs, 2-NH^B), 7.89 (1H, bs, 2-NH^A), 7.76 (2H, m, H3′), 2.89 (3H, d, J_{CH_3-NH} = 5.0 Hz, NH−CH_3). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 164.3 (C2), 163.2 (C4), 148.3 (C6), 142.7 (C1′), 136.0 (C5), 133.2 (C3′), 122.7 (C2′), 119.1 (CN), 106.0 (C4′), 27.6 (NH−CH_3). Rotamer B: δ 163.8 (C2), 161.9 (C6), 151.0 (C4), 143.6 (C1′), 136.5 (C5), 132.8 (C3′), 121.8 (C2′), 119.4 (CN), 104.8 (C4′) 26.2 (NH−CH_3). UV/vis (DMSO): λ_{max} = 574 nm. ESI MS *m*/*z*: 270.2 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{12}N_7O$ $[M + H]^+$ 270.1097, found 270.1098.

*N^4-Methyl-5-nitroso-N^6-[4-(trifluoromethyl)phenyl]pyrimidine-2,4,6-triamine (**4b**).* Treatment of **3b** (100 mg, 0.32 mmol) with methylamine (33% ethanolic solution, 15 μL) in DMF by general procedure B (rt, 16 h) gave **4b** (90 mg, 90%) as an orange solid with mp = 220 °C. ^{1}H NMR (DMSO-d_6): δ 14.16 (1H, s, 6-NH, A), 11.39 (1H, q, J_{NH-CH_3} = 5.0 Hz, 4-NH, B), 10.62 (1H, s, 6-NH, B), 9.02 (1H, q, J_{NH-CH_3} = 4.9 Hz, 4-NH, A), 8.26 (2H, m, H2′, B), 8.07 (2H, m, H2′, A), 7.96 and 7.94 (2H, bs, 2-NH_2, A), 7.84 (2H, bs, 2-NH_2, B), 7.64–7.68 (4H, m, H3′, A and B), 2.97 (3H, d, J_{CH_3-NH} = 4.9 Hz, CH_3, A), 2.90 (3H, d, J_{CH_3-NH} = 5.0 Hz, CH_3, B). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 164.4 (C2), 163.2 (C4), 148.4 (C6), 141.9 (C1′, $J_{C1'-F}$ = 1.3 Hz), 136.0 (C5), 126.0 (C3′, $J_{C3'-F}$ = 3.8 Hz), 124.4 (CF_3, J_{C-F} = 271.5 Hz), 124.2 (C4′, $J_{C4'-F}$ = 32.4 Hz), 122.8 (C2′), 27.6 (NH−CH_3). Rotamer B: δ 164.0 (C2), 162.0 (C6), 151.2 (C4), 142.9 (C1′, $J_{C1'-F}$ = 1.2 Hz), 136.5 (C5), 125.6 (C3′, $J_{C3'-F}$ = 3.8 Hz), 124.6 (CF_3, J_{C-F} = 271.5 Hz), 123.3 (C4′, $J_{C4'-F}$ = 32.8 Hz), 122.2 (C2′) 26.2 (NH−CH_3). UV/vis (DMSO): λ_{max} = 570 nm. ESI MS *m*/*z*: 335.1 $[M + Na]^+$, 313.1 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{12}F_3N_6O$ $[M + H]^+$ 313.1019, found 313.1018.

*Methyl 4-[(2-Amino-4-(methylamino)-5-nitrosopyrimidin-6-yl)-amino]benzoate (**4c**).* Treatment of **3c** (121 mg, 0.40 mmol) with methylamine (33% ethanolic solution, 18 μL) in DMF by general procedure B (rt, 24 h) gave **4c** (77 mg, 64%) as a pink solid with mp = 223–228 °C. ^{1}H NMR (DMSO-d_6): Rotamer A: δ 14.19 (1H, s, 6-NH), 9.00 (1H, q, J_{NH-CH_3} = 4.8 Hz, 4-NH), 8.01 (2H, m, H2′), 7.95 and 7.94 (2H, bs, 2-NH_2), 7.91 (2H, m, H3′), 3.84 (3H, s, O−CH_3), 2.97 (3H, d, J_{CH_3-NH} = 4.8 Hz, N−CH_3). Rotamer B: δ 11.38 (1H, q, J_{NH-CH_3} = 5.0 Hz, 4-NH), 10.56 (1H, s, 6-NH), 8.22 (2H, m, 2′-H), 7.90 (2H, m, 3′-H), 7.85 (2H, bs, 2-NH_2), 3.84 (3H, s, O−CH_3), 2.90 (3H, d, J_{CH_3-NH} = 5.0 Hz, N−CH_3). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 165.9 (C4′−CO), 164.4 (C2), 163.2 (C4), 148.2 (C6), 142.8 (C1′), 136.0 (C5), 129.8 (C3′), 124.9 (C4′), 122.1 (C2′), 52.2 (O−CH_3), 27.6 (N−CH_3). Rotamer B: δ 166.1 (C4′−CO), 164.0 (C2), 161.8 (C6), 151.1 (C4), 143.7 (C1′), 136.5 (C5), 129.8 (C3′), 123.9 (C4′), 121.4 (C2′), 52.1 (O−CH_3), 26.2 (N−CH_3). UV/vis (DMSO): λ_{max} = 570 nm. ESI MS *m*/*z*: 325.2 $[M + Na]^+$, 303.2 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{15}N_6O_3$ $[M + H]^+$ 303.1200, found 303.1199.

*N^6-(4-Chlorophenyl)-N^4-methyl-5-nitrosopyrimidine-2,4,6-triamine (**4d**).* Treatment of **3d** (100 mg, 0.36 mmol) with methylamine (33% ethanolic solution, 16 μL) in DMF by general procedure B (rt, 6 h) gave **4d** (78 mg, 78%) as a pink solid with mp = 261 °C. ^{1}H NMR (DMSO-d_6): Rotamer A: δ 14.13 (1H, s, 6-NH), 8.95 (1H, q, J_{NH-CH_3} = 4.9 Hz, 4-NH), 7.88 (2H, m, H2′), 7.85 (2H, bs, 2-NH_2), 7.38 (2H, m, H3′), 2.96 (3H, d, J_{CH_3-NH} = 4.9 Hz, N−CH_3). Rotamer B: δ 11.44 (1H, q, J_{NH-CH_3} = 5.0 Hz, 4-NH), 10.42 (1H, s, 6-NH), 8.05 (2H, m, H2′), 7.75 (2H, bs, 2-NH_2), 7.36 (2H, m, H3′), 2.89 (3H, d, J_{CH_3-NH} = 5.0 Hz, N−CH_3). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 164.4 (C2), 163.2 (C4), 148.4 (C6), 137.0 (C1′), 135.9 (C5), 128.9 (C3′), 128.3 (C4′), 124.2 (C2′), 27.6 (N−CH_3). Rotamer B: δ 164.1 (C2), 161.6 (C6), 151.6 (C4), 138.1 (C1′), 136.3 (C5), 128.3 (C3′), 127.3 (C4′), 123.9 (C2′), 26.2 (N−CH_3). UV/vis (DMSO): λ_{max} = 564 nm. ESI MS *m*/*z*: 301.1 $[M + Na]^+$, 279.1 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{12}ClN_6O$ $[M + H]^+$ 279.0755, found 279.0758.

*N^4-Methyl-5-nitroso-N^6-phenylpyrimidine-2,4,6-triamine (**4e**).* Treatment of **3e** (100 mg, 0.41 mmol) with methylamine (33% ethanolic solution, 19 μL) in DMF by general procedure B (rt, 8 h) gave **4e** (65 mg, 65%) as a red solid with mp = 260 °C. ^{1}H NMR (DMSO-d_6): Rotamer A: δ 14.12 (1H, s, 6-NH), 8.94 (1H, q, J_{NH-CH_3} = 4.9 Hz, 4-NH), 7.84 (2H, m, H2′), 7.81 (2H, bs, 2-NH_2), 7.35 (2H, m, H3′), 7.13 (1H, m, H4′), 2.96 (3H, d, J_{CH_3-NH} = 4.9 Hz, N−CH_3). Rotamer B: δ 11.48 (1H, q, J_{NH-CH_3} = 5.0 Hz, 4-NH), 10.28 (1H, s, 6-NH), 7.98 (2H, m, H2′), 7.72 (2H, bs, 2-NH_2), 7.33 (2H, m, H3′), 7.09 (1H, m, H4′), 2.89 (3H, d, J_{CH_3-NH} = 5.0 Hz, N−CH_3). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 164.5 (C2), 163.3 (C4), 148.5 (C6), 138.0 (C1′), 136.0 (C5), 129.1 (C3′), 124.5 (C4′), 122.7 (C2′), 27.6 (N−CH_3). Rotamer B: δ 164.2 (C2), 161.6 (C6), 151.3 (C4), 138.1 (C1′), 136.3 (C5), 128.6 (C3′), 123.6 (C4′), 122.3 (C2′), 26.1 (N−CH_3). UV/vis (DMSO): λ_{max} = 564 nm. ESI MS *m*/*z*: 267.1 $[M + Na]^+$, 245.1 $[M + H]^+$. HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{13}N_6O$ $[M + H]^+$ 245.1145, found 245.1144.

*N^4-Methyl-5-nitroso-N^6-(p-tolyl)pyrimidine-2,4,6-triamine (**4f**).* Treatment of **3f** (100 mg, 0.39 mmol) with methylamine (33% ethanolic solution, 18 μL) in DMF by general procedure B (rt, 3 h) gave **4f** (68 mg, 68%) as a red solid with mp = 240 °C. ^{1}H NMR (DMSO-d_6): Rotamer A: δ 14.12 (1H, s, 6-NH), 8.91 (1H, q, J_{NH-CH_3} = 4.9 Hz, 4-NH), 7.77 (2H, bs, 2-NH_2), 7.71 (2H, m, H2′), 7.15 (2H, m, H3′), 2.95 (3H, d, J_{CH_3-NH} = 4.9 Hz, N−CH_3), 2.28 (3H, s, 4′-CH_3). Rotamer B: δ 11.50 (1H, q, J_{NH-CH_3} = 5.0 Hz, 4-NH), 10.21 (1H, s, 6-NH), 7.83 (2H, m, H2′), 7.67 (2H, bs, 2-NH_2), 7.13 (2H, m, H3′), 2.89 (3H, d, J_{CH_3-NH} = 5.0 Hz, N−CH_3), 2.28 (3H, s, 4′-CH_3).

^{13}C NMR (DMSO-d_6): Rotamer A: δ 164.5 (C2), 163.3 (C4), 148.4 (C6), 136.2 (C5), 135.4 (C1′), 133.8 (C4′), 129.5 (C3′), 122.6 (C2′), 27.5 (N−CH_3), 20.7 (4′-CH_3). Rotamer B: δ 164.3 (C2), 161.4 (C6), 151.4 (C4), 136.5 (C5), 135.9 (C1′), 132.7 (C4′), 129.0 (C3′), 122.4 (C2′), 26.1 (N−CH_3), 20.6 (4′-CH_3). UV/vis (DMSO): λ_{max} = 562 nm. ESI MS m/z: 281.1 $[M + Na]^+$, 259.2 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{12}H_{15}N_6O$ $[M + H]^+$ 259.1301, found 259.1302.

*4-[(2-Amino-4-(methylamino)-5-nitrosopyrimidin-6-yl)amino]-phenol (**4g**).* Treatment of **3g** (118 mg, 0.45 mmol) with methylamine (33% ethanolic solution 20 μL) in DMF by general procedure B (rt, 24 h) gave **4g** (71 mg, 59%) as a red solid with mp = 273 °C (decomp.). ^{1}H NMR (DMSO-d_6): Rotamer A: δ 14.12 (1H, s, 6-NH), 9.43 (1H, s, 4′-OH), 8.84 (1H, q, J_{NH-CH_3} = 4.9 Hz, 4-NH), 7.66 (2H, m, 2-NH_2), 7.62 (2H, m, H2′), 6.74 (2H, m, H3′), 2.94 (3H, d, J_{CH_3-NH} = 4.9 Hz, N−CH_3). Rotamer B: δ 11.54 (1H, q, J_{NH-CH_3} = 5.0 Hz, 4-NH), 10.09 (1H, s, 6-NH), 9.27 (1H, s, 4′-OH), 7.68 (2H, m, H2′), 7.57 (2H, m, 2-NH_2), 6.72 (2H, m, H3′), 2.88 (3H, d, J_{CH_3-NH} = 5.0 Hz, N−CH_3). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 164.5 (C2), 163.3 (C4), 154.6 (C4′), 148.2 (C6), 135.8 (C5), 129.2 (C1′), 124.2 (C2′), 115.5 (C3′), 27.5 (N−CH_3). Rotamer B: δ 164.4 (C2), 161.2 (C6), 154.0 (C4′), 151.5 (C4), 136.2 (C5), 130.5 (C1′), 124.3 (C2′), 115.0 (C3′), 26.1 (N−CH_3). UV/vis (DMSO): λ_{max} = 546 nm. ESI MS m/z: 283.1 $[M + Na]^+$, 261.1 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{11}H_{13}N_6O_2$ $[M + H]^+$ 261.1094, found 261.1094.

*N^6-(4-Aminophenyl)-N^4-methyl-5-nitrosopyrimidine-2,4,6-triamine (**4h**).* Treatment of **3h** (100 mg, 0.38 mmol) with methylamine (33% ethanolic solution, 17 μL) in DMF by general procedure B (rt, 12 h) gave **4h** (74 mg, 75%) as a red solid with mp = 239 °C. ^{1}H NMR (DMSO-d_6): δ 14.18 (1H, s, 6-NH, A), 11.57 (1H, q, J_{CH_3-NH} = 5.0 Hz, 4-NH, B), 9.94 (1H, s, 6-NH, B), 8.79 (1H, q, J_{CH_3-NH} = 4.9 Hz, 4-NH, A), 7.59 and 7.58 (2H, 2-NH_2, A), 7.49−7.52 (4H, m, 2-NH_2, H2′, B), 7.48 (2H, m, H2′, A), 6.55 (2H, m, H3′, A), 6.54 (2H, m, H3′, B), 5.10 (2H, bs, 4′-NH_2, A), 4.95 (2H, bs, 4′-NH_2, B), 2.94 (3H, d, J_{CH_3-NH} = 4.9 Hz, N−CH_3, A), 2.88 (3H, d, J_{CH_3-NH} = 5.0 Hz, N−CH_3, B). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 164.4 (C2), 163.3 (C4), 147.9 (C6), 146.2 (C4′), 135.7 (C5), 126.4 (C1′), 123.9 (C2′), 114.1 (C3′), 27.5 (N−CH_3). Rotamer B: δ 164.4 (C2), 160.9 (C6), 151.6 (C4), 145.6 (C4′), 136.1 (C5), 127.8 (C1′), 124.2 (C2′), 113.7 (C3′), 26.0 (N−CH_3). UV/vis (DMSO): λ_{max} = 482 nm. ESI MS m/z: 282.1 $[M + Na]^+$, 260.1 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{11}H_{13}N_7ONa$ $[M + Na]^+$ 282.1073, found 282.1074.

*4-[(2-Amino-4-(cyclopropylamino)-5-nitrosopyrimidin-6-yl)-amino]benzonitrile (**5a**).* Treatment of **3a** (120 mg, 0.44 mmol) with cyclopropylamine (28 mg, 0.48 mmol) in DMF by general procedure B (conv., 80 °C, 5 h) gave **5a** (62 mg, 48%) as a violet solid with mp = 267 °C. ^{1}H NMR (DMSO-d_6): δ 14.13 (1H, s, 6-NH, A), 11.62 (1H, s, J_{NH-CH} = 5.6 Hz, 4-NH, B), 10.66 (1H, s, 6-NH, B), 8.97 (1H, d, J_{NH-CH} = 5.4 Hz, 4-NH, A), 8.31 (2H, m, H2′, B), 8.08 (2H, m, H2′, A), 7.99−8.07 (4H, m, 2-NH_2, A and B), 7.75−7.79 (4H, m, H3′, A and B), 3.20 (1H, m, CH_{cypr}, A), 3.09 (1H, m, CH_{cypr}, B), 0.79−0.83 (4H, m, $CH_2{}^A{}_{cypr}$, A and B), 0.72 (2H, m, $CH_2{}^B{}_{cypr}$, A), 0.66 (2H, m, $CH_2{}^B{}_{cypr}$, B). ^{13}C NMR (DMSO- d_6): Rotamer A: δ 164.2 (C4), 164.1 (C2), 148.1 (C6), 142.7 (C1′), 135.9 (C5), 133.2 (C3′), 122.8 (C2′), 119.1 (CN), 106.0 (C4′), 24.4 (CH_{cypr}), 6.1 (CH_{2cypr}). Rotamer B: δ 163.9 (C2), 161.8 (C6), 151.8 (C4), 143.5 (C1′), 136.0 (C5), 132.8 (C3′), 121.9 (C2′), 119.4 (CN), 104.9 (C4′), 22.8 (CH_{cypr}), 7.0 (CH_{2cypr}). UV/vis (DMSO): λ_{max} = 570 nm. ESI MS m/z: 296.3 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{14}H_{14}N_7O$ $[M + H]^+$ 296.1254, found 296.1254.

*N^4-Cyclopropyl-5-nitroso-N^6-[4-(trifluoromethyl)phenyl]-pyrimidine-2,4,6-triamine (**5b**).* Treatment of **3b** (100 mg, 0.32 mmol) with cyclopropylamine (20 mg, 0.35 mmol) in DMF by general procedure B (conv., 80 °C, 12 h) gave **5b** (45 mg, 42%) as a violet solid with mp = 228−230 °C. ^{1}H NMR (DMSO-d_6): δ 14.13 (1H, s, 6-NH, A), 11.16 (1H, d, J_{NH-CH} = 5.7 Hz, 4-NH, B), 10.63 (1H, s, 6-NH, B), 8.95 (1H, d, J_{NH-CH} = 5.4 Hz, 4-NH, A), 8.26 (2H, m, H2′, B), 8.08 (2H, m, H2′, A), 7.91−8.01 (4H, m, 2-NH_2, A and B), 7.64−7.68 (4H, m, H3′, A and B), 3.20 (1H, m, CH_{cypr}, A), 3.10 (1H, m, CH_{cypr}, B), 0.79−0.83 (4H, m, $CH_2{}^A{}_{cypr}$, A and B), 0.73 (2H, m, $CH_2{}^B{}_{cypr}$, A), 0.65 (2H, m, $CH_2{}^B{}_{cypr}$, B). ^{13}C NMR (DMSO- d_6): Rotamer A: δ 164.4 (C4), 164.1 (C2), 148.3 (C6), 141.9 (C1′, $J_{C1'-F}$ = 1.3 Hz), 135.9 (C5), 129.0 (C3′, $J_{C3'-F}$ = 3.9 Hz), 124.4 (CF_3, J_{C-F} = 270.9 Hz), 124.3 (C4′, $J_{C4'-F}$ = 32.1 Hz), 122.8 (C2′), 24.4 (CH_{cypr}), 6.1 (CH_{2cypr}). Rotamer B: δ 164.1 (C2), 161.8 (C6), 151.9 (C4), 142.8 (C1′, $J_{C1'-F}$ = 1.3 Hz), 136.0 (C5), 125.6 (C3′, $J_{C3'-F}$ = 3.8 Hz), 124.6 (CF_3, J_{C-F} = 271.3 Hz), 123.4 (C4′, $J_{C4'-F}$ = 31.8 Hz), 122.3 (C2′), 22.8 (CH_{cypr}), 7.0 (CH_{2cypr}). UV/vis (DMSO): λ_{max} = 568 nm. ESI MS m/z: 361.1 $[M + Na]^+$, 339.1 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{14}H_{14}F_3N_6O$ $[M + H]^+$ 339.1175, found 339.1175.

*Methyl 4-[(2-Amino-4-(cyclopropylamino)-5-nitrosopyrimidin-6-yl)amino]benzoate (**5c**).* Treatment of **3c** (100 mg, 0.33 mmol) with cyclopropylamine (21 mg, 0.36 mmol) in DMF (10 mL) by general procedure B (conv., 70 °C, 12 h) gave **5c** (92 mg, 85%) as a red solid with mp = 211 °C. ^{1}H NMR (DMSO-d_6): δ 14.16 (1H, s, 6-NH, A), 11.66 (1H, d, J_{NH-CH} = 5.6 Hz, 4-NH, B), 10.59 (1H, s, 6-NH, B), 8.94 (1H, d, J_{NH-CH} = 5.4 Hz, 4-NH, A), 8.22 (2H, m, H2′, B), 8.02 (2H, m, H2′, A), 7.98 (2H, bs, 2-NH_2, B), 7.94 (2H, bs, 2-NH_2, A), 7.91 (2H, m, H3′, A), 7.90 (2H, m, H3′, B), 3.84 (6H, s, $COOCH_3$, A and B), 3.20 (1H, m, CH_{cypr}, A), 3.10 (1H, m, CH_{cypr}, B), 0.79−0.83 (4H, m, $CH_2{}^A{}_{cypr}$, A and B), 0.73 (2H, m, $CH_2{}^B{}_{cypr}$, A), 0.66 (2H, m, $CH_2{}^B{}_{cypr}$, B). ^{13}C NMR (DMSO- d_6): Rotamer A: δ 165.9 (C4′−CO), 164.3 (C2), 164.1 (C4), 148.2 (C6), 142.8 (C1′), 135.9 (C5), 130.2 (C3′), 124.9 (C4′), 122.2 (C2′), 52.2 ($COOCH_3$), 24.4 (CH_{cypr}), 6.1 (CH_{2cypr}). Rotamer B: δ 166.1 (C4′−CO), 164.1 (C2), 161.7 (C6), 151.9 (C4), 143.6 (C1′), 136.0 (C5), 129.8 (C3′), 124.0 (C4′), 121.5 (C2′), 52.1 ($COOCH_3$), 22.8 (CH_{cypr}), 7.0 (CH_{2cypr}). UV/vis (DMSO): λ_{max} = 568 nm. ESI MS m/z: 351.1 $[M + Na]^+$, 329.1 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{15}H_{16}N_6O_3Na$ $[M + Na]^+$ 351.1176, found 351.1174.

*N^6-(4-Chlorophenyl)-N^4-cyclopropyl-5-nitrosopyrimidine-2,4,6-triamine (**5d**).* Treatment of **3d** (100 mg, 0.36 mmol) with cyclopropylamine (22 mg, 0.39 mmol) in DMF by general procedure B (conv., 90 °C, 5 h) gave **5d** (80 mg, 73%) as a red solid with mp = 220 °C. ^{1}H NMR (DMSO- d_6): δ 14.11 (1H, s, 6-NH, A), 11.74 (1H, d, J_{NH-CH} = 5.6 Hz, 4-NH, B), 10.46 (1H, s, 6-NH, B), 8.92 (1H, d, J_{NH-CH} = 5.4 Hz, 4-NH, A), 8.05 (2H, m, H2′, B), 7.89 (2H, m, H2′, A), 7.86 and 7.92 (4H, bs and m, 2-NH_2, A and B), 7.38 (2H, m, H3′, A), 7.36 (2H, m, H3′, B), 3.18 (1H, m, CH_{cypr}, A), 3.08 (1H, m, CH_{cypr}, B), 0.78−0.82 (4H, m, $CH_2{}^A{}_{cypr}$, A and B), 0.71 (2H, m, $CH_2{}^B{}_{cypr}$, A), 0.64 (2H, m, $CH_2{}^B{}_{cypr}$, B). ^{13}C NMR (DMSO- d_6): Rotamer A: δ 164.4 (C2), 164.1 (C4), 148.3 (C6), 137.0 (C1′), 135.8 (C5), 128.9 (C3′), 128.3 (C4′), 124.3 (C2′), 24.4 (CH_{cypr}), 6.1 (CH_{2cypr}). Rotamer B: δ 164.2 (C2), 161.5 (C6), 152.0 (C4), 138.1 (C1′), 135.9 (C5), 128.3 (C3′), 127.4 (C4′), 124.0 (C2′), 22.8 (CH_{cypr}), 7.0 (CH_{2cypr}). UV/vis (DMSO): λ_{max} = 564 nm. ESI MS m/z: 327.1 $[M + Na]^+$, 305.1 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{13}H_{13}ClN_6ONa$ $[M + Na]^+$ 327.0731, found 327.0730.

*N^4-Cyclopropyl-5-nitroso-N^6-phenylpyrimidine-2,4,6-triamine (**5e**).* Treatment of **3e** (100 mg, 0.41 mmol) with cyclopropylamine (26 mg, 0.45 mmol) in DMF by general procedure B (conv., 90 °C, 12 h) gave **5e** (81 mg, 74%) as a violet solid with mp = 222 °C. ^{1}H NMR (DMSO- d_6): δ 14.09 (1H, s, 6-NH, A), 11.77 (1H, d, J_{NH-CH} = 5.6 Hz, 4-NH, B), 10.29 (1H, s, 6-NH, B), 8.86 (1H, d, J_{NH-CH} = 5.4 Hz, 4-NH, A), 7.98 (2H, m, H2′, B), 7.79−7.86 (6H, m, 2-NH_2, A and B; H2′, A), 7.35 (2H, m, H3′, A), 7.35 (2H, m, H3′, B), 7.14 (1H, m, H4′, A), 7.10 (1H, m, H4′, B), 3.19 (1H, m, CH_{cypr}, A), 3.09 (1H, m, CH_{cypr}, B), 0.78−0.83 (4H, m, $CH_2{}^A{}_{cypr}$, A and B), 0.72 (2H, m, $CH_2{}^B{}_{cypr}$, A), 0.64 (2H, m, $CH_2{}^B{}_{cypr}$, B). ^{13}C NMR (DMSO- d_6): Rotamer A: δ 164.5 (C2), 164.2 (C4), 148.4 (C6), 138.0 (C1′), 135.9 (C5), 129.1 (C3′), 124.6 (C4′), 122.7 (C2′), 24.4 (CH_{cypr}), 6.1 (CH_{2cypr}). Rotamer B: δ 164.3 (C2), 161.4 (C6), 152.1 (C4), 139.0 (C1′), 135.8 (C5), 128.5 (C3′), 123.7 (C4′), 122.4 (C2′), 22.7 (CH_{cypr}), 7.0 (CH_{2cypr}). UV/vis (DMSO): λ_{max} = 562 nm. ESI MS m/z: 293.1 $[M + Na]^+$, 271.1 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{13}H_{15}N_6O$ $[M + H]^+$ 271.1301, found 271.1302.

*N^4-Cyclopropyl-5-nitroso-N^6-(p-tolyl)pyrimidine-2,4,6-triamine (**5f**).* Treatment of **3f** (100 mg, 0.39 mmol) with cyclopropylamine (25

mg, 0.43 mmol) in DMF by general procedure B (conv., 90 °C, 3 h) gave **5f** (75 mg, 68%) as a red solid with mp = 193−195 °C. ^{1}H NMR (DMSO-d_6): δ 14.08 (1H, s, 6-NH, A), 11.72 (1H, d, J_{NH-CH} = 5.5 Hz, 4-NH, B), 10.21 (1H, s, 6-NH, B), 8.81 (1H, d, J_{NH-CH} = 5.3 Hz, 4-NH, A), 7.82 (2H, m, H2′, B), 7.76−7.80 (4H, m, 2-NH_2, A and B), 7.71 (2H, m, H2′, A), 7.15 (2H, m, H3′, A), 7.13 (2H, m, H3′, B), 3.18 (1H, m, CH_{cypr}, A), 3.08 (1H, m, CH_{cypr}, B), 2.28 (6H, s, 4′-CH_3, A and B), 0.77−0.82 (4H, m, $CH_2{}^A{}_{cypr}$, A and B), 0.71 (2H, m, $CH_2{}^B{}_{cypr}$, A), 0.63 (2H, m, $CH_2{}^B{}_{cypr}$, B). ^{13}C NMR (DMSO- d_6): Rotamer A: δ 164.5 (C2), 164.1 (C4), 148.3 (C6), 135.8 (C5), 135.3 (C1′), 133.8 (C4′), 129.5 (C3′), 122.6 (C2′), 24.4 (CH_{cypr}), 20.7 (C4′−CH_3), 6.1 (CH_{2cypr}). Rotamer B: δ 164.3 (C2), 161.3 (C6), 152.1 (C4), 136.4 (C1′), 135.8 (C5), 132.8 (C4′), 129.0 (C3′), 122.5 (C2′), 22.7 (CH_{cypr}), 20.7 (C4′−CH_3), 7.0 (CH_{2cypr}). UV/vis (DMSO): λ_{max} = 562 nm. ESI MS *m*/*z*: 307.2 [M + Na]$^+$, 285.2 [M + H]$^+$. HRMS (ESI) *m*/*z*: calcd for $C_{14}H_{17}N_6O$ [M + H]$^+$ 285.1458, found 285.1458.

*4-[(2-Amino-4-(cyclopropylamino)-5-nitrosopyrimidin-6-yl)-amino]phenol (**5g**).* Treatment of **3g** (147 mg, 0.56 mmol) with cyclopropylamine (35 mg, 0.62 mmol) in DMF by general procedure B (conv., 80 °C, 8 h) gave **5g** (92 mg, 58%) as an orange solid with mp = 274−279 °C. ^{1}H NMR (DMSO-d_6): δ 14.09 (1H, s, 6-NH, A), 11.58 (1H, d, J_{NH-CH} = 5.7 Hz, 4-NH, B), 10.12 (1H, s, 6-NH, B), 9.44 (1H, s, 4′-OH, A), 9.28 (1H, s, 4′-OH, B), 8.77 (1H, d, J_{NH-CH} = 5.4 Hz, 4-NH, A), 7.61−7.73 (8H, m, 2-NH_2, A and B; H2′, A and B), 6.74 (2H, m, H3′, A), 6.72 (2H, m, H3′, B), 3.17 (1H, m, CH_{cypr}, A), 3.07 (1H, m, CH_{cypr}, B), 0.76−0.82 (4H, m, $CH_2{}^A{}_{cypr}$, A and B), 0.71 (2H, m, $CH_2{}^B{}_{cypr}$, A), 0.63 (2H, m, $CH_2{}^B{}_{cypr}$, B). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 164.5 (C2), 164.1 (C4), 154.6 (C4′), 148.2 (C6), 135.7 (C5), 129.2 (C1′), 124.2 (C2′), 115.5 (C3′), 24.4 (CH_{cypr}), 6.1 (CH_{2cypr}). Rotamer B: δ 164.4 (C2), 161.0 (C6), 154.1 (C4′), 152.2 (C4), 135.7 (C5), 130.4 (C1′), 124.4 (C2′), 115.0 (C3′), 22.7 (CH_{cypr}), 7.0 (CH_{2cypr}). UV/vis (DMSO): λ_{max} = 550 nm. ESI MS *m*/*z*: 309.1 [M + Na]$^+$, 287.1 [M + H]$^+$. HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{15}N_6O_2$ [M + H]$^+$ 287.1251, found 287.1251.

*N^6-(4-Aminophenyl)-N^4-cyclopropyl-5-nitrosopyrimidine-2,4,6-triamine (**5h**).* Treatment of **3h** (100 mg, 0.38 mmol) with cyclopropylamine (24 mg, 0.42 mmol) in DMF by general procedure B (conv., 90 °C, 24 h) gave **5h** (99 mg, 92%) as a red solid with mp = 236−237 °C. ^{1}H NMR (DMSO-d_6): δ 14.15 (1H, s, 6-NH, A), 11.89 (1H, d, J_{NH-CH} = 5.7 Hz, 4-NH, B), 9.96 (1H, s, 6-NH, B), 8.70 (1H, d, J_{NH-CH} = 5.4 Hz, 4-NH, A), 7.57−7.64 (4H, m, 2-NH_2, A and B), 7.50 (2H, m, H2′, B), 7.48 (2H, m, H2′, A), 6.55 (2H, m, H3′, A), 6.53 (2H, m, H3′, B), 5.11 (2H, bs, 4′-NH_2, A), 4.96 (2H, bs, 4′-NH_2, B), 3.16 (1H, m, CH_{cypr}, A), 3.07 (1H, m, CH_{cypr}, B), 0.75−0.81 (4H, m, $CH_2{}^A{}_{cypr}$, A and B), 0.70 (2H, m, $CH_2{}^B{}_{cypr}$, A), 0.62 (2H, m, $CH_2{}^B{}_{cypr}$, B). ^{13}C NMR (DMSO- d_6): Rotamer A: δ 164.4 (C2), 164.1 (C4), 147.8 (C6), 146.2 (C4′), 135.7 (C5), 126.3 (C1′), 123.9 (C2′), 114.1 (C3′), 24.3 (CH_{cypr}), 6.1 (CH_{2cypr}). Rotamer B: δ 164.5 (C2), 160.7 (C6), 152.3 (C4), 145.6 (C4′), 135.7 (C5), 127.7 (C1′), 124.3 (C2′), 113.7 (C3′), 22.6 (CH_{cypr}), 7.0 (CH_{2cypr}). UV/vis (DMSO): λ_{max} = 516 nm. ESI MS *m*/*z*: 308.1 [M + Na]$^+$, 286.1 [M + H]$^+$. HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{16}N_7O$ [M + H]$^+$ 286.1410, found 286.1410.

*4-[(2,4-Diamino-5-nitrosopyrimidin-6-yl)amino]benzonitrile (**6a**).* Treatment of **3a** (100 mg, 0.37 mmol) with ammonia (25% aqueous solution, 20 mL) by general procedure B (conv., 50 °C, 4 h) gave **6a** (42 mg, 45%) as an orange solid with mp > 300 °C. ^{1}H NMR (DMSO-d_6): δ 13.92 (1H, s, 6-NH, A), 10.68 (1H, s, 6-NH, B), 10.28 (1H, d, J_{GEM} = 4.6 Hz, 4-NH^A, B), 8.49 (1H, bs, 4-NH^A, A), 8.32 (2H, m, H2′, B), 8.07−8.10 (3H, m, H2′, A; 4-NH^B, B), 7.91 (1H, bs, 2-NH^A, A), 7.84 (1H, bs, 2-NH^A, B), 7.75−7.80 (5H, m, H3′, A; H3′, B; 2-NH^B, A), 7.72 (1H, bs, 4-NH^B, A), 7.69 (1H, bs, 2-NH^B, B). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 165.9 (C4), 164.6 (C2), 148.1 (C6), 142.7 (C1′), 136.2 (C5), 133.2 (C3′), 122.7 (C2′), 119.1 (CN), 105.9 (C4′). Rotamer B: δ 164.1 (C2), 162.0 (C6), 150.9 (C4), 143.6 (C1′), 137.4 (C5), 132.8 (C3′), 121.8 (C2′), 119.4 (CN), 104.8 (C4′). UV/vis (DMSO): λ_{max} = 350, 578 nm. ESI MS *m*/*z*: 278.1 [M + Na]$^+$, 256.1 [M + H]$^+$. HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{10}N_7O$ [M + H]$^+$ 256.0941, found 256.0941.

*5-Nitroso-N^6-[4-(trifluoromethyl)phenyl]pyrimidine-2,4,6-triamine (**6b**).* Treatment of **3b** (100 mg, 0.32 mmol) with ammonia (25% aqueous solution, 20 mL) by general procedure B (conv., 50 °C, 5 h) gave **6b** (34 mg, 36%) as a red solid with mp = 253−255 °C. ^{1}H NMR (DMSO-d_6): δ 13.92 (1H, s, 6-NH, A), 10.65 (1H, s, 6-NH, B), 10.32 (1H, d, J_{GEM} = 4.7 Hz, 4-NH^A, B), 8.48 (1H, bs, 4-NH^A, A), 8.26 (2H, m, H2′, B), 8.06−8.09 (3H, m, H2′, A; 4-NH^B, B), 7.84 (1H, bs, 2-NH^A, A), 7.76 (1H, bs, 2-NH^B, A), 7.74 (1H, bs, 2-NH^A, B), 7.72 (1H, bs, 4-NH^B, A), 7.64−7.68 (5H, m, H3′, A; H3′, B; 2-NH^B, B). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 166.0 (C4), 164.7 (C2), 148.3 (C6), 141.4 (C1′, $J_{C1'-F}$ = 1.3 Hz), 136.3 (C5), 126.0 (C3′, $J_{C3'-F}$ = 3.9 Hz), 124.5 (CF_3, J_{C-F} = 3270.8 Hz), 124.2 (C4′, $J_{C4'-F}$ = 32.0 Hz), 122.8 (C2′). Rotamer B: δ 164.3 (C2), 162.1 (C6), 151.0 (C4), 142.9 (C1′, $J_{C1'-F}$ = 1.3 Hz), 137.4 (C5), 125.6 (C3′, $J_{C3'-F}$ = 3.9 Hz), 124.6 (CF_3, J_{C-F} = 271.7 Hz), 123.3 (C4′, $J_{C4'-F}$ = 32.1 Hz), 122.2 (C2′). UV/vis (DMSO): λ_{max} = 346, 576 nm. ESI MS *m*/*z*: 321.1 [M + Na]$^+$, 299.1 [M + H]$^+$. HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{10}F_3N_6O$ [M + H]$^+$ 299.0862, found 299.0863.

*Methyl 4-[(2,4-Diamino-5-nitrosopyrimidin-6-yl)amino]benzoate (**6c**).* Treatment of **3c** (100 mg, 0.32 mmol) with ammonia (25% aqueous solution, 20 mL) by general procedure B (conv., 50 °C, 20 h) gave **6c** (46 mg, 50%) as a pink solid with mp = 295−299 °C. ^{1}H NMR (DMSO-d_6): Rotamer A: δ 13.95 (1H, s, 6-NH), 8.47 (1H, bs, 4-NH^A), 8.02 (2H, m, H2′), 7.91 (2H, m, H3′), 7.85 (1H, bs, 2-NH^A), 7.75−7.77 (1H, m, 2-NH^B), 7.71 (1H, bs, 4-NH^B), 3.84 (3H, s, $COOCH_3$). Rotamer B: δ 10.60 (1H, s, 6-NH), 10.31 (1H, d, J_{GEM} = 4.7 Hz, 4-NH^A), 8.23 (2H, m, H2′), 8.07 (1H, d, J_{GEM} = 4.7 Hz, 4-NH^B), 7.90 (2H, m, H3′), 7.75−7.77 (1H, m, 2-NH^A), 7.67 (1H, m, 2-NH^B), 3.84 ($COOCH_3$). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 166.0 (C4), 165.9 (C4′−CO), 164.7 (C2), 148.1 (C6), 142.8 (C1′), 136.2 (C5), 130.2 (C3′), 124.8 (C4′), 122.1 (C2′), 52.2 ($COOCH_3$). Rotamer B: δ 166.1 (C4′−CO), 164.2 (C2), 162.0 (C6), 150.9 (C4), 143.8 (C1′), 137.4 (C5), 129.8 (C3′), 123.8 (C4′), 121.4 (C2′), 52.1 ($COOCH_3$). UV/vis (DMSO): λ_{max} = 348, 576 nm. ESI MS *m*/*z*: 311.2 [M + Na]$^+$, 289.2 [M + H]$^+$. HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{12}N_6O_3Na$ [M + Na]$^+$ 311.0863, found 311.0863.

*N^6-(4-Chlorophenyl)-5-nitrosopyrimidine-2,4,6-triamine (**6d**).* Treatment of **3d** (100 mg, 0.36 mmol) with ammonia (25% aqueous solution, 20 mL) by general procedure B (conv., 50 °C, 3 h) gave **6d** (55 mg, 58%) as an orange solid with mp = 274−277 °C. ^{1}H NMR (DMSO-d_6): Rotamer A: δ 13.88 (1H, s, 6-NH), 8.41 (1H, bs, 4-NH^A), 7.88 (2H, m, H2′), 7.76 (1H, m, 2-NH^A), 7.65−7.68 (2H, m, 2-NH^B and 4-NH^B), 7.38 (2H, m, H3′). Rotamer B: δ 10.45 (1H, s, 6-NH), 10.45 (1H, d, J_{GEM} = 4.8 Hz, 4-NH^A), 8.05 (2H, m, H2′), 8.02 (1H, d, J_{GEM} = 4.8 Hz, 4-NH^B), 7.65−7.68 (1H, m, 2-NH^A), 7.58 (1H, bs, 2-NH^B), 7.36 (2H, m, H3′). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 165.9 (C4), 164.7 (C2), 148.3 (C6), 137.0 (C1′), 136.2 (C5), 128.8 (C3′), 128.2 (C4′), 124.2 (C2′). Rotamer B: δ 164.3 (C2), 161.8 (C6), 151.0 (C4), 138.2 (C1′), 137.3 (C5), 128.3 (C3′), 127.2 (C4′), 123.9 (C2′). UV/vis (DMSO): λ_{max} = 340, 564 nm. ESI MS *m*/*z*: 287.1 [M + Na]$^+$, 265.1 [M + H]$^+$. HRMS (ESI) *m*/*z*: calcd for $C_{10}H_{10}ClN_6O$ [M + H]$^+$ 265.0599, found 265.0599.

*5-Nitroso-N^6-phenylpyrimidine-2,4,6-triamine (**6e**).* Treatment of **3e** (100 mg, 0.38 mmol) with ammonia (25% aqueous solution, 20 mL) by general procedure B (conv., 50 °C, 3 h) gave **6e** (63 mg, 72%) as a pink solid with mp = 266 °C. ^{1}H NMR (DMSO- d_6): Rotamer A: δ 13.88 (1H, s, 6-NH), 8.38 (1H, s, 4-NH^A), 7.83 (2H, m, H2′), 7.71 (1H, m, 2-NH^A), 7.61−7.63 (2H, m, 2-NH^B and 4-NH^B), 7.35 (2H, m, H3′), 7,13 (1H, m, H4′). Rotamer B: δ 10.40 (1H, d, J_{GEM} = 4.7 Hz, 4-NH^A), 10.30 (1H, s, 6-NH), 7.97−8.00 (3H, m, H2′ and 4-NH^B), 7.61−7.63 (1H, m, 2-NH^A), 7.53 (1H, bs, 2-NH^B), 7.33 (2H, m, H3′), 7.09 (1H, m, H4′). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 166.0 (C4), 164.8 (C2), 148.4 (C6), 138.0 (C1′), 136.2 (C5), 129.0 (C3′), 124.5 (C4′), 122.7 (C2′). Rotamer B: δ 164.5 (C2), 161.7 (C6), 151.1 (C4), 139.1 (C1′), 137.2 (C5), 128.5 (C3′), 123.6 (C4′), 122.4 (C2′). UV/vis (DMSO): λ_{max} = 342, 568 nm. ESI MS *m*/*z*: 253.1 [M + Na]$^+$, 231.1 [M + H]$^+$. HRMS (ESI) *m*/*z*: calcd for $C_{10}H_{10}N_6ONa$ [M + Na]$^+$ 253.0808, found 253.0808.

*5-Nitroso-N^6-(p-tolyl)pyrimidine-2,4,6-triamine (**6f**).* Treatment of **3f** (100 mg, 0.39 mmol) with ammonia (25% aqueous solution, 20

mL) by general procedure B (conv., 50 °C, 14 h) gave **6f** (66 mg, 70%) as an orange solid with mp = 250−251 °C. ^{1}H NMR (DMSO-d_6): Rotamer A: δ 13.88 (1H, s, 6-NH), 8.35 (1H, bs, 4-NH^A), 7.71 (2H, m, H2′), 7.67 (1H, m, 2-NH^A), 7.56−7.60 (2H, m, 2-NH^B and 4-NH^B), 7.15 (2H, m, H3′), 2.28 (3H, s, CH_3). Rotamer B: δ 10.41 (1H, d, J_{GEM} = 5.0 Hz, 4-NH^A), 10.23 (1H, s, 6-NH), 7.96 (1H, d, J_{GEM} = 5.0 Hz, 4-NH^B), 7.83 (2H, m, H2′), 7.56−7.60 (1H, m, 2-NH^A), 7.49 (1H, bs, 2-NH^B), 7.13 (2H, m, 3′-H), 2.29 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 166.0 (C4), 164.8 (C2), 148.3 (C6), 136.2 (C5), 135.3 (C1′), 133.7 (C4′), 129.5 (C3′), 122.6 (C2′), 20.6 (CH_3). Rotamer B: δ 164.5 (C2), 161.6 (C6), 151.1 (C4), 137.2 (C5), 136.5 (C1′), 132.7 (C4′), 128.9 (C3′), 122.5 (C2′), 20.6 (CH_3). UV/vis (DMSO): λ_{max} = 340, 564 nm. ESI MS m/z: 267.2 [M + Na]$^+$, 245.2 [M + H]$^+$. HRMS (ESI) m/z: calcd for $C_{11}H_{13}N_6O$ [M + H]$^+$ 245.1145, found 245.1145.

4-[(2,4-Diamino-5-nitrosopyrimidin-6-yl)amino]phenol (**6g**). Treatment of **3g** (100 mg, 0.38 mmol) with ammonia (25% aqueous solution, 20 mL) by general procedure B (conv., 50 °C, 14 h) gave **6g** (48 mg, 51%) as an orange solid with mp = 288 °C (decomp.). ^{1}H NMR (DMSO-d_6): Rotamer A: δ 13.88 (1H, s, 6-NH), 8.28 (1H, bs, 4-NH^A), 7.60 (2H, m, H2′), 7.56 (1H, bs, 2-NH^A), 7.52 (1H, bs, 4-NH^B), 7.46−7.49 (1H, m, 2-NH^B), 6.73 (2H, m, H3′). Rotamer B: δ 10.44 (1H, d, J_{GEM} = 3.4 Hz, 4-NH^A), 10.11 (1H, s, 6-NH), 7.90 (1H, d, J_{GEM} = 3.4 Hz, 4-NH^B), 7.67 (2H, m, H2′), 7.46−7.49 (1H, m, 2-NH^A), 7.40 (1H, bs, 2-NH^B), 6.72 (2H, m, H3′). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 165.9 (C4), 164.90 (C2), 154.9 (C4′), 148.1 (C6), 136.1 (C5), 129.0 (C1′), 124.2 (C2′), 115.6 (C3′). Rotamer B: δ 164.6 (C2), 161.4 (C6), 154.1 (C4′), 151.2 (C4), 137.1 (C5), 130.4 (C1′), 124.4 (C2′), 115.0 (C3′). UV/vis (DMSO): λ_{max} = 334, 550−560 nm. ESI MS m/z: 269.1 [M + Na]$^+$, 247.7 [M + H]$^+$. HRMS (ESI) m/z: calcd for $C_{10}H_{10}N_6O_2Na$ [M + Na]$^+$ 269.0757, found 269.0757.

N^6-(4-Aminophenyl)-5-nitrosopyrimidine-2,4,6-triamine (**6h**). Treatment of **3h** (100 mg, 0.38 mmol) with ammonia (25% aqueous solution, 20 mL) by general procedure B (conv., 50 °C, 28 h) gave **6h** (71 mg, 77%) as a red solid with mp = 268−270 °C. ^{1}H NMR (DMSO-d_6): δ 13.94 (1H, s, 6-NH, A), 10.47 (1H, d, J_{GEM} = 5.1 Hz, 4-NH^A, B), 9.97 (1H, s, 6-NH, B), 8.23 (1H, bs, 4-NH^A, A), 7.88 (1H, d, J_{GEM} = 5.1 Hz, 4-NH^B, B), 7.49−7.51 (4H, m, H2′, B; 4-NH^B and 2-NH^A, A), 7.47 (2H, m, H2′), 7.41−7.43 (2H, m, 2-NH^A B; 2-NH^B, A), 7.35 (1H, m, 2-NH^B, B), 6.55 (2H, m, H3′, A), 6.54 (2H, m, H3′, B), 4.97−5.14 (4H, m, 4′-NH$_2$, A; 4′-NH$_2$, B). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 165.9 (C4), 164.8 (C2), 147.9 (C6), 146.2 (C4′), 136.0 (C5), 126.3 (C1′), 123.9 (C2′), 114.1 (C3′). Rotamer B: δ 164.6 (C2), 161.1 (C6), 151.3 (C4), 145.5 (C4′), 137.1 (C5), 127.1 (C1′), 124.3 (C2′), 113.7 (C3′). UV/vis (DMSO): λ_{max} = 330, 422 nm. ESI MS m/z: 268.2 [M + Na]$^+$, 246.2 [M + H]$^+$. HRMS (ESI) m/z: calcd for $C_{10}H_{12}N_7O$ [M + H]$^+$ 246.1097, found 246.1097.

N^6-(4-(Dimethylamino)phenyl)-5-nitrosopyrimidine-2,4,6-triamine (**6i**). Treatment of **3i** (200 mg, 0.69 mmol) with ammonia (25% aqueous solution, 30 mL) by general procedure B (conv., 60 °C, 5 h) gave **6i** (160 mg, 77%) as a black solid with mp = 251−254 °C. ^{1}H NMR (DMSO-d_6): δ 13.97 (1H, s, 6-NH, A), 10.46 (1H, d, J_{GEM} = 5.2 Hz, 4-NH^A, B), 10.10 (1H, s, 6-NH, B), 8.26 (1H, bs, 4-NH^A, A), 7.88 (1H, d, J_{GEM} = 5.2 Hz, 4-NH^B, B), 7.69 (2H, m, H2′, B), 7.63 (2H, m, H2′, A), 7.52 (1H, bs, 2-NH^A, A), 7.51 (1H, bs, 4-NH^B, A), 7.45 (2H, m, 2-NH^B, A; 2-NH^A, B), 7.38 (1H, bs, 2-NH^B, B), 6.68−6.71 (4H, m, H3′, A and B), 2.89 (6H, s, N(CH$_3$)$_2$, A), 2.88 (6H, s, N(CH$_3$)$_2$, B). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 165.9 (C4), 164.8 (C2), 148.0 (C4′), 147.9 (C6), 136.1 (C5), 126.9 (C1′), 123.8 (C2′), 112.6 (C3′), 40.4 (N(CH$_3$)$_2$). Rotamer B: δ 164.6 (C2), 161.2 (C6), 151.3 (C4), 147.5 (C4′), 137.2 (C5), 128.6 (C1′), 124.1 (C2′), 112.5 (C3′), 40.6 (N(CH$_3$)$_2$). UV/vis (DMSO): λ_{max} = 278, 330, 428 nm. ESI MS m/z: 296.1 [M + Na]$^+$, 274.1 [M + H]$^+$. HRMS (ESI) m/z: calcd for $C_{12}H_{16}N_7O$ [M + H]$^+$ 274.1410, found 274.1411.

General Procedure C: Synthesis of Acetamides 7a−f and 7i. A mixture of 5-nitrosopyrimidine **6a−f** or **6i** in acetic anhydride (10 mL per 1 mmol of **6**) was stirred at 80 °C (conv.). After completion (TLC), the reaction mixture was evaporated to dryness (in vacuum), and the final product **7a−f** or **7i** was obtained by silica gel column chromatography (5% or 10% MeOH in $CHCl_3$) as a solid.

N-{2-amino-6-[(4-cyanophenyl)amino]-5-nitrosopyrimidin-4-yl}-acetamide (**7a**). Treatment of **6a** (100 mg, 0.39 mmol) by general procedure C (30 min) gave **7a** (20 mg, 17%) as a green solid with mp = 224 °C. ^{1}H NMR (DMSO-d_6): δ 13.25 (1H, s, 6-NH, A), 12.61 (1H, s, 4-NH, B), 10.96 (1H, s, 6-NH, B), 10.59 (1H, s, 4-NH, A), 8.52−8.62 (4H, m, 2-NH$_2$, A and B), 8.27 (2H, m, H2′, B), 8.09 (2H, m, H2′, A), 7.80−7.83 (4H, m, H3′, A and B), 2.49 (3H, s, CH_3CO, B), 2.45 (3H, s, CH_3CO, A). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 169.6 (CO), 163.9 (C2), 162.3 (C4), 147.3 (C6), 141.9 (C1′), 136.5 (C5), 133.3 (C3′), 123.2 (C2′), 119.0 (CN), 106.76 (C4′), 26.0 (CH_3). Rotamer B: δ 172.7 (CO), 163.8 (C2), 162.2 (C6), 145.2 (C4), 143.1 (C1′), 136.5 (C5), 132.9 (C3′), 122.6 (C2′), 119.33 (CN), 105.7 (C4′), 27.6 (CH_3). UV/vis (DMSO): λ_{max} = 600 nm. ESI MS m/z: 320.1 [M + Na]$^+$, 298.1 [M + H]$^+$. HRMS (ESI) m/z: calcd for $C_{13}H_{11}N_7O_2Na$ [M + Na]$^+$ 320.0866, found 320.0863.

N-{2-Amino-5-nitroso-6-[(4-(trifluoromethyl)phenyl)amino]-pyrimidin-4-yl}acetamide (**7b**). Treatment of **6b** (200 mg, 0.67 mmol) by general procedure C (10 min) gave **7b** (116 mg, 51%) as a green solid, which was crystallized (from acetone) to afford green crystals with mp = 240−243 °C. ^{1}H NMR (DMSO-d_6): δ 13.25 (1H, s, 6-NH, A), 12.65 (1H, s, 4-NH, B), 10.94 (1H, bs, 6-NH, B), 10.57 (1H, bs, 4-NH, A), 8.44−8.55 (4H, m, 2-NH$_2$, A and B), 8.20 (2H, m, H2′, B), 8.06 (2H, m, H2′, A), 7.68−7.71 (4H, m, H3′, A and B), 2.50 (3H, s, CH_3CO, B), 2.46 (3H, s, CH_3CO, A). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 169.7 (CO), 163.9 (C2), 162.3 (C4), 147.5 (C6), 141.1 (C1′), 136.5 (C5), 124.9 (C4′, $J_{C4'-F}$ = 32.2 Hz), 124.4 (CF_3, J_{C-F} = 271.5 Hz), 126.1 (C3′, $J_{C3'-F}$ = 3.8 Hz), 123.4 (C2′), 26.0 (CH_3). Rotamer B: δ 172.8 (CO), 163.9 (C2), 162.3 (C6), 145.3 (C4), 142.3 (C1′), 136.5 (C5), 125.7 (C4′, $J_{C4'-F}$ = 3.8 Hz), 124.5 (CF_3, J_{C-F} = 271.8 Hz), 124.1 (C3′, $J_{C3'-F}$ = 33.0 Hz), 123.1 (C2′), 27.6 (CH_3). UV/vis (DMSO): λ_{max} = 598 nm. ESI MS m/z: 363.0 [M + Na]$^+$, 341.0 [M + H]$^+$. HRMS (ESI) m/z: calcd for $C_{13}H_{12}F_3N_6O_2$ [M + H]$^+$ 341.0968, found 341.0968.

Methyl 4-[(4-Acetamido-2-amino-5-nitrosopyrimidin-6-yl)-amino]benzoate (**7c**). Treatment of **6c** (100 mg, 0.35 mmol) by general procedure C (15 min) gave **7c** (40 mg, 35%) as a green solid with mp = 247−248 °C. ^{1}H NMR (DMSO-d_6): δ 13.32 (1H, s, 6-NH, A), 12.65 (1H, s, 4-NH, B), 10.90 (1H, s, 6-NH, B), 10.57 (1H, s, 4-NH, A), 8.47−8.57 (4H, m, 2-NH$_2$, A and B), 8.18 (2H, m, H2′, B), 8.02 (2H, m, H2′, A), 7.92−7.95 (4H, m, H3′, A and B), 3.84−3.85 (COOCH$_3$, m, 6H, A and B), 2.50 (3H, s, CH_3CO, B), 2.45 (3H, s, CH_3CO, A). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 169.6 (CO), 165.88 (**C**OOCH$_3$), 163.9 (C2), 162.3 (C4), 147.3 (C6), 141.9 (C1′), 136.5 (C5), 130.2 (C3′), 125.5 (C4′), 122.7 (C2′), 52.3 (COO**C**H$_3$), 26.0 (CH_3). Rotamer B: δ 172.8 (CO), 166.0 (**C**OOCH$_3$), 163.9 (C2), 162.1 (C6), 145.3 (C4), 143.1 (C1′), 136.5 (C5), 129.8 (C3′), 124.7 (C4′), 122.2 (C2′), 52.2 (COO**C**H$_3$), 27.6 (CH_3). UV/vis (DMSO): λ_{max} = 596 nm. ESI MS m/z: 353.1 [M + Na]$^+$, 331.1 [M + H]$^+$. HRMS (ESI) m/z: calcd for $C_{14}H_{14}N_6O_4Na$ [M + Na]$^+$ 353.0968, found 353.0968.

N-{2-Amino-6-[(4-chlorophenyl)amino]-5-nitrosopyrimidin-4-yl}-acetamide (**7d**). Treatment of **6d** (300 mg, 1.13 mmol) by general procedure C (30 min) gave **7d** (135 mg, 39%) as a green solid, which was crystallized (from methanol) to afford green crystals with mp = 230 °C. ^{1}H NMR (DMSO-d_6): Rotamer A: δ 13.23 (1H, s, 6-NH), 10.51 (1H, s, 4-NH), 8.44 (2H, bs, 2-NH$_2$), 7.86 (2H, m, H2′), 7.41 (2H, m, H3′), 2.45 (3H, s, CH_3). Rotamer B: δ 12.72 (1H, s, 4-NH), 10.76 (1H, s, 6-NH), 8.39 and 8.38 (2H, bs, 2-NH$_2$), 7.98 (2H, m, H2′), 7.40 (2H, m, H3′), 2.49 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 169.7 (CO), 163.9 (C2), 162.2 (C4), 147.5 (C6), 136.4 (C5), 136.2 (C1′), 129.1 (C4′), 128.9 (C3′), 124.8 (C2′), 26.0 (CH_3). Rotamer B: δ 172.8 (CO), 164.0 (C2), 161.9 (C6), 145.3 (C4), 137.5 (C1′), 136.4 (C5), 128.4 (C3′), 128.2 (C4′), 124.8 (C2′), 27.6 (CH_3). UV/vis (DMSO): λ_{max} = 592 nm. ESI MS m/z: 329.0 [M + Na]$^+$, 307.0 [M + H]$^+$. HRMS (ESI) m/z: calcd for $C_{12}H_{11}ClN_6O_2Na$ [M + Na]$^+$ 329.0524, found 329.0523.

N-[2-Amino-5-nitroso-6-(phenylamino)pyrimidin-4-yl]acetamide (**7e**). Treatment of **6e** (189 mg, 0.82 mmol) by general procedure C

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(30 min) gave **7e** (62 mg, 28%) as a green solid with mp = 229−231 °C. ^{1}H NMR (DMSO-d_6): Rotamer A: δ 13.28 (1H, s, 6-NH), 10.48 (1H, s, 4-NH), 8.40 (2H, bs, 2-NH $_2$), 7.82 (2H, m, H2′), 7.38 (2H, m, H3′), 7.18 (1H, m, H4′), 2.46 (3H, s, CH_3). Rotamer B: δ 12.76 (1H, s, 4-NH), 10.64 (1H, s, 6-NH), 8.35 and 8.32 (2H, bs, 2-NH_2), 7.92 (2H, m, H2′), 7.37 (2H, m, H3′), 7.15 (1H, m, H4′), 2.50 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 169.7 (CO), 163.9 (C2), 162.1 (C4), 147.6 (C6), 137.1 (C1′), 136.4 (C5), 129.1 (C3′), 125.2 (C4′), 123.1 (C2′), 26.0 (CH_3). Rotamer B: δ 172.9 (CO), 164.0 (C2), 161.9 (C6), 145.4 (C4), 138.4 (C1′), 136.5 (C5), 128.6 (C3′), 124.4 (C4′), 123.3 (C2′), 27.6 (CH_3). UV/vis (DMSO): λ_{max} = 590 nm. ESI MS m/z: 295.2 $[M + Na]^+$, 273.2 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{12}H_{12}N_6O_2Na$ $[M + Na]^+$ 295.0913, found 295.0914.

*N-[2-Amino-5-nitroso-6-(p-tolylamino)pyrimidin-4-yl]acetamide (**7f**).* Treatment of **6f** (184 mg, 0.77 mmol) by general procedure C (60 min) gave **7f** (94 mg, 43%) as a green solid with mp = 238 °C. ^{1}H NMR (DMSO-d_6): Rotamer A: δ 13.29 (1H, s, 6-NH), 10.46 (1H, s, 4-NH), 8.36 (2H, bs, 2-NH_2), 7.69 (2H, m, H2′), 7.18 (2H, m, H3′), 2.46 (3H, s, CO−CH_3), 2.29 (3H, s, 4′-CH_3). Rotamer B: δ 12.79 (1H, s, 4-NH), 10.58 (1H, s, 6-NH), 8.30 and 8.28 (2H, bs, 2-NH_2), 7.77 (2H, m, H2′), 7.16 (2H, m, H3′), 2.49 (3H, s, CO−CH_3), 2.30 (3H, s, 4′-CH_3). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 169.7 (CO), 163.9 (C2), 162.1 (C4), 147.5 (C6), 136.3 (C5), 134.5 and 129.6 (C1′ and C4′), 129.6 (C3′), 123.1 (C2′), 26.0 (CO−CH_3), 20.74 (4′-CH_3). Rotamer B: δ 172.9 (CO), 164.1 (C2), 161.7 (C6), 145.4 (C4), 136.3 (C5), 135.9 (C1′), 133.6 (C4′), 129.0 (C3′), 123.4 (C2′), 27.6 (CO−CH_3), 20.7 (4′-CH_3). UV/vis (DMSO): λ_{max} = 586 nm. ESI MS m/z: 309.2 $[M + Na]^+$, 287.2 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{13}H_{14}N_6O_2Na$ $[M + Na]^+$ 309.1070, found 309.1069.

*N-(2-Amino-6-(4-(dimethylamino)phenylamino)-5-nitrosopyrimidin-4-yl)acetamide (**7i**).* Treatment of **6i** (100 mg, 0.37 mmol) by general procedure C (rt, 20 min) gave **7i** (56 mg, 48%) as a black solid with mp = 220−222 °C. ^{1}H NMR (DMSO-d_6): δ 13.44 (1H, s, 6-NH, A), 12.89 (1H, s, 4-NH, B), 10.48 (1H, s, 6-NH, B), 10.40 (1H, s, 4-NH, A), 8.25 and 8.24 (2H, bs, 2-NH_2, A), 8.18 and 8.17 (2H, bs, 2-NH_2, B), 7.62−7.65 (4H, m, H2′, A and B), 6.69−6.73 (4H, m, H3′, A and B), 2.90 (6H, s, $N(CH_3)_2$, A), 2.89 (6H, s, $N(CH_3)_2$, B), 2.49 (3H, s, CO−CH_3, B), 2.46 (3H, s, CO−CH_3, A). ^{13}C NMR (DMSO-d_6): Rotamer A: δ 169.7 (CO), 163.8 (C2), 161.9 (C4), 148.2 (C4′), 147.1 (C6), 136.1 (C5), 125.8 (C1′), 124.2 (C2′), 112.55 (C3′), 40.3 ($N(CH_3)_2$), 26.0 (CO−CH_3). Rotamer B: δ 172.9 (CO), 164.0 (C2), 161.2 (C6), 148.0 (C4′), 145.5 (C4), 136.2 (C5), 127.7 (C1′), 124.8 (C2′), 112.3 (C3′), 40.5 ($N(CH_3)_2$), 27.6 (CO−CH_3). UV/vis (DMSO): λ_{max} = 458 nm. ESI MS m/z: 338.1 $[M + Na]^+$, 316.1 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{14}H_{18}N_7O_2$ $[M + H]^+$ 316.1516, found 316.1516.

■ ASSOCIATED CONTENT

Supporting Information

Temperature dependence of the ^{1}H NMR spectra of compound **5e**; ^{1}H and ^{13}C NMR, HRMS, and UV−vis spectra of the new compounds; and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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