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An aqueous medium synthesis and tautomerism study of 3(5)-amino-1,2,4-triazoles

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ABSTRACT

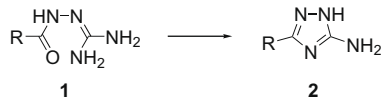
A catalyst-free highly efficient synthesis of 3(5)-amino-5(3)-(het)aryl-1,2,4-triazoles in aqueous medium was performed using conventional heating and microwave irradiation. The tautomerism in the products was investigated using NMR spectroscopy and X-ray crystallography. The effects of the substitution, temperature, solvents, and concentration on the tautomerism were studied. The triazoles were found to exist in 1*H*-forms, the 4*H*-form was not observed either in solid state or in solution. In general, 5-amino-1,2,4-triazoles were electronically preferred in the tautomeric equilibrium, but some exceptions from the established relationship were also identified.

1,2,4-Triazoles represent a class of heterocyclic compounds of significant importance in agriculture and medicine.[1] They are also used in metalloorganic chemistry as polyfunctional ligands.[2] Among 1,2,4-triazoles, 3(5)-amino-1,2,4-triazoles have been recognized, primarily, as valuable synthons for the construction of more complex structures, particularly biologically active fused heterocycles (e.g., 1,2,4-triazolo[1,5-*a*]pyrimidines[3] and 1,2,4-triazolo[1,5-*a*][1,3,5]triazines[4]).

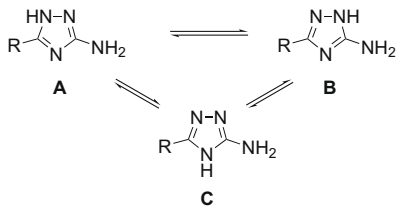
The most straightforward and commonly used method for the preparation of 3(5)-amino-1,2,4-triazoles **2** involves the cyclocondensation of amidoguanidines **1** (Scheme 1). However, the use of a high temperature (often above the melting point)[5] or the presence of a strong base[5e] in the reaction complicated the work-up and led to decreased yields of the products. Herein we describe a method which avoids these drawbacks and leads to 3(5)-amino-1,2,4-triazoles via a simple and eco-friendly procedure.

Tautomerism in five-membered heterocyclic systems is an intriguing phenomenon, which has been recognized for a long time.[6] A knowledge of the tautomeric preferences and the factors affecting the equilibrium are essential for understanding the reactivity of compounds in chemical processes and their effects on biological systems. Due to annular prototropic tautomerism, 1,2,4-triazoles, particularly amino-1,2,4-triazoles without substituents on the ring nitrogen atoms, *a priori* can exist in three forms, namely, 3-amino-1*H*-1,2,4-triazoles (**A**), 5-amino-1*H*-1,2,4-triazoles (**B**), and 3-amino-4*H*-1,2,4-triazoles (**C**) (Scheme 2). A number of theoretical reports[7] have appeared in the area of tautomerism in amino-1,2,4-triazoles, but experimental studies have often ignored this phenomenon and some data were misinterpreted. In this Letter, we present a study on the tautomerism in 3(5)-amino-5(3)-(het)aryl-1,2,4-triazoles using NMR spectroscopy and X-ray crystallography.

Green chemistry, which is an essential part of process development in modern chemistry, has also begun to influence medicinal chemistry significantly.[9] The design of an environmentally friendly synthesis includes elaboration of methods able to avoid or minimize the formation of byproducts, the selection of a safe solvent, and effective use of energy. Water is considered to be the best solvent for sustainable chemistry.[10] We found that



Scheme 1.



Scheme 2.

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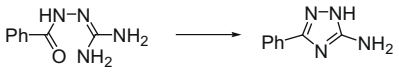
Table 1
Synthesis of triazoles **2a–j** via cyclocondensation of amidoguanidines **1** under conventional heating

1 **2**

Triazole	R	Reaction time (h)	Volume[a] (ml)	Yield (%)	Mp (°C) (lit.)
2a	Ph	4	20	97	186–187 (186–187)[5e]
2b	4-MeC_6H_4	4	20	98	209 (207)[8a]
2c	4-$MeOC_6H_4$	8	40	96	226 (224–226)[5e]
2d	4-FC_6H_4	3	20	95	188–189
2e	4-ClC_6H_4	6	60[b]	94	229–230 (227–229)[5e]
2f	2-Furyl	6	20	95	211–212 (204–206)[8b]
2g	2-Thienyl	8	30	97	214
2h	2-Pyridyl	4	20	92	220–221 (217)[8c]
2i	3-Pyridyl	6	20	98	224–225 (223)[8c]
2j	4-Pyridyl	6	20	98	272–274 (276–278)[5d]

[a] Volume of water per 1 g of **1**.
[b] 40% ethanol was used as solvent.

Table 2
Optimization of the microwave-assisted synthesis of **2a**



1a **2a**

Microwave power (W)	Reaction time (s)	Yield (%)
50	420	94
100	150	100
150	120	88
200	70	82

(het)arylamidoguanidines **1**, upon heating in water, underwent quantitative cyclocondensation with elimination of a water molecule affording 3(5)-amino-5(3)-(het)aryl-1,2,4-triazoles **2** (Table 1).[11] The reaction provided the products in excellent purity and did not require the presence of base or catalyst. The solubility of the starting (het)arylamidoguanidines **1** was found to be a limiting factor of the reaction and increasing the volume of water or using a co-solvent (ethanol) was required for some less soluble amidoguanidines **1**. However, when ethanol was used as the sole solvent instead of water, the conversion of **1a** into 3(5)-amino-5(3)-phenyl-1,2,4-triazole (**2a**) did not proceed to completion even after 3 days of heating under reflux.

Microwave irradiation is an alternative source of energy, which allows highly effective use of the heat produced, reduces reaction times and often improves yields. Microwave-assisted syntheses have found extensive applications in heterocyclic chemistry,[12] and a number of methods for the preparation of 1,2,4-triazoles using microwave irradiation have been reported.[13] However, no data on microwave-based syntheses of 3(5)-amino-1,2,4-triazoles are available. Since water is an excellent solvent for microwave-assisted reactions,[14] and provided it is a suitable medium for cyclocondensation of **1** under conventional heating, we attempted to use it as a solvent in the microwave-initiated synthesis. Four regimes with fixed microwave irradiation power were applied using a CEM 'Discover' apparatus and 100 W was found to be optimal microwave power for the cyclization of **1a** (Table 2).[15] These conditions were then applied successfully for the preparation of other 3(5)-amino-5(3)-(het)aryl-1,2,4-triazoles (**2**) (Table 3). We attempted to prepare **2a** by heating **1a** in ethanol using similar irradiation conditions. However, a longer reaction time (5 min) was required and the isolated yield was lower (86%).

Table 3
Microwave-assisted synthesis of triazoles **2a–j** in water, 100 W

1 **2**

Triazole	R	Reaction time (s)	Yield (%)
2a	Ph	150	100
2b	4-MeC_6H_4	165	100
2c	4-$MeOC_6H_4$	165	100
2d	4-FC_6H_4	150	90
2e	4-ClC_6H_4	180	100
2f	2-Furyl	165	100
2g	2-Thienyl	180	100
2h	2-Pyridyl	150	84
2i	3-Pyridyl	150	100
2j	4-Pyridyl	150	88

The structures of the compounds prepared and in particular their tautomerism were investigated using both NMR spectroscopy, which is considered to be the most informative and accurate method for solutions,[16] and X-ray crystallography, which provides comprehensive structural information in the solid state.[16b,c]

The 1,2,4-triazoles **2** were found to exist in amino forms; imino forms were disfavored according to literature data.[17] Of the three tautomeric forms theoretically possible due to annular tautomerism (Scheme 2), forms **A** and **B** were found to be present in the solutions of triazoles **2**, while form **C** was not observed under the experimental conditions.

The equilibrium between the tautomers was established rapidly and the compositions did not change with time. Identical spectra for the tautomeric system **A**–**B** were observed on dissolving the samples and after equilibration of the solution overnight.

Table 4
Tautomerism in 3(5)-amino-1,2,4-triazoles in DMSO-d_6 solution

A **B**

Triazole	R	^{1}H NMR signals of tautomeric forms **A** and **B** in DMSO-d_6 (0.1 M), ppm				K_T	$-\Delta G_{298}$ (kJ mol^{-1})
		3(5)-NH_2		N(1)-H			
		A	**B**	**A**	**B**		
2a	Ph	5.29	6.05	13.20	12.04	8.2	5.2
2b	4-MeC_6H_4	5.25	6.01	13.09	11.96	6.1	4.4
2c	4-MeOC_6H_4	5.21	5.99	12.99	11.90	5.0	4.0
2d	4-FC_6H_4	5.31	6.04	13.18	12.05	14.2	6.6
2e	4-ClC_6H_4	5.37	6.10	13.25	12.12	20.6	7.5
2f	2-Furyl	5.29	6.07	13.20	12.07	13.6	6.5
2g	2-Thienyl	5.34	6.09	13.16	12.02	22.9	7.8
2h	2-Pyridyl	5.33	6.08	13.45	12.23	1.6	1.2
2i	3-Pyridyl	5.42	6.18	13.41	12.22	25.2	8.0
2j	4-Pyridyl	5.48	6.22	13.64	12.35	30.1	8.4

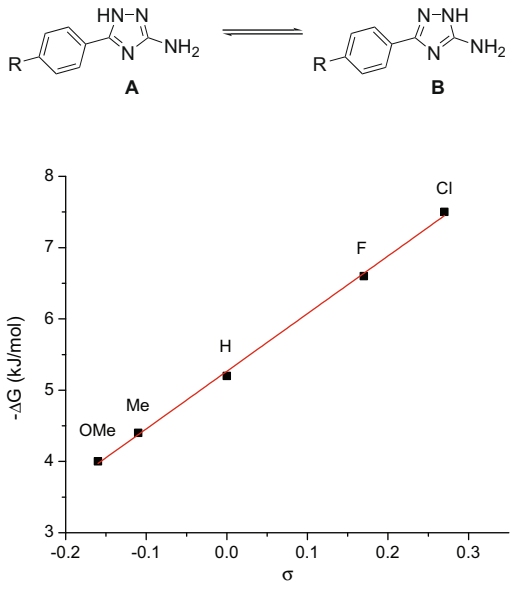


Figure 1. Correlation of -ΔG for the tautomeric equilibrium of 3-amino-5-aryl- and 5-amino-3-aryl-1,2,4-triazoles with the Hammett constant (σ) of the R group.

The NH and NH_2 signals of tautomers **A** and **B** in the ^{1}H NMR spectra in DMSO were quite distinct allowing calculation of K_T values (Table 4). 5-Amino-1,2,4-triazoles **B** were identified to be the predominant tautomers. The substituent showed significant effects on the equilibrium between tautomeric forms **A** and **B**. This effect was strongly dependent on the electronic properties of the substituents. It was found that the K_T and ΔG_{298} values correlated well with the Hammett constants[18] of the substituents on the phenyl ring of **2a–e**: $-\Delta G_{298} = 8.086\sigma + 5.265$, $R^2 = 0.998$ (Fig. 1). Therefore, the thermodynamic stability of form **B** in comparison with **A** increased together with the electron-withdrawing properties of the substituents. This relationship could also be extended to some heterocyclic, that is, 3-pyridyl, 4-pyridyl, and 2-thienyl substituents at C3(5) of the 1,2,4-triazole ring. However, experimental results for compounds 2f,**h** with 2-furyl and especially 2-pyridyl substituents at these positions were outside this correlation. At first glance, this observation could be attributed to possible intramolecular hydrogen bonding between N1–H and the nitrogen atom of the pyridyl and the oxygen atom of the furyl moieties in form **A**. The intramolecular hydrogen bonding N1–H···X (X = O, N) would prevent movement of the tautomeric equilibrium toward 'electronically' favored form **B** despite the strong electron-withdrawing effect of the heterocycles. However, this explanation became wide open to criticism by detailed analysis of further experiments. The signals of N(1)–H in the ^{1}H NMR spectra appeared at the same range and had similar line widths for all triazoles **2**. Increasing the concentration of the samples from 0.1 to 1.0 M caused a ~0.2 ppm downfield shift of the signals (particularly NH and NH_2) in the ^{1}H NMR spectra without affecting K_T. Heating the sample should disfavor systems stabilized by intramolecular hydrogen bonding and would shift the equilibrium to form **B**. However, no significant changes in K_T were observed for **2f,h** at elevated temperatures, similarly to triazoles **2** without potential intramolecular hydrogen bonding. The signals of the tautomers **A** and **B** appeared clearly in the ^{1}H NMR spectra in DMSO-d_6 solution and coalesced only on heating (Fig. 2). Interestingly, addition of nonpolar $CDCl_3$ to the DMSO-d_6 solution of triazoles 2f,**h** did not strengthen the intramolecular hydrogen bonding as expected. In contrast, the rate of the tautomeric exchange became too fast to be observed on the NMR time-scale. Only one set of signals appeared in the NMR spectra when a mixture of DMSO-d_6 and $CDCl_3$ (1:1) was used as solvent for the experiment, as exemplified in Figure 2. Therefore, the "anomalous" thermodynamic stability of tautomeric forms **A** for **2f,h** as well as the effect of solvents on the rate of tautomeric exchange is still to be revealed.

Unsymmetrical 3,5-disubstituted 1,2,4-triazoles have been known to crystallize in the form of the tautomer bearing an electron-acceptor substituent at position 3 and an electron-donor substituent at position 5.[19] Surprisingly, we found that the presence of forms **A** and **B** in the crystal was possible even for compounds bearing substituents with considerably different electronic properties. Thus, two compounds, that is, 5-amino-3-phenyl-1,2,4-triazole and 3-amino-5-phenyl-1,2,4-triazole (**2a**) crystallized together in the same crystal (Fig. 3) despite the fact that the K_T value for their equilibrium in DMSO-d_6 solution was 8.2. Conversely, **2h** with a K_T in DMSO-d_6 solution equal to 1.6, crystallized solely as 5-amino-3-(pyridin-2-yl)-1,2,4-triazole (form **B**) (Fig. 4).

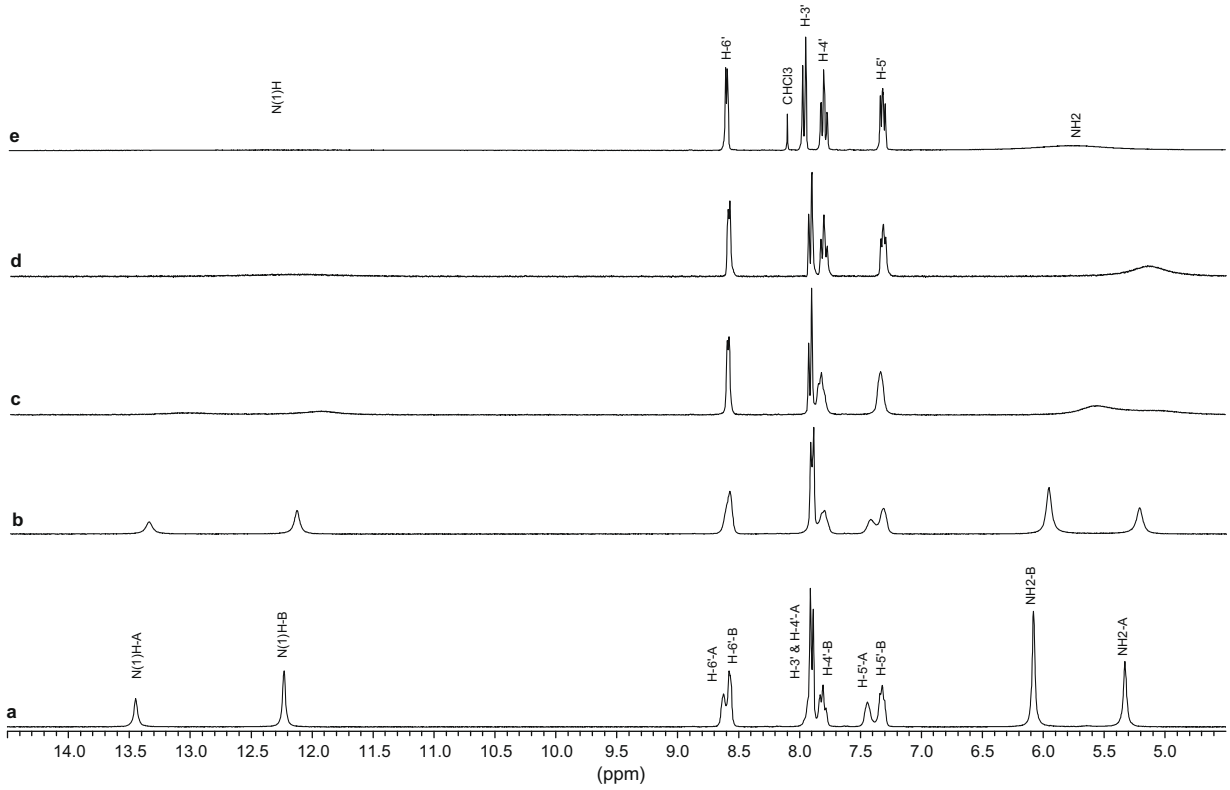


Figure 2. ^{1}H NMR spectra (300 MHz) of 3(5)-amino-5(3)-(pyridin-2-yl)-1,2,4-triazole (**2h**) 0.1 M solution in DMSO-d_6, 27 °C (a); 50 °C (b); 100 °C (c); 150 °C (d); 0.1 M solution in DMSO-d_6–$CDCl_3$ (1:1), 27 °C (e).

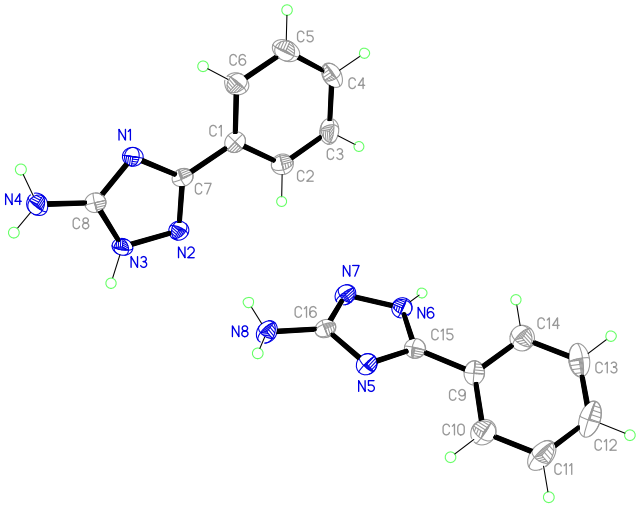


Figure 3. X-ray structure of **2a**, CCDC 717328.[20]

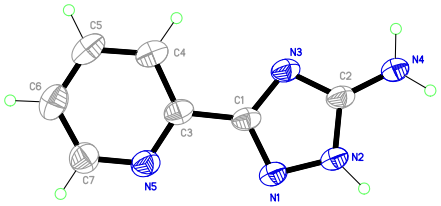


Figure 4. X-ray structure of **2h**, CCDC 717327.[21]

In conclusion, an efficient and environmentally friendly method for the preparation of 3(5)-amino-1,2,4-triazoles has been developed and some aspects of the tautomerism in these compounds have been described.

Acknowledgments

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11. *General procedure for the conventional synthesis of 3(5)-amino-5(3)-het(aryl)-1,2,4-triazoles (**2**)*: (Het)arylamidoguanidines (**1**) were heated under reflux in water (see Table 1 for volume and time). After cooling, the precipitated products **2** were filtered, washed with ice-cold water and dried. The purity of **2** was satisfactory; for analysis, the samples were recrystallized from water or aq EtOH (**2e**,**g**). The reaction can be scaled-up from 0.5 g to 20 g without significant changes in the yields. Compound **2a**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.29* and 6.05 (two s, 2H, NH_2), 7.32 (t, ^3J 7.2 Hz, 1H, H-4′), 7.39 (t, ^3J 7.2 Hz, 2H, H-3′ and -5′), 7.89 (d, ^3J 6.8 Hz, 2H, H-2′ and -6′), 12.04 and 13.20* (two s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 125.4 (C-3′ and -5′), 128.1 (C-4′), 128.3 (C-2′ and -6′), 132.3 (C-1′), 152.4*, 157.3, 158.4 and 164.4* (C-3 and -5). Compound **2b**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.32 (s, 3H, Me), 5.25* and 6.01 (two s, 2H, NH_2), 7.19 (d, ^3J 7.9 Hz, 2H, H-3′ and -5′), 7.77 (d, ^3J 7.9 Hz, 2H, H-2′ and -6′), 11.96 and 13.09* (two s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.8 (Me), 125.4 (C-3′ and -5′), 128.9 (C-2′ and -6′), 129.6 (C-1′), 137.4 and 139.1* (C-4′), 152.5*, 157.3, 158.5 and 164.2* (C-3 and -5). Compound **2c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (s, 3H, OMe), 5.21* and 5.99 (two s, 2H, NH_2), 6.95 (d, ^3J 8.7 Hz, 2H, H-3′ and -5′), 7.81 (d, ^3J 8.7 Hz, 2H, H-2′ and -6′), 11.90 and 12.99* (two s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.0 (OMe), 113.8 (C-3′ and -5′), 125.0 (C-1′), 126.8 (C-2′ and -6′), 152.3*, 157.2, 158.4 and 164.2* (C-3 and -5), 159.4 and 160.1* (C-4′). Compound **2d**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.31* and 6.04 (two s, 2H, NH_2), 7.22 (dd, ^3J 8.7, $^3J_{HF}$ 8.7 Hz, 2H, H-3′ and -5′), 7.91 (dd, ^3J 8.7, $^4J_{HF}$ 5.7 Hz, 2H, H-2′ and -6′), 12.05 and 13.18* (two s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 115.2 (d, $^2J_{CF}$ 22.3 Hz, C-3′ and -5′), 127.2 (d, $^3J_{CF}$ 8.2 Hz, C-2′ and -6′), 128.9 (d, $^4J_{CF}$ 2.9 Hz, C-1′), 157.3 and 157.5 (C-3 and -5), 162.1 (d, $^1J_{CF}$ 244.6 Hz, C-4′). Compound **2e**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.37* and 6.10 (two s, 2H, NH_2), 7.46 (d, ^3J 8.3 Hz, 2H, H-3′ and -5′), 7.88 (d, ^3J 8.3 Hz, 2H, H-2′ and -6′), 12.12 and 13.25* (two s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 126.9 (C-3′ and -5′), 128.4 (C-2′ and -6′), 131.2 (C-1′), 132.6 (C-4′), 157.4 (C-3 and -5). Compound **2f**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.29* and 6.07 (two s, 2H, NH_2), 6.54 (dd, ^3J 3.0 and 1.5 Hz, 1H, H-4′), 6.67 (d, ^3J 3.0 Hz, 1H, H-3′), 7.68 (d, ^3J 1.5 Hz, 1H, H-5′), 12.07 and 13.20* (two s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 107.4 (C-4′), 111.2 (C-3′), 142.5 (C-5′), 147.6 (C-2′), 152.1 and 156.9 (C-3 and -5). Compound **2g**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.34* and 6.09 (two s, 2H, NH_2), 7.07 (dd, ^3J 4.9 and 3.4 Hz, 1H, H-4′), 7.40 (d, ^3J 3.0 Hz, 1H, H-3′), 7.46 (d, ^3J 4.9 Hz, 1H, H-5′), 12.02 and 13.16* (two s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 124.2 (C- 4′), 125.4 (C-5′), 127.4 (C-3′), 135.5 (C-2′), 154.7 and 157.1 (C-3 and -5). Compound **2h**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.33* and 6.08 (two s, 2H, NH_2), 7.25–7.51 (m, 1H, H-5′), 7.74–8.00 (m, 2H, H-3′ and -4′), 8.52–8.69 (m, 1H, H-6′), 12.23 and 13.45* (two s, 1H, NH); ^{13}C NMR^{13}C NMR (75 MHz, DMSO-d_6): δ 120.7* and 120.9 (C-5′), 123.0 and 124.3* (C-3′), 136.5 and 137.5* (C-4′), 146.5* and 150.7 (C-2′), 149.2 (C-6′), 151.6*, 157.2, 158.6 and 164.4* (C-3 and -5). Compound **2i**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.42* and 6.18 (two s, 2H, NH_2), 7.43 (dd, ^3J 7.5 and 4.9 Hz, 1H, H-5′), 8.18 (dt, ^3J 7.9, ^4J 1.7 Hz, 1H, H-4′), 8.54 (dd, ^3J 4.2, ^4J 1.5 Hz, 1H, H-6′), 9.06 (d, ^4J 1.5 Hz, 1H, H-2′), 12.22 and 13.41* (two s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 123.6 (C-5′), 127.9 (C-3′), 132.4 (C-4′), 146.5 (C-2′), 149.0 (C-6′), 156.1 and 157.5 (C-3 and -5). Compound **2j**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.48* and 6.22 (two s, 2H, NH_2), 7.78 (dd, ^3J 4.5, ^4J 1.5 Hz, 2H, H-3′ and -5′), 8.60 (d, ^3J 5.7 Hz, 2H, H-2′ and -6′), 12.35 and 13.64* (two s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 119.5 (C-3′ and -5′), 139.2 (C-4′), 149.9 (C-2′ and -6′), 156.4 and 157.6 (C-3 and -5). *—signals of minor tautomers **A**.
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