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ORIGINAL PAPER

A simple and convenient synthesis of tautomeric (6 or 2)-hydroxy-4-methyl-(2 or 6)-oxo-1-(substituted phenyl)-(1,2 or 1,6)-dihydropyridine-3-carbonitriles

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Abstract A simple and convenient synthesis of tautomeric (6 or 2)-hydroxy-4-methyl-(2 or 6)-oxo-1-(substituted phenyl)-(1,2 or 1,6)-dihydropyridine-3-carbonitriles from ethyl acetoacetate and 2-cyano-*N*-(substituted phenyl)ethanamides using microwave-assisted chemistry is presented. The structure of the obtained product was confirmed by the use of FT-IR, NMR, UV, and MS techniques. The presence of tautomeric forms (6-hydroxy-4-methyl-2-oxo-1-(substituted phenyl)-1,2-dihydropyridine-3-carbonitrile and 2-hydroxy-4-methyl-6-oxo-1-(substituted phenyl)-1,6-dihydropyridine-3-carbonitrile) and the state of equilibrium of the obtained product in DMSO-d_6 was studied by ^{1}H and ^{13}C NMR spectroscopy, as well as B3LYP/6-311++G(d,p) and GIAO/WP04/aug-cc-pVDZ theoretical calculations.

Keywords Microwave assisted synthesis · Heterocycles · Cyclizations · Ab initio calculations · Tautomerism

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Introduction

Many naturally occurring and synthetic compounds containing a 2-pyridone ring have a broad spectrum of biological activity [1–3]. Some of them are cardiotonic agents for the treatment of heart failure [4–7], whereas others possess antitumor [8, 9], antibacterial [10], or some other biological activities [1, 2, 11–15]. Many 3-cyano-2-pyridone derivatives are used in the manufacture of dyes and pigments, stabilizers for polymers and varnishes, additives for fuels and lubricants, acid–base indicators, and other practically important materials [2].

The 3-cyano-2-pyridones can be obtained by different procedures using various starting compounds [1, 2, 16, 17]. Microwave-assisted synthesis has also been used to obtain 2-pyridones and their derivatives [18–23]. 6-Hydroxy-4-methyl-2-oxo-1-(substituted phenyl)-1,2-dihydro-pyridine-3-carbonitriles are compounds which are mostly used as coupling components in the synthesis of various pyridone azo dyes and pigments as well as other pyridone dyes and pigments [24–35]. These 2-pyridones described in the literature were obtained using different procedures. Matsui et al. [24] prepared 6-hydroxy-4-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonitrile from aniline, ethyl cyanoacetate, and ethyl acetoacetate using the procedure described earlier by Chen and Wang [36]. 6-Hydroxy-4-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonitrile was also obtained by condensation of acetoacetanilide with methyl cyanoacetate or of methyl acetoacetate with cyanoacetanilide in ethanol with the addition of potassium hydroxide [28, 34]. This pyridone was also prepared from ethyl 2-cyano-2-[1-methyl-3-oxo-3-(phenylamino)-propylidine]acetate which was synthesized by the reaction of ethyl cyanoacetate and acetoacetanilide in the presence of sodium ethoxide [37]. 6-Hydroxy-4-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonitrile

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and 1-(4-chlorophenyl)-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile were in addition prepared from ethyl 2-cyano-3-methyl-4-phenylcarbamoyl-2-butenoate or its 4-chlorophenyl derivative, respectively, and base [38]. 1-(4-Ethoxycarbonylphenyl)-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile was prepared by the reaction of ethyl 4-aminobenzoate and diketene, followed by condensation with ethyl cyanoacetate [33]. The ester was then hydrolyzed to give the carboxy derivative.

To our knowledge all of the known procedures suffer from long reaction times, use of strong base, and/or require several steps to produce the desired pyridine derivatives usually in low to moderate yields. Herein, we report a simple, convenient, and efficient microwave-assisted synthesis of products consisting of the tautomeric pyridone 6-hydroxy-4-methyl-2-oxo-1-(substituted phenyl)-1,2-dihydropyridine-3-carbonitriles **a** and 2-hydroxy-4-methyl-6-oxo-1-(substituted phenyl)-1,6-dihydropyridine-3-carbonitriles **b** (Scheme 1). Atom numbering in the corresponding pyridone tautomers **a** and **b** has been defined arbitrarily and is given in Scheme 1.

Results and discussion

A series of 16 reaction products, consisting of a mixture of tautomers **a** and **b** (Scheme 1), was synthesized using microwave irradiation starting from ethyl acetoacetate and corresponding 2-cyano-*N*-(substituted phenyl)ethanamides in the presence of freshly powdered potassium hydroxide. Starting 2-cyano-*N*-(substituted phenyl)ethanamides were synthesized according to previously published methods [39–41]. Microwave synthesis (MW) was performed in a dedicated microwave reactor in an open vessel. An attempt was made to perform synthesis in a closed vessel but much lower yields were obtained. Reactions were also carried out in a domestic commercial microwave oven as well. The conventional synthesis was also performed.

In order to optimize reaction conditions irradiation power (100–600 W), reaction time (1–30 min), and reactant molar ratio, the reaction between 2-cyano-*N*-phenylethanamide, ethyl acetoacetate, and freshly powdered potassium hydroxide was used as a model reaction. The optimized reactant ratios were found to be 1.0 equiv. 2-cyano-*N*-phenylethanamide, 3.9 equiv. ethyl acetoacetate, and 2.0 equiv. potassium hydroxide in the open vessel reaction in a dedicated microwave reactor. Optimized reaction time was found to be 10 min at 150 W. The isolated yield of the product **1** is 78 %. All other products were synthesized according to established optimized reaction conditions and results are given in Table 1.

The obtained products were characterized by melting point, FT-IR, NMR, UV, and MS data, as well as elemental analysis (Supplementary Material). When reactions were run in the closed vessel, ethanol was used as solvent. Reactions were performed at 140 °C but the isolated yields (20–25 %) were several times lower than in the open vessel. Also reactions were run in an open vessel in the domestic commercial microwave oven. These reactions were run using the optimized reactant ratio obtained in the dedicated microwave reactor and without stirring during irradiation (10 min). The higher irradiation power (300 W) than in the dedicated microwave reactor was needed to obtain yields of 30–50 %. Although not much lower yields were obtained in comparison to the dedicated microwave reactor, synthesis in domestic commercial microwave ovens cannot be advised owing to safety and reproducibility reasons [42]. In addition, conventional synthesis of all pyridones was performed using optimal reactant ratio in ethanol at reflux temperature. In comparison to the conventional method, microwave synthesis gives products in higher yields (e.g., compound **1**: 78 % in the microwave vs. 40 % in the conventional synthesis) and in a shorter reaction time (10 min vs. 3 h). A similar trend was found for other compounds, and results are given in Table S1.

The preliminary study of the ^{1}H and ^{13}C NMR spectra of the obtained products indicated the existence of two compounds that could not be separated using chromatographic techniques. A detailed study on the assignments of the

Scheme 1

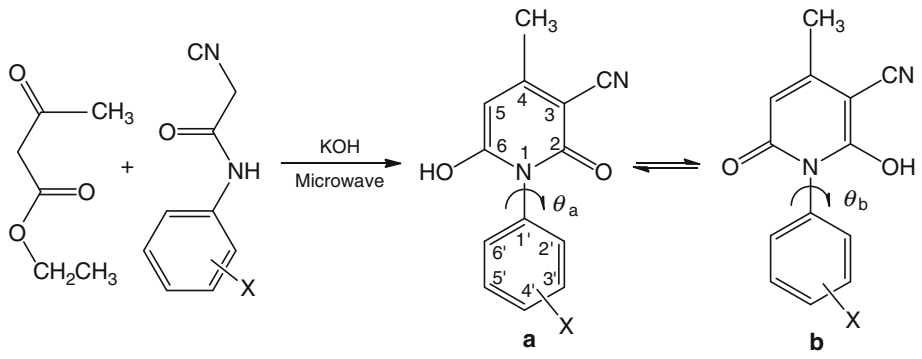


Table 1 Yields and melting points of the obtained product (MW synthesis)

Compound	X	Yield/%[a]	M.p./°C
1	H	78	281–283
2	4-CH_3	72	284–285
3	4-OCH_3	60	270–273
4	4-NO_2	73	238–242
5	4-$COCH_3$	42	227–230
6	4-OH	50	286–288
7	4-I	57	288–289
8	4-Cl	64	285–287
9	4-Br	64	276–278
10	4-F	74	284–285
11	3-CF_3	66	315–317
12	3-Cl	59	275–278
13	3-Br	52	278–280
14	3-OCH_3	47	250–252
15	3-CH_3	54	284–285
16	3-$COCH_3$	52	243–245

[a] Purification performed by chloroform washing

Table 2 Percentage of tautomers **a** and **b** and equilibrium constant K_T

Compound	**a**/%	**b**/%	K_T^a
1	43	57	1.33
2	70	30	0.43
3	23	77	3.35
4	27	73	2.70
5	73	27	0.37
6	100	0	0.00
7	75	25	0.33
8	68	32	0.47
9	60	40	0.67
10	41	59	1.44
11	0	100	–
12	45	55	1.22
13	54	46	0.85
14	80	20	0.25
15	30	70	2.33
16	43	57	1.33

K_T^a = [**b**]/[**a**]; proportions are determined by ratio of integrated H5 signal in DMSO-d_6

^{1}H and ^{13}C NMR signals of the synthesized compounds was undertaken using homonuclear correlated spectroscopy (H,H-COSY), heteronuclear single quantum coherence (^{1}H–^{13}C HSQC), and heteronuclear multiple bond correlation (^{1}H–^{13}C HMBC) techniques. The results were used for characterization and study of the state of equilibrium, i.e., the state of tautomeric interconversion, of forms **a** and **b** (Scheme 1) in DMSO-d_6 solution. Most of the synthesized compounds, according to our knowledge, are reported for the first time, and for known compounds **2**–**4**, **8**, **12**, **15**, and **17** corresponding NMR spectral data are not available in the literature.

It was not a new notion that pyridones exist in solution or in the solid state as an appropriate equilibrium of tautomeric or dimeric forms [43, 44]. This equilibrium in solution is mainly affected by substituent electronic effects as well as solvent properties [45, 46]. Slow proton exchange in the prototropic equilibrium allowed observation of separate signals in ^{1}H and ^{13}C NMR spectra which was used for qualitative and quantitative determination of each form in the tautomeric mixture. The integral of H5 NMR signal was the main indication and the parameter used for determination of pyridone tautomer ratio in DMSO-d_6. In the ^{1}H NMR spectra of compound **1** singlets at 5.69 and 6.09 ppm are unequivocally assigned to H5 of forms **1a** and **1b**, respectively. This methodology was applied to the NMR data of the other compounds, and results of tautomer percentages and K_T determination are given in Table 2. Additionally, quantitative ^{13}C NMR spectra with inverse-gated ^{1}H decoupling were recorded. Analysis of the obtained results indicated that a good agreement of the tautomer determination existed for the methyl group proton at C4 and C2–C6 carbon atoms of the pyridone ring (example given for compound **1**; Fig. S1). Results of density functional theory (DFT) calculations of ^{1}H and ^{13}C NMR chemical shifts (performed by GIAO/WP04/aug-cc-pVDZ model and PCM-type calculation to include DMSO solvation) are given in Tables S2 and S3. The analysis of the ^{1}H–^{13}C correlated spectra provided precise proton and carbon signal assignments. Examples are given for compound **15**: HMBC in Fig. S2, and HSQC in Fig. S3. Connectivity found in the HMBC spectra helped to distinguish the quaternary carbons of the pyridone core.

Results from Table 2 indicate the complex influence of electronic substituent effects on the tautomeric equilibria. Linear correlations of the negative logarithm value of the equilibrium constant, pK_T, with Hammett substituent constant, $\sigma_{m/p}$ [47], was found for electron-acceptor substituted compounds (Fig. S4 and Table S4). The slopes of correlation lines pK_T versus $\sigma_{m/p}$ are negative, and the proportionality constants ρ indicate significant sensitivity of pK_T to substituent effects. The negative sign means reverse behavior, i.e., the contribution of tautomer **b** in the equilibrium increases, although the electron-withdrawing ability of the substituents, measured by σ, increases. A non-linear relation of pK_T versus $\sigma_{m/p}$, which includes fluoro-substituted pyridone owing to its significant electron-donating character [47], was found for electron-donor

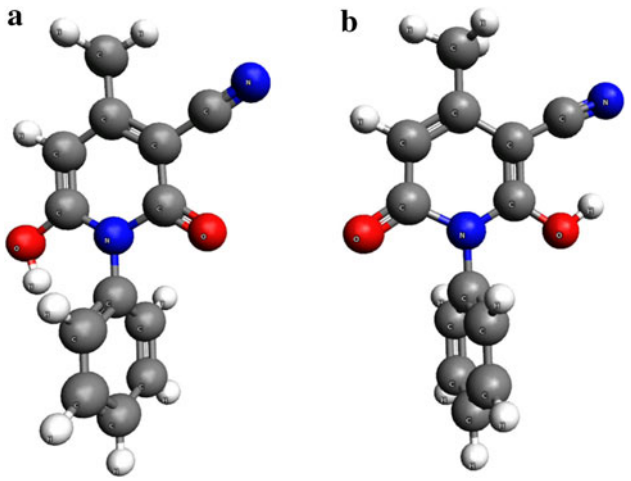


Fig. 1 Optimized geometries of tautomers **1a** and **1b**

substituted compounds (Fig. S4). Transmission of the resonance substituent effect is significantly affected by the non-planarity of the molecule (Table S5; angles θ_a and θ_b), thereby influencing the π-electron delocalization and the state of tautomeric equilibrium. Moreover, contributions of the solvent effects (DMSO) could not be neglected: dipolarity, polarizability, and solute/solvent hydrogen bonding interaction—hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) interaction—significantly contribute to the tautomer stability. Generally, it could be observed that solvent HBA effect is more pronounced for compound **6** such that tautomer **a** predominates (Table 2) owing to the presence of a proton-donating site, i.e., OH group. As the contribution of solvent HBA effect decreases, owing to decreasing substituent proton-donating capabilities (compounds **2**, **1**, **10**, **15**, and **3**, respectively; Fig. S4) K_T increases, i.e., contribution of tautomer **b** increases.

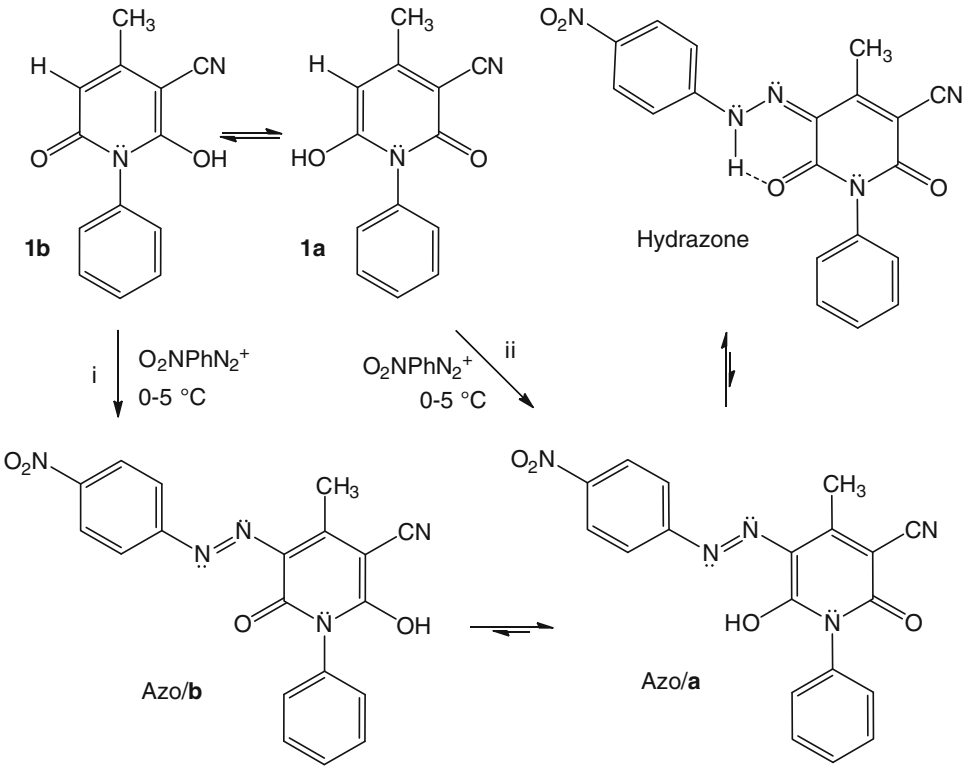
Also, we carried out ab initio studies to calculate energies of both tautomers. The obtained results in the gas phase indicate higher stability of tautomer **b** (0.5–11.4 kJ/mol) for all compounds owing to the existence of an intramolecular hydrogen bond between hydroxy and cyano groups. On the other hand, calculations of the solvation free energy have shown that tautomers **a** are better solvated in DMSO (difference in solvation free energy between tautomer **a** and **b** is from 0.1 to 8.9 kJ/mol), thus indicating a higher stability of form **a** in solution. Detailed experimental and theoretical investigation on the solvent- and temperature-dependent pyridone tautomeric equilibrium and tautomerization mechanism is a matter of current study. In Fig. 1 the optimized geometry of tautomers **1a** and **1b**, obtained by the use of B3LYP method with 6-311G(d,p) basis set, is given. Also, some elements of optimized geometries are given in Table S5.

The determination of thermodynamic parameters for the keto–enol equilibrium of **1** in DMSO-d_6 indicated the endothermic nature of this process [48], which is in accordance with the low temperature influence on the equilibrium shift observed in the NMR spectra (Fig. S5). The NMR spectra of compound **1** were recorded at 343 K (Fig. S5) to confirm thermally induced tautomerization, i.e., slow proton exchange in prototropic equilibrium of compound **1**. The prototropic interconversion could be accomplished via [1,5]- [49] or less probably [1,7]-hydrogen transfer, as well as by intermolecular double proton transfer, prototropic interconversion with cyclic associate participation [50], supported by the high tendency of pyridone to dimerize (self-association) [51].

The synthesized pyridones showed an interesting feature (presented in case of pyridone **1**): its diazotization (Scheme 2) produced azo derivatives which are easily rearranged to more stable hydrazone form [48].

Spectral assignment of (*Z*)-6-hydroxy-4-methyl-5-[2-(4-nitrophenyl)hydrazono]-2,6-dioxo-1-phenyl-1,2,5,6-tetrahydro-3-carbonitriles is given in the ^{1}H NMR spectrum of unpurified, as well as purified product (Figs. S6 and S7, respectively). Additionally, the theoretical calculations showed that the hydrazone form is 62.8 kJ/mol more stable than azo/**b** form mainly because of the formation of an intramolecular hydrogen bond (Scheme 2). On the other hand, calculations have shown that azo/**a** tautomer is not a minimum on the potential energy surface. All B3LYP/6-311++G(d,p) optimizations, which started from azo/**a** geometry, optimized to much more stable hydrazone geometry. Theoretical calculations and NMR results clearly indicate that if both tautomers (azo/**a** and azo/**b**; Scheme 2) are obtained by diazotization of pyridone **1** subsequent hydrogen rearrangements drive the equilibrium to the more stable hydrazone form. Diazotization of form **1b** could take place either following path i and consecutive tautomerization azo/**b** to azo/**a** or by prototropic equilibrium shifts to form **1a** followed by diazotization (path ii) (Scheme 2). Reactivity of the diazonium salt depends on the substituent groups that are present on the starting pyridone. From the kinetic point of view electrophilic attack at C5 by *para*-nitrophenyldiazonium ion significantly depends on charge density at this carbon. DFT calculation showed higher negative charges at C5 for tautomer **a** in all compounds (Tables S2 and S3), and thus, it could be supposed that there is a higher probability that reaction takes place at C5 of form **a**. Moreover, the results of geometry optimization of pyridone showed that the hydroxyl group at C6 and the pyridone ring are co-planar; thus, the higher extent of overlapping (n,π-conjugation) of oxygen lone pairs (p-orbitals) and π-electrons of the pyridone ring contributes to an increased electron density at C5 carbon. It is expected that the close vicinity of the electron-donating hydroxyl group in form **a** at C6 could participate in a stabilization of the activated complex, and more

Scheme 2



favorable reaction pathway ii could be operative in that way. Studies of solvent and substituent intramolecular charge transfer properties of pyridones and dyes, using UV and time-dependent density functional theory (TD-DFT) methods, will be the focus of forthcoming work. Generally speaking, the dye synthesis gave a product containing unreacted pyridone form **b** and azo dye product. The pure pyridone azo dye absorbed at a higher wavelength (batochromic shift; $\lambda_{max} = 430$ nm) owing to larger mobility of electronic densities (extended π-resonance) through the overall π-electronic systems. The obtained dyes are red, whereas the starting pyridone is white-yellowish. The high commercial importance of such dyes as coloring materials warrants intensive dye synthesis and further study of azo–hydrazone tautomerism study, as well as their solvatochromic and substituent-dependent properties.

In summary, this simple, convenient, and rapid one-pot microwave procedure, which gives the title tautomeric pyridones in good yield with high purity, can be useful in the preparation of dyes and pigments as well as pharmaceutically important compounds.

Experimental

All commercially available chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA). 2-Cyano-*N*-(substituted phenyl)ethanamides were synthesized according to literature methods [39–41]. All NMR spectral measurements were performed on a Bruker Avance III 500 spectrometer (500.26 MHz for ^{1}H, 125.80 MHz for ^{13}C) equipped with broadband 5 mm probe (BBO). The spectra were recorded at room temperature in deuterated dimethyl sulfoxide (DMSO-d_6). The chemical shifts were expressed in ppm values referenced to $\delta_H = 2.5$ and $\delta_C = 39.5$ ppm in ^{1}H and ^{13}C NMR spectra, respectively. Coupling constants J were expressed in Hz. ^{1}H NMR spectra of compound **1** were recorded at 343 K. 2D COSY, HMBC, and HSQC spectra were also recorded on a Bruker Avance III 500 spectrometer. Standard pulse sequences were used for 2D spectra. COSY spectra were recorded at spectral widths of 5 kHz in both $F2$ and $F1$ domains; 1K × 512 data points were acquired with 32 scans per increment and relaxation delays of 2.0 s. Data processing was performed on a 1K × 1K data matrix. Inverse-detected 2D heteronuclear correlated spectra were measured over 512 complex points in $F2$ and 256 increments in $F1$, collecting 128 (HSQC) or 256 (HMBC) scans per increment with relaxation delays of 1.0 s. The HMBC experiments were optimized for a coupling of 8 Hz. Fourier transform was done on a 512 × 512 data matrix. $\pi/2$-shifted sine squared window functions were used along $F1$ and $F2$ axes for all 2D spectra. UV data were obtained using a Shimadzu 1,700 UV–Vis spectrophotometer in ethanol as solvent at

5×10^{-5} mol dm^{-3}. Fourier transform infrared (FT-IR) spectra were obtained using an FT-IR BOMEM MB 100 in the form of KBr pellets. Elemental analysis (C, H, N, and O) was performed using a VARIO EL III elemental analyzer, and F, Cl, Br, and I content was calculated by subtraction; results agreed favorably with calculated values. The mass spectra were obtained on FinniganMAT 8230 (EI, 70 eV) and on Agilent technologies 6210 TOF LC/MS (high resolution mass spectrometry, HRMS) instruments (LC: series 1200). Microwave synthesis was performed in a Milestone MycroSYNTH reactor.

General procedure for pyridone synthesis under microwave irradiation

A mixture of ethyl acetoacetate (4.9 mmol), 2-cyano-*N*-(substituted phenyl)ethanamides (1.25 mmol), and freshly powdered potassium hydroxide (2.5 mmol) was placed in a glass vial, equipped with condenser, and irradiated with stirring using the following method: ramp time 1 min at 150 W and hold time 10 min at 150 W. The obtained product was suspended in hot water, acidified with diluted HCl, filtrated, and washed with water and chloroform.

General procedure for pyridone synthesis using conventional method

A mixture of ethyl acetoacetate (30.0 mmol), 2-cyano-*N*-(substituted phenyl)ethanamides (12.0 mmol), and freshly powdered potassium hydroxide (20.0 mmol) was placed in a three-necked flask, equipped with condenser, thermometer, and magnetic stirrer, and heated for 3 h under reflux. The obtained product was suspended in hot water, acidified with diluted HCl, filtrated, and washed with water and chloroform.

*6-Hydroxy-4-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonitrile (**1a**, $C_{13}H_{10}N_2O_2$) and 2-hydroxy-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbonitrile* (**1b**, $C_{13}H_{10}N_2O_2$)
White-yellowish crystalline solid; yield 78 %; m.p.: 281–283 °C (Ref. [52] 280–283 °C).

6-Hydroxy-4-methyl-1-(4-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**2a**, $C_{14}H_{12}N_2O_2$) and *2-hydroxy-4-methyl-1-(4-methylphenyl)-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**2b**, $C_{14}H_{12}N_2O_2$)
White-yellowish crystalline solid; yield 72 %; m.p.: 284–285 °C; HRMS: *m/z* (MH^+) calcd for $C_{14}H_{13}N_2O_2$ 241.0996, found 241.0972; IR (KBr): $\bar{\nu}$ = 514, 655, 816, 1,036, 1,104, 1,131, 1,181, 1,232, 1,415, 1,538, 1,664 (C=O), 2,216 (C≡N), 2,507, 2,608, 2,932, 3,078, 3,419 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 326 (16,420) nm (mol^{-1} dm^3 cm^{-1}).

2a: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.27 (s, 3H, 4-CH_3), 2.35 (s, 3H, 4′-CH_3), 5.69 (s, 1H, 5-H), 7.07 (AA′XX′, J = 8.2 Hz, 2H, $C_6H_4CH_3$), 7.27 (AA′XX′, J = 8.6 Hz, 2H, $C_6H_4CH_3$), 12.60 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.9 (4-CH_3), 21.0 (4′-CH_3), 88.6 (C3), 92.7 (C5), 117.8 (C≡N), 128.4 (C2′, C6′), 129.7 (C3′, C5′), 133.0 (C1′), 138.0 (C4′), 159.4 (C4), 161.1 (C2), 162.5 (C6) ppm.

2b: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.90 (s, 3H, 4-CH_3), 2.36 (s, 3H, 4′-CH_3), 6.08 (s, 1H, 5-H), 7.14 (AA′XX′, J = 8.4 Hz, 2H, $C_6H_4CH_3$), 7.31 (AA′XX′, J = 8.4 Hz, 2H, $C_6H_4CH_3$), 12.60 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.0 (4′-CH_3), 21.9 (4-CH_3), 83.6 (C3), 99.0 (C5), 115.5 (C≡N), 128.3 (C2′, C6′), 130.2 (C3′, C5′), 135.2 (C1′), 138.6 (C4′), 153.3 (C4), 161.2 (C6), 171.9 (C2) ppm.

6-Hydroxy-1-(4-methoxyphenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**3a**, $C_{14}H_{12}N_2O_3$) and *2-hydroxy-1-(4-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**3b**, $C_{14}H_{12}N_2O_3$)
Yellowish crystalline solid; yield 60 %; m.p.: 270–273 °C; HRMS: *m/z* (MH^+) calcd for $C_{14}H_{13}N_2O_3$ 255.0751, found 255.0762; IR (KBr): $\bar{\nu}$ = 551, 633, 770, 825, 1,036, 1,172, 1,255, 1,302, 1,410, 1,512, 1,665 (C=O), 2,218 (C≡N), 2,514, 2,605, 2,835, 2,972, 3,074, 3,422 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 323 (18,460) nm (mol^{-1} dm^3 cm^{-1}).

3a: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.28 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 5.69 (s, 1H, 5-H), 7.00 (AA′XX′, J = 7.2 Hz, 2H, $C_6H_4OCH_3$), 7.12 (AA′XX′, J = 7.2 Hz, 2H, $C_6H_4OCH_3$), 12.73 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.0 (CH_3), 55.5 (OCH_3), 89.0 (C3), 92.6 (C5), 114.4 (C3′, C5′), 1,17.8 (C≡N), 128.0 (C1′), 129.6 (C2′, C6′), 159.3 (C4), 159.4 (C4′), 161.2 (C2), 162.7 (C6) ppm.

3b: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.91 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.07 (s, 1H, 5-H), 7.03 (AA′XX′, J = 7.4 Hz, 2H, $C_6H_4OCH_3$), 7.18 (AA′XX′, J = 7.4 Hz, 2H, $C_6H_4OCH_3$), 12.73 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.0 (CH_3), 55.6 (OCH_3), 83.6 (C3), 99.0 (C5), 114.8 (C3′, C5′), 115.6 (C≡N), 129.7 (C2′, C6′), 130.3 (C1′), 153.6 (C4), 159.5 (C4′), 161.5 (C6), 171.9 (C2) ppm.

6-Hydroxy-4-methyl-1-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**4a**, $C_{13}H_9N_3O_4$) and *2-hydroxy-4-methyl-1-(4-nitrophenyl)-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**4b**, $C_{13}H_9N_3O_4$)
Yellow crystalline solid; yield 73 %; m.p.: 238–242 °C; HRMS: *m/z* (MH^+) calcd for $C_{13}H_{10}N_3O_4$ 272.0691, found 272.0666; IR (KBr): $\bar{\nu}$ = 639, 751, 856, 1,112, 1,346, 1,411, 1,514, 1,575, 1,654 (C=O), 1,718, 2,221 (C≡N), 2,501, 2,594, 3,085, 3,308, 3,426 (O–H) cm^{-1}; UV–Vis

(ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 335 (15,760) nm (mol^{-1} dm^3 cm^{-1}).

4a: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.28 (s, 3H, CH_3), 5.69 (s, 1H, 5-H), 7.65 (AA′XX′, J = 10 Hz, 2H, $C_6H_4NO_2$), 8.32 (AA′XX′, J = 10 Hz, 2H, $C_6H_4NO_2$), 12.10 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.9 (CH_3), 88.1 (C3), 95.9 (C5), 118.0 (C≡N), 124.1 (C3′, C5′), 130.3 (C2′, C6′), 141.0 (C4′), 146.3 (C1′), 159.0 (C4), 160.9 (C2), 161.3 (C6) ppm.

4b: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.93 (s, 3H, CH_3), 6.13 (s, 1H, 5-H), 7.76 (AA′XX′, J = 10 Hz, 2H, $C_6H_4NO_2$), 8.36 (AA′XX′, J = 10 Hz, 2H, $C_6H_4NO_2$), 12.10 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.5 (CH_3), 83.4 (C3), 99.4 (C5), 114.9 (C≡N), 124.7 (C3′, C5′), 130.4 (C2′, C6′), 143.2 (C4′), 147.6 (C1′), 152.1 (C4), 162.0 (C6), 172.1 (C2) ppm.

1-(4-Acetylphenyl)-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**5a**, $C_{15}H_{12}N_2O_3$) and *1-(4-acetylphenyl)-2-hydroxy-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**5b**, $C_{15}H_{12}N_2O_3$)

Brownish crystalline solid; yield 42 %; m.p.: 227–230 °C; HRMS: *m/z* (MH$^+$) calcd for $C_{15}H_{13}N_2O_3$ 269.0927, found 269.0921; IR (KBr): $\bar{\nu}$ = 643, 822, 958, 1,010, 1,267, 1,450, 1,531, 1,666, 1,687 (C=O), 2,219 (C≡N), 2,489, 2,593, 3,071, 3,433 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 331 (24,040) nm (mol^{-1} dm^3 cm^{-1}).

5a: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 2.62 (s, 3H, C(O)CH_3), 5.66 (s, 1H, 5-H), 7.38 (AA′XX′, J = 8.5 Hz, 2H, $C_6H_4C(O)CH_3$), 8.03 (AA′XX′, J = 8.5 Hz, 2H, $C_6H_4C(O)CH_3$) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.8 (CH_3), 26.9 (C(O)*C*H$_3$), 87.3 (C3), 93.2 (C5), 117.8 (C≡N), 128.8 (C3′, C5′), 129.0 (C2′, C6′), 136.5 (C4′), 139.9 (C1′), 158.9 (C4), 160.7 (C2), 161.0 (C6), 197.4 (*C*(O)CH$_3$) ppm.

5b: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.92 (s, 3H, CH_3), 2.63 (s, 3H, C(O)CH_3), 6.13 (s, 1H, 5-H), 7.47 (AA′XX′, J = 8.5 Hz, 2H, $C_6H_4C(O)CH_3$), 8.08 (AA′XX′, J = 8.5 Hz, 2H, $C_6H_4C(O)CH_3$) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.6 (CH_3), 26.9 (C(O)*C*H$_3$), 83.4 (C3), 99.1 (C5), 115.1 (C≡N), 129.0 (C2′, C6′), 129.3 (C3′, C5′), 137.0 (C4′), 141.5 (C1′), 152.3 (C4), 162.0 (C6), 171.9 (C2), 197.4 (*C*(O)CH$_3$) ppm.

6-Hydroxy-1-(4-hydroxyphenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**6a**, $C_{13}H_{10}N_2O_3$)

Gray-brownish crystalline solid; yield 50 %; m.p.: 286–288 °C; HRMS: *m/z* (MH$^-$) calcd for $C_{13}H_9N_2O_3$ 241.0612, found 241.0618; IR (KBr): $\bar{\nu}$ = 543, 633, 768, 830, 1,030, 1,127, 1,168, 1,281, 1,407, 1,442, 1,511, 1,528, 1,665 (C=O), 2,220 (C≡N), 2,513, 2,612, 3,060, 3,519 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 331 (23,080) nm (mol^{-1} dm^3 cm^{-1}); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 5.69 (s, 1H, 5-H), 6.82 (AA′XX′, J = 8.6 Hz, 2H, C_6H_4OH), 6.98 (AA′XX′, J = 8.8 Hz, 2H, C_6H_4OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.0 (CH_3), 89.1 (C3), 92.5 (C5), 115.7 (C3′, C5′), 117.8 (C≡N), 126.4 (C1′), 129.5 (C2′, C6′), 157.6 (C4′), 159.5 (C4), 161.3 (C2), 161.4 (C6) ppm.

6-Hydroxy-1-(4-iodophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**7a**, $C_{13}H_9IN_2O_2$) and *2-hydroxy-1-(4-iodophenyl)-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**7b**, $C_{13}H_9IN_2O_2$)

Grayish crystalline solid; yield 57 %; m.p.: 288–289 °C; HRMS: *m/z* (MH$^+$) calcd for $C_{13}H_{10}IN_2O_2$ 352.9806, found 352.9782; IR (KBr): $\bar{\nu}$ = 512, 590, 637, 760, 811, 1,009, 1,231, 1,269, 1,416, 1,524, 1,665 (C=O), 2,480, 2,223 (C≡N), 2,664, 3,091, 3,426 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 328 (6,720) nm (mol^{-1} dm^3 cm^{-1}).

7a: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 5.66 (s, 1H, 5-H), 7.05 (AA′XX′, J = 10 Hz, 2H, C_6H_4I), 7.82 (AA′XX′, J = 10 Hz, 2H, C_6H_4I), 8.65 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.8 (CH_3), 88.0 (C3), 92.8 (C5), 94.6 (C4′), 117.5 (C≡N), 130.8 (C2′, C6′), 135.3 (C1′), 137.8 (C3′, C5′), 159.2 (C4), 160.6 (C2), 160.8 (C6) ppm.

7b: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.91 (s, 3H, CH_3), 6.08 (s, 1H, 5-H), 7.11 (AA′XX′, J = 10 Hz, 2H, C_6H_4I), 7.87 (AA′XX′, J = 10 Hz, 2H, C_6H_4I), 8.65 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.7 (CH_3), 83.4 (C3), 99.0 (C5), 95.4 (C4′), 115.1 (C≡N), 130.7 (C2′, C6′), 137.3 (C1′), 138.3 (C3′, C5′), 152.5 (C4), 162.1 (C6), 171.8 (C2) ppm.

1-(4-Chlorophenyl)-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**8a**, $C_{13}H_9ClN_2O_2$) and *1-(4-chlorophenyl)-2-hydroxy-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**8b**, $C_{13}H_9ClN_2O_2$)

White crystalline solid; yield 64 %; m.p.: 285–287 °C; HRMS: *m/z* (MH$^+$) calcd for $C_{13}H_{10}ClN_2O_2$ 261.0450, found 261.0425; IR (KBr): $\bar{\nu}$ = 515, 638, 738, 817, 1,021, 1,094, 1,232, 1,312, 1,416, 1,492, 1,536, 1,665 (C=O), 2,218 (C≡N), 2,507, 2,612, 2,928, 3,074, 3,428 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 328 (24,040) nm (mol^{-1} dm^3 cm^{-1}).

8a: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 5.66 (s, 1H, 5-H), 7.28 (AA′XX′, J = 8.6 Hz, 2H, C_6H_4Cl), 7.53 (AA′XX′, J = 8.6 Hz, 2H, C_6H_4Cl) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.0 (CH_3), 88.2 (C3), 93.1 (C5), 117.9 (C≡N), 129.3 (C3′, C5′), 130.7 (C2′, C6′), 133.2 (C4′), 134.7 (C1′), 159.5 (C4), 161.0 (C2), 161.2 (C6) ppm.

8b: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.92 (s, 3H, CH_3), 6.10 (s, 1H, 5-H), 7.36 (AA′XX′, J = 8.8 Hz, 2H,

C_6H_4Cl), 7.55 (AA′XX′, $J = 8.4$ Hz, 2H, C_6H_4Cl) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.9$ (CH_3), 83.5 (C3), 99.3 (C5), 115.4 (C≡N), 129.8 (C3′, C5′), 130.7 (C2′, C6′), 133.8 (C4′), 136.6 (C1′), 152.9 (C4), 162.5 (C6), 172.1 (C2) ppm.

1-(4-Bromophenyl)-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**9a**, $C_{13}H_9BrN_2O_2$) and *1-(4-bromophenyl)-2-hydroxy-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**9b**, $C_{13}H_9BrN_2O_2$)

White crystalline solid; yield 64 %; m.p.: 276–278 °C; HRMS: *m/z* (MH^+) calcd for $C_{13}H_{10}BrN_2O_2$ 302.9750, found 302.9762; IR (KBr): $\bar{\nu} = 513$, 596, 633, 770, 812, 1017, 1,133, 1,246, 1,416, 1,488, 1,545, 1,663 (C=O), 2,219 (C≡N), 2,616, 3,419 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 323 (15,360) nm (mol^{-1} dm^3 cm^{-1}).

9a: ^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.26$ (s, 3H, CH_3), 5.66 (s, 1H, 5-H), 7.24 (AA′XX′, $J = 8.4$ Hz, 2H, C_6H_4Br), 7.66 (AA′XX′, $J = 8.4$ Hz, 2H, C_6H_4Br), 12.80 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.0$ (CH_3), 88.0 (C3), 93.1 (C5), 117.9 (C≡N), 122.4 (C4′), 131.1 (C3′, C5′), 132.7 (C2′, C6′), 135.2 (C1′), 159.4 (C4), 160.9 (C2), 162.4 (C6) ppm.

9b: ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.92$ (s, 3H, CH_3), 6.09 (s, 1H, 5-H), 7.28 (AA′XX′, $J = 8.4$ Hz, 2H, C_6H_4Br), 7.72 (AA′XX′, $J = 8.6$ Hz, 2H, C_6H_4Br), 12.80 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.9$ (CH_3), 83.6 (C3), 99.3 (C5), 115.4 (C≡N), 121.7 (C4′), 131.1 (C3′, C5′), 132.2 (C2′, C6′), 137.1 (C1′), 152.9 (C4), 161.2 (C6), 172.1 (C2) ppm.

1-(4-Fluorophenyl)-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**10a**, $C_{13}H_9FN_2O_2$) and *1-(4-fluorophenyl)-2-hydroxy-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**10b**, $C_{13}H_9FN_2O_2$)

White-brownish crystalline solid; yield 74 %; m.p.: 284–285 °C; HRMS: *m/z* (MH^+) calcd. for $C_{13}H_{10}FN_2O_2$ 245.0746, found 245.0721; IR (KBr): $\bar{\nu} = 537$, 643, 655, 797, 832, 1,132, 1,156, 1,224, 1,380, 1,408, 1,509, 1,572, 1,637, 1,663 (C=O), 1,637, 2,221 (C≡N), 3,434 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 321 (17,980) nm (mol^{-1} dm^3 cm^{-1}).

10a: ^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.27$ (s, 3H, CH_3), 5.67 (1H, s, 5-H), 7.29 (t, $J = 5$ Hz, 4H, C_6H_4F), 12.70 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 20.8$ (CH_3), 87.8 (C3), 92.8 (C5), 115.7 (C3′), 116.2 (C5′), 117.6 (C≡N), 130.7 (C6′), 131.6 (C2′), 133.6 (C1′), 159.1 (C4), 160.6 (C2), 161.1 (C6), 162.8 (C4′) ppm.

10b: ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.92$ (s, 3H, CH_3), 6.09 (s, 1H, 5-H), 7.35 (t, $J = 5$ Hz, 4H, C_6H_4F), 12.70 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.7$ (CH_3), 83.4 (C3), 99.0 (C5), 115.0 (C≡N), 115.9 (C3′), 116.4 (C5′), 130.5 (C2′), 130.6 (C6′), 133.7 (C1′), 152.9 (C4), 160.8 (C6), 162.3 (C4′), 171.7 (C2) ppm.

6-Hydroxy-4-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carbonitrile (**11b**, $C_{14}H_9F_3N_2O_2$)

Grayish crystalline solid; yield 66 %; m.p.: 315–317 °C; HRMS: *m/z* (MH^-) calcd for $C_{14}H_8F_3N_2O_2$ 293.0519, found 293.0543; IR (KBr): $\bar{\nu} = 570$, 626, 657, 706, 807, 1,071, 1,133, 1,249, 1,330, 1,405, 1,461, 1,570, 1,645 (C=O), 2,229 (C≡N), 2,610, 2,851, 3,077, 3,431 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 303 (7,940) nm (mol^{-1} dm^3 cm^{-1}); ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.92$ (s, 3H, CH_3), 6.18 (s, 1H, 5-H), 7.67 (d, $J = 7.6$ Hz, 6′-H), 7.76 (d, $J = 7.4$ Hz, 4′-H), 7.82-7.89 (m, 2H, 2′-H, 5′-H), 12.81 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.9$ (CH_3), 83.6 (C3), 99.5 (C5), 115.3 (C≡N), 126.1 (C4′), 126.7 (CF_3), 130.2 (C2′), 130.8 (C5′), 131.0 (C6′), 133.3 (C3′), 138.5 (C1′), 152.7 (C4), 162.5 (C6), 172.3 (C2) ppm.

1-(3-Chlorophenyl)-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**12a**, $C_{13}H_9ClN_2O_2$) and *1-(3-chlorophenyl)-2-hydroxy-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**12b**, $C_{13}H_9ClN_2O_2$)

Grayish crystalline solid; yield 59 %; m.p.: 275–278 °C; HRMS: *m/z* (MH^-) calcd for $C_{13}H_8ClN_2O_2$ 259.0255, found 259.0279; IR (KBr): $\bar{\nu} = 581$, 627, 690, 745, 789, 818, 1,078, 1,134, 1,297, 1,379, 1,406, 1,489, 1,546, 1,662 (C=O), 2,219 (C≡N), 2,594, 3,073, 3,445 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 323 (12,080) nm (mol^{-1} dm^3 cm^{-1}).

12a: ^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.28$ (s, 3H, CH_3), 5.67 (s, 1H, 5-H), 7.21–7.26 (m, 1H, 6′-H), 7.42 (t, $J = 2.2$ Hz, 1H, 4′-H), 7.50–7.54 (m, 1H, 2′-H), 7.55 (d, $J = 1.2$ Hz, 1H, 5′-H), 12.90 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.0$ (CH_3), 88.6 (C3), 93.2 (C5), 117.9 (C≡N), 127.7 (C6′), 128.7 (C4′), 130.7 (C5′), 130.8 (C2′), 133.3 (C3′), 137.2 (C1′), 159.4 (C4), 161.3 (C2), 162.4 (C6) ppm.

12b: ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.94$ (s, 3H, CH_3), 6.10 (s, 1H, 5-H), 7.28–7.34 (m, 1H, 6′-H), 7.49 (t, $J = 2.2$ Hz, 1H, 4′-H), 7.50–7.54 (m, 1H, 2′-H), 7.57 (d, $J = 1.2$ Hz, 1H, 5′-H), 12.90 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.8$ (CH_3), 83.6 (C3), 99.3 (C5), 115.3 (C≡N), 127.8 (C6′), 129.0 (C4′), 129.4 (C2′), 131.3 (C5′), 133.9 (C3′), 139.1 (C1′), 152.8 (C4), 161.0 (C6), 172.1 (C2) ppm.

1-(3-Bromophenyl)-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**13a**, $C_{13}H_9BrN_2O_2$) and *1-(3-bromophenyl)-2-hydroxy-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**13b**, $C_{13}H_9BrN_2O_2$)

Grayish crystalline solid; yield 52 %; m.p.: 278–280 °C; HRMS: *m/z* (MH^-) calcd for $C_{13}H_8BrN_2O_2$ 302.9750,

found 302.9775; IR (KBr): $\bar{\nu}$ = 676, 685, 730, 770, 786, 825, 1,036, 1,070, 1,134, 1,229, 1,246, 1,311, 1,408, 1,474, 1,545, 1,660 (C=O), 2,219 (C≡N), 2,593, 2,924 (CH_3), 3,066, 3,435 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 323 (9,480) nm (mol^{-1} dm^3 cm^{-1}).

13a: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.26 (s, 3H, CH_3), 5.65 (s, 1H, 5-H), 7.35 (d, J = 7.8 Hz, 1H, 6′-H), 7.46–7.51(m, 1H, 4′-H), 7.61–7.72 (m, 2H, 2′-H, 5′-H), 12.88 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.0 (CH_3), 87.6 (C3), 93.3 (C5), 117.9 (C≡N), 121.5 (C2′), 128.2 (C6′), 128.3 (C4′), 131.5 (C5′), 131.7 (C3′), 137.4 (C1′), 159.2 (C4), 161.1 (C2), 162.5 (C6) ppm.

13b: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.93 (s, 3H, CH_3), 6.10 (s, 1H, 5-H), 7.27 (d, J = 6.8 Hz, 1H, 6′-H), 7.40–7.45 (m, 1H, 4′-H), 7.52–7.60 (m, 2H, 2′-H, 5′-H), 12.88 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.8 (CH_3), 83.5 (C3), 99.3 (C5), 115.3 (C≡N), 122.0 (C2′), 128.1 (C6′), 128.6 (C4′), 131.0 (C5′), 132.2 (C3′), 139.2 (C1′), 152.8 (C4), 161.3 (C6), 172.1 (C2) ppm.

6-Hydroxy-1-(3-methoxyphenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**14a**, $C_{14}H_{12}N_2O_3$) and *2-hydroxy-1-(3-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**14b**, $C_{14}H_{12}N_2O_3$)

Gray crystalline solid; yield 47 %; m.p.: 250–252 °C; HRMS: *m/z* (MH^-) calcd for $C_{14}H_{11}N_2O_3$ 255.0751, found 255.0775; IR (KBr): $\bar{\nu}$ = 513, 636, 701, 768, 821, 1,050, 1,120, 1,289, 1,412, 1,491, 1,539, 1,609, 1,663 (C=O), 2,218 (C≡N), 3,072, 3,436 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 316 (10,580) nm (mol^{-1} dm^3 cm^{-1}).

14a: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.29 (s, 3H, 4-CH_3), 3.75 (s, 3H, 3′-OCH_3), 5.70 (s, 1H, 5-H), 6.79 (dd, J = 0.75 Hz, 7 Hz, 1H, 6′-H), 6.84 (t, J = 2.2 Hz, 1H, 2′-H), 7.00 (dd, J = 2 Hz, 6 Hz, 1H, 4′-H), 7.38 (t, J = 8.2 Hz, 1H, 5′-H), 12.70 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.8 (4-CH_3), 55.3 (3′-OCH_3), 88.9 (C3), 92.3 (C5), 114.1 (C2′), 114.2 (C4′), 117.4 (C≡N), 120.5 (C6′), 129.7 (C5′), 136.4 (C1′), 159.5 (C4), 159.8 (C3′), 160.8 (C2), 162.1 (C6) ppm.

14b: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.94 (s, 3H, 4-CH_3), 3.77 (s, 3H, 3′-OCH_3), 6.08 (s, 1H, 5-H), 6.82 (d, J = 1 Hz, 1H, 6′-H), 6.90 (t, J = 2.2 Hz, 1H, 2′-H), 7.03 (dd, J = 2 Hz, 6.5 Hz, 1H, 4′-H), 7.41 (t, J = 8.3 Hz, 1H, 5′-H), 12.70 (bs, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.5 (4-CH_3), 55.4 (C3′-OCH_3), 83.4 (C3), 98.8 (C5), 1,14.1 (C2′), 114.7 (C4′), 115.2 (C≡N), 120.4 (C6′), 130.2 (C5′), 138.6 (C1′), 152.9 (C4), 160.1 (C3′), 160.6 (C6), 171.7 (C2) ppm.

6-Hydroxy-4-methyl-1-(3-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**15a**, $C_{14}H_{12}N_2O_2$) *and 2-hydroxy-4-methyl-1-(3-methylphenyl)-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**15b**, $C_{14}H_{12}N_2O_2$)

Grayish crystalline solid; yield 54 %; m.p.: 284–285 °C (Ref. [53] 278–281 °C).

1-(3-Acetylphenyl)-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**16a**, $C_{15}H_{12}N_2O_3$) and *1-(3-acetylphenyl)-2-hydroxy-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile* (**16b**, $C_{15}H_{12}N_2O_3$)

Gray crystalline solid; yield 52 %; m.p.: 243–245 °C; HRMS: *m/z* ($M+CH_3COO–H_2O–H^-$) calcd for $C_{17}H_{11}N_2O_4$ 267.0751, found 267.0775; IR (KBr): $\bar{\nu}$ = 589, 635, 698, 757, 820, 1,037, 1,133, 1,239, 1,281, 1,412, 1,557, 1,662 (C=O), 2,216 (C≡N), 2,356, 2,598, 3,446 (O–H), 3,537 cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 324 (10,380) nm (mol^{-1} dm^3 cm^{-1}).

16a: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.29 (s, 3H, CH_3), 2.61 (s, 3H, C(O)CH_3), 5.70 (s, 1H, 5-H), 7.53 (d, J = 8 Hz, 1H, 6′-H), 7.64-7.62 (m, 1H, 2′-H), 7.89 (t, J = 2 Hz, 4′-H), 8.03 (t, J = 7.7 Hz, 5′-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.1 (CH_3), 27.1 (C(O)*C*H_3), 88.2 (C3), 93.2 (C5), 117.9 (C≡N), 128.4 (C2′), 128.8 (C4′), 130.2 (C6′), 133.5 (C5′), 136.3 (C1′), 138.4 (C3′), 159.6 (C4), 161.1 (C2), 162.6 (C6), 197.5 (*C*(O)CH_3) ppm.

16b: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.93 (s, 3H, CH_3), 2.59 (s, 3H, C(O)CH_3), 6.13 (s, 1H, 5-H), 7.58 (d, J = 8 Hz, 1H, 6′-H), 7.64–7.62 (m, 1H, 2′-H), 7.82 (t, J = 2 Hz, 4′-H), 8.03 (t, J = 7.7 Hz, 5′-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.0 (CH_3), 27.0 (C(O)*C*H_3), 83.7 (C3), 99.4 (C5), 115.4 (C≡N), 128.5 (C2′), 128.6 (C4′), 129.7 (C6′), 133.7 (C5′), 138.0 (C1′), 138.2 (C3′), 153.0 (C4), 161.4 (C6), 172.2 (C2), 197.5 (*C*(O)CH_3) ppm.

(Z)-4-Methyl-5-[2-(4-nitrophenyl)hydrazono]-2,6-dioxo-1-phenyl-1,2,5,6-tetrahydropyridine-3-carbonitrile (**17**, $C_{19}H_{13}N_5O_4$)

The azo dye was synthesized by the diazotization of pyridone **1** with 4-nitrophenyldiazonium chloride [54]. The obtained material was filtrated, washed with distilled water, and recrystallized from methanol and finally purified by flash chromatography. Dark red powder; yield 64 %; m.p.: >300 °C; IR (KBr): $\bar{\nu}$ = 586, 632, 689, 700, 739, 749, 771, 796, 847, 872, 952, 1,110, 1,152, 1,167, 1,214, 1,260, 1,339, 1,407, 1,423, 1,507, 1,644, 1,697 (C=O), 2,221 (C≡N), 2,852, 2,923, 3,082, 3,116, 3,444 (O–H) cm^{-1}; UV–Vis (ethanol, $c = 5 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 430 (24,560) nm (mol^{-1} dm^3 cm^{-1}); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.63 (s, 3H, 4-CH_3), 7.32-7.34

(m, 2H, 5′-H, 3′-H), 7.46–7.49 (m, 1H, 4′-H), 7.51–7.54 (m, 2H, 2′-H, 6′-H), 7.91 (AA′XX′, $J = 9.0$ Hz, 2H, C_6H_4–NO_2), 8.30 (AA′XX′, $J = 9.5$ Hz, 2H, C_6H_4–NO_2), 14.26 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 16.6$ (CH_3), 103.4 (C5), 114.7 (C3), 117.6 (C≡N), 125.5 (C_6H_4–NO_2), 125.9 (C4′), 128.8 (C_6H_4–NO_2), 128.8 (C3′, C5′), 129.0 (C2′, C6′), 133.8 (C1′), 144.4 (C_6H_4–NO_2), 146.5 (C_6H_4–NO_2), 159.6 (C2), 159.9 (C4), 160.2 (C6) ppm.

Ab initio theoretical calculation method

The geometry optimizations were carried out by the B3LYP method with the standard basis set 6-311G(d,p). Harmonic vibrational frequencies were evaluated at the same level to confirm the nature of the stationary points found (to confirm that optimized geometry corresponds to a local minimum that has only real frequencies), and to account for the zero point vibrational energy (ZPVE) correction. Global minima were found for every molecule considering pyridone tautomeric forms **a** and **b**, and rotational isomers of *meta*-substituted derivatives. Solvent (DMSO) was simulated with the standard polarized continuum model (PCM). Theoretical calculation of chemical shifts on optimized geometries can provide a good basis for the estimation of experimental data. Quantum chemical calculation of ^{1}H and ^{13}C NMR chemical shifts (method GIAO, WP04 functional and aug-cc-pVDZ basis set, and PCM for inclusion of solvation effect) were done. Tautomer electronic energies and atomic charges (ChelpG method) were calculated on B3LYP/6-311G(d,p) optimized geometries with the B3LYP/6-311++G(3df,3pd) method. All calculations were done with the Gaussian03 program package [55].

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