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1,6-Naphthyridin-7(6H)-ones: Synthesis and optical properties

Anissa Beghennou,^a Geoffrey Gontard,^a Héloïse Dossmann,^a Kévin Passador,^a Serge Thorimbert,^a Vincent Corcé*^a and Candice Botuha*^a

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Efficient synthesis of original 1,6-naphthyridin-7(6H)-ones and their optical properties are described. Powerful fluorescent properties including dual fluorescence, solvatochromism, acidochromism, large Stokes shifts and high quantum yields are evidenced, suitable for biological applications or as luminescent devices in materials science.

Introduction

Naphthyridines represent an important scaffold in medicinal chemistry.¹ A large variety of structures containing a naphthyridine core exhibits anti-viral,² anti-cancer³ or anti-Alzheimer's disease⁴ activities. In addition to these biological properties, certain naphthyridines display interesting optical features and have been used as fluorescent probes for thiols,⁵ guanosine monophosphate (GMP)⁶ and glucopyranoside detection⁷ but also as fluorescent organic nanoparticles⁸ or emitting materials.^{9,10} These structures have also been used as ligands for the formation of fluorescent complexes with aluminium,¹¹ boron^{12,13} and copper.¹⁴ Among all naphthyridine isomers, the 1,6-naphthyridines derivatives possess a wide range of pharmaceutical properties.¹⁵ More particularly, the 1,6-naphthyridin-4(6H)-one derivatives have attracted considerable efforts in the last decade. Recent researches introduced these structures as MET inhibitors¹⁶ or bearing antiviral properties (Fig. 1).^{17,18} In addition, Knochel and co-workers demonstrated that 1,6-naphthyridines are highly fluorescent structures with high quantum yield and tunable emission.¹⁹ Fluorescent probes containing 1,6-naphthyridine scaffolds such as benzo-fused 1,6-naphthyridines and chromeno-fused 1,6-naphthyridines have also proved to have highly optical properties (Fig. 1).^{20,21} Starting from these observations, we were interested to investigate optical properties of 1,6-naphthyridin-7-one analogues. Surprisingly, little work has been described concerning these specific structures.²² Recent patents mention preparation of 1,6-naphthyridin-7-ones for use as Mat2A inhibitors for oncology applications²³

but also as matrix metalloproteinase inhibitors,²⁴ kinase inhibitors²⁵ and modulators of TGR5 (Fig. 1).²⁶ However, no examples of optical properties were reported in the literature and few general synthetic routes are available. The lack of general methods to obtain these structures led us to develop a short reaction procedure in order to gain insight their optical properties. Herein, we report a convenient synthesis of 8-substituted 1,6-naphthyridin-7(6H)-ones and theoretical studies and photophysical properties of 1,6-naphthyridin-7(6H)-ones are described to help to rationalize experimental results and to get deep insight of their ability to be a powerful new class of organic fluorescent small molecules.

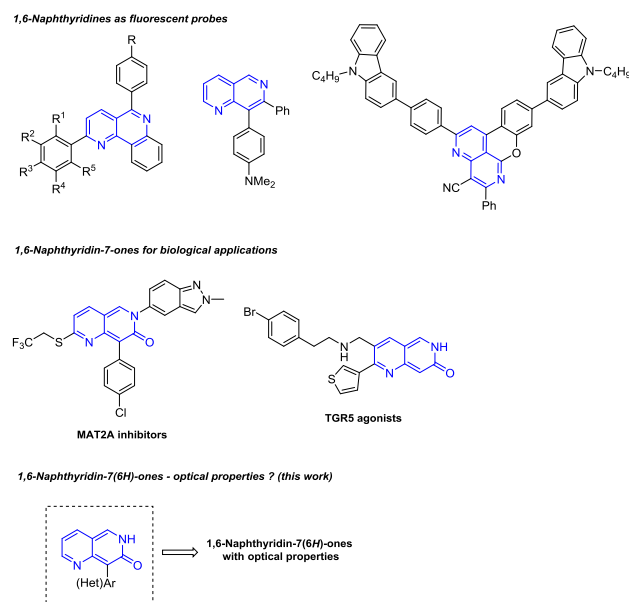
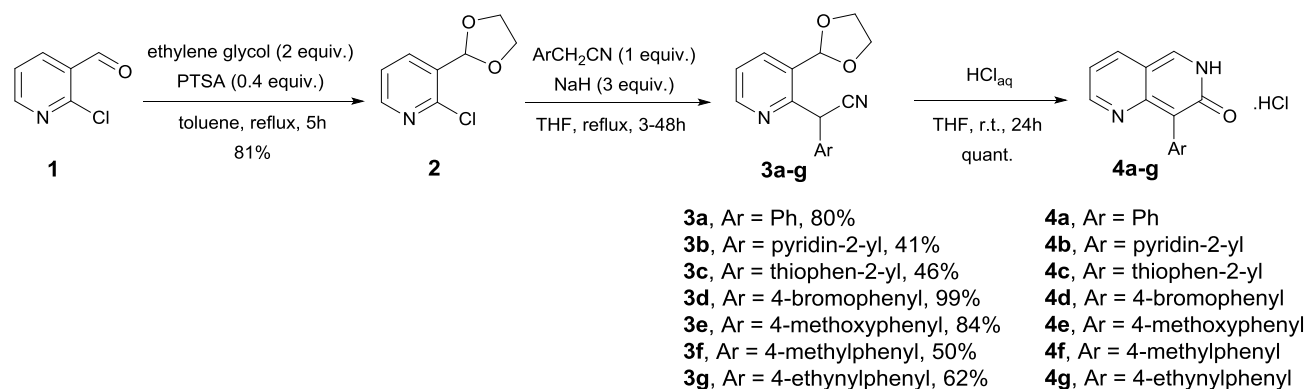


Fig. 1. Examples of 1,6-naphthyridines as fluorescent probes (top) and of 1,6-naphthyridinones for biological applications (middle). 1,6-naphthyridinones described in this work (bottom).

^a Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, IPCM, F-75005 Paris, France

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ARTICLE



Scheme 1 Synthesis of 8-substituted 1,6-naphthyridin-7(6H)-ones 4.

Results and discussion

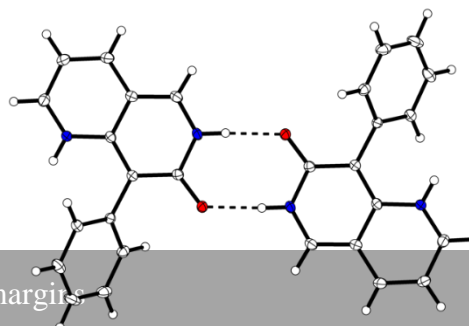
The naphthyridine core was synthesized in 4 steps from commercially available 2-chloro-3-formylpyridine **1** (Scheme 1). The reaction of chloropyridine **1** with ethylene glycol afforded the acetal **2** which subsequently reacted with a panel of 2-arylated acetonitriles **3** in the presence of a slight excess of sodium hydride in refluxing THF. Under these conditions, the nucleophilic aromatic substitution took smoothly place and the corresponding adducts **3** were obtained in moderate to excellent yields. A panel of different substituents at the 4-position of the (hetero)aryls with various electronic properties notably electron-donating groups (Me, OMe) and electron withdrawing groups (thiophenyl and 2-pyridyl) is well tolerated. Halogen groups such as bromine allow the possibility to further post-functionalize the naphthyridinone by Pd-catalyzed cross-coupling reactions. Finally, ethynyl group was employed to run a possible click alkyne-azide cycloaddition for further ligation to a biomolecule. By contrast, phenylsulfonyl- imidazolyl- 4-trifluoromethylphenyl- and 4-nitrophenylacetonitriles failed to react under the reaction conditions, even after 48h of reaction. We assumed that the corresponding sodium anions generated after deprotonation with sodium hydride showed a decreased in their reactivity due to the high electron-withdrawing character of the substituents. This observation is fully in line with the work of Arseniadys and co-workers on the reactivity of nitrile-stabilized anions.²⁷ Interestingly, when 4-(dimethylamino)phenyl acetonitrile was employed as reactant, an unexpected product was obtained. Rather than getting the nucleophilic aromatic substitution compound, the self-condensation adduct 2,3-bis(4-

(dimethylamino)phenyl)acrylonitrile was obtained as the main product.

Finally, an acidic treatment of compounds **3** in a mixture of THF and aqueous hydrochloric acid led to the removal of the acetal and assisted the cyclization step, furnishing the expected 8-substituted naphthyridin-7(6H)-ones **4** as their hydrochloride salts in a quantitative yield. As their related compounds containing a 2-hydroxypyridine system (such as isoquinolinones, 2,6- and 2,7-naphthyridin-3-ones), 1,6-naphthyridin-7(6H)-ones **4** may exist under lactim-enol and lactam-keto tautomeric forms in the ground state. In solid-state, the lactam-keto tautomer is predominant as shown by X-ray analysis performed on crystals of **4a** (Fig. 2).

With this set of naphthyridinones in hand, we first recorded the absorption and emission spectra in a PBS solution due to the hydrochloride salts. It is noteworthy that all the strategies employed to get the free bases of the corresponding hydrochloride salts and isolate the neutral naphthyridinones failed (See general procedure of compounds **4**). Nevertheless, for optical measurement in PBS, the neutral form is assumed to be the major form (according to the pKa value of the pyridine ring) and its absorption and fluorescence properties have been analyzed. PBS solutions of naphthyridinones remain stable for months without any decrease in the optical properties.

Naphthyridinones **4a** and **4c-g** present a maximum of absorption centred around 415 nm (see SI for spectra) which is in accordance with absorption maxima recorded for 2,6- and



2,7-naphthyridin-3-ones assigned to $\pi \rightarrow \pi^*$ transition of the lactam form.²⁸ Interestingly, the analogue **4b** bearing a pyridyl substituent in the 8-position exhibits two absorption bands centred at 323 nm and 420 nm.

Fig. 2. X-Ray crystallographic structure of **4a**. Hydrogen bonding association are represented. Chlorine atoms have been removed for the sake of clarity.

This particular behaviour could be assigned to the equilibrium between the lactam and lactim forms, induced by a hydrogen bond between the lactim function with the nitrogen of the pyridyl substituent that stabilizes the species. This phenomenon has already been observed with the 4-(pyridine-2-yl)isoquinolin-3-ol.²⁹ In addition, after an excitation at 420 nm corresponding to the lactam-form, all naphthyridinones **4** present a single fluorescent emission from 500 to 540 nm (Fig. S1-S7). The presence of a pyridine ring in the naphthyridinone structure led us to investigate the influence of pH on optical properties. Absorption spectra of **4a** in water were thus recorded in acidic conditions. After addition of increasing amounts of concentrated aqueous hydrochloric acid solution, the absorption maximum at 416 nm decreased and a new band appeared at 458 nm along with a new maximum absorption band at 303 nm which is compatible with the presence of two new species, certainly lactam and lactim protonated forms of **4a** respectively (Fig. 3). The emission intensity of **4a** upon excitation at 415 nm was then determined as a function of pH for values comprised between 2 and 8. A maximum of fluorescence intensity centred at 537 nm is observed for pH > 5 corresponding to the neutral form of the naphthyridinone **4a** (Fig. 3, inset). At low pH, where the protonated form of lactam-**4a** should be predominant, emission is completely quenched.

This feature is of interest notably for the development of pH-sensitive fluorescent probes. Naphthyridinones and isoquinolinones are known to exhibit fluorescent features along with a strong solvatochromism.^{19,29} Interestingly, only one absorption band is observed at 416 nm in water and PBS (Table 1). To deeper explore these properties, absorption spectra of **4a** were recorded in various solvents as reported in Table 1 (see SI for spectra). In all organic solvents, naphthyridinone **4a** shows an intense absorption band around 350 nm ($\epsilon = 3785$ to $5220 \text{ M}^{-1}\text{cm}^{-1}$, Table 1) accompanied with a less intense band at 453-484 nm which have been assigned to the lactim and lactam forms respectively. Interestingly, the presence of the lactam form is enhanced as the polarity of the solvent increase. This phenomenon is more marked in polar protic solvents which could be rationalized by the stabilization of the lactam form by intermolecular hydrogen-bond with the solvent (Figure S8). In water and PBS **4a** exhibits a blue-shifted single band at 414-416 nm originated from lactam form.

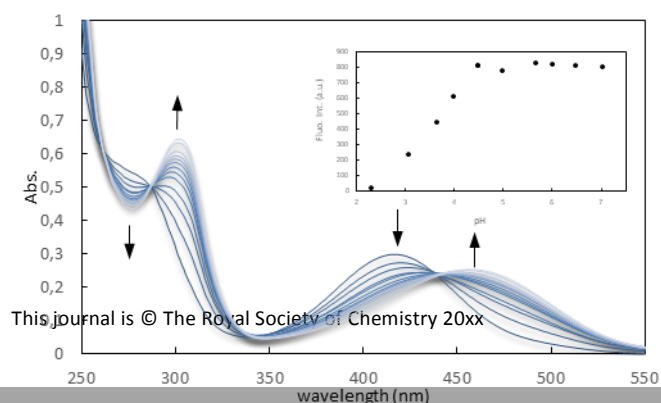


Fig. 3 Photometric titration ($[\mathbf{4a}] = 10^{-4} \text{ M}$) in water solution upon addition of aqueous hydrochloric acid (pH 2-8). Inset: Fluorimetric acid-base titration of **4a**.

Furthermore, the emission spectra of **4a** were also recorded in different solvents (Table 1). Upon excitation of the lactim form at 350-360 nm, in aprotic solvents with moderate polarity (CH_3CN , CHCl_3 and THF), single emissions at around 420 nm were obtained with modest Stokes shift and high quantum yield ($\phi_F = 0.5$ in CHCl_3). In contrast, in high polar protic and aprotic solvents (DMSO, DMF, MeOH and EtOH), dual emission was observed with similar intensities at 452 and 541 nm. In that configuration, large Stokes shifts (up to 9140 cm^{-1}) were obtained albeit with low quantum yields ($\phi_F < 0.03$) indicating a possible structural rearrangement in the excited state, like proton transfer or charge transfer (CT). In contrast, when excited in PBS and water at the excitation wavelength 416 nm corresponding to the lactam form, **4a** shows a single blue-shifted emission at 537 nm with low quantum yield.

Solvent	$\lambda_{\text{abs}}^{[a]}$ (nm)	ϵ ($\text{M}^{-1}\cdot\text{cm}^{-1}$)	$\lambda_{\text{em}}^{[b]}$ (nm)	Stokes Shift (cm^{-1}) ^[c]	$\Phi_{\text{em}}^{[d]}$
Acetone	353	5220	424	4743	0.08
CHCl_3	364	4560	429	4162	0.50
THF	356	4373	439	5310	0.27
CH_3CN	349, 459	3785	418	4729	0.14
MeOH	379, 478	2280	426/548	8137	< 0.01
EtOH	365, 484	2324	446/547	9140	< 0.01
DMF	355, 453	5120	452/540	6047	0.03
DMSO	356, 461	3655	452/541	5965	0.05
H_2O	416	3510	537	5416	0.01
PBS	414	4441	537	5532	0.02

Table 1. Absorption and emission maxima of **4a** in various solvents. [a] First λ_{abs} value corresponds to the maximum absorption wavelength (with $[\mathbf{4a}] = 10^{-4} \text{ mol}\cdot\text{L}^{-1}$); [b] λ_{em} to the emission band wavelength maximum observed after excitation at the maximum absorption wavelength (for $[\mathbf{4a}] = 10^{-5} \text{ mol}\cdot\text{L}^{-1}$). [c] Stokes shift defined as the wavelength difference between the absorption and emission peak maxima. [d] Fluorescence quantum yields measured using a 0.1 M H_2SO_4 solution of quinine sulfate ($\phi_F = 0.55$) as a reference.

A most striking feature of this behaviour is that the emission colours of **4a** in different solvents can easily be distinguished by the naked eye in different solvents (Fig. 4). As it has been observed for 3-hydroxyisoquinolines, the solvatochromic behaviour of **4a** showing two distinct bands in absorption and emission could be attributed to the presence of lactam and lactim forms in equilibrium.²⁹

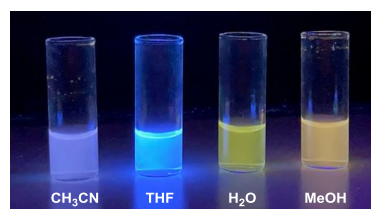


Fig. 4. Emission colours of **4a** in various solvents after excitation at 365 nm (with $[\mathbf{4a}] = 10^{-4} \text{ mol}\cdot\text{L}^{-1}$).

By analogy with parent 3-hydroxyisoquinolines, lactim form of **4a** would correspond to the high energy band whereas lactam

form of **4a** would be responsible for the low energy band, especially in polar protic solvents. These assumptions were probed and confirmed by time-dependent density functional theory (TD-DFT) calculations. The absorption spectrum of the lactam and lactim tautomers in DMF were computed at the M06-2X/aug-cc-pvdz level as well as the emission wavelength of their first excited electronic state. A large Stokes shift (ca. 110 nm / 6857 cm⁻¹) is predicted for both tautomers. These TD-DFT calculations thus support the observed dual emission due to tautomeric forms of **4a** and the large Stokes shifts experimentally observed. The analysis of **4a** (lactam and lactim) natural transition orbitals (NTO) shows that for both tautomers, the first transition occurs partly via an ICT from the phenyl ring in the 8-position to the naphthyridinone part, in particular on the pyridine core (Fig. 5 and SI). Therefore, strategic substitution at lactam/lactim and phenyl ring (donor) and at pyridine (acceptor) could lead to an additive effect to improve ICT properties of resulting push-pull π -conjugated system. Such strategy is known to induce red-shifted emissions and brighter fluorescent molecules.^{30,31} Note that the substitution effect on the phenyl ring was already observed in this work with the studied naphthyridinones series **4** which exhibit variation in their absorption and emission properties depending on the Ar substituent (see SI).

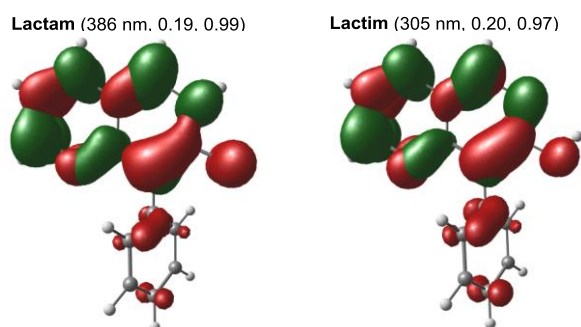


Fig. 5. NTO of the first transition of the **4a** lactam and lactim tautomers. In brackets are indicated the excitation energy, the corresponding oscillator strength and the associated weight of the transition (isosurface value of 0.04). Red color indicates a decrease in density, green color, an increase upon the transition.

Furthermore, large Stokes shift and strong solvatochromic properties emitting different colours of light, especially white, are highly desired criteria especially for the confection of luminescent devices in material sciences. Among all classes of fluorophores, single-compound fluorophores achieving white light emission represent a significant improvement in devices manufacturing compared to combinations of blue, green and red emitters requiring complex mixture and balancing.

As described above, we were pleased to observe a dual fluorescence emission for **4a** in polar solvents such as DMF and a white light emission observable by eyesight under UV illumination at 365 nm (Fig. 6A). The chromaticity CIE 1931 coordinates were calculated and found to be (0.25, 0.33), consolidating our observations (Fig. 6B), opening up promising perspectives in the development of organic emitting materials.

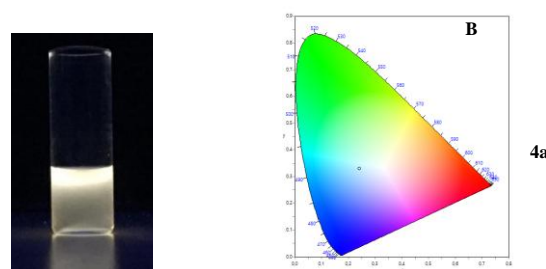


Fig. 6. (A) Emission colour of **4a** in DMF at 365 nm (with [4a] = 10⁻⁴ mol.L⁻¹); (B) Chromaticity diagram of **4a**.

The intrinsic mechanism associated with the dual emission can originate from several factors.^{32–34} However, a photo-induced tautomerization or excited state intramolecular transfer (ESIPT) have been reported to be responsible of dual emission in similar system.³⁵ Indeed, compounds with enolizable protons possessing an intramolecular hydrogen bond could undergo an ESIPT which often give excited state enol tautomer and excited state keto tautomer emissions. In our case, dual fluorescence resulting from ESIPT is possible since lactim-lactam tautomerization could arise from an intramolecular proton transfer in a four membered ring system in the excited state. Therefore, we can assume that the shortest wavelength observed mainly in moderate polar solvent at 450 nm after excitation at 350 nm is the local emission of the lactim form. Whereas, the longest wavelength at 540 nm represents the lactam form of the naphthyridinone **4a** generated by a proton transfer of the lactim isomer in the excited state. To the best of our knowledge, this work is the first report of naphthyridinones possessing a lactim-lactam equilibrium depicting dual fluorescence. However, more detailed time-resolved studies are necessary to give a conclusive identification of this dual process and in-depth photo-physical studies of these compounds is currently ongoing in our laboratory to answer these questions.

Conclusions

To sum up, we disclosed a concise synthetic pathway to access 8-substituted 1,6-naphthyridin-7(6H)-ones in good yields. For all these novel structures, we described the absorption spectra and photophysical fluorescence properties in various solvent as well as the study of acid-base titration for one representative example. These results show that 1,6-naphthyridin-7(6H)-ones exhibit dual fluorescence, a solvatochromic and acidochromic behaviour depending on the media. Large Stokes shift in protic solvent were observed and high quantum yields in aprotic solvent, up to 0.5 in CHCl₃, were obtained. These unique fluorescence properties clearly indicate that 1,6-naphthyridin-7(6H)-ones could be used as pH-sensitive fluorescent probes but also as potential full organic white light emitters. Future work in our group will be focused on strategic substitution of 1,6-naphthyridin-7(6H)-ones cores leading to optical properties enhancement, by way of fluorescence emission tuning, and better understanding of the photophysical mechanisms involved.

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Conflicts of interest

There are no conflicts to declare.

Experimental

Synthetic procedures,

2-chloro-3-(1,3-dioxolan-2-yl)pyridine (2). To a stirred solution of 2-chloro-3-pyridine carboxaldehyde (2 g, 14 mmol) and ethylene glycol (1.58 mL, 28.2 mmol) in toluene (50 mL) was added *p*-toluenesulfonic acid hydrate (PTSA, H₂O) (1.06 g, 5.6 mmol). The reaction mixture was refluxed for 5 h with a Dean-Stark apparatus. After cooling to room temperature, a saturated aqueous solution of Na₂CO₃ was added. The compound was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Cyclohexane/ethyl acetate 7/3) to afford the title compound as a white solid. *m* = 2.1 g. Yield: 81%. ¹H NMR (400 MHz, Chloroform-*d*): δ 8.41 (dd, 1H, *J* = 4.8, 1.9 Hz), 7.95 (dd, 1H, *J* = 7.4, 1.7 Hz), 7.29 (dd, 1H, *J* = 7.4, 4.8 Hz), 6.11 (s, 1H), 4.19-4.06 (m, 4H). ¹³C NMR (100 MHz, Chloroform-*d*): δ 150.5, 149.9, 136.7, 132.0, 122.5, 100.2, 65.6. HRMS (ESI⁺): calcd for C₈H₉ClNO₂: 186.0316, found: *m/z* 186.0317 [M+H]⁺.

General procedure for the synthesis of compounds 3:

Sodium hydride (3 equiv., 60% in oil) was added to a stirred solution of 2-chloro-3-(1,3-dioxolan-2-yl)pyridine **2** (1 equiv.) in dry THF (0.27 M). Arylacetonitrile (2 equiv.) was added in one portion and the reaction mixture was refluxed. The solution was cooled to room temperature and quenched by addition of water. The compound was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Cyclohexane/Et₂O 6/4) to afford the title compound.

2-[3-(1,3-dioxolan-2-yl)pyridin-2-yl]-2-phenylacetonitrile (3a). The compound is obtained from **2** (100 mg, 0.54 mmol), phenylacetonitrile (113 μL, 1.08 mmol) and NaH (65 mg, 1.62 mmol) in 2 mL of THF for 3 h of reaction time. Colorless oil, *m* = 114.6 mg, Yield: 80%. ¹H NMR (400 MHz, Chloroform-*d*): δ 8.58 (dd, 1H, *J* = 4.8, 1.6 Hz), 7.81 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.35-7.38 (m, 2H), 7.18-7.28 (m, 4H), 5.82 (s, 1H), 5.77 (s, 1H), 3.95-4.06 (m, 4H). ¹³C NMR (100 MHz, Chloroform-*d*): δ 153.3, 150.2, 135.7, 134.7, 131.0, 130.4, 129.0, 128.2, 123.1, 119.4, 100.7, 65.4, 65.2, 41.4. HRMS (ESI⁺): calcd for C₁₆H₁₄N₂O₂H: 267.1128; found: 267.1128 [M+H]⁺.

2-[3-(1,3-dioxolan-2-yl)pyridin-2-yl]-2-(pyridine-2-yl)acetonitrile 3b: The compound is obtained from **2** (150 mg, 0.81 mmol), 2-pyridylacetonitrile (181 μL, 1.62 mmol) and NaH (98 mg, 2.43 mmol)

in 3 mL of THF for 24 h of reaction time. Pale yellow oil. *m* = 90 mg, Yield: 41%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.63 (dd, *J* = 4.7, 1.8 Hz, 1H), 8.54 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.98 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.82 (td, *J* = 7.7, 1.8 Hz, 1H), 7.48 (dd, *J* = 7.8, 4.7 Hz, 1H), 7.38 – 7.28 (m, 2H), 6.23 (s, 1H), 6.08 (s, 1H), 4.13 – 3.92 (m, 4H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 155.1, 152.9, 150.7, 149.8, 138.0, 136.4, 132.1, 124.1, 123.6, 122.8, 119.3, 100.5, 65.5, 65.4, 44.1. HRMS (ESI⁺): calcd for C₁₅H₁₃N₃O₂H: 268.1081; found: 268.1082 [M+H]⁺.

2-[3-(1,3-dioxolan-2-yl)pyridin-2-yl]-2-(thiophen-2-yl)acetonitrile (3c). The compound is obtained from **2** (100 mg, 0.54 mmol), 2-thienylacetonitrile (114 μL, 1.08 mmol) and NaH (65 mg, 1.62 mmol) in 2 mL of THF for 20 h of reaction time. Brown oil, *m* = 67.5 mg, Yield: 46%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.71 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.90 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.31 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.27 (d, *J* = 5.0 Hz, 1H), 7.17 (d, *J* = 3.5 Hz, 1H), 6.97 (dd, *J* = 5.0, 3.8 Hz, 1H), 6.15 (s, 1H), 5.92 (s, 1H), 4.08 – 4.16 (m, 4H). ¹³C NMR (100 MHz, Chloroform-*d*) δ 152.8, 150.3, 136.4, 135.7, 130.8, 127.4, 126.9, 126.7, 123.4, 118.6, 100.8, 65.3, 65.2, 37.2. HRMS (ESI⁺): calcd for C₁₄H₁₂N₂O₂SH: 273.0692; found: 273.0694 [M+H]⁺.

2-(4-bromophenyl)-2-[3-(1,3-dioxolan-2-yl)pyridin-2-yl]acetonitrile (3d). The compound is obtained from **2** (500 mg, 2.7 mmol), 4-bromophenylacetonitrile (1.06 g, 5.4 mmol) and NaH (325 mg, 8.1 mmol) in 10 mL of THF for 5 h of reaction time. *m* = 930 mg, Yield: 99%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.65 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.29 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.87 (s, 1H), 5.84 (s, 1H), 4.20 – 4.04 (m, 4H). ¹³C NMR (100 MHz, Chloroform-*d*) δ 153.0, 150.6, 135.8, 133.9, 132.2, 131.1, 130.1, 123.3, 122.6, 118.9, 101.0, 65.5, 65.4, 41.0. HRMS (ESI⁺): calcd for C₁₆H₁₃BrN₂O₂H: 345.0233 / 347.0213; found: 345.0234 / 347.0212 [M+H]⁺.

2-[3-(1,3-dioxolan-2-yl)pyridin-2-yl]-2-(4-methoxyphenyl)acetonitrile (3e). The compound is obtained from **2** (200 mg, 1.08 mmol), 4-methoxyphenylacetonitrile (293 μL, 2.16 mmol) and NaH (130 mg, 3.24 mmol) in 4 mL of THF for 48 h of reaction time. The product was purified twice on silica gel (Cyclohexane/Et₂O 5/5 then DCM/MeOH 1%). Yellow oil, *m* = 270 mg, Yield: 84%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.66 (d, *J* = 4.7, 1.2 Hz, 1H), 7.94 (d, *J* = 7.7, 1.2 Hz, 1H), 7.45 (dd, *J* = 7.7, 4.7 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.99 (2s, 2H), 4.13-3.99 (m, 4H), 3.73 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 159.4, 153.9, 150.7, 136.7, 131.0, 129.7, 127.7, 123.8, 120.4, 114.7, 100.5, 65.5, 65.4, 55.6, 39.8 (overlap with solvent). HRMS (ESI⁺): calcd for C₁₇H₁₆N₂O₃Na: 319.1053; found: 319.1054 [M+Na]⁺.

2-[3-(1,3-dioxolan-2-yl)pyridin-2-yl]-2-(4-methylphenyl)acetonitrile (3f). The compound is obtained from **2** (100 mg, 0.54 mmol), 4-methylphenylacetonitrile (143 μL, 1.08 mmol) and NaH (65 mg, 1.62 mmol) in 2 mL of THF for 24 h of reaction time. Yellow oil, *m* = 75 mg, Yield: 50%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.66 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.88 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.28 (m, 1H), 7.14 (d, *J* = 8.0, 2H), 5.85 (2s, 2H), 4.18 – 3.99 (m, 4H), 2.31 (s, 3H). ¹³C NMR (100 MHz, Chloroform-*d*) δ 153.6, 150.2, 138.1, 135.4, 131.6, 131.0, 129.7, 128.1, 122.9, 119.4, 100.6, 65.3, 65.2, 41.3, 21.1. HRMS (ESI⁺): calcd for C₁₇H₁₆N₂O₂H: 281.1285; found: 281.1285 [M+H]⁺.

2-[3-(1,3-dioxolan-2-yl)pyridine-2-yl]-2-(4-ethynylphenyl)acetonitrile (3g). The compound is obtained from **2** (440 mg, 2.34 mmol), 2-(4-((trimethylsilyl)ethynyl)phenyl)acetonitrile (1 g, 4.68 mmol) and NaH (282 mg, 7.02 mmol) in 9 mL of THF for 20 h of reaction time. The deprotection of the terminal alkyne occurred during the reaction. Purification by gel silica chromatography (Cyclohexane/Et₂O 3/7). Brown oil, m = 420 mg, Yield: 62%. ¹H NMR (400 MHz, Chloroform-d) δ 8.65 (dd, J = 4.8, 1.8 Hz, 1H), 7.89 (dd, J = 7.8, 1.8 Hz, 1H), 7.47 – 7.41 (m, 4H), 7.29 (dd, J = 7.8, 4.8 Hz, 1H), 5.88 (s, 1H), 5.86 (s, 1H), 4.14 – 4.05 (m, 5H), 3.07 (s, 1H). ¹³C NMR (100 MHz, Chloroform-d) δ 153.0, 150.4, 135.7, 135.3, 132.6, 131.0, 128.3, 123.1, 122.2, 118.8, 100.8, 82.9, 78.0, 65.3, 65.2, 41.3. HRMS (ESI⁺): calcd for C₁₈H₁₄N₂O₂H: 291.1128; found: 291.1129 [M+H]⁺.

General procedure for synthesis of compound 4:

A 37% w/w aqueous solution of hydrochloric acid (328 μL, 3.94 mmol, 3 equiv.) was added to a stirred solution of the corresponding aryl-2-[3-(1,3-dioxolan-2-yl)aryl-2-yl]acetonitrile **3** in THF (0.1 M). The solution was stirred at room temperature for 20 h. The mixture was concentrated under vacuum to yield the corresponding naphthyridinone **4** as a hydrochloride salt. Attempts to get the free bases form of **4**, either through an acid-base extraction or by neutralization with stoichiometric quantity of bases or by a column chromatography using basic aluminum oxide remained unsuccessful.

8-phenyl-6,7-dihydro-1,6-naphthyridin-7-one, hydrochloride salt (4a). The compound is obtained from compound **3a** (350 mg, 1.3 mmol) in 13 mL of THF. Orange powder m = 338 mg, quantitative Yield. Mp > 300°C. ¹H NMR (400 MHz, Deuterium Oxide) δ 9.25 (s, 1H), 9.09 (dd, J = 8.3, 1.7 Hz, 1H), 8.85 (dd, J = 5.6, 1.7 Hz, 1H), 7.70–7.64 (m, 3H), 7.62–7.58 (m, 1H), 7.48 (d, 2H). ¹³C NMR (100 MHz, Deuterium Oxide) δ 162.1, 153.3, 151.7, 146.8, 141.6, 130.4, 129.9, 129.8, 129.1, 117.1, 115.5, 115.0. HRMS (ESI⁺): calcd for C₁₄H₁₀N₂O₂H: 223.0866; found: 223.0866 [M+H]⁺.

8-(pyridin-2-yl)-6,7-dihydro-1,6-naphthyridin-7-one, hydrochloride salt (4b). The compound is obtained from compound **3b** (114 mg, 0.45 mmol) in 4.5 mL of THF. Yellow powder, m = 115 mg, quantitative Yield, Mp > 300°C. ¹H NMR (400 MHz, Deuterium Oxide) δ 8.32 (d, J = 6.8 Hz, 1H), 8.28 (d, J = 6.9 Hz, 2H), 7.97 (ddd, J = 8.6, 7.0, 1.3 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.40 (t, J = 6.9 Hz, 1H), 7.23 (t, J = 7 Hz, 1H), 7.12 (s, 1H). ¹³C NMR (100 MHz, Deuterium Oxide) δ 148.6, 143.9, 142.5, 141.2, 139.5, 139.2, 121.4, 121.0, 117.5, 117.3, 116.9, 83.1, 65;1. HRMS (ESI⁺): calcd for C₁₃H₉N₃O₂H: 224.0818; found: 224.0818 [M+H]⁺.

8-(thiophen-2-yl)-6,7-dihydro-1,6-naphthyridin-7-one, hydrochloride salt (4c). The compound is obtained from compound **3c** (67.5 mg, 0.25 mmol) in 2.5 mL of THF. Black solid, m = 65 mg, quantitative Yield. Mp > 300°C. ¹H NMR (300 MHz, Deuterium Oxide) δ 9.24 (s, 1H), 9.06 (d, J = 8.4 Hz, 1H), 8.91 (d, J = 5.5 Hz, 1H), 7.83 (d, J = 5.1 Hz, 1H), 7.61 (dd, J = 8.5, 5.5 Hz, 1H), 7.36 (m, 2H). ¹³C NMR (100 MHz, Deuterium Oxide) δ 161.8, 153.5, 151.0, 146.9, 142.9, 130.8, 129.9, 128.8, 128.2, 117.3, 115.3, 108.7. HRMS (ESI⁺): Calcd for C₁₂H₈N₂OSH 229.0430; found 229.0432 [M+H]⁺.

8-(4-bromophenyl)-6,7-dihydro-1,6-naphthyridin-7-one, hydrochloride salt (4d). The compound is obtained from compound **3d** (565 mg, 1.63 mmol) in 16 mL of THF. m = 540 mg, Yield: 99%.

Mp > 300°C. ¹H NMR (400 MHz, Deuterium Oxide) δ 9.27 (s, 1H), 9.09 (dd, J = 8.4, 1.7 Hz, 1H), 8.88 (dd, J = 5.6, 1.7 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.61 (dd, J = 8.4, 5.6 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H). ¹³C NMR (100 MHz, Deuterium Oxide) δ 153.3, 151.7, 147.1, 132.9, 132.3, 128.2, 123.6, 117.1, 115.5. HRMS (ESI⁺): calcd for C₁₄H₉BrN₂O₂H: 300.9971 / 302.9951; found: 300.9972 / 302.9950 [M+H]⁺.

8-(4-methoxyphenyl)-6,7-dihydro-1,6-naphthyridin-7-one, hydrochloride salt (4e). The compound is obtained from compound **3e** (50 mg, 0.17 mmol) in 1.7 mL of THF. Orange solid, m = 53 mg, quantitative Yield. Mp > 300°C. ¹H NMR (400 MHz, Deuterium Oxide) δ 9.22 (s, 1H), 9.09 (dd, J = 8.4, 1.7 Hz, 1H), 8.86 (dd, J = 5.6, 1.7 Hz, 1H), 7.58 (dd, J = 8.4, 5.6 Hz, 1H), 7.44 – 7.42 (m, 2H), 7.24 – 7.21 (m, 2H), 3.94 (s, 3H). ¹³C NMR (100 MHz, Deuterium Oxide) δ 162.3, 159.9, 153.2, 151.7, 146.4, 141.5, 131.9, 121.3, 117.0, 115.6, 115.2, 114.6, 55.4. HRMS (ESI⁺): calcd for C₁₅H₁₂N₂O₂H: 253.0972; found 253.0972[M+H]⁺.

8-(4-methylphenyl)-6,7-dihydro-1,6-naphthyridin-7-one, hydrochloride salt (4f). The compound is obtained from compound **3f** (108 mg, 0.38 mmol) in 4 mL of THF. Orange solid, m = 107 mg, quantitative Yield. Mp > 300°C. ¹H NMR (400 MHz, Deuterium Oxide) δ 9.22 (s, 1H), 9.07 (dd, J = 8.4, 1.7 Hz, 1H), 8.85 (dd, J = 5.6, 1.7 Hz, 1H), 7.58 (dd, J = 8.3, 5.6 Hz, 1H), 7.48 (d, J = 7.9 Hz, 2H), 7.36 (d, 2H), 2.47 (s, 3H). ¹³C NMR (100 MHz, Deuterium Oxide) δ 162.1, 153.2, 151.6, 146.4, 141.5, 140.3, 130.3, 130.2, 125.8, 117.0, 115.5, 115.0, 20.5. HRMS (ESI⁺): Calcd for C₁₅H₁₂N₂O₂H: 237.1022; found 237.1025 [M+H]⁺.

8-(4-ethynylphenyl)-6,7-dihydro-1,6-naphthyridin-7-one, hydrochloride salt (4g). The compound is obtained from compound **3g** (338 mg, 1.16 mmol) in 12 mL of THF. Yellow solid, m = 320 mg, quantitative Yield. Mp > 300°C. ¹H NMR (400 MHz, Deuterium Oxide) δ 9.24 (s, 1H), 9.08 (dd, J = 8.4, 1.7 Hz, 1H), 8.84 (dd, J = 5.6, 1.7 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.58 (dd, J = 8.3, 5.6 Hz, 1H), 7.47 (d, J = 8.6 Hz, 2H), 3.67 (s, 1H). ¹³C NMR (100 MHz, Deuterium Oxide) δ 161.8, 153.4, 151.7, 147.1, 141.5, 133.3, 130.7, 130.0, 122.9, 117.2, 115.5, 114.0, 83.2, 79.6. HRMS (ESI⁺): calcd for C₁₆H₁₀N₂O₂H: 247.0866, found: 247.0866 [M+H]⁺.

Crystallography.

A single crystal was selected, mounted and transferred into a cold nitrogen gas stream. Intensity data was collected with a Bruker Kappa-APEX2 system using micro-source Cu-Kα radiation. Unit-cell parameters determination, data collection strategy, integration and absorption correction were carried out with the Bruker APEX2 suite of programs. The structure was solved with SHELXT and refined anisotropically by full-matrix least-squares methods with SHELXL using WinGX. The structure was deposited at the Cambridge Crystallographic Data Centre with number CCDC 2193379 and can be obtained free of charge via www.ccdc.cam.ac.uk.

Theoretical calculations.

(Time-dependent(TD))-Density Functional Theory (DFT) including geometry optimizations, frequency and single-point energy calculations were performed with the Minnesota M06-2X hybrid functional coupled to the correlation consistent

augmented aug-cc-pvdz basis set. The DMF or the THF solvent were mimicked with the Polarizable Continuum Model (PCM) model. Definitions of the basis sets were obtained from the Basis Set Exchange library. Computed structures and absorption spectra shown in this work have been depicted using the Chemcraft software. The emission band from the first singlet excited state of lactam and lactim taking into account the solvent effect was computed in several steps using the external iteration approach to include the solvation effects of the various implied states (ground state, (vertical and relaxed) 1st excited state).

Author Contributions

We strongly encourage authors to include author contributions and recommend using [CRediT](#) for standardised contribution descriptions. Please refer to our general [author guidelines](#) for more information about authorship.

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