# New Convenient Synthesis of Fluorescent 1,8-Naphthyridines and the Metal-Sensing Properties of the Dyes

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*Received: 10.03.2014; Accepted after revision: 11.04.2014*

**Abstract:** A new and efficient approach to a series of highly fluorescent non-aggregating donor–acceptor 1,8-naphthyridines is described. Examination of the photophysical properties of the 1,8-naphthyridines revealed that the presence of donor–acceptor functionality leads to bright green fluorescence with solvatochromism in solvents of differing polarities. The application of these molecules in metal sensing was also explored.

**Key words:** 1,8-naphthyridines, lactones, non-aggregating, solvatochromism, metal sensing

1,8-Naphthyridines and their benzannulated derivatives represent an important class of heterocyclic compounds that possess a variety of pharmacological activities.[1] These compounds have shown great potential in nucleic acid biology, for example, as markers for DNA motifs or DNA intercalators.[2] Naphthyridines have also recently found use as nanomaterials,[3] chemodosimeters,[4] and light harvesters.[5]

Planar 1,8-naphthyridines are nonfluorescent in nature as a result of weak ($\pi^*$, n) radiative transitions from the lowest state and of rapid intersystem crossing.[6] The tendency of planar 1,8-naphthyridines to aggregate through noncovalent interactions, such as parallel and antiparallel $\pi$–$\pi$ stacking, leads to a bathochromic shift in the photoluminescence and reduces its quantum efficiency, thereby limiting the applications of these compounds as organic electronic materials.[7] In an attempt to design new fluorescent naphthyridine derivatives, we proposed a strategy of equipping the molecule with electron-donating and electron-withdrawing moieties to modulate the HOMO/LUMO energy levels and to strengthen radiative transitions.

We therefore designed several new arylated and fused naphthyridines containing donor (D) and acceptor (A) moieties, as shown in Figure 1. To suppress aggregation, this molecular design induces nonplanarity through the presence of a methyl group or methylene linker on the naphthyridine ring; this inhibits intermolecular $\pi$–$\pi$ interactions, while permitting tuning of the electronic characteristics (HOMO/LUMO levels) by means of donor and acceptor groups to enhance selective metal-binding signals by an intramolecular charge-transfer (ICT) mechanism.

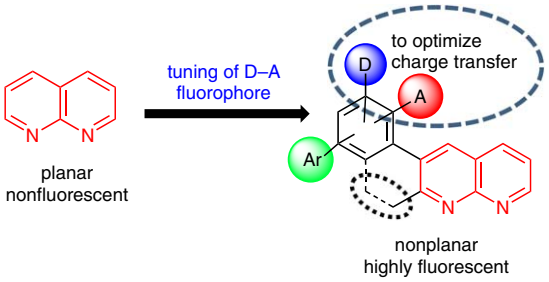


**Figure 1** Strategy for designing non-aggregating donor–acceptor 1,8-naphthyridines

We have recently demonstrated that controlled tuning and swapping of donor and acceptor moieties can be used to produce a marked modulation of the optical properties of fluorenes,[8] fluoranthenes,[9] pyrenylarenes,[10] benzo[*f*]quinolines, and benzo[*f*]acridines,[11] potentially useful in electroluminescent organic devices. More recently, we have identified a fluoranthene dye, FLUN-550, as a fluorescent probe for the quantification of intracellular lipid droplets.[12] Here, we report the synthesis of a novel series of non-aggregating, donor–acceptor fluorescent naphthyridines, their interesting photophysical properties, and their applications in metal sensing.

One of the most common approaches for the synthesis of 1,8-naphthyridines and their benzannulated derivatives is the Friedlander strategy.[13] Recently, Suárez-Ortiz et al.[14] reported the synthesis of benzo[*b*][1,8]naphthyridin-5-ones from silyl α-keto alkynes by using a nickel(II) cyanide/carbon monoxide/potassium cyanide catalytic system in an aqueous medium. In an attempt to prepare donor–acceptor naphthyridines, we devised a new protocol that exploits the reactive centers of pyran-2-ones, as shown in Scheme 1. The key intermediates, the 2*H*-pyran-2-ones **3a**–**e**, were readily prepared from ketene *S*,*S*-acetals and substituted acetophenones by means of Tominaga's protocol (Scheme 1).[15] To prepare compounds with a donor functionality, the methylsulfanyl group of substrates **3a**–**e** was replaced by a piperidine moiety to give 6-aryl-2-oxo-4-piperidin-1-yl-2*H*-pyran-3-carbonitriles **4a**–**e** in excellent yields (Scheme 1).[16]

Lactones **4a**–**e** have three electrophilic centers at C-2, C-4, and C-6, the last of which is highly reactive towards nucleophiles because of the extended conjugation and the presence of an electron-withdrawing substituent at the 3-position of the pyranone ring. Finally, Michael addition of

***SYNLETT*** 2014, 25, 1542–1546
Advanced online publication: 23.05.2014
DOI: 10.1055/s-0033-1339113; Art ID: st-2014-d0211-l
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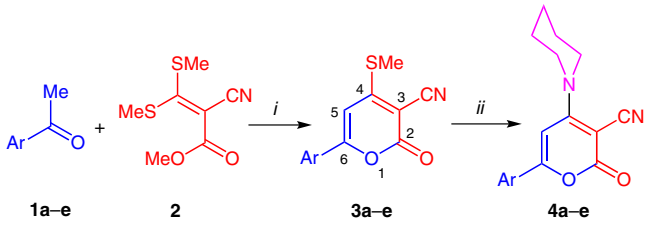



**Scheme 1** Synthesis of 6-aryl-2-oxo-4-piperidin-1-yl-2*H*-pyran-3-carbonitriles **4a**–**e**. *Reagents and conditions*: (i) KOH, DMSO, r.t.; (ii) piperidine, MeOH, reflux.

the conjugate base of 1-(2-methyl-1,8-naphthyridin-3-yl)ethanone[17] (**5**) at the C-6 position of the 2*H*-pyran-2-ones **4a**–**e**, followed by decarboxylation and intramolecular cyclization, gave the functionalized 1,8-naphthyridines **6a**–**e** in good yields (Scheme 2 and Table 1).[18] A plausible reaction mechanism for the formation of substituted naphthyridines **6a**–**e** is shown in Scheme 2.

**Table 1** Synthesis of Substituted 1,8-Naphthyridines **6a**–**e**

| Product | Ar | Yield[a] (%) |
|---|---|---|
| **6a** | Ph | 65 |
| **6b** | 4-$ClC_6H_4$ | 67 |
| **6c** | 4-$BrC_6H_4$ | 64 |
| **6d** | 4-$MeOC_6H_4$ | 70 |
| **6e** | 4-Tol | 61 |

[a] Isolated yield after purification by column chromatography.

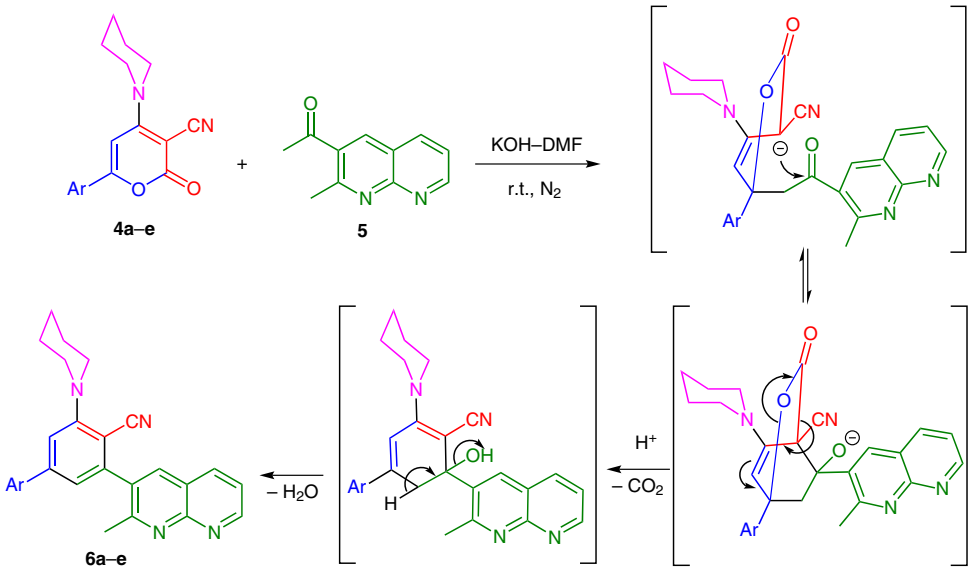
The photophysical properties of **6a**–**e** were examined by UV/vis and fluorescence spectroscopy in dichloromethane. The electronic absorbance maxima ($\lambda_{max,abs}$), emission maxima ($\lambda_{max,em}$), and the fluorescence quantum yield ($\Phi_f$) for the synthesized molecules are summarized in Table 2. The fluorescence quantum yields of **6a**–**e** ranged from 9% to 21%, relative to harmine (see Supporting Information, Figure S1).

**Table 2** Photophysical Properties of 1,8-Naphthyridines **6a**–**e**

| Compound | $\lambda_{max,abs}$[a] (nm) | $\lambda_{max,em}$[b] (nm) | $\varepsilon \times 10^4$[c] ($M^{-1}$ $cm^{-1}$) | Stokes shift[d] ($cm^{-1}$) | $\Phi_f$[e] (%) |
|---|---|---|---|---|---|
| **6a** | 347 | 457 | 0.86 | 7000 | 21 |
| **6b** | 353 | 458 | 0.91 | 6500 | 16 |
| **6c** | 351 | 464 | 1.15 | 7000 | 9 |
| **6d** | 361 | 455 | 1.18 | 5800 | 14 |
| **6e** | 351 | 454 | 1.12 | 6500 | 16 |

[a] Absorption maximum in $CH_2Cl_2$.
[b] Fluorescence maxima.
[c] Molar extinction coefficient.
[d] Stokes shift ($cm^{-1}$) = $(1/\lambda_{abs} - 1/\lambda_{em})$.
[e] Fluorescence quantum yield relative to harmine in 0.1 M aq $H_2SO_4$ as a standard ($\Phi$ = 45%).

Intramolecular rotation in flexible structures promotes nonradiative decay processes that cause energy loss and fluorescence quenching. Partial or complete inhibition of free rotation induces rigidity in the fluorophore, promoting radiative decay.[19] To inhibit possible nonradiative transitions in **6a**–**e**, we attempted to induce rigidity in the naphthyridine system by incorporating a methylene linker between the naphthyridine moiety and the benzene ring. We therefore synthesized a series of 5,6-dihydronaphtho[2,1-*b*]-1,8-naphthyridines **8a**–**e** in good yields by treating a mixture of the appropriate pyrancarbonitrile **4a**–**e** with 8,9-dihydrobenzo[*b*]-1,8-naphthyridin-6(7*H*)-one (**7**)[20] and potassium hydroxide in *N*,*N*-dimethylformamide under an inert atmosphere (Table 3).




**Scheme 2** Plausible reaction mechanism for the synthesis of functionalized 1,8-naphthyridines **6a**–**e**

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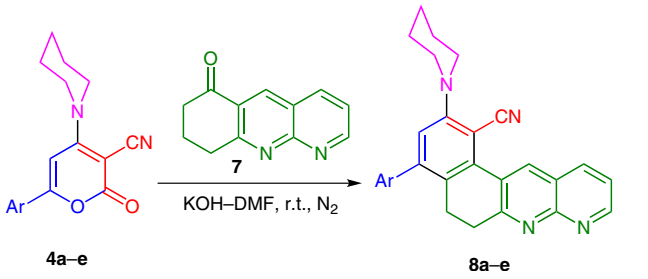
**Table 3** Synthesis of 5,6-Dihydronaphtho[2,1-*b*]-1,8-naphthyridines **8a–e**




| Product | Ar | Yield[a] (%) |
|---|---|---|
| **8a** | Ph | 62 |
| **8b** | 4-$ClC_6H_4$ | 54 |
| **8c** | 4-$BrC_6H_4$ | 56 |
| **8d** | 4-$MeOC_6H_4$ | 52 |
| **8e** | 4-Tol | 60 |

[a] Isolated yields after purification by column chromatography.

As expected, rigidification of the flexible parts of fluorophore reduced the nonradiative pathway and nearly doubled the fluorescence quantum yields for products **8a–e** (Table 4). Compounds **8a–e** showed photoluminescence in the blue-green region ($\lambda_{PL}$ = 482–488 nm) in dichloromethane ($10^{-6}$ M), with Stokes shifts ranging from 5600 to 6700 $cm^{-1}$ (see Supporting Information, Figure S1).

**Table 4** Photophysical Properties of 5,6-Dihydronaphtho[2,1-*b*]-1,8-naphthyridines **8a–e**

| Compound | $\lambda_{max,abs}$[a] (nm) | $\lambda_{max,em}$[b] (nm) | $\varepsilon \times 10^4$[c] ($M^{-1}$ $cm^{-1}$) | Stokes shift[d] ($cm^{-1}$) | $\Phi_f$[e] (%) |
|---|---|---|---|---|---|
| **8a** | 369 | 488 | 1.28 | 6700 | 49 |
| **8b** | 378 | 482 | 0.88 | 5700 | 40 |
| **8c** | 380 | 482 | 0.82 | 5600 | 43 |
| **8d** | 370 | 486 | 1.01 | 6500 | 42 |
| **8e** | 376 | 487 | 1.09 | 6100 | 48 |

[a] Absorption maxima in $CH_2Cl_2$.
[b] Fluorescence maxima.
[c] Molar extinction coefficient.
[d] Stokes shift ($cm^{-1}$) = $(1/\lambda_{abs} - 1/\lambda_{em})$.
[e] Fluorescence quantum yield relative to harmine in 0.1 M aq $H_2SO_4$ as a standard ($\Phi$ = 45%).

To examine the non-aggregating behavior of the highly fluorescent product **8a**, we examined the effects of concentration on its photoluminescence in dichloromethane (Figure 2). It is evident from the photoluminescence spectrum of **8a** that the fluorescence intensity gradually increased at concentrations of up to $2.5 \times 10^{-4}$ M but then decreased at concentrations above $10^{-2}$ M as a result of concentration quenching. At all concentrations, the emission band of **8a** corresponded exclusively to that of the monomer at 488 nm. No bathochromic shift or additional peaks for aggregate formation were observed, confirming the absence of the intermolecular π–π interactions or stacking.

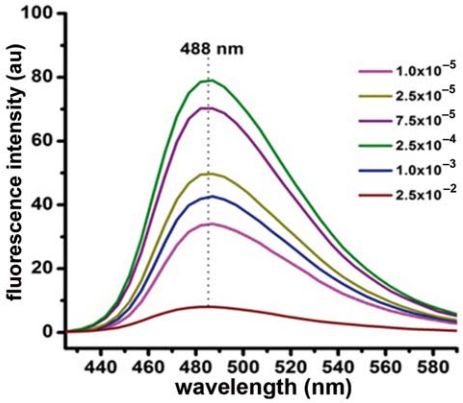



**Figure 2** Fluorescence spectra of **8a** at concentrations of $10^{-5}$ to $10^{-2}$ M in dichloromethane

To investigate the stabilization of the ground and excited states of the synthesized 5,6-dihydronaphtho[2,1-*b*]-1,8-naphthyridines, we examined the absorption and photoluminescence spectra of **8a** in a series of solvents of differing polarity indices, and we did not observe any significant changes in the absorption spectra. Interestingly, on changing the solvent, bathochromic shifts in the photoluminescence were observed from 461 nm in nonpolar cyclohexane to 488 nm in moderately polar dichloromethane to 517 nm in highly polar *N*,*N*-dimethylformamide (Figure 3).

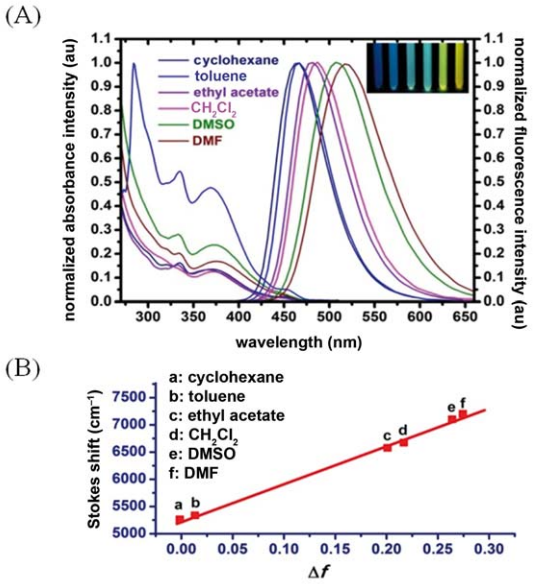



**Figure 3** (A) Solvatochromism, and (B) Lippert–Mataga plot of naphthyridine **8a** in solvents of increasing polarity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The solvent sensitivity of the emission band of naphthyridine **8a** was further examined by means of a Lippert–Mataga plot. Figure 3 shows the changes in the emission wavelength and the Stokes shift with respect to solvent polarity. A linear correlation ($r^2 = 0.995$) between the Stokes shift and the orientation polarizability ($\Delta f$) with a large solvatochromism slope (6902.48) confirmed the charge-transfer nature of the emissive state of **8a** (see Supporting Information, Table S1). The positive solvatochromism revealed that the excited state is strongly stabilized by solvent molecules and has a high intramolecular charge-transfer character and a large dipole moment compared with the ground state.

To examine the metal-binding nature of the designed fluorescent donor–acceptor naphthyridines, they were screened with a series of alkali ($Li^+$, $Na^+$, $K^+$, and $Cs^+$), alkaline ($Mg^{2+}$, $Ca^{2+}$, and $Ba^{2+}$), and transition-metal ions ($Mn^{2+}$, $Ni^{2+}$, $Co^{2+}$, $Cu^{2+}$, and $Zn^{2+}$) in acetonitrile solution. Compound **8a** was selected for detailed binding studies because of its good quantum yield. Photoluminescence studies in the presence of the various metal ions revealed that naphthyridine **8a** showed complete fluorescence quenching in the presence of zinc(2+) ions, but no fluorescence enhancement was observed with any of the ions studied. Gradual addition of zinc(2+) ions (from 0 to 10 equivalents) to a solution of **8a** successively decreased the fluorescence, as shown in Figure 4. The fluorescence intensity was dramatically reduced in the presence of 1.3 equivalents of zinc(2+) ions, complete loss of fluorescence occurring at $2.5 \times 10^{-4}$ M ($I/I_o = 0.03$, where $I$ and $I_o$ are the fluorescence intensities in the presence and absence of zinc ions, respectively).

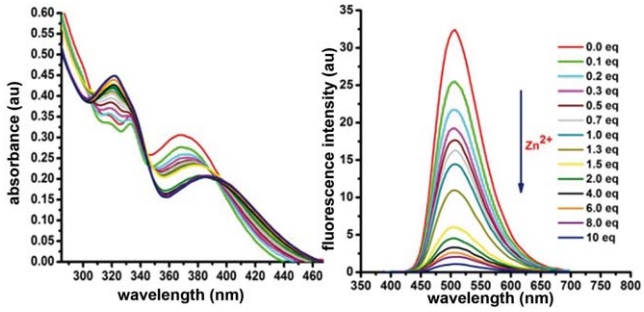


**Figure 4** Absorption and emission spectra of naphthyridine **8a** ($2.5 \times 10^{-5}$ M) in acetonitrile ($\lambda_{ex}$ 370 nm) upon titration with $Zn^{2+}$ (0 to $2.5 \times 10^{-4}$ M)

The addition of zinc(2+) ions might alter the energy of one of the triplet states so that the efficiency of S1/Tn intersystem crossing becomes more efficient upon coordination, leading to fluorescence quenching. Note that there are reports in the literature on many of fluorescent sensors for zinc, with applications in ratiometric detection and bioimaging.[21]

We also studied the binding mode of naphthyridine **8a** with zinc(2+) by means of $^1$H NMR spectroscopy in acetonitrile-$d_3$–deutereochloroform (4:1 v/v) (Figure 5). Large downfield shifts of the protons of the naphthyridine moiety ($H_a$, $H_b$, $H_c$) were observed upon addition of zinc(2+). The downfield shift can be rationalized in terms of the electron affinity of the bound cation.

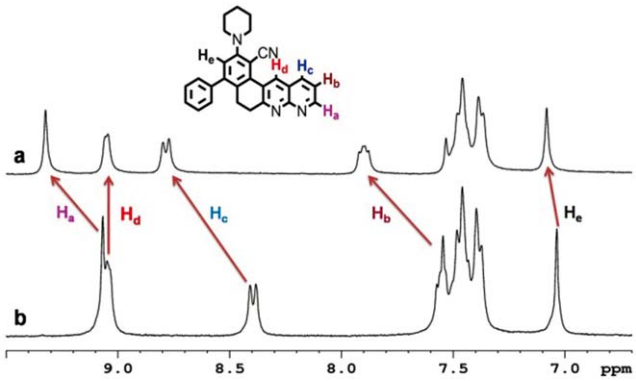


**Figure 5** Portion of the $^1$H NMR spectrum of naphthyridine **8a** (a) in the presence and (b) the absence of $Zn^{2+}$ ions

The stoichiometry of the **8a**–zinc(2+) complex was established by the method of continuous variation (Job plot)[22] (see Supporting Information, Figure S2); this showed that **8a** forms a 2:1 complex with zinc(2+). Electrospray-ionization mass spectrometric analysis showed a peak at $m/z$ = 995.0 corresponding to [(**8a**$_2$·$Zn^{2+}$) + $ClO_4^-$] (see Supporting Information, Figure S3).

The relative selectivity of the ligand **8a** towards zinc(2+) was verified by screening with a series of other metal ions ($Li^+$, $Na^+$, $K^+$, $Cs^+$, $Mg^{2+}$, $Ca^{2+}$, $Ba^{2+}$, $Mn^{2+}$, $Ni^{2+}$, $Co^{2+}$, and $Cu^{2+}$) under the same conditions (see Supporting Information, Figure S4). We found that of the metal ions tested, only zinc(2+) ions exhibited a marked fluorescence quenching (33-fold).

The equilibrium binding constant for the **8a**–zinc(2+) complex was evaluated for 2:1 ligand–metal complexation by using a nonlinear expression[23] for the fluorescence titration curve; this revealed strong complexation with a binding constant (β) of $3.9 \times 10^{10}$ $M^{-2}$. From the fluorimetric titration curve,[24] we estimated the detection limit of **8a** for zinc(2+) to be $8.9 \times 10^{-6}$ M (see Supporting Information, Figure S5). Furthermore, $I_o$–I increased linearly with increasing concentration of zinc(2+) (0 M to $3.3 \times 10^{-5}$ M) when **8a** was used at a concentration of $2.5 \times 10^{-5}$ M (see Supporting Information, Figure S6).

In conclusion, we have synthesized a new class of non-aggregating donor–acceptor-based fluorescent benzannulated 1,8-naphthyridines and have demonstrated an efficient method for their synthesis through C–C bond formation without the use of a transition-metal catalyst. These molecules showed interesting photophysical properties with high fluorescence quantum yields. We also discovered a metal-sensing application of naphthyridine **8a**, which shows 33-fold fluorescence quenching in the presence of zinc(2+). Further studies on these molecules for their application as bioprobes are underway.

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## Acknowledgment

We gratefully acknowledge financial support from CSIR, New Delhi, India, under Network Projects (BSC0102 and BSC0114). The spectroscopic data provided by SAIF, CDRI is gratefully acknowledged. The CSIR-CDRI communication number for this article is 8657.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

## References and Notes

(1) (a) You, Q.-D.; Li, Z.-Y.; Huang, C.-H.; Yang, Q.; Wang, X.-J.; Guo, Q. L.; Chen, X.-G.; He, X.-G.; Li, T.-K.; Chern, J.-W. *J. Med. Chem.* **2009**, *52*, 5649. (b) Lv, K.; Liu, M.-L.; Feng, L.-S.; Sun, L.-Y.; Sun, Y.-X.; Wei, Z.-Q.; Guo, H.-Q. *Eur. J. Med. Chem.* **2012**, *47*, 619.

(2) (a) Nakatani, K.; Sando, S.; Saito, I. *J. Am. Chem. Soc.* **2000**, *122*, 2172. (b) Lu, S.-H.; Selvi, S.; Fang, J.-M. *J. Org. Chem.* **2007**, *72*, 117.

(3) (a) Chen, Y.; Li, J.-L.; Tong, G. S. M.; Lu, W.; Fu, W.-F.; Lai, S.-W.; Che, C. M. *Chem. Sci.* **2011**, *2*, 1509. (b) Borzsonyi, G.; Alsbaiee, A.; Beingessner, R. L.; Fenniri, H. *J. Org. Chem.* **2010**, *75*, 7233.

(4) (a) Li, Z.; Yu, M.; Zhang, L.; Yu, M.; Liu, J.; Wei, L.; Zhang, H. *Chem. Commun.* **2010**, *46*, 7169. (b) Yu, M.-M.; Li, Z.-X.; Wei, L.-H.; Wei, D.-H.; Tang, M. S. *Org. Lett.* **2008**, *10*, 5115.

(5) Kukrek, A.; Wang, D.; Hou, Y.; Zong, R.; Thummel, R. *Inorg. Chem.* **2006**, *45*, 10131.

(6) Wormell, P.; Lacey, A. R. *Chem. Phys.* **1987**, *118*, 71.

(7) (a) Sadhukhan, N.; Bera, J. K. *Inorg. Chem.* **2009**, *48*, 978. (b) Koizumi, T.; Tanaka, K. *Inorg. Chim. Acta* **2004**, *357*, 3666. (c) Chen, Y.; Zhao, X.-J.; Gan, X.; Fu, W.-F. *Inorg. Chim. Acta* **2008**, *361*, 2335.

(8) Goel, A.; Chaurasia, S.; Dixit, M.; Kumar, V.; Prakash, S.; Jena, B.; Verma, J. K.; Jain, M.; Anand, R. S.; Manoharan, S. S. *Org. Lett.* **2009**, *11*, 1289.

(9) Goel, A.; Kumar, V.; Chaurasia, S.; Rawat, M.; Prasad, R.; Anand, R. S. *J. Org. Chem.* **2010**, *75*, 3656.

(10) Goel, A.; Kumar, V.; Nag, P.; Bajpai, V.; Kumar, B.; Singh, C.; Prakash, S.; Anand, R. S. *J. Org. Chem.* **2011**, *76*, 7474.

(11) Goel, A.; Kumar, V.; Singh, S. P.; Sharma, A.; Prakash, S.; Singh, C.; Anand, R. S. *J. Mater. Chem.* **2012**, *22*, 14880.

(12) Goel, A.; Sharma, A.; Kathuria, M.; Bhattacharjee, A.; Verma, A.; Mishra, P. R.; Nazir, A.; Mitra, K. *Org. Lett.* **2014**, *16*, 756.

(13) Marco-Contelles, J.; Pérez-Mayoral, E.; Samadi, A.; Do Carmo Carreiras, M.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652.

(14) Suárez-Ortiz, G. A.; Sharma, P.; Amézquita-Valencia, M.; Arellano, I.; Cabrera, A.; Rosas, N. *Tetrahedron Lett.* **2011**, *52*, 1641.

(15) Tominaga, Y.; Ushirogouchi, A.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1984**, *32*, 3384.

(16) (a) Goel, A.; Dixit, M.; Chaurasia, S.; Kumar, A.; Raghunandan, R.; Maulik, P. R.; Anand, R. S. *Org. Lett.* **2008**, *10*, 2553. (b) Goel, A.; Verma, D.; Dixit, M.; Raghunandan, R.; Maulik, P. R. *J. Org. Chem.* **2006**, *71*, 804. (c) Goel, A.; Singh, S. P.; Kumar, A.; Kant, R.; Maulik, P. R. *Org. Lett.* **2009**, *11*, 5122.

(17) Reddy, K. V.; Mogilaiah, K.; Sreenivasulu, B. *J. Indian Chem. Soc.* **1986**, *63*, 443.

(18) **Naphthyridines 6a–e and 8a–e; General Procedure**
A mixture of the appropriate carbonitrile **4a–e** (1 mmol) with 1-(2-methyl-1,8-naphthyridin-3-yl)ethanone (**5**; 1.2 mmol) or 8,9-dihydrobenzo[*b*]-1,8-naphthyridin-6(7*H*)-one (**7**; 1.2 mmol) and KOH (1.5 mmol) in anhyd DMF (5 mL) was stirred at r.t. under $N_2$ for 25–30 min. When the reaction was complete (TLC), the mixture was poured onto crushed ice with vigorous stirring then neutralized with 10% aq HCl. The resulting precipitate was collected by filtration and purified by column chromatography (silica gel, $CHCl_3$–MeOH).
**3-(2-Methyl-1,8-naphthyridin-3-yl)-5-piperidin-1-yl-biphenyl-4-carbonitrile (6a)**
Yellow solid; yield: 262 mg (65%); mp 130–132 °C ($CHCl_3$–MeOH); $R_f$ = 0.54 ($CHCl_3$–MeOH, 24:1); IR (KBr): 2932 (s), 2852 (s), 2213 (s), 1656 (m), 1591 (m), 1553 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, TMS): δ = 1.52–1.96 (m, 6 H), 2.74 (s, 3 H), 3.19–3.42 (m, 4 H), 7.03–7.71 (m, 8 H), 7.98–8.30 (m, 2 H), 9.03–9.23 (m, 1 H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$): δ = 24.0, 24.4, 26.1, 53.4, 105.0, 116.9, 117.1, 120.8, 121.3, 121.9, 127.2, 128.8, 129.0, 133.9, 136.8, 137.4, 139.4, 144.8, 146.3, 153.8, 155.5, 158.2, 160.9; MS (ESI): *m/z* = 405 $[M + H]^+$; HRMS: *m/z* $[M + H]^+$ calcd for $C_{27}H_{25}N_4$: 405.2079; found: 405.2130.
**4-Phenyl-2-piperidin-1-yl-5,6-dihydronaphtho[2,1-*b*]-1,8-naphthyridine-1-carbonitrile (8a)**
Yellow solid; yield: 257 mg (62%); mp 194–196 °C ($CHCl_3$–MeOH); $R_f$ = 0.60 ($CHCl_3$–MeOH, 24:1); IR (KBr): 2939 (s), 2850 (w) 2214 (s), 1584 (s), 1443 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$,TMS): δ = 1.48–1.72 (m, 2 H), 1.74–2.01 (m, 4 H), 2.67–3.02 (m, 2 H), 3.03–3.41 (m, 6 H), 7.00 (s, 1 H), 7.10–7.65 (m, 6 H), 8.31 (d, *J* = 6.2 Hz, 1 H), 8.90–9.25 (m, 2 H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$): δ = 23.9, 25.9, 26.1, 33.4, 53.8, 102.8, 119.1, 120.5, 121.7, 121.9, 127.0, 128.1, 128.5, 128.8, 130.7, 135.1, 137.5, 137.8, 139.9, 146.4, 153.8, 155.2, 157.7, 163.9; MS (ESI): *m/z* = 417 $[M + H]^+$; HRMS: *m/z* $[M + H]^+$ calcd for $C_{28}H_{25}N_4$: 417.2079; found: 417.2085.

(19) Wu, J.; Liu, W.; Ge, J.; Zhang, H.; Wang, P. *Chem. Soc. Rev.* **2011**, *40*, 3483.

(20) Majewicz, T. G.; Caluwe, P. *J. Org. Chem.* **1975**, *40*, 3407.

(21) (a) Hirano, T.; Kikuchi, K.; Urano, Y.; Higuchi, T.; Nagano, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 1052. (b) Nolan, E. M.; Lippard, S. J. *Acc. Chem. Res.* **2009**, *42*, 193. (c) Tamanini, E.; Katewa, A.; Sedger, L. M.; Todd, M. H.; Watkinson, M. *Inorg. Chem.* **2009**, *48*, 319. (d) Xu, Z.; Yoon, J.; Spring, D. R. *Chem. Soc. Rev.* **2010**, *39*, 1996. (e) Lau, Y. H.; Rutledge, P. J.; Watkinson, M.; Todd, M. H. *Chem. Soc. Rev.* **2011**, *40*, 2848.

(22) Neupane, L. N.; Park, J.-Y.; Park, J. H.; Lee, K.-H. *Org. Lett.* **2013**, *15*, 254.

(23) (a) Obare, S. O.; Murphy, C. J. *New J. Chem.* **2001**, *25*, 1600. (b) Obare, S. O.; Murphy, C. J. *Inorg. Chem.* **2001**, *40*, 6080. (c) Fahrni, C. J.; O'Halloran, T. V. *J. Am. Chem. Soc.* **1999**, *121*, 11448. (d) Buccella, D. J.; Horowitz, A.; Lippard, S. J. *J. Am. Chem. Soc.* **2011**, *133*, 4101.

(24) (a) Shortreed, M.; Kopelman, R.; Kuhn, M.; Hoyland, B. *Anal. Chem.* **1996**, *68*, 1414. (b) Wang, H.; Xue, L.; Jiang, H. *Org. Lett.* **2011**, *13*, 3844. (c) Xu, Z.; Xiao, Y.; Qian, X.; Cui, J.; Cui, D. *Org. Lett.* **2005**, *7*, 889. (d) Shen, L.; Lu, X.; Tian, H.; Zhu, W. *Macromolecules* **2011**, *44*, 5612.

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