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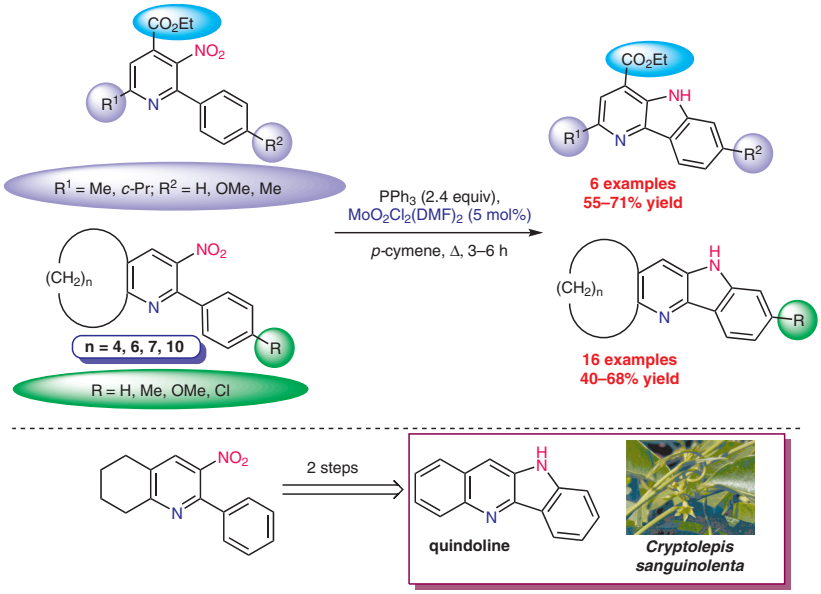
Synthesis of δ-Carbolines and the Alkaloid Quindoline through a Molybdenum-Catalyzed Cadogan Cyclization and their Photoluminescent Properties

Vladislav Yu. Shuvalov[a,b]
Anna S. Rupp[a]
Anna K. Kuratova[a]
Alexander S. Fisyuk[a,b]
Andrey A. Nefedov[c]
Galina P. Sagitullina*[a]

[a] Department of Organic Chemistry, F. M. Dostoevsky Omsk State University, 55a Mira Ave., 644077 Omsk, Russian Federation
sagitullina@chemomsu.ru
[b] Laboratory of New Organic Materials, Omsk State Technical University, 11 Mira Ave., 644050 Omsk, Russian Federation
[c] N. N. Vorozhtsov Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 Lavrentiev Ave., 630090 Novosibirsk, Russian Federation



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Abstract Cadogan reductive cyclization of substituted 2-aryl-3-nitropyridines to give δ-carbolines was performed under $MoO_2Cl_2(DMF)_2$ catalysis with triphenylphosphine as a ligand. A new approach for the synthesis of the alkaloid quindoline based on a Mo(VI)-catalyzed Cadogan reductive cyclization of 2-phenyl-3-nitro-5,6,7,8-tetrahydroquinoline followed by aromatization of the resulting 2,3,4,10-tetrahydro-1*H*-indolo[3,2-*b*]quinoline is proposed. Various *o*-nitroarylpyridines, obtained by reacting acylpyruvates and cyclic hydroxymethylene ketones with nitroacetophenone enamines, were used as starting compounds for the preparation of δ-carbolines. The synthesized δ-carbolines were found to act as phosphors; their photophysical properties were studied and a structure–property relationship was revealed.

Key words quindoline, carbolines, Cadogan cyclization, nitro compounds, acylpyruvates, cyclic hydroxymethylene ketones

Malaria is one of the most dangerous infectious diseases and is the main cause of death (mostly in children under five years old) in developing countries, where more than a million people die every year because of it. The appearance in the 20th century in Thailand and Colombia of a new type of chloroquine-resistant malarial plasmodium, *Plasmodium falciparum*, caused a surge in malarial disease. This resulted in an emergency situation, as no vaccine or antimalarial drug active against this *P. falciparum* strain, the most deadly malaria parasite, was available and, consequently, efforts were made to produce them (Figure 1).[1] Several scientific research groups were engaged in antimalarial drug design, but the only success was achieved by the group of Tu Youyou, who screened 1000 species of wild plants and extracted artemisinin from *Artemisia annua*.[2] As a result, Tu Youyou, the program manager for artemisinin, was awarded a half share in the Nobel Prize in Physiology or Medicine for 2015.[3,4]

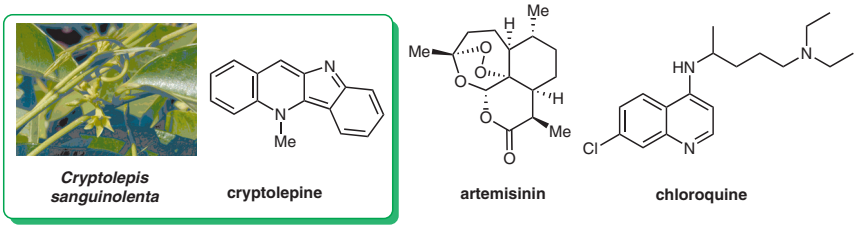


Figure 1 Antimalarial drugs

The development of new antimalarial drugs is an urgent task, because artemisinin-resistant strains of *P. falciparum* have already been found in Cambodia, Myanmar, Thailand, Vietnam, and Madagascar.[5] Mutations in one of the genes of the malaria plasmodium are the cause of drug resistance.[6]

Quindoline and cryptolepine are major alkaloids, and isocryptolepine is a minor alkaloid of the *Cryptolepis sanguinolenta*, a plant that grows in West and Central Africa. The root-bark extract of this plant is used in traditional medicine to treat various types of fever, including tuberculosis and malaria.[7] Quindoline is a synthetic precursor of cryptolepine, which is an anhydro base of a quaternary quindolinium salt in structure.

Over the past 40 years, many structural analogues of natural quindoline and cryptolepine have been synthesized; the biological activities of these analogues is often higher than that of the natural alkaloids.[8]

δ-Carbolines (5*H*-indolo[3,2-*b*]pyridines) exhibit antimalarial activity and extremely high antifungal and antibacterial activity, as well as inhibitory activity against the kinesin protein (KSP) involved into the proliferation of cancer cells, cytotoxicity to HeLa cells, and affinity for adenosine A3 receptors.[9] δ-Carbolines and benzo-δ-carbolines show fluorescent properties, which permits the use of fluorescence spectroscopy and microscopy to quantify their antimalarial activity and to determine their subcellular localization in DNA-containing parasite structures.[10]

In two reviews, 15 methods for the synthesis of quindoline have been reported.[11] The most effective was the synthesis of quindoline through the reduction of 1,3-bis(2-nitrophenyl)propan-2-one to a diamino ketone that undergoes spontaneous cyclization to form 2-(2-aminobenzyl)-1*H*-indole, which undergoes oxidative cyclization to form quindoline.[11] The reviews cites no examples of the synthesis of quindoline from 2-arylnitropyridines.

Most δ-carbolines have been synthesized from substituted pyridines and indoles.[12a–c] Crucially, new methods for the synthesis of δ-carbolines by the Pd-catalyzed reaction of 2-iodoanilines with *N*-tosylenynamines include a Larock indolization stage, a Ts group elimination, electrocyclization, and oxidative aromatization; the compounds can also be prepared by Ni-catalyzed or metal-free [2+2+2] cycloaddition reactions of *N*-(2-cyanophenyl)-*N*-(phenylethynyl)methanesulfonamide with internal alkynes.[12d–e]

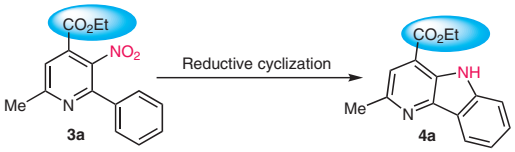
Here, we report, for the first time, a synthesis of δ-carbolines through a $MoO_2Cl_2(DMF)_2$-catalyzed Cadogan reaction, together with a new method for obtaining the alkaloid quindoline. In addition, the photophysical properties of the resulting δ-carbolines were studied. The dioxomolybdenum(VI)-catalyzed Cadogan reaction has recently been successfully used for the synthesis of indoles and carbazoles.[13]

First, we optimized the conditions for the reductive cyclization of 2-aryl-3-nitropyridines **3** to δ-carbolines **4**. Heating pyridine **3a** in the presence of ethane-1,2-diylbis(diphenylphosphine) (DPPE) under solvent-free condition afforded δ-carboline **4a** in trace amounts. The optimal conditions for the synthesis of **4a** involve the use of PPh_3 as a reducing agent and $MoO_2Cl_2(DMF)_2$ as a catalyst (Table 1).

3-Nitropyridines **3a–f** were obtained by cyclocondensation of acylpyruvate **1a** (R^2 = Me) or **1b** (R^2 = cyclopropyl) with nitroenamines **2a–c** (R^1 = H, OMe, Me). A one-pot synthesis of pyridines **3** was performed in acetic acid at 35 °C. δ-Carbolines **4a–f** were synthesized by reductive Cadogan cyclization under Mo(VI) catalysis with triphenylphosphine as a reducing agent [Scheme 1; see Supporting Information (SI) for details].

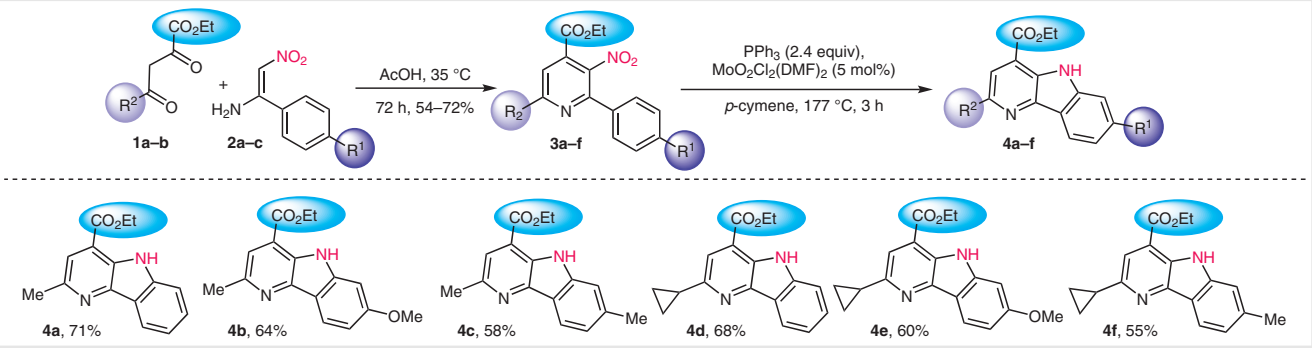
Cyclocondensation of cyclic hydroxymethylene ketones **5** with nitroacetophenone enamines **2a–d** resulted in the formation of 3-nitropyridines **6a–p**. Subsequent Mo(VI)-catalyzed Cadogan reaction afforded a series of δ-carbolines **7a–p** with a fused pyridine ring (Scheme 2, see SI).

Table 1 Optimization of the Cadogan Reaction[a]



Entry	Reductant	Solvent	Temp (°C)	Catalyst[b]	Time (h)	Yield[c] (%)
1	DPPE[d]	–	150	–	5	traces
2	PPh_3[e]	*p*-cymene	177	–	10	34
3	PPh_3[e]	toluene	110	$MoO_2Cl_2(DMF)_2$	24	15
4	PPh_3[e]	*p*-cymene	177	$MoO_2Cl_2(DMF)_2$	3	71

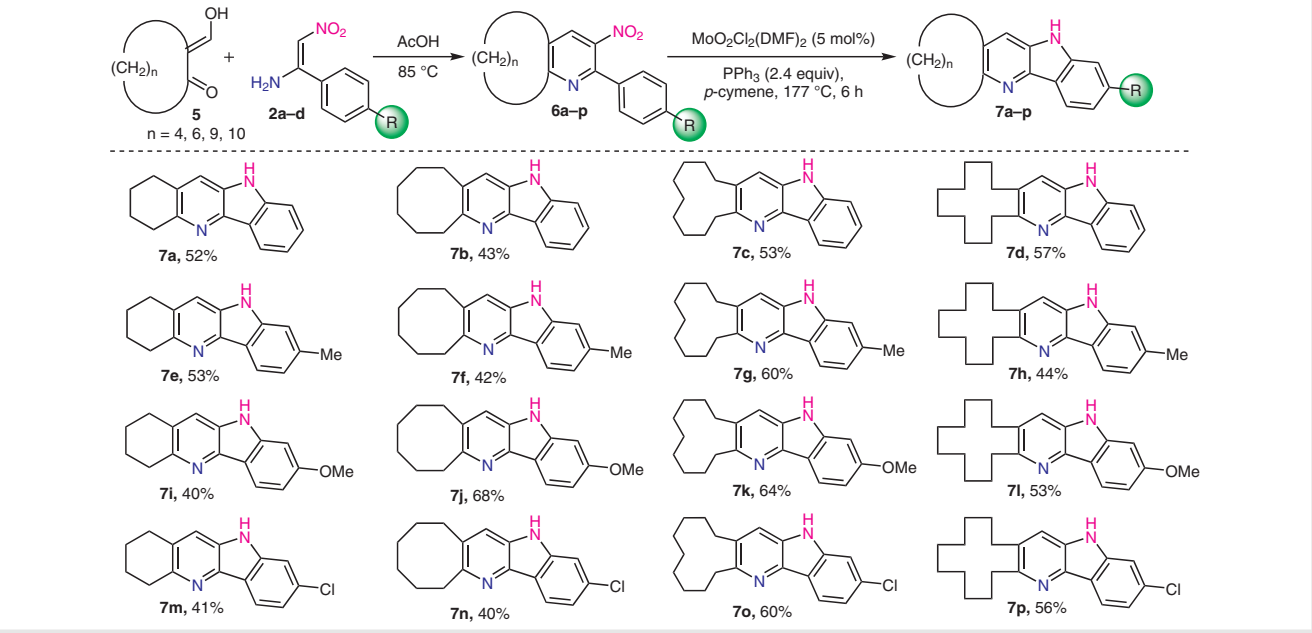
[a] All reactions were conducted with 1 mmol of **3a** under N_2.
[b] 5 mol%.
[c] Isolated yield after column chromatography.
[d] 1.1 mmol.
[e] 2.4 mmol.



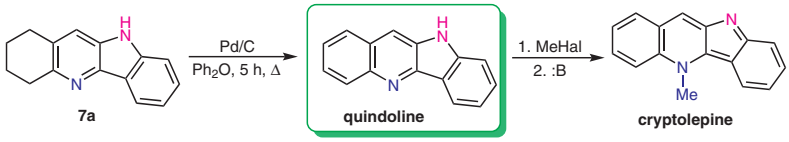
Scheme 1 Mo-catalyzed Cadogan cyclization of 3-nitropyridines **3** to 4-ethoxycarbonyl-δ-carbolines **4**

The final stage of the synthesis of the alkaloid quindoline involved aromatization of the cyclohexane ring of the δ-carboline **7a** (Scheme 3).

Absorption spectra of 4-ethoxycarbonyl-δ-carbolines **4a–f** in ethanol solution showed four bands with λ_{max} = 250–264, 277–280, 331–340 (**4a**,**c**,**d**,**f**), and 378–388 nm (**4a**,**c**,**d**,**f**). The molar attenuation coefficients of these compounds were in the range 6.2×10^3 to 9.3×10^3 L × mol^{-1} × cm^{-1} (see Table S1 in the SI). In the case of compounds **4b**,**e**, which have a methoxy group on the benzene ring, the last two bands overlapped to form a strong broad band at 370–377 nm, while the attenuation coefficient increased to 13.6×10^3 to 14.4×10^3 L × mol^{-1} × cm^{-1} (Table S1 in the SI). Compounds **4a–f** are phosphors, emitting light in the 450–460 nm region (Figure 2); however, they are characterized by low quantum yields (0.05–0.18).



Scheme 2 Dioxomolybdenum-catalyzed reductive cyclization of 3-nitro-*o*-pyridinophanes to form δ-carbolines with a lipophilic bridge



Scheme 3 Synthesis of alkaloid quindoline by aromatization of **7a**; :B = Base (OH^-).

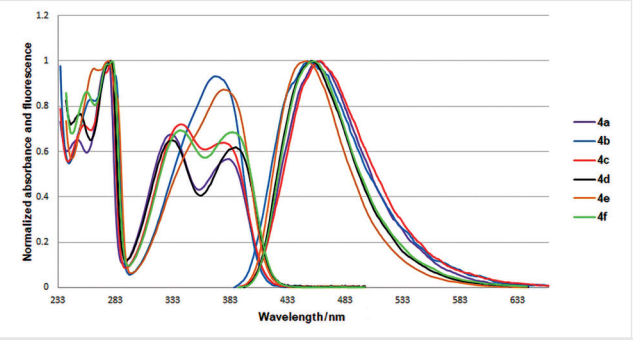


Figure 2 Normalized absorption and fluorescence spectra of dilute solutions of compounds **4a–f** in EtOH

The absorption spectra of δ-carbolines **7a–p**, recorded under the same conditions, showed two main bands at 261–264 and 311–316 nm. The band in the long-wavelength region of the spectrum had a shoulder, which was most pronounced for compounds **7a–d**, which contain no substituents on the benzene core. In the case of the methoxy-substituted derivatives **7i–l**, the shoulder overlapped with the main band to give a broad signal with a maximum at 316–330 nm. The molar attenuation coefficients for compounds **7a–p** were in the range 14.6×10^3 to 20.3×10^3 $L \times mol^{-1} \times cm^{-1}$ (Table S2 in the SI).

A comparison of the absorption spectra of tetra-, hexa-, nona-, and decamethylene-substituted δ-carbolines showed that the positions of the absorption maxima for compounds **7a–d** (261, 311–312 nm), **7e–h** (262–264, 315–323 nm), **7i–l** (264, 323–330 nm), and **7m–p** (263–264, 314–316 nm) do not depend on the size of the methylene chain. Upon excitation with UV light, ethanolic solutions of compounds **7a–p** produced a strong photoluminescence, emitting blue light (368–389 nm) with a quantum yield of 0.11–0.54. Introduction of the methoxy group to the C(7) atom of the benzene ring of compounds **7i–l** led to an increase in the quantum yield (0.45–0.54) and to a hypsochromic shift ($^{max}\lambda_{em}$ = 368–372 nm) in the luminescence spectrum. For the chlorine-substituted carbolines **7m–p**, a hypsochromic shift was also observed ($^{max}\lambda_{em}$ = 369–373 nm); however, the quantum yield decreased (0.11–0.12).

In summary, we have developed, for the first time, a catalytic two-step synthesis of substituted δ-carbolines[14] and a three-step synthesis of quindoline alkaloid from available starting compounds. We also studied the photophysical properties of the products and we revealed a structure–property relationship.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612416.

References and Notes

(1) (a) Lai, T. K.; Chatterjee, A.; Banerji, J.; Sarkar, D.; Chattopadhyay, N. *Helv. Chim. Acta* **2008**, *91*, 1975. (b) Gamo, F.-J.; Sanz, L. M.; Vidal, J.; de Cozar, C.; Alvarez, E.; Lavandera, J.-L.; Vanderwall, D. E.; Green, D. V. S.; Kumar, V.; Hasan, A.; Brown, J. R.; Peishoff, C. E.; Cardon, L. R.; Garcia-Bustos, J. F. *Nature* **2010**, *465*, 305.

(2) (a) Denisov, E. T.; Solodova, S. L.; Denisova, T. G. *Russ. Chem. Rev.* **2010**, *79*, 981. (b) Wiesner, J.; Ortman, R.; Jomaa, H.; Schlitzer, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 5274; *Angew. Chem.* **2003**, *115*, 5432.

(3) Tu, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 10210; *Angew. Chem.* **2016**, *128*, 10366.

(4) Kumar, A.; Katiyar, S. B.; Agarwal, A.; Chauhan, P. M. *Curr. Med. Chem.* **2003**, *10*, 1137.

(5) (a) Andriantsoanirina, V.; Ratsimbasoa, A.; Bouchier, C.; Jahevitra, M.; Rabearimanana, S.; Radrianjafy, R.; Andrianaranjaka, V.; Randriantsoa, T.; Rason, M. A.; Tichit, M.; Rabarijaona, L. P.; Mercereau-Puijalon, O.; Durand, R.; Ménard, D. *Antimicrob. Agents Chemother.* **2009**, *53*, 4588. (b) Noedl, H.; Se, Y.; Schaecher, K.; Smith, B. L.; Socheat, D.; Fukuda, M. M. *N. Engl. J. Med.* **2008**, *359*, 2619. (c) Ashley, E. A.; Dhorda, M.; Fairhurst, R. M.; Amaratunga, C.; Lim, P.; Suon, S.; Sreng, S.; Anderson, J. M.; Mao, S.; Sam, B.; Sopha, C.; Chuor, C. M.; Nguon, C.; Sovannaroth, S.; Pukrittayakamee, S.; Jittamala, P.; Chotivanich, K.; Chutasmit, K.; Suchatsoonthorn, C.; Runcharoen, R.; Hien, T. T.; Thuy-Nhien, N. T.; Thanh, N. V.; Phu, N. H.; Htut, Y.; Han, K. T.; Aye, K. H.; Mokuolu, O. A.; Olaosebikan, R. R.; Folaranmi, O. O.; Mayxay, M.; Khanthavong, M.; Hongvanthong, B.; Newton, P. N.; Onyamboko, M. A.; Fanello, C. I.; Tshefu, A. K.; Mishra, N.; Valecha, N.; Phyo, A. P.; Nosten, F.; Yi, P.; Tripura, R.; Borrmann, S.; Bashraheil, M.; Peshu, J.; Faiz, M. A.; Ghose, A.; Hossain, M. A.; Samad, R.; Rahman, M. R.; Hasan, M. M.; Islam, A.; Miotto, O.; Amato, R.; MacInnis, B.; Stalker, J.; Kwiatkowski, D. P.; Bozdech, Z.; Jeeyapant, A.; Cheah, P. Y.; Sakulthaew, T.; Chalk, J.; Intharabut, B.; Silamut, K.; Lee, S. J.; Vihokhern, B.; Kunasol, C.; Imwong, M.; Tarning, J.; Taylor, W. J.; Yeung, S.; Woodrow, C. J.; Flegg, J. A.; Das, D.; Smith, J.; Venkatesan, M.; Plowe, C. V.; Stepniewska, K.; Guerin, P. J.; Dondorp, A. M.; Day, N. P.; White, N. J. *N. Engl. J. Med.* **2014**, *371*, 411.

(6) Le Bras, J.; Durand, R. *Fundam. Clin. Pharmacol.* **2003**, *17*, 147.

(7) (a) Grellier, P.; Ramiaramanana, L.; Millerioux, V.; Deharo, E.; Schrevel, J.; Frappier, F.; Trigalo, F.; Bodo, B.; Pousset, J.-L. *Phytother. Res.* **1996**, *10*, 317. (b) Cimanga, K.; De Bruyne, T.; Pieters, L.; Vlietinck, A. J.; Turger, C. A. *J. Nat. Prod.* **1997**, *60*, 688.

(8) (a) Dassonneville, L.; Bonjean, K.; De Pauw-Gillet, M.-C.; Colson, P.; Houssier, C.; Quetin-Leclercq, J.; Angenot, L.; Bailly, C. *Biochemistry* **1999**, *38*, 7719. (b) Kumar, E. V. K. S.; Etukala, J. R.; Ablordeppey, S. Y. *Mini-Rev. Med. Chem.* **2008**, *8*, 538. (c) Lavrado, J.; Moreira, R.; Paulo, A. *Curr. Med. Chem.* **2010**, *17*, 2348. (d) Wang, W.; Yin, R.; Zhang, M.; Yu, R.; Hao, C.; Zhang, L.; Jiang, T. *J. Med. Chem.* **2017**, *60*, 2840. (e) Wright, C. W.; Addae-Kyereme, J.; Breen, A. G.; Brown, J. E.; Cox, M. F.; Croft, S. L.; Gökçek, Y.; Kendrick, H.; Phillips, R. M.; Pollet, P. L. *J. Med. Chem.* **2001**, *44*, 3187.

(9) (a) Mazu, T. K.; Etukala, J. R.; Jacob, M. R.; Khan, S. I.; Walker, L. A.; Ablordeppey, S. Y. *Eur. J. Med. Chem.* **2011**, *46*, 2378. (b) Ishiyama, H.; Ohshita, K.; Abe, T.; Nakata, H.; Kobayashi, J. *Bioorg. Med. Chem.* **2008**, *16*, 3825.

(10) (a) Bonjean, K.; De Pauw-Gillet, M. C.; Defresne, M. P.; Colson, P.; Houssier, C. H.; Dassonneville, L.; Bailly, C.; Greimers, R.; Wright, C.; Quetin-Leclercq, J.; Tits, M.; Angenot, L. *Biochemistry* **1998**, *37*, 5136. (b) Arzel, E.; Rocca, P.; Grellier, P.; Labaeid, M.; Frappier, F.; Gueritte, F.; Gaspard, C.; Marsais, F.; Godard, A.; Quéguiner, G. *J. Med. Chem.* **2001**, *44*, 949. (c) Lavrado, J.; Cabal, G. G.; Prudêncio, M.; Mota, M. M.; Gut, J.; Rosenthal, P. J.; Díaz, C.; Guedes, R. C.; dos Santos, D. J. V. A.; Bichenkova, E.; Douglas, K. T.; Moreira, R.; Paulo, A. *J. Med. Chem.* **2011**, *54*, 734. (d) Nogueira, C. R.; Lopes, L. M. X. *Molecules* **2011**, *16*, 2146. (e) Corbett, Y.; Herrera, L.; Gonzalez, J.; Cubilla, L.; Capson, T. L.; Coley, P. D.; Kursar, T. A.; Romero, L. I.; Ortega-Barria, E. *Am. J. Trop. Med. Hyg.* **2004**, *70*, 119.

(11) (a) Méndez, M. V.; Bracca, A. B. J.; Kaufman, T. S. *Synthesis* **2018**, *50*, 1417. (b) Parvatkar, P. T.; Parameswaran, P. S. *Curr. Org. Synth.* **2016**, *13*, 58.

(12) (a) Smirnova, O. B.; Golovko, T. V.; Granik, V. G. *Pharm. Chem. J.* **2010**, *44*, 654; translated from Khim.-Farm. Zh. 2010, 44, 6. (b) Gupta, A.; Kamble, B.; Moola Joghee, N.; Chandrasekar, M. J. N. *Curr. Org. Synth.* **2012**, *9*, 377. (c) Cao, J.; Xu, Y.; Kong, Y.; Cui, Y.; Hu, Z.; Wang, G.; Deng, Y.; Lai, G. *Org. Lett.* **2012**, *14*, 38. (d) Wang, G.; You, X.; Gan, Y.; Lui, Y. *Org. Lett.* **2017**, *19*, 110. (e) Wen, H.; Cao, W.; Liu, Y.; Wang, L.; Chen, P.; Tang, Y. *J. Org. Chem.* **2018**, *83*, 13308.

(13) (a) Sanz, R.; Escribano, J.; Pedrosa, M. R.; Aguado, R.; Arnáiz, F. J. *Adv. Synth. Catal.* **2007**, *349*, 713. (b) Yamamoto, Y.; Yamada, S.; Nishiyama, H. *Adv. Synth. Catal.* **2011**, *353*, 701. (c) Yamamoto, Y.; Ohkubo, E.; Shibuya, M. *Adv. Synth. Catal.* **2017**, *359*, 1747. (d) de Noronha, R. G.; Fernandes, A. C. *Curr. Org. Chem.* **2012**, *16*, 33. (e) Huleatt, P. B.; Lau, J.; Chua, S.; Tan, Y. L.; Duong, H. A.; Chai, C. L. L. *Tetrahedron Lett.* **2011**, *52*, 1339. (f) Nykaza, T. V.; Ramirez, A.; Harrison, T. S.; Luzung, M. R.; Radosevich, A. T. *J. Am. Chem. Soc.* **2018**, *140*, 3103.

(14) **Ethyl 5*H*-Pyrido[3,2-*b*]indole-4-carboxylates 4a–j; General Procedure**

A solution of the appropriate ethyl 3-nitroisonicotinate **3a–f** (1 mmol), PPh_3 (0.629 g, 2.4 mmol), and $MoO_2Cl_2(DMF)_2$ (0.017 g, 0.05 mmol) in *p*-cymene (10 mL) was refluxed with constant stirring under N_2. The solvent was removed under reduced pressure, and the residue was purified by column chromatography [silica gel, toluene then PE–EtOAc (1:1)], followed by crystallization from *i*-PrOH.

Ethyl 2-Methyl-5*H*-pyrido[3,2-*b*]indole-4-carboxylate (4a)

Light-yellow crystals; yield: 180 mg (71%); mp 130–131 °C (*i*-PrOH). IR (KBr): 3391, 2985, 1687, 1475, 1240, 1212, 1097, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.48 (t, *J* = 7.1 Hz, 3 H), 2.80 (s, 3 H), 4.50 (q, *J* = 7.1 Hz, 2 H), 7.30 (ddd, *J* = 7.9, 6.8, 1.4 Hz, 1 H), 7.45–7.55 (m, 2 H), 7.69 (s, 1 H), 8.40 (d, *J* = 7.9 Hz, 1 H), 9.50 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 24.1, 61.7, 111.4, 118.4, 118.6, 120.6, 121.2, 121.5, 128.4, 130.5, 141.0, 144.0, 149.9, 166.4. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.89; H, 5.57; N, 10.96.