


 Cite this: *RSC Adv.*, 2021, 11, 25624



Received 8th June 2021

Accepted 19th July 2021

DOI: 10.1039/d1ra04425g

rsc.li/rsc-advances

Access to 6-hydroxy indolizines and related imidazo[1,5-*a*]pyridines through the S_N2 substitution/condensation/tautomerization cascade process†

 Guiyun Duan,‡ Hao Liu,‡ Liqing Zhang, Chunhao Yuan,  Yongchao Li and Yanqing Ge *

A simple and efficient cascade reaction was developed for the construction of hydroxy substituted indolizines from pyrrole-2-carbaldehydes and commercially available 4-halogenated acetoacetic esters. Their optical properties were also evaluated.

Introduction

Indolizine, a biostere for indole, is commonly found in numerous natural products and pharmaceuticals. Indolizine derivatives exhibit diverse biological activities such as anti-HIV, anti-inflammatory, anti-tubercular, and anticancer activities.^{1–5} They are also used in dyes and optical materials owing to their bright colors.^{6–11} As a consequence, much effort has been devoted to their synthesis and functionalization, and thus many methods have been developed.^{12–14} In addition to classical Scholtz or Tschichibabin reactions, a variety of straightforward and efficient methods have been reported in recent years^{15–20} including 1,3-dipolar cycloaddition of pyridinium salts and intramolecular cyclization catalyzed by transition metals and intermolecular cyclization. Despite the efficiency of these methods, they suffer from the requirement of specific pre-organized substrates, necessity of expensive metal catalysts, multistep synthesis, and a lack of product diversity. Moreover, no method has been reported for the preparation of indolizines bearing a hydroxyl group.

Recently, we synthesized a series of indolizine and related N-bridgehead heterocycles *via* a cascade reaction (Scheme 1a).²¹ To achieve the related pyrazolo[1,5-*a*]pyridines through a shorter and convenient route, a simple and efficient synthetic method was also reported subsequently using commercially accessible starting materials (Scheme 1b).²² Based on the results obtained in our laboratory, we expected that a cascade reaction

of pyrrole-2-carbaldehyde **1** with 4-halogenated acetoacetic ester **2** might be successful in the presence of a weak base (Scheme 1). In continuation of our effort to search for new fluorophores for imaging,^{23–26} herein, we report a simple and efficient method for the synthesis of hydroxy substituted indolizines *via* an S_N2 substitution/condensation/tautomerization cascade process in a metal-free fashion. Their optical properties were also evaluated.

Results and discussion

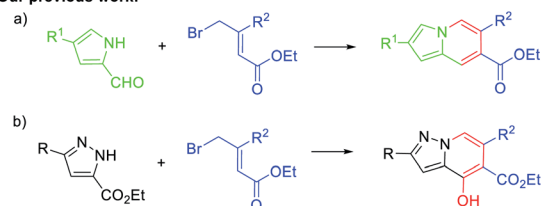
Initially, commercially available pyrrole-2-formaldehyde and ethyl 4-chloro-3-oxobutanoate **2a** were selected for the experimental design. However, only the dimerization product of **2a** was obtained. Subsequently, we optimized the reaction conditions using 4-propionyl-pyrrole-2-formaldehyde **1a** and ethyl 4-chloro-3-oxobutanoate **2a** as the model substrates. To our delight, the desired cyclized product **3a** was obtained in an acceptable 56% yield in the presence of K₂CO₃ (Table 1, entry 1). The reaction even progressed very well at room temperature

Department of Pharmacy, Shandong First Medical University, Shandong Academy of Medical Sciences, Taian, Shandong 271016, P. R. China. E-mail: geyanqing2016@126.com; Fax: +86-538-6229741; Tel: +86-538-6229741

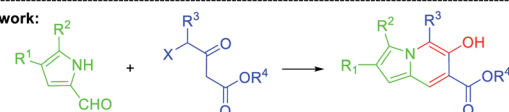
† Electronic supplementary information (ESI) available: ¹H NMR, ¹³C NMR and HRMS spectra of compounds **3a–3l** and **5a–5e**. CCDC 2081693. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra04425g

‡ Guiyun Duan and Hao Liu contributed equally.

Our previous work:

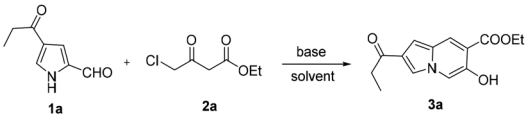


This work:

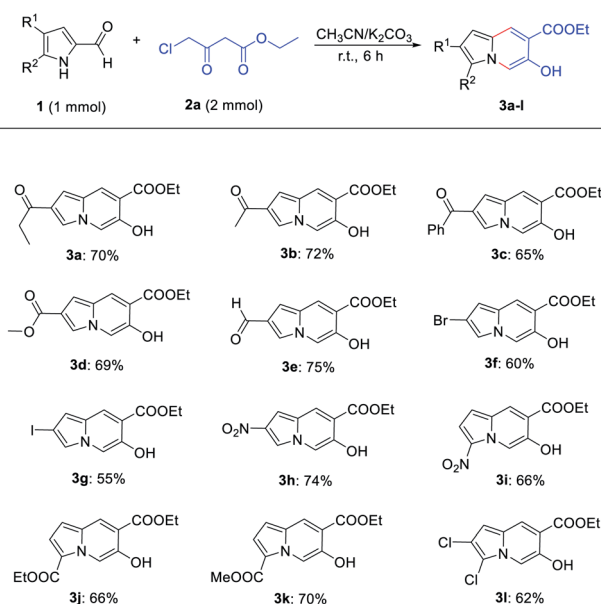
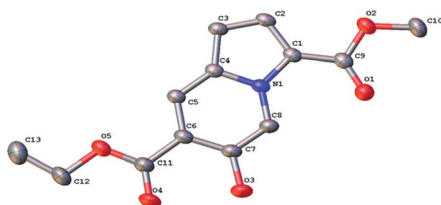
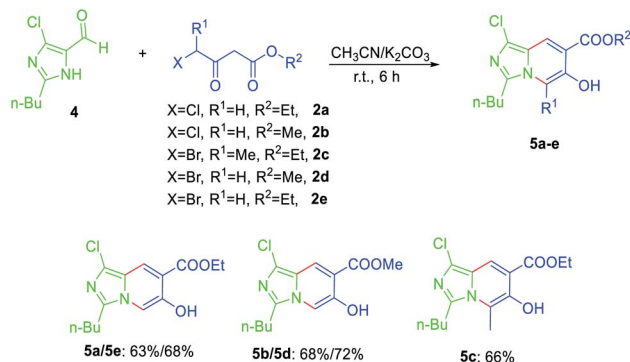


Scheme 1 Access to indolizines *via* a cascade reaction.



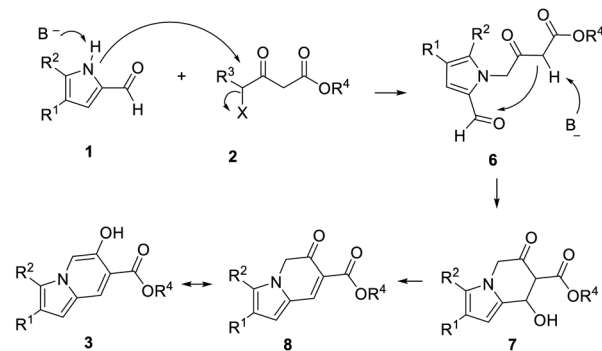
Table 1 Optimization of reaction conditions^a


Entry	Base	T (°C)	Solvent	Time	Yield (%)
1	K ₂ CO ₃	50	MeCN	6 h	56
2	K ₂ CO ₃	25	MeCN	6 h	70
3	DBU	25	MeCN	6 h	54
4	Cs ₂ CO ₃	25	MeCN	6 h	63
5	NaOH	25	MeCN	6 h	42
6	<i>t</i> -BuOK	25	MeCN	6 h	59
7	NaOAc	25	MeCN	6 h	12
8	CsOAc	25	MeCN	6 h	26
9	K ₂ CO ₃	25	DMF	6 h	67
10	K ₂ CO ₃	25	EtOH	6 h	60
11	K ₂ CO ₃	25	Acetone	6 h	62

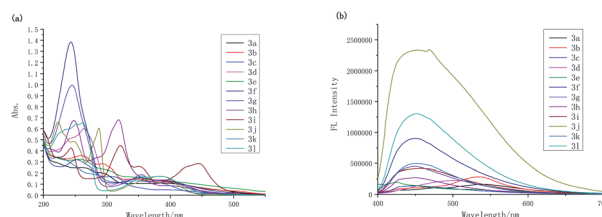
^a 1 mmol **1a**, 2 mmol **2a**, 3 mmol base, and 10 mL solvent were used.Scheme 2 Substrate scope of pyrrole-2-formaldehyde. Reaction conditions: **1** (1 mmol), **2** (2 mmol), K₂CO₃ (3 mmol), CH₃CN (10 mL), 20 °C, 6 h.Fig. 1 X-ray crystal structure of compound **3k**.Scheme 3 Substrate scope studies of 4-halogenated acetoacetic ester. Reaction conditions: **4** (1 mmol), **2** (2 mmol), K₂CO₃ (3 mmol), CH₃CN (10 mL), 20 °C, 6 h.

(entry 2). Other bases such as DBU, Cs₂CO₃, NaOH, *t*-BuOK, NaOAc, and CsOAc were then evaluated. However, the yields decreased, especially for a weak base (NaOAc) (entries 3–8). Regarding the effect of solvents, no improvement in the yield was obtained when the reaction was carried out in DMF, EtOH, and acetone (entries 9–11).

Then, the reactions of various substituted pyrrole-2-formaldehyde were tested (Scheme 2). Generally, the desired products were obtained in moderate-to-good yields when the pyrroles contained electron-withdrawing groups at the 4- or 5-position. However, no product was obtained for pyrrole-2-formaldehyde, presumably due to the reduction of nucleophilicity of the pyrrole ring. The structure of compound **3k** was confirmed by X-ray crystal structure analysis (Fig. 1, CCDC 2081693†).



Scheme 4 The proposed mechanism.

Fig. 2 UV-vis and FL spectra of compounds **3a**–**3l**.

Next, the applicability of this cascade reaction was expanded to the synthesis of imidazo[1,5-*a*]pyridine, furnishing the desired product **5a** in 61% yield. The scope of the 4-halogenated acetoacetic ester was also evaluated (Scheme 3). The results indicate that the halogen and alkyl groups on position 4 and the ether group hardly influenced the yields.

Based on the above mentioned results and our previous work, we propose a mechanism as shown in Scheme 4. First, S_N2 substitution of 4-halogenated acetoacetic ester **2** and pyrrole-2-formaldehyde **1** yields intermediate **6**. Subsequently, cyclized intermediate **7** is formed through intramolecular nucleophilic substitution. Finally, the desired products **3** are obtained through dehydration and tautomerism.

To advance our efforts to search for new fluorophores for cell imaging and their strong luminescence, we investigated the UV-vis and fluorescence spectra of these new compounds (Fig. 2). Compounds **3a–3l** show similar absorptions at *ca.* 250 nm (Table S1†), which should be assigned to the π–π* electronic transition originating from the indolizine ring. Notably, the substituent and their position on the indolizine ring slightly affect these absorption peaks. However, the weak absorption bands between 290 nm and 445 nm due to n–π* electronic transition are especially different for compounds **3h** and **3i** containing a strong electron-withdrawing group (NO₂). The maximum emission bands of **3c**, **3e**, and **3f** are similar (425–455 nm, Table S1†), while those of **3a**, **3b**, and **3d** are 540 nm, 535 nm, and 505 nm, respectively, with a much higher red shift.

Conclusions

In summary, we developed an efficient cascade reaction to construct indolizines and related imidazo[1,5-*a*]pyridines with a hydroxyl group, which is difficult to introduce through other methods. The structure was confirmed by single-crystal X-ray diffraction analysis. The compounds showed strong fluorescence in a dilute solution. Further studies on the optical properties of these indolizines are in progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Innovative Research Programs of Higher Education of Shandong Province (2019KJC009), the Science Fund of Shandong Province for Excellent Young Scholars (ZR2017JL015) and the Natural Science Foundation of China (21801180).

Notes and references

- 1 K. M. Dawood and A. A. Abbas, Inhibitory activities of indolizine derivatives: a patent review, *Expert Opin. Ther. Pat.*, 2020, **30**, 695–714.
- 2 W. Huang, T. Zuo, H. Jin, Z. Liu, Z. Yang, X. Yu, L. Zhang and L. Zhang, Design, synthesis and biological evaluation of

indolizine derivatives as HIV-1 VIF–ElonginC interaction inhibitors, *Mol. Diversity*, 2013, **17**, 221–243.

- 3 R. S. Kumar, P. Antonisamy, A. I. Almansour, N. Arumugam, G. Periyasami, M. Altaf, H. R. Kim and K. B. Kwon, Functionalized spirooxindole-indolizine hybrids: stereoselective green synthesis and evaluation of anti-inflammatory effect involving TNF- α and nitrite inhibition, *Eur. J. Med. Chem.*, 2018, **152**, 417–423.
- 4 S. Park, E. H. Kim, J. Kim, S. H. Kim and I. Kim, Biological evaluation of indolizine–chalcone hybrids as new anticancer agent, *Eur. J. Med. Chem.*, 2018, **144**, 435–443.
- 5 Y. Xue, J. Tang, X. Ma, Q. Li, B. Xie, Y. Hao, H. Jin, K. Wang, G. Zhang, L. Zhang and L. Zhang, Synthesis and biological activities of indolizine derivatives as alpha-7 nAChR agonists, *Eur. J. Med. Chem.*, 2016, **115**, 94–108.
- 6 E. Kim, Y. Lee, S. Lee and S. B. Park, Discovery, Understanding, and bioapplication of organic fluorophore: a case study with an indolizine-based novel fluorophore, Seoul-Fluor, *Acc. Chem. Res.*, 2015, **48**, 538–547.
- 7 A. J. Huckaba, A. Yella, L. E. McNamara, A. E. Steen, J. S. Murphy, C. A. Carpenter, G. D. Punecky, N. I. Hammer, M. K. Nazeeruddin, M. Gratzel and J. H. Delcamp, Molecular design principles for near-infrared absorbing and emitting indolizine dyes, *Chem.–Eur. J.*, 2016, **22**, 15536–15542.
- 8 W. E. Meador, S. A. Autry, R. N. Bessetti, J. N. Gayton, A. S. Flynt, N. I. Hammer and J. H. Delcamp, Water-soluble NIR absorbing and emitting indolizine cyanine and indolizine squaraine dyes for biological imaging, *J. Org. Chem.*, 2020, **85**, 4089–4095.
- 9 R. Ji, A. Liu, S. Shen, X. Cao, F. Li and Y. Ge, An indolizine-rhodamine based FRET fluorescence sensor for highly sensitive and selective detection of Hg²⁺ in living cells, *RSC Adv.*, 2017, **7**, 40829–40833.
- 10 Y. Ge, A. Liu, J. Dong, G. Duan, X. Cao and F. Li, A simple pH fluorescent probe based on new fluorophore indolizine for imaging of living cells, *Sens. Actuators, B*, 2017, **247**, 46–52.
- 11 X. Zheng, R. Ji, X. Cao and Y. Ge, FRET-based ratiometric fluorescent probe for Cu²⁺ with a new indolizine fluorophore, *Anal. Chim. Acta*, 2017, **978**, 48–54.
- 12 B. Sadowski, J. Klajn and D. T. Gryko, Recent advances in the synthesis of indolizines and their π -expanded analogues, *Org. Biomol. Chem.*, 2016, **14**, 7804–7828.
- 13 D. Yadagiri, M. Rivas and V. Gevorgyan, Denitrogenative transformations of pyridotriazoles and related compounds: synthesis of N-containing heterocyclic compounds and beyond, *J. Org. Chem.*, 2020, **85**, 11030–11046.
- 14 S. Dong, X. Fu and X. Xu, [3 + 2]-Cycloaddition of catalytically generated pyridinium ylide: a general access to indolizine derivatives, *Asian J. Org. Chem.*, 2020, **9**, 1133–1143.
- 15 (a) R. R. Liu, J. J. Hong, C. J. Lu, M. Xu, J. R. Gao and Y. X. Jia, Indolizine synthesis *via* oxidative cross-coupling/cyclization of alkenes and 2-(pyridin-2-yl)acetate derivatives, *Org. Lett.*, 2015, **17**, 3050–3053; (b) C. Dohmen, H. Ihmels, R. Kreienmeier and B. O. Patrick, Synthesis of a crystallochromic indolizine dye by a base- and cataly-



- free photochemical route, *Chem. Commun.*, 2019, **55**, 11071–11074.
- 16 (a) Y. Liu, H. Hu, J. Zhou, W. Wang, Y. He and C. Wang, Synthesis of indolizine derivatives containing eight-membered rings *via* a gold-catalyzed twofold hydroarylation of diynes, *Org. Biomol. Chem.*, 2017, **15**, 5016–5024; (b) B. Cheng, H. Li, S. Duan, X. Zhang, Y. He, Y. Li, Y. Li, T. Wang and H. Zhai, Application of primary halogenated hydrocarbons for the synthesis of 3-aryl and 3-alkyl indolizines, *Org. Biomol. Chem.*, 2020, **18**, 6253–6257; (c) X. Wu, P. Zhao, X. Geng, J. Zhang, X. Gong, Y. D. Wu and A. X. Wu, Synthesis of indolizines from pyridinium 1,4-zwitterionic thiolates and propiolic acid derivatives *via* a formal [4 + 1] pathway, *Org. Lett.*, 2017, **19**, 3319–3322.
- 17 (a) T. Jin, Z. Tang, J. Hu, H. Yuan, Y. Chen, C. Li, X. Jia and J. Li, Direct oxidative cleavage of multiple C_{sp3}–H bonds and a C–C bond in 2-(pyridin-2-yl)acetate derivatives: formal [3 + 1 + 1] synthesis of 3-(pyridin-2-yl)indolizine skeletons, *Org. Lett.*, 2018, **20**, 413–416; (b) F. Sirindil, S. Golling, R. Lamare, J. M. Weibel, P. Pale and A. Blanc, Synthesis of indolizine and pyrrolo[1,2-*a*]azepine derivatives *via* a gold(i)-catalyzed three-step cascade, *Org. Lett.*, 2019, **21**, 8997–9000; (c) Y.-H. Zhang, Y.-H. Yuan, S.-Y. Zhang, Y.-Q. Tu and J.-M. Tian, Asymmetric intramolecular Friedel–Crafts reaction catalyzed by a spiropyrrolidine organocatalyst: Enantioselective construction of indolizine and azepine frameworks, *Tetrahedron Lett.*, 2018, **59**, 4015–4018.
- 18 (a) T. Douglas, A. Pordea and J. Dowden, Iron-catalyzed indolizine synthesis from pyridines, diazo compounds, and alkynes, *Org. Lett.*, 2017, **19**, 6396–6399; (b) A. S. Kulandai Raj, K. C. Tan, L. Y. Chen, M. J. Cheng and R. S. Liu, Gold-catalyzed bicyclic annulations of 4-methoxy-1,2-dienyl-5-yne with isoxazoles to form indolizine derivatives *via* an Au-*p*-allene intermediate, *Chem. Sci.*, 2019, **10**, 6437–6442.
- 19 (a) C. Jadala, V. Ganga Reddy, N. Hari Krishna, N. Shankaraiah and A. Kamal, Base-mediated 1,3-dipolar cycloaddition of pyridinium bromides with bromoallyl sulfones: a facile access to indolizine scaffolds, *Org. Biomol. Chem.*, 2020, **18**, 8694–8701; (b) J. Li, S. Zhang and H. Zou, One-pot chemoselective domino condensation to form fused pyrrolo-pyrazino-indolizines framework: discovery of novel AIE molecules, *Org. Chem. Front.*, 2020, **7**, 1218–1223.
- 20 (a) C.-J. Lu, X. Yu, Y.-T. Chen, Q.-B. Song and H. Wang, Indolizine synthesis *via* copper-catalyzed cyclization of gem difluoroalkenes and 2-(pyridin-2-yl)acetate derivatives, *Org. Chem. Front.*, 2020, **7**, 2313–2318; (b) S. Jin, L. Wang, H. Han, X. Liu, Z. Bu and Q. Wang, Assembly of functionalized *p*-extended indolizine polycycles through dearomative [3 + 2] cycloaddition/oxidative decarbonylation, *Chem. Commun.*, 2021, **57**, 359–362.
- 21 (a) Y. Q. Ge, J. Jia, H. Yang, X. T. Tao and J. W. Wang, The synthesis, characterization and optical properties of novel pyrido[1,2-*a*]benzimidazole derivatives, *Dyes Pigm.*, 2011, **88**, 344–349; (b) Y. Ge, J. Jia, H. Yang, G. Zhao, F. Zhan and J. Wang, A facile approach to indolizines *via* tandem reaction, *Heterocycles*, 2009, **78**, 725–736.
- 22 P. Yan, G. Duan, R. Ji and Y. Ge, A simple and efficient synthesis of new fluorophore 4-hydroxy pyrazolo[1,5-*a*]pyridines through a tandem reaction, *Tetrahedron Lett.*, 2018, **59**, 2426–2429.
- 23 (a) Y. Ge, X. Zheng, R. Ji, S. Shen and X. Cao, A new pyrido[1,2-*a*]benzimidazole-rhodamine FRET system as an efficient ratiometric fluorescent probe for Cu²⁺ in living cells, *Anal. Chim. Acta*, 2017, **965**, 103–110; (b) Y. Ge, R. Ji, S. Shen, X. Cao and F. Li, A ratiometric fluorescent probe for sensing Cu²⁺ based on new imidazo[1,5-*a*]pyridine fluorescent dye, *Sens. Actuators, B*, 2017, **245**, 875–881; (c) G. Duan, G. Zhang, S. Yuan, R. Ji, L. Zhang and Y. Ge, A pyrazolo[1,5-*a*]pyridine-based ratiometric fluorescent probe for sensing Cu²⁺ in cell, *Spectrochim. Acta, Part A*, 2019, **219**, 173–178; (d) Y. Ge, A. Liu, R. Ji, S. Shen and X. Cao, Detection of Hg²⁺ by a FRET ratiometric fluorescent probe based on a novel pyrido[1,2-*a*]benzimidazole-rhodamine system, *Sens. Actuators, B*, 2017, **251**, 410–415.
- 24 (a) Y. Ge, X. Xing, A. Liu, R. Ji, S. Shen and X. Cao, A novel imidazo[1,5-*a*]pyridine-rhodamine FRET system as an efficient ratiometric fluorescent probe for Hg²⁺ in living cells, *Dyes Pigm.*, 2017, **146**, 136–142; (b) Y. Li, S. Qi, C. Xia, Y. Xu, G. Duan and Y. Ge, A FRET ratiometric fluorescent probe for detection of Hg²⁺ based on an imidazo[1,2-*a*]pyridine-rhodamine system, *Anal. Chim. Acta*, 2019, **1077**, 243–248; (c) A. Liu, R. Ji, S. Shen, X. Cao and Y. Ge, A ratiometric fluorescent probe for sensing sulfite based on a pyrido[1,2-*a*]benzimidazole fluorophore, *New J. Chem.*, 2017, **41**, 10096–10100; (d) Z. Xu, Z. Chen, A. Liu, R. Ji, X. Cao and Y. Ge, A ratiometric fluorescent probe for detection of exogenous mitochondrial SO₂ based on a FRET mechanism, *RSC Adv.*, 2019, **9**, 8943–8948.
- 25 (a) F. Chen, A. Liu, R. Ji, Z. Xu, J. Dong and Y. Ge, A FRET-based probe for detection of the endogenous SO₂ in cells, *Dyes Pigm.*, 2019, **165**, 212–216; (b) D. Zhang, A. Liu, R. Ji, J. Dong and Y. Ge, A mitochondria-targeted and FRET-based ratiometric fluorescent probe for detection of SO₂ derivatives in water, *Anal. Chim. Acta*, 2019, **1055**, 133–139; (c) G. Zhang, R. Ji, X. Kong, F. Ning, A. Liu, J. Cui and Y. Ge, A FRET based ratiometric fluorescent probe for detection of sulfite in food, *RSC Adv.*, 2019, **9**, 1147–1150; (d) G. Song, A. Liu, H. Jiang, R. Ji, J. Dong and Y. Ge, A FRET-based ratiometric fluorescent probe for detection of intrinsically generated SO₂ derivatives in mitochondria, *Anal. Chim. Acta*, 2019, **1053**, 148–154.
- 26 Y. Ge, P. Wei, T. Wang, X. Cao, D. Zhang and F. Li, A simple fluorescent probe for monitoring pH in cells based on new fluorophore pyrido[1,2-*a*]benzimidazole, *Sens. Actuators, B*, 2018, **254**, 314–320.

