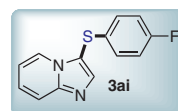
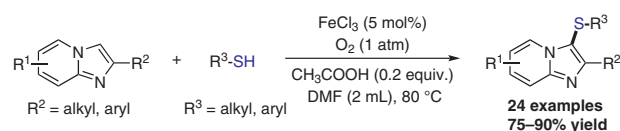


Aerobic Iron(III)-Catalyzed Direct Thiolation of Imidazo[1,2-*a*]-pyridine with Thiols

Ling Qin^aHui-bin Wu^aLidong Weng^bQun Shen^{*b}Huoji Chen^{*b} 

HeLa cells: IC50 = 9.37 μM
 A-549 cells: IC50 = 4.25 μM
 BGC-823 cells: IC50 = 5.22 μM
 normal cell line (VEC): IC50 >100 μM

^a Department of Pharmaceutics, Nanfang Hospital, Southern Medical University, Guangzhou 510515, P. R. of China

^b School of Traditional Chinese Medicine, Southern Medical University, Shatainan road 1023th, Guangzhou 510515, P. R. of China
 sq@smu.edu.cn
 chenhuoji@smu.edu.cn

[§] These authors contributed equally to this work.

Received: 10.03.2020

Accepted after revision: 31.03.2020

Published online: 21.04.2020

DOI: 10.1055/s-0040-1707517; Art ID: so-2020-d0010-op

License terms:

© 2020. The Author(s). This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Abstract A novel and efficient iron(III)-catalyzed regioselective C-3 sulfenylation of imidazo[1,2-*a*]pyridines with thiols under oxygen atmosphere has been developed. The reaction proceeds in moderate to good yields with a broad range of substrates, providing a novel, efficient and green route for accessing synthetically useful C3-sulfenated imidazo[1,2-*a*]pyridines. Moreover, the fluoride-containing C3-sulfenated imidazo[1,2-*a*]pyridine **3ai** exhibited superior anticancer activity and good safety profiles.

Key words iron-catalyzed, thiolation, imidazo[1,2-*a*]pyridine, thiols, anticancer activity

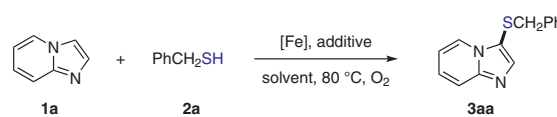
The imidazo[1,2-*a*]pyridine ring system is a significant azaheterocycle^{1,2} that exists in a large number of pharmaceutical and natural products^{3–6} showing a range of biological properties, such as antiviral,⁷ antiherpes,⁸ antiulcer⁹ and antiapoptotic activities.¹⁰ Moreover, these compounds also represent a pivotal structural scaffold in functional materials such as fluorescent dyes.¹¹ Thus, substituted imidazo[1,2-*a*]pyridines have attracted the continuous interest of organic chemists^{12–15} and great efforts have been devoted the development of synthetic methodologies to access this class of compound.^{16,17}

The presence of a C–S bond on an azaaromatic nucleus can contribute prominent biological activities.¹⁸ Many elegant formylation processes have been developed for the sulfenylation at C3 of imidazo[1,2-*a*]pyridines.^{19–28} However, there is no report on iron-catalyzed sulfenylation of imidazo[1,2-*a*]pyridine derivatives with thiols.

Iron is inexpensive, environmentally friendly, low in toxicity, easy to use, and stable in performance. Therefore, iron-catalyzed organic conversions have recently attracted great interest from the synthetic community.^{29,30} As a part of our ongoing studies focusing on iron-catalyzed cross-coupling reactions,^{31,32} herein, we wish to report a novel and mild protocol for the C-3 sulfenylation of imidazo[1,2-*a*]pyridines using thiols in the presence of iron(III) catalyst under ambient conditions.

We began our study by investigating the thiolation of imidazo[1,2-*a*]pyridine with thiols (Table 1). Optimization of the reaction conditions showed that the solvent played a crucial role in reaction efficiency, with DMF being optimal for the C-3 thiolation of imidazo[1,2-*a*]pyridine under atmospheric pressure of dioxygen (entries 1–5). Furthermore, FeCl₃ was superior to other Fe catalysts, such as FeCl₂, FeBr₃, FeBr₂, or Fe(NO₃)₃ (entries 6–9). Addition of acetic acid greatly promoted the FeCl₃-catalyzed C-3 thiolation reaction of **1a** (entries 10–17). Increasing the reaction temperature led to a higher reaction rate, but the yields and conversions were not improved, with starting material being recovered. Finally, in the absence of Fe catalyst or oxygen atmosphere, no desired product was obtained (entries 18 and 19). These studies led to the following conditions being taken as optimal: **1a** (0.3 mmol), **2a** (0.4 mmol), 5 mol% FeCl₃ and 20 mol% CH₃COOH in 2 mL of DMF at 80 °C for 12 h under atmosphere of oxygen.

With the optimized conditions in hand, the substrate scope with respect to imidazo[1,2-*a*]pyridines was first examined; the results are summarized in Scheme 1. A variety of imidazo[1,2-*a*]pyridines bearing electron-withdrawing or electron-donating groups afforded the desired products in good yields. Imidazo[1,2-*a*]pyridines bearing electron-donating methyl groups at the 5-, 6-, 7-, and 8-positions smoothly reacted with benzyl mercaptan (**2a**) to give the corresponding C3-sulfenated imidazo[1,2-*a*]pyridine

Table 1 Optimization of Reaction Conditions^a


Entry	[Fe]	Additive	Solvent	Yield (%) ^b
1	FeCl ₃	–		35
2	FeCl ₃	–	dioxane	27
3	FeCl ₃	–	toluene	32
4	FeCl ₃	–	DCE	22
5	FeCl ₃	–	DMF	42
6	FeCl ₂	–	DMF	31
7	FeBr ₃	–	DMF	25
8	FeBr ₂	–	DMF	22
9	Fe(NO ₃) ₃	–	DMF	18
10	FeCl ₃	TsOH	DMF	47
11	FeCl ₃	HCl	DMF	54
12	FeCl ₃	CH ₃ COOH	DMF	88
13	FeCl ₃	CF ₃ COOH	DMF	73
14	FeCl ₃	CH ₃ SO ₃ H	DMF	71
15	FeCl ₃	CF ₃ SO ₃ H	DMF	66
16	FeCl ₃	C ₆ H ₅ OH	DMF	67
17	FeCl ₃	C ₆ H ₅ COOH	DMF	72
18	–	CH ₃ COOH	DMF	n.d.
19 ^c	FeCl ₃	CH ₃ COOH	DMF	n.d.

^a Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.3 mmol), **2a** (0.4 mmol), Fe catalyst (5 mol%), additive (20 mol%) and solvent (2 mL), at 80 °C under O₂ (1 atm) for 12 h.

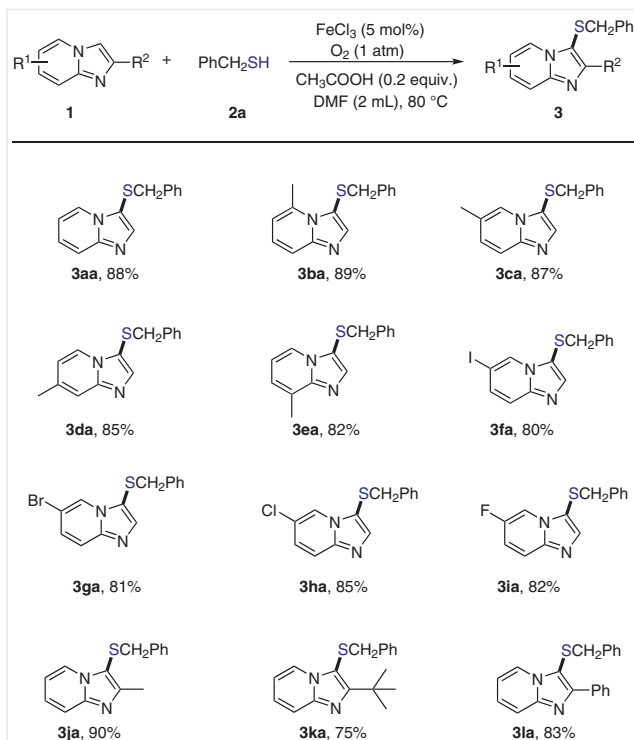
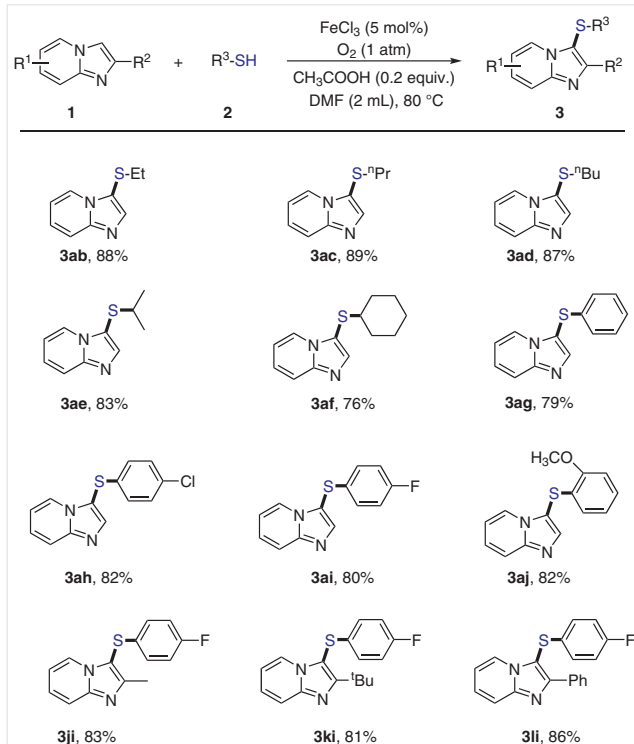
^b Isolated yield.

^c N₂ atmosphere.

3aa–ia in good yields. Notably, halogen substituents were well tolerated and provided the corresponding fluoro-, chloro-, and bromo-products **3ga–ia** in 82, 85, and 81% yields, respectively. Substrates with a range of substituents at C2 were also applicable to this reaction (**3ja–la**).

Next, the scope of the reaction with thiols was examined; the results are illustrated in Scheme 2. The reaction of both aliphatic and aromatic thiols proceeded smoothly and the corresponding C-3 sulfenated products were obtained in 76–89% yields. Aliphatic secondary thiols, such as propane-2-thiol and cyclohexane thiol, reacted smoothly with imidazo[1,2-*a*]pyridine **1a** to afford the corresponding C3-sulfenated products **3ae–af**. Aromatic thiols bearing electron-withdrawing or electron-donating groups afforded the desired products **3ag–baj** in good yields. Notably, the reaction could afford C3-sulfenated products **3ji**, **3ki**, and **3li** in good yields when carried out using 2-substituted imidazo[1,2-*a*]pyridines as substrates with 4-fluorothiophenol.

Recently, we found that the fluorine-containing compounds could exhibit anticancer activity.³³ This result prompted us to screen fluorine-containing C-3 sulfenated

**Scheme 1** Substrate scope of the reaction with imidazo[1,2-*a*]pyridines**Scheme 2** Substrate scope of the reaction with thiols

imidazo[1,2-*a*]pyridines as antitumor agents against three human cancer cell lines (HeLa, A-549 and BGC-823) and a normal cell line (VEC) in vitro using MTT cell proliferation

assays (Table 2). The data reveal that fluorine-containing C-3 sulfenated imidazo[1,2-*a*]pyridine **3ai** exhibited superior anticancer activity (HeLa cells ($IC_{50} = 9.37 \mu\text{M}$), A-549 cells ($IC_{50} = 4.25 \mu\text{M}$) and BGC-823 cells ($IC_{50} = 5.22 \mu\text{M}$)) and good safety profiles ($IC_{50} > 100 \mu\text{M}$ against VEC).

Table 2 The Inhibiting Effect of Fluorine-Containing C3-Sulfenated Imidazo[1,2-*a*]pyridines to HeLa, A-549 and BGC-823 Cell Lines In Vitro

Compd.	Normal cells IC_{50} ($\mu\text{mol}\cdot\text{L}^{-1}$) ^a	Cancer cells IC_{50} ($\mu\text{mol}\cdot\text{L}^{-1}$) ^a		
	VEC	HeLa	A-549	BGC-823
3ia	55.4	38.3	18.7	21.6
3ai	>100	9.37	4.25	5.22
3ki	92.2	15.2	9.32	8.62
3ji	91.8	18.7	12.8	13.0
3li	90.3	20.1	14.5	16.6
3aa	52.2	33.1	20.7	25.3

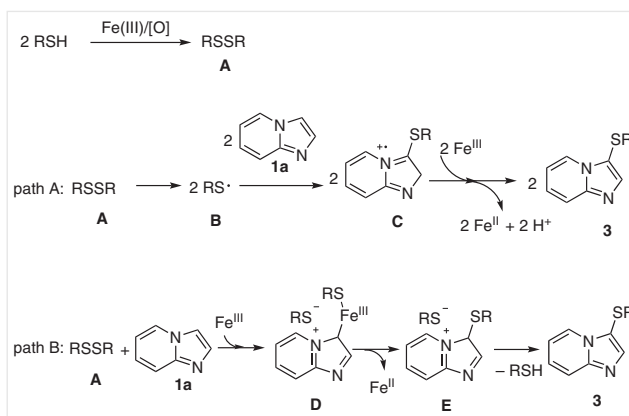
^a IC_{50} values are the mean of three independent experiments run in triplicate.

To gain some insight into the reaction mechanism, a control experiment was then carried out, wherein the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was found to suppress the reaction (Scheme 3), suggesting that this transformation is probably a radical process.



Scheme 3 Control experiments

Based on the control experiment and on previous work,^{28,31} a plausible reaction mechanism is proposed in Scheme 4. Initially, disulfide **A** is generated from sodium phenylsulfinate. Subsequently, the thio radical **B** is produced via direct radical cracking and then undergoes radical addition to imidazo[1,2-*a*]pyridine to form intermediate **C**. Finally, a single-electron oxidation followed by aromatization leads to the product **3** (Path A).³⁴ However, other reaction mechanism may also be possible. For example, disulfide **A** could react with imidazo[1,2-*a*]pyridine and Fe^{III} to form the Fe–C bonded intermediate **D**.³⁰ Then, intermediate **D** could undergo reductive elimination to form intermediate **E**. Finally, deprotonation of intermediate **E** would lead to product **3** (Path B).



Scheme 4 Possible reaction mechanism

In conclusion, we have developed a new iron(III)-catalyzed method for the regioselective C-3 sulfenylation of imidazo[1,2-*a*]pyridines with thiols under an oxygen atmosphere. The reaction proceeds in moderate to good yields with a broad range of substrates, providing a novel efficient and green route for accessing synthetically useful C3-sulfenated imidazo[1,2-*a*]pyridines. Moreover, the fluoride-containing C3-sulfenated imidazo[1,2-*a*]pyridine **3ai** exhibited superior anticancer activity and good safety profiles. This topic is currently being further studied in our laboratory.

¹H and ¹³C NMR spectra were recorded with a BRUKER DRX-400 spectrometer using CDCl_3 as solvent and TMS as an internal standard. IR spectra were obtained either as potassium bromide discs or as liquid films between two potassium bromide pellets. GC-MS analyses were obtained using electron ionization. HRMS analyses were obtained with a LCMS-IT-TOF mass spectrometer. TLC analyses were performed using commercial 100–400 mesh silica gel plates, and visualization was effected at 254 nm.

General Procedure

A mixture of imidazo[1,2-*a*]pyridine **1** (0.3 mmol), thiol **2** (0.4 mmol), CH_3COOH (0.2 equiv, 0.06 mmol) and FeCl_3 (5 mol %) in DMF (2 mL) was stirred at 80 °C under air for 24 h. The reaction mixture was diluted with H_2O (15 mL), extracted with EtOAc (3 × 15 mL) and the combined organic extracts were dried over MgSO_4 . After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel to afford desired product **3**.

3-(Benzylthio)imidazo[1,2-*a*]pyridine (**3aa**)^{19c}

Yield: 88% (63 mg); yellow oil.

¹H NMR (400 MHz, CDCl_3): $\delta = 8.05$ (s, 1 H), 7.57–7.77 (m, 2 H), 7.17 (t, $J = 5.2$ Hz, 4 H), 6.96 (d, $J = 6.0$ Hz, 2 H), 6.69 (t, $J = 6.4$ Hz, 1 H), 3.79 (s, 2 H).

¹³C NMR (100 MHz, CDCl_3): $\delta = 141.6, 137.7, 128.6, 128.5, 128.3, 127.3, 127.0, 125.3, 124.1, 117.7, 112.4, 41.5$.

3-(Benzylthio)-5-methylimidazo[1,2-*a*]pyridine (**3ba**)^{19e}

Yield: 89% (68 mg); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.57 (s, 1 H), 7.50 (d, *J* = 8.8 Hz, 1 H), 7.06–7.20 (m, 4 H), 6.93 (m, 2 H), 6.46 (d, *J* = 6.8 Hz, 1 H), 3.83 (s, 2 H), 2.83 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 144.4, 138.2, 136.9, 129.4, 128.7, 128.6, 128.5, 127.3, 125.8, 116.2, 114.3, 45.7, 21.0.

3-(Benzylthio)-6-methylimidazo[1,2-*a*]pyridine (3ca)^{19e}

Yield: 89% (66 mg); white solid; mp 155–156 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.70 (s, 1 H), 7.60 (s, 1 H), 7.48 (d, *J* = 9.2 Hz, 1 H), 7.10–7.19 (m, 3 H), 6.97–7.03 (m, 3 H), 3.79 (s, 2 H), 2.20 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 141.4, 138.0, 128.7, 128.5, 128.4, 127.3, 122.0, 121.8, 117.0, 41.8, 18.1.

3-(Benzylthio)-7-methylimidazo[1,2-*a*]pyridine (3da)^{19e}

Yield: 85% (65 mg); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.91 (d, *J* = 6.4 Hz, 1 H), 7.58 (s, 1 H), 7.35 (s, 1 H), 7.14–7.16 (m, 3 H), 6.98 (d, *J* = 5.2 Hz, 2 H), 6.54 (d, *J* = 6.8 Hz, 1 H), 3.78 (s, 2 H), 2.36 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 141.3, 137.8, 136.7, 128.6, 128.5, 127.3, 123.2, 116.2, 115.1, 41.6, 21.2.

3-(Benzylthio)-8-methylimidazo[1,2-*a*]pyridine (3ea)^{19e}

Yield: 82% (63 mg); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.93 (d, *J* = 6.8 Hz, 1 H), 7.63 (s, 1 H), 7.15–7.27 (m, 3 H), 6.99–7.01 (d, 3 H), 6.65 (t, *J* = 6.8 Hz, 1 H), 3.80 (s, 2 H), 2.60 (s, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 147.6, 140.6, 137.7, 128.6, 128.5, 127.4, 127.3, 124.5, 121.8, 113.7, 112.5, 41.5, 16.6.

3-(Benzylthio)-6-iodoimidazo[1,2-*a*]pyridine (3fa)^{19e}

Yield: 82% (88 mg); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 8.00 (s, 1 H), 7.60 (s, 1 H), 7.28–7.33 (m, 2 H), 7.10–7.19 (m, 3 H), 6.91–6.93 (m, 2 H), 3.78 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 145.9, 141.7, 137.6, 133.3, 129.2, 128.6, 128.5, 127.8, 118.5, 113.6, 75.8, 42.1.

3-(Benzylthio)-6-bromoimidazo[1,2-*a*]pyridine (3ga)^{19e}

Yield: 81% (77 mg); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.94 (s, 1 H), 7.66 (s, 1 H), 7.43 (d, *J* = 9.2 Hz, 1 H), 7.10–7.19 (m, 4 H), 6.92–6.94 (m, 2 H), 3.78 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 142.2, 137.6, 128.8, 128.6, 128.5, 127.7, 124.4, 118.2, 107.4, 41.9.

3-(Benzylthio)-6-chloroimidazo[1,2-*a*]pyridine (3ha)^{19e}

Yield: 85% (70 mg); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.89 (s, 1 H), 7.71 (s, 1 H), 7.51 (d, *J* = 9.2 Hz, 1 H), 7.13–7.19 (m, 4 H), 6.95 (d, *J* = 6.8 Hz, 2 H), 3.80 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 142.3, 137.6, 128.6, 127.6, 126.8, 122.2, 121.0, 118.0, 41.9.

3-(Benzylthio)-6-fluoroimidazo[1,2-*a*]pyridine (3ia)

Yield: 82% (63 mg); yellow oil.

IR (KBr): 2968, 2854, 1542, 1459, 1367, 737 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.40 (m, 1 H), 7.79 (m, 1 H), 7.68 (s, 1 H), 7.17–7.15 (m, 3 H), 6.98 (d, *J* = 5.2 Hz, 2 H), 6.54 (m, 1 H), 3.78 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 153.8 (*J* = 232.0 Hz), 142.2, 128.5, 118.6 (*J* = 9.0 Hz), 118.5, 117.3 (*J* = 25.0 Hz), 117.0, 111.4 (*J* = 31.0 Hz), 114.0, 41.9.

HRMS (EI): *m/z* calcd for C₁₄H₁₁FN₂S: 258.0629; found: 258.0627.

3-(Benzylthio)-2-methylimidazo[1,2-*a*]pyridine (3ja)^{19e}

Yield: 90% (69 mg); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 8.07 (d, *J* = 6.5 Hz, 1 H), 7.53 (d, *J* = 8.9 Hz, 1 H), 7.13–7.22 (m, 4 H), 6.92 (d, *J* = 6.8 Hz, 2 H), 6.73 (t, *J* = 6.8 Hz, 1 H), 3.75 (s, 2 H), 2.26 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 150.9, 143.4, 137.7, 132.2, 128.7, 128.5, 127.2, 125.6, 124.0, 116.6, 112.1, 40.1, 13.5.

3-(Benzylthio)-2-(*tert*-butyl)imidazo[1,2-*a*]pyridine (3ka)^{19e}

Yield: 75% (67 mg); white solid; mp 89–90 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.98 (d, *J* = 6.8 Hz, 1 H), 7.55 (d, *J* = 8.8 Hz, 1 H), 7.00–7.13 (m, 5 H), 6.58 (t, *J* = 6.6 Hz, 1 H), 3.79 (s, 2 H), 1.54 (s, 9 H).

¹³C NMR (100 MHz, CDCl₃): δ = 161.0, 145.1, 137.3, 128.7, 128.6, 127.3, 125.1, 123.5, 116.9, 111.8, 108.1, 41.1, 34.0, 30.7.

3-(Benzylthio)-2-phenylimidazo[1,2-*a*]pyridine (3la)

Yield: 75% (79 mg); white solid; mp 96–98 °C.

IR (KBr): 2975, 2884, 1466, 1394, 1373, 1367, 741 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.43 (d, *J* = 6.8 Hz, 1 H), 7.78 (d, *J* = 8.8 Hz, 1 H), 7.61 (s, 1 H), 7.31–7.59 (m, 5 H), 7.13–7.23 (m, 5 H), 6.88 (t, *J* = 7.0 Hz, 1 H), 3.91 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 146.2, 142.5, 130.2, 129.9, 127.2, 127.1, 126.4, 125.9, 124.6, 123.7, 121.4, 119.7, 118.0, 113.0, 43.3.

HRMS (EI): *m/z* calcd for C₂₀H₁₆N₂S: 316.1038; found: 316.1034.

3-(Ethylthio)imidazo[1,2-*a*]pyridine (3ab)^{19e}

Yield: 88% (47 mg); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 8.53 (s, 1 H), 8.01 (s, 1 H), 7.66 (s, 1 H), 7.25 (s, 1 H), 6.91 (t, *J* = 5.6 Hz, 1 H), 2.62 (q, *J* = 6.4 Hz, 2 H), 1.19 (t, *J* = 6.0 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 147.4, 141.0, 128.4, 122.5, 121.9, 117.3, 113.1, 40.0, 13.9.

3-(Propylthio)imidazo[1,2-*a*]pyridine (3ac)^{19e}

Yield: 89% (51 mg); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 8.48 (s, 1 H), 7.89 (s, 1 H), 7.65 (s, 1 H), 7.25 (s, 1 H), 6.91 (t, *J* = 5.6 Hz, 1 H), 2.59 (t, *J* = 6.4 Hz, 2 H), 1.55 (q, *J* = 6.8 Hz, 2 H), 0.96 (t, *J* = 6.0 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 147.5, 141.0, 128.4, 125.1, 124.3, 117.9, 112.6, 37.7, 23.0, 12.9.

3-(Butylthio)imidazo[1,2-*a*]pyridine (3ad)^{19e}

Yield: 87% (54 mg); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 8.43 (d, *J* = 6.8 Hz, 1 H), 7.77 (s, 1 H), 7.64 (d, *J* = 9.2 Hz, 1 H), 7.24 (t, *J* = 8.0 Hz, 1 H), 6.92 (t, *J* = 6.8 Hz, 1 H), 2.61 (t, *J* = 7.2 Hz, 2 H), 1.36–1.52 (m, 4 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 147.3, 140.8, 125.2, 124.1, 117.9, 114.0, 112.7, 35.4, 31.7, 21.5, 13.56.

3-(Isopropylthio)imidazo[1,2-*a*]pyridine (3ae)^{19e}

Yield: 83% (48 mg); yellow oil.

^1H NMR (400 MHz, CDCl_3): δ = 8.46 (s, 1 H), 7.88 (s, 1 H), 7.65 (s, 1 H), 7.25 (s, 1 H), 6.91 (t, J = 5.6 Hz, 1 H), 3.03–3.06 (m, 1 H), 1.20 (d, J = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 141.7, 136.2, 123.5, 116.3, 115.2, 112.6, 39.8, 23.1.

3-(Cyclohexylthio)imidazo[1,2-*a*]pyridine (3af)^{19e}

Yield: 76% (53 mg); yellow oil.

^1H NMR (400 MHz, CDCl_3): δ = 8.43 (d, J = 6.8 Hz, 1 H), 7.77 (s, 1 H), 7.64 (d, J = 9.2 Hz, 1 H), 7.24 (t, J = 8.0 Hz, 1 H), 6.92 (t, J = 6.8 Hz, 1 H), 2.67–2.74 (m, 1 H), 1.59–1.89 (m, 5 H), 1.19–1.34 (m, 5 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 147.3, 140.8, 125.2, 124.1, 117.9, 114.0, 112.7, 32.6, 25.9, 25.5, 21.4.

3-(Phenylthio)imidazo[1,2-*a*]pyridine (3ag)²⁸

Yield: 79% (54 mg); white solid; mp 84–87 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.16 (d, J = 6.8 Hz, 1 H), 7.96 (s, 1 H), 7.67 (d, J = 6.8 Hz, 1 H), 7.26 (t, J = 6.8 Hz, 1 H), 7.16 (t, J = 7.2 Hz, 2 H), 7.09 (t, J = 7.2 Hz, 1 H), 6.95 (d, J = 8.0 Hz, 2 H), 6.82 (t, J = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 148.1, 142.4, 135.2, 129.3, 126.2, 126.0, 124.9, 124.3, 118.1, 113.2, 110.7.

3-((4-Chlorophenyl)thio)imidazo[1,2-*a*]pyridine (3ah)^{19g}

Yield: 82% (64 mg); yellow solid; mp 146–147 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.18 (d, J = 6.8 Hz, 1 H), 7.99 (s, 1 H), 7.71 (d, J = 6.8 Hz, 1 H), 7.31 (t, J = 6.8 Hz, 2 H), 7.16 (d, J = 8.4 Hz, 1 H), 6.92 (d, J = 8.4 Hz, 1 H), 6.91–6.86 (m, 2 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 148.2, 142.5, 133.7, 132.2, 129.4, 127.5, 126.2, 124.1, 118.2, 113.4, 110.2.

3-((4-Fluorophenyl)thio)imidazo[1,2-*a*]pyridine (3ai)²⁸

Yield: 80% (59 mg); white solid; mp 82–84 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.16 (d, J = 6.8 Hz, 1 H), 7.97 (s, 1 H), 7.69 (t, J = 3.6 Hz, 1 H), 7.50 (d, J = 2.4 Hz, 1 H), 7.16 (d, J = 8.8 Hz, 2 H), 6.91–6.86 (m, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.7 (d, J = 242.2 Hz), 148.2, 142.6, 130.9 (d, J = 4.8 Hz), 128.8 (d, J = 7.6 Hz), 126.3, 124.2, 118.3, 116.5 (d, J = 22.4 Hz), 113.4, 110.2.

3-((2-Methoxyphenyl)thio)imidazo[1,2-*a*]pyridine (3aj)^{19g}

Yield: 82% (63 mg); white solid; mp 145–146 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.25 (d, J = 6.8 Hz, 1 H), 7.98 (s, 1 H), 7.71 (d, J = 9.0 Hz, 1 H), 7.33–7.27 (m, 1 H), 7.12 (t, J = 6.8 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 2 H), 6.70 (t, J = 7.6 Hz, 1 H), 6.39 (d, J = 7.6 Hz, 1 H), 3.94 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 155.8, 142.4, 127.0, 126.2, 125.8, 124.5, 133.6, 121.3, 117.9, 112.9, 110.7, 55.8.

3-((4-Fluorophenyl)thio)-2-methylimidazo[1,2-*a*]pyridine (3ji)^{19g}

Yield: 83% (64 mg); white solid; mp 85–87 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.16 (m, 1 H), 7.59 (t, J = 8.8 Hz, 1 H), 7.26 (d, J = 6.8 Hz, 1 H), 6.95–6.83 (m, 1 H), 6.83 (t, J = 6.0 Hz, 3 H), 2.59 (d, J = 6.0 Hz, 1 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.8 (d, J = 244.9 Hz), 148.0, 142.2, 130.0 (d, J = 3.1 Hz), 128.5 (d, J = 7.9 Hz), 126.0, 124.1, 118.2, 116.3 (d, J = 22.1 Hz), 113.2, 111.1.

2-(tert-Butyl)-3-((4-fluorophenyl)thio)imidazo[1,2-*a*]pyridine (3ki)^{19g}

Yield: 81% (73 mg); white solid; mp 89–91 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.12 (d, J = 6.8 Hz, 1 H), 7.68 (d, J = 8.8 Hz, 1 H), 7.23 (t, J = 6.8 Hz, 1 H), 6.89–6.74 (m, 5 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.3 (d, J = 242.2 Hz), 145.7, 130.9 (d, J = 3.0 Hz), 126.4 (d, J = 7.8 Hz), 125.7, 123.5, 117.3, 116.3 (d, J = 22.4 Hz), 112.7, 104.7.

2-Phenyl-3-((4-fluorophenyl)thio)imidazo[1,2-*a*]pyridine (3li)

Yield: 86% (83 mg); white solid; mp 93–95 °C.

IR (KBr): 2967, 2929, 2857, 1517, 1469, 1376, 724 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 8.18 (d, J = 6.8 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 1 H), 7.35–7.26 (m, 5 H), 7.10 (t, J = 6.8 Hz, 1 H), 7.01 (t, J = 6.8 Hz, 2 H), 6.90 (t, J = 8.8 Hz, 2 H), 6.79 (t, J = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.7 (d, J = 244.7 Hz), 148.4, 142.0, 137.2, 130.3 (d, J = 3.1 Hz), 129.1, 128.2 (d, J = 4.0 Hz), 127.9, 125.9, 123.2, 119.8, 116.5, 116.3 (d, J = 22.2 Hz), 115.7, 110.3.

HRMS (EI): m/z calcd for $\text{C}_{19}\text{H}_{13}\text{FN}_2\text{S}$: 320.0785; found: 320.0783.

MTT Assay

The fluoride-containing C3-sulfenated imidazo[1,2-*a*]pyridines were screened for in vitro cytotoxicity against three human cancer cell lines (HeLa, A-549 and BGC-823) and a normal cell line (VEC) by MTT assay. In vitro, the cytotoxic activities of gossypol and fluoride-containing gossypol Schiff base derivatives were determined by the MTT cytotoxicity assay, which was performed in 96-well plates. The tumor cell line panel consisted of HeLa (human cervical carcinoma), A-549 (human lung carcinoma), BGC-823 (human gastric carcinoma), and VEC (human vascular endothelial cells) (final concentration in the growth medium was $2\text{--}4 \times 10^4 \text{ mL}^{-1}$). The MTT solution (20 μL in each well) was added after cells had been treated with the drug for 48 h and the cells were incubated for a further 4 h at 37 °C. The purple formazan crystals were dissolved in 150 μL DMSO. After 5 min, the plates were read on an automated microplate spectrophotometer at 570 nm. Assays were performed in triplicate in three independent experiments. The concentration required for 50% inhibition of cell viability (IC_{50}) was calculated. In all of these experiments, three replicate wells were used to determine each point.

Funding Information

Funding was provided by the Natural Science Foundation of Guangdong Province (2017A030310021), the Science and Technology Program of Guangdong Province (2017A050506027, 2017B090912005) and the Science and Technology Program of Guangzhou (201807010053).

Acknowledgment

The authors wish to thank Dr. Lidong Weng for his invaluable insight during the development of this work.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0039-1690903>.

References

- Gueiffier, A.; Viols, H.; Galtier, C.; Blache, Y.; Chavignon, O.; Teulade, J. C.; Chapat, J. P. *Heterocycl. Commun.* **1994**, *1*, 83.
- Salgado-Zamora, H.; Taylor, E. C. *Heterocycl. Commun.* **2006**, *12*, 307.
- Du, B.; Shan, A.; Zhang, Y.; Zhong, X.; Chen, D.; Cai, K. *Am. J. Med. Sci.* **2014**, *347*, 178.
- Frett, B.; McConnell, N.; Smith, C. C.; Wang, Y.; Shah, N. P.; Li, H. Y. *Eur. J. Med. Chem.* **2015**, *94*, 123.
- Gueiffier, E.; Gueiffier, C. A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888.
- Alonso, J. M.; Oehlich, D.; Ahnaou, A.; Drinkenburg, W.; Mackie, C.; Andres, J. I.; Lavreysen, H.; Cid, J. M. *J. Med. Chem.* **2012**, *55*, 2688.
- Puerstinger, G.; Paeshuyse, J.; De Clercq, E.; Neyts, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 390.
- Gudmundsson, K. S.; Johns, B. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2735.
- Heidari, A. J. *Data Min. Genomics Proteomics* **2016**, *7*, 125.
- Enguehard-Gueiffier, C.; Fauvelle, F.; Debouzy, J. C.; Peinnequin, A.; Thery, I.; Dabouis, V.; Gueiffier, A. *Eur. J. Pharm. Sci.* **2005**, *24*, 219.
- Mutai, T.; Tomoda, H.; Ohkawa, T.; Yabe, Y.; Araki, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 9522.
- Li, Q.; Zhou, M.; Han, L.; Cao, Q.; Wang, X.; Zhao, L.; Zhou, J.; Zhang, H. *Chem. Biol. Drug Des.* **2015**, *86*, 849.
- Cao, H.; Lei, S.; Li, N.; Chen, L.; Liu, J.; Cai, H.; Tan, J. *Chem. Commun.* **2015**, *51*, 1823.
- Lei, S.; Mai, Y.; Yan, C.; Mao, J.; Cao, H. *Org. Lett.* **2016**, *18*, 3582.
- Chezal, J. M.; Moreau, E.; Delmas, G.; Gueiffier, A.; Blache, Y.; Grassy, G.; Teulade, J. C. *J. Org. Chem.* **2001**, *66*, 6576.
- Mitra, S.; Ghosh, M.; Mishra, S.; Hajra, A. *J. Org. Chem.* **2015**, *80*, 8275.
- Kim, H.; Byeon, M.; Jeong, E.; Baek, Y.; Jeong, S. J.; Um, K.; Son, J. Y. *Adv. Synth. Catal.* **2019**, *361*, 2094.
- Wu, Q.; Zhao, D.; Qin, X.; Lan, J.; You, J. *Chem. Commun.* **2011**, *47*, 9188.
- (a) Mohan, D. C.; Rao, S. N.; Ravi, C.; Adimurthy, S. *Asian J. Org. Chem.* **2014**, *3*, 609. (b) Liu, W.; Wang, S.; Jiang, Y.; He, P.; Zhang, Q.; Cao, H. *Asian J. Org. Chem.* **2015**, *4*, 312. (c) Li, Z.; Hong, J.; Zhou, X. *Tetrahedron* **2011**, *67*, 3690. (d) Hamdouchi, C.; de Blas, J.; Ezquerro, J. *Tetrahedron* **1999**, *55*, 541. (e) Cao, H.; Chen, L.; Liu, J.; Cai, H.; Deng, H.; Chen, G.; Yan, C.; Chen, Y. *RSC Adv.* **2015**, *5*, 22356. (f) Ravi, C.; Chandra, Mohan. D.; Adimurthy, S. *Org. Biomol. Chem.* **2016**, *14*, 2282. (g) Zheng, Z.; Qi, D.; Shi, L. *Catal. Commun.* **2015**, *66*, 83. (h) Li, J.; Li, C.; Yang, S.; An, Y.; Wu, W.; Jiang, H. *J. Org. Chem.* **2016**, *81*, 7771.
- (a) Hiebel, M.-A.; Berteina-Raboin, S. *Green Chem.* **2015**, *17*, 937. (b) Bagdi, A. K.; Mitra, S.; Ghosh, M.; Hajra, A. *Org. Biomol. Chem.* **2015**, *13*, 3314. (c) Huang, X.; Wang, S.; Li, B.; Wang, X.; Ge, Z.; Li, R. *RSC Adv.* **2015**, *5*, 22654. (d) Ding, Y.; Wu, W.; Zhao, W.; Li, Y.; Xie, P.; Huang, Y.; Liu, Y.; Zhou, A. *Org. Biomol. Chem.* **2016**, *14*, 1428. (e) Wang, D.; Guo, S.; Zhang, R.; Lin, S.; Yan, Z. *RSC Adv.* **2016**, *6*, 54377. (f) Ji, X.-M.; Zhou, S.-J.; Chen, F.; Zhang, X.-G.; Tang, R.-Y. *Synthesis* **2015**, 659. (g) Yan, K.; Yang, D.; Sun, P.; Wei, W.; Liu, Y.; Li, G.; Lu, S.; Wang, H. *Tetrahedron Lett.* **2015**, *56*, 4792. (h) Zhu, W.; Ding, Y.; Bian, Z.; Xie, P.; Xu, B.; Tang, Q.; Wu, W.; Zhou, A. *Adv. Synth. Catal.* **2016**, *358*, 2215.
- Hamdouchi, C.; Sanchez, C.; Ezquerro, J. *Synthesis* **1998**, 867.
- Patil, S. M.; Kulkarni, S.; Mascarenhas, M.; Sharma, R.; Roopan, S. M.; Roychowdhury, A. *Tetrahedron* **2013**, *69*, 8255.
- Gao, Z.; Zhu, X.; Zhang, R. *RSC Adv.* **2014**, *4*, 19891.
- Ravi, C.; Mohan, C. D.; Adimurthy, S. *Org. Lett.* **2014**, *16*, 2978.
- Maddi, R. R.; Shirsat, P. K.; Kumar, S.; Meshram, H. M. *Chemistry Select* **2017**, *2*, 1544.
- Bochis, R. J.; Olen, L. E.; Fisher, M. H.; Reamer, R. A.; Wilks, G.; Taylor, J. E.; Olson, G. J. *Med. Chem.* **1981**, *24*, 1483.
- Ravi, C.; Joshi, A.; Adimurthy, S. *Eur. J. Org. Chem.* **2017**, 3646.
- Rahaman, R.; Das, S.; Barman, P. *Green Chem.* **2015**, *20*, 141.
- (a) Jia, F.; Li, Z. *Org. Chem. Front.* **2014**, *1*, 194. (b) Yang, X.-H.; Song, R.-J.; Xie, Y.-X.; Li, J.-H. *ChemCatChem* **2016**, *8*, 2429. (c) Piontek, A.; Bisz, E.; Szostak, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 11116. (d) Sreedevi, R.; Saranya, S.; Rohit, K. R.; Anilkumar, G. *Adv. Synth. Catal.* **2019**, *361*, 2236. (e) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. A.; Liu, X. *Chem. Soc. Rev.* **2015**, *44*, 291.
- Bauer, I.; Knölker, H.-J. *Chem. Rev.* **2015**, *115*, 3170.
- Xiang, S.; Chen, H.; Liu, Q. *Tetrahedron Lett.* **2016**, *57*, 3870.
- Wu, W.; Wang, Z.; Shen, Q.; Liu, Q.; Chen, H. *Org. Biomol. Chem.* **2019**, *17*, 6753.
- Zeng, L.; Deng, Y.; Weng, L.; Yang, Z.; Chen, H.; Liu, Q. *Natural Sci.* **2017**, *9*, 312.
- Yi, S.; Li, M.; Mo, W.; Hu, X.; Hu, B.; Sun, N.; Jin, L.; Shen, Z. *Tetrahedron Lett.* **2016**, *57*, 1912.