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

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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 azaheterocycle1-2 that exists in a large number of pharmaceutical and natural products3-6 showing a range of biological properties, such as antiviral,7 antitherpes,8 antiulcer9 and antiapoptotic activities.10 Moreover, these compounds also represent a pivotal structural scaffold in functional materials and pharmaceuticals such as fluorescent dyes.11 Thus, substituted imidazo[1,2-a]pyridines have attracted the continuous interest of organic chemists12-15 and great efforts have been devoted to 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, Fe(NO3)3 (entries 6–9). Addition of acetic acid greatly promoted the FeCl3-catalysed 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 derivatives.
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Table 1  Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Fe]</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield (%)</th>
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<td>–</td>
<td>–</td>
<td>35</td>
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<tr>
<td>2</td>
<td>FeCl₃</td>
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<td>27</td>
</tr>
<tr>
<td>3</td>
<td>FeCl₃</td>
<td>–</td>
<td>toluene</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
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<td>DCE</td>
<td>22</td>
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<td>DMF</td>
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<td>8</td>
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<td>–</td>
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<tr>
<td>9</td>
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<td>–</td>
<td>DMF</td>
<td>18</td>
</tr>
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<td>DMF</td>
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<tr>
<td>18</td>
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<td>CH₃COOH</td>
<td>DMF</td>
<td>n.d.</td>
</tr>
<tr>
<td>19</td>
<td>–</td>
<td>CH₃COOH</td>
<td>DMF</td>
<td>n.d.</td>
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</table>

* 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.  
* Isolated yield.  
* 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. This result prompted us to screen fluorine-containing C-3 sulfenated 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 (IC50 = 9.37 μM), A-549 cells (IC50 = 4.25 mM) and BGC-823 cells (IC50 = 5.22 μM)) and good safety profiles (IC50 >100 μM against VEC).

### Table 2

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Normal cells IC50 (μmol·L⁻¹)</th>
<th>Cancer cells IC50 (μmol·L⁻¹)</th>
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<tr>
<td></td>
<td>VEC</td>
<td>HeLa</td>
</tr>
<tr>
<td>3ia</td>
<td>55.4</td>
<td>38.3</td>
</tr>
<tr>
<td>3ai</td>
<td>&gt;100</td>
<td>9.37</td>
</tr>
<tr>
<td>3ki</td>
<td>92.2</td>
<td>15.2</td>
</tr>
<tr>
<td>3ji</td>
<td>91.8</td>
<td>18.7</td>
</tr>
<tr>
<td>3li</td>
<td>90.3</td>
<td>20.1</td>
</tr>
<tr>
<td>3la</td>
<td>52.2</td>
<td>33.1</td>
</tr>
</tbody>
</table>

*IC50 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**

Based on the control experiment and on previous work, 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 (Path A). However, other reaction mechanism may also be possible. For example, disulfide A could react with imidazo[1,2-a]pyridine and FeIII to form the Fe–C bonded intermediate D. 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**

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 CDCl3 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 using 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), CH3COOH (0.2 equiv, 0.06 mmol) and FeCl3 (5 mol %) in DMF (2 mL) was stirred at 80 °C under air for 24 h. The reaction mixture was diluted with H2O (15 mL), extracted with EtOAc (3 × 15 mL) and the combined organic extracts were dried over MgSO4. 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-(Benzythio)imidazo[1,2-a]pyridine (3aa) ¹⁵e

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

¹H NMR (400 MHz, CDCl3): δ = 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, CDCl3): δ = 141.6, 137.7, 128.6, 128.5, 128.3, 127.3, 127.0, 124.1, 117.7, 112.4, 41.5.

3-(Benzythio)-5-methylimidazo[1,2-a]pyridine (3ba) ¹⁵e

Yield: 89% (68 mg); yellow oil.
3-(Benzylthio)-6-fluorimidazo[1,2-a]pyridine (3ca)

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 = 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.

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

3-(Benzylthio)-6-methylimidazo[1,2-a]pyridine (3da)

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, 138.7, 136.7, 128.6, 128.5, 127.3, 123.2, 116.2, 115.1, 41.6, 21.2.

3-(Benzylthio)-7-methylimidazo[1,2-a]pyridine (3ea)

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, 146.0, 137.7, 128.6, 128.5, 127.4, 127.3, 124.5, 121.8, 113.7, 112.5, 41.5, 16.6.

3-(Benzylthio)-8-methylimidazo[1,2-a]pyridine (3ea)

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-iodoimidazo[1,2-a]pyridine (3fa)

Yield: 82% (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-bromoimidazo[1,2-a]pyridine (3ga)

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, 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.

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

Yield: 75% (67 mg); white solid; mp 96–98 °C.

IR (KBr): 2975, 2884, 1466, 1393, 1373, 741 cm–1.

3-(Benzylthio)-2-tert-butylimidazo[1,2-a]pyridine (3ka)

Yield: 75% (67 mg); white solid; mp 96–98 °C.

HRMS (EI): m/z calcd for C22H17N9S: 316.1038; found: 316.1034.

3-(Ethylthio)imidazo[1,2-a]pyridine (3ab)

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, 113.0, 40.0, 13.9.

3-(Propylthio)imidazo[1,2-a]pyridine (3ac)

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, 122.5, 121.9, 117.9, 112.6, 37.7, 23.0, 12.9.

3-(Butylthio)imidazo[1,2-a]pyridine (3ad)

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).
13C NMR (100 MHz, CDCl3): δ = 147.3, 140.8, 125.2, 124.1, 117.9, 114.0, 112.7, 35.4, 31.7, 21.5, 13.56.

3-((4-Fluorophenyl)thio)imidazo[1,2-a]pyridine (3ae)¹⁵
Yield: 83% (48 mg); yellow oil.
1H NMR (400 MHz, CDCl3): 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).
13C NMR (100 MHz, CDCl3): 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)¹⁶
Yield: 76% (53 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), 2.67–2.74 (m, 1 H), 1.59–1.89 (m, 5 H), 1.19–1.34 (m, 5 H).
13C NMR (100 MHz, CDCl3): 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, CDCl3): 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).
13C NMR (100 MHz, CDCl3): 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-Chlorophenylthio)imidazo[1,2-a]pyridine (3ah)¹⁹
Yield: 86% (83 mg); white solid; mp 93–95 °C.
IR (KBr): 2957, 2857, 1517, 1459, 1376, 724 cm⁻¹.
1H NMR (400 MHz, CDCl3): δ = 8.18 (d, J = 6.8 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 1 H), 7.23 (t, J = 6.8 Hz, 1 H), 6.85–6.74 (m, 5 H).
13C NMR (100 MHz, CDCl3): 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.

3-(4-Fluorophenyl)thio)-2-methylimidazo[1,2-a]pyridine (3ji)¹⁹
Yield: 83% (64 mg); white solid; mp 85–87 °C.
1H NMR (400 MHz, CDCl3): 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).
13C NMR (100 MHz, CDCl3): 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, 111.8, 116.3 (d, J = 22.1 Hz), 113.2, 111.1.

2-(tert-Butyl)-3-(4-fluorophenylthio)imidazo[1,2-a]pyridine (3ki)¹⁹
Yield: 81% (73 mg); white solid; mp 89–91 °C.
1H NMR (400 MHz, CDCl3): 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).
13C NMR (100 MHz, CDCl3): 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-fluorophenylthio)imidazo[1,2-a]pyridine (3li)
Yield: 86% (83 mg); white solid; mp 93–95 °C.
HRMS (EI): m/z calcd for C₂₉H₂₉FN₅S²⁻: 320.0785; found: 320.0783.

MTT Assay
The fluorine-containing C3-sulfenyl 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 fluorine-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 2–4 x 10⁻⁴ M). 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 further 4 h at 37 °C. The purple form azan 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 (IC₅₀) was calculated. In all of these experiments, three replicate wells were used to determine each point.

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Supporting Information

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