# Supporting Information

# Metal- and base-free regioselective thiolation of methyl

# C(sp<sup>3</sup>)–H bond in 2-picoline *N*-oxides

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# **Table of Contents**

1.	General Experimental	SI-2
2.	General Procedure	SI-2
3.	Synthesis of Omeprazole Sulfide and Rabeprazole Sulfide	SI-14
4.	Green Chemistry Metrics Analysis	.SI-16
5.	References	.SI-22
6.	Spectra Data	SI-22

#### **1.General Experimental**

The preparation experiments were performed under air or an argon atmosphere in oven dried glassware. Solvents used as reaction media were distilled immediately before use: THF was distilled from Na/benzophenone ketyl, DCM and DCE were distilled from calcium hydride, DMF was obtained from vacuum distillation. All reagents were purchased at the highest commercial quality and used without further purification. Reactions were monitored by thin layer chromatography (TLC) using ultra violet light (UV) as the visualizing agent. Nuclear magnetic resonance spectra (NMR) were recorded on Bruker AV-400 instruments and were calibrated using residual undeuterated solvent as an internal reference (<sup>1</sup>H NMR: CHC1<sub>3</sub> 7.26 ppm, <sup>13</sup>C NMR: CHC1<sub>3</sub> 77.16 ppm). High resolution mass spectra (HRMS) were recorded on a hybrid IT-TOF mass spectrometer (Shimadzu LCMS-IT-TOF, Kyoto, Japan). The following abbreviations were used to indicate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sep = septet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet).

#### **2. General Procedure**

#### **General Procedure I: Oxidation of Pyridines**



Pyridine derivative (1.0 eq) was dissolved in DCM (0.3 M) and mCPBA (1.2 eq) was added and stirred at room temperature overnight until the reaction was complete as indicated by TLC. The reaction mixture was concentrated in vacuo and chromatographed gradiently on silica gel with DCM/MeOH (100:1~50:1) to afford product 1.

#### **General Procedure II:**



To a solution of compound 1 (1.0 eq.) in EA (0.4 M) was added TFAA (2.5 eq.). The

resulting solution was stirred and heated to reflux for several hours (typically one to four hours) until the reaction was complete as indicated by TLC. The solution was cooled down to r.t. and concentrated in vacuo to give compound **2**, which was good enough to go to the next step.

To a solution of compound **2** (1.0 eq.) in toluene (0.8 M) was added R<sup>1</sup>-SH (1.0 eq.) and TBAB (0.2 eq.). The resulting solution was stirred and heated to reflux for several hours (typically one to five hours) until the reaction was complete as indicated by TLC. After cooled down to r.t., sat. aqueous Na<sub>2</sub>CO<sub>3</sub> were added to the reaction mixture and extracted with EA for three times. The combined organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo and the crude product was purified by flash column chromatography using PE~PE/EA (50:1~1:3) to afford product **3**.

#### 2-methylpyridine 1-oxide (1a)

This compound was obtained from commercial sources.



#### 3-bromo-2-methylpyridine 1-oxide (1b)

Following General Procedure I, using 3-bromo-2-methylpyridine (2.0 g, 11.6 mmol), **1b** was obtained (1.6 g, 73% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.25 (d, *J* = 6.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.02 (t, *J* = 7.2 Hz, 1H), 2.70 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  149.8, 138.6, 129.5, 122.9, 122.2, 17.4. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>6</sub>H<sub>7</sub>BrNO 187.9706; Found 187.9701.

#### 4-bromo-2-methylpyridine 1-oxide (1c)

Following General Procedure I, using 4-bromo-2-methylpyridine (2.0 g, 11.6 mmol), **1c** was obtained (2.2 g, 100% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  8.22 (d, *J* = 6.8 Hz, 1H), 7.77 (s, 1H), 7.57 (d, *J* = 6.4 Hz 1H), 2.50 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  150.4, 140.1, 129.5, 126.9, 118.9, 17.7. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>6</sub>H<sub>7</sub>BrNO 187.9706; Found 187.9706.

CO<sub>2</sub>Me

0-

MeO<sub>2</sub>C

#### 3-(methoxycarbonyl)-2-methylpyridine 1-oxide (1d)

Following General Procedure I, using methyl 2-methylnicotinate (2.0 g, 13.2 mmol), **1d** was obtained (1.86 g, 84% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.41 (d, *J* = 6.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 3.95 (s, 3H), 2.79 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  165.1, 151.0, 141.5, 129.6, 127.1, 122.3, 52.8, 14.7. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>8</sub>H<sub>10</sub>NO<sub>3</sub>: 168.0655; Found 168.0653.

#### 5-(methoxycarbonyl)-2-methylpyridine 1-oxide (1e)

Following General Procedure I, using 5-(methoxycarbonyl)-2-methylpyridine (2.0 g, 13.2 mmol), **1e** was obtained (2.2 g, 100% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.84 (s, 1H), 7.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 3.96 (s, 3H), 2.58 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  163.3, 153.0, 140.0, 127.2, 126.1, 125.8, 52.6, 17.8. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>8</sub>H<sub>10</sub>NO<sub>3</sub>: 168.0655; Found 168.0660.

#### 2,3,5-trimethylpyridine 1-oxide (1f)



This compound was obtained from commercial sources.



#### 2,4-dimethylpyridine 1-oxide (1g)

Following General Procedure I, using 2,4-dimethylpyridine (5.0 g, 46.7 mmol), **1g** was obtained (5.8 g, 100% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.15 (d, *J* = 6.8 Hz, 1H), 7.07 (s, 1H), 6.96 (d, *J* = 6.8 Hz, 1H), 2.50 (s, 3H), 2.32 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ 148.1, 138.5, 137.4, 127.1, 124.3, 20.1, 17.6. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>7</sub>H<sub>10</sub>NO: 124.0757; Found 124.0760.



Following General Procedure I, using 2,6-dimethylpyridine (5.0 g, 46.6 mmol), **1h** was obtained (4.4 g, 77% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.02-6.93 (m,

3H), 2.39 (s, 6H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) & 148.9, 124.9, 123.9, 18.1. HRMS (+ESI-TOF) m/z: [M+H]<sup>+</sup> Calcd for C<sub>7</sub>H<sub>10</sub>NO: 124.0757; Found 124.0763.

#### 2,3,5-trimethyl-4-nitropyridine 1-oxide (1i)

This compound was obtained from commercial sources.

#### 2,3-dimethyl-4-nitropyridine 1-oxide (1j)

This compound was obtained from commercial sources.

#### ò⁻ 2-ethylpyridine 1-oxide (1k)

This compound was obtained from commercial sources.

# 4-fluoro-2-methylpyridine 1-oxide (11)

This compound was obtained from commercial sources.

# Ò-4-methoxy-2-methylpyridine 1-oxide (1m)

This compound was obtained from commercial sources.

# 0-

#### 2-methylquinoline 1-oxide (1n)

This compound was obtained from commercial sources.

#### 2-methylpyrazine 1-oxide (10)

This compound was obtained from commercial sources.

Ô



NO<sub>2</sub>







OMe



#### 2,3-dimethylpyrazine 1-oxide (1p)

This compound was obtained from commercial sources.

## 4-methoxy-2,3,5-trimethylpyridine 1-oxide (1q)

This compound was obtained from commercial sources.



#### 4-(3-methoxypropoxy)-2,3-dimethylpyridine 1-oxide (1r)

This compound was obtained from commercial sources.



#### 2-((p-tolylthio)methyl)pyridine (3a)

Following General Procedure II, using **1a** (507 mg, 4.65 mmol), the title compound was obtained (770 mg, 77% yield) as a pale yellow oil. The spectroscopic data are consistent with data previously reported.<sup>1</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.53 (d, *J* = 4.8 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.29-7.22 (m, 3H), 7.15-7.13 (m, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.21 (s, 2H), 2.29 (s, 3H).



#### 2-((m-tolylthio)methyl)pyridine (3b)

Following General Procedure II, using **1a** (523 mg, 4.79 mmol), the title compound was obtained (730 mg, 71% yield) as a deep yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.54 (d, *J* = 4.4 Hz, 1H), 7.62-7.58 (m, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.16-7.7.13 (m, 4H), 6.98 (t, *J* = 4.0 Hz, 1H), 4.26 (s, 2H), 2.28 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.4, 148.9, 138.2, 136.3, 135.3, 129.8, 128.4, 126.9, 126.1, 122.7, 121.7, 40.1, 21.0. HRMS (+ESITOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>14</sub>NS 216.0841; Found 216.0840.

#### 2-(((4-methoxyphenyl)thio)methyl)pyridine (3c)



Following General Procedure II, using **1a** (505 mg, 4.63 mmol), the title compound was obtained (747 mg, 70% yield) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.51(d, *J* = 4.8 Hz, 1H), 7.59-7.55 (m, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.13 (dd, *J* = 5.2, 6.8 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 4.13 (s, 2H), 3.75 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.3, 158.1, 149.3, 136.6, 134.0, 125.6, 123.3, 122.0, 114.6, 55.3, 42.7. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>14</sub>NOS 232.0791; Found 232.0777.

#### 2-(((4-chlorophenyl)thio)methyl)pyridine (3d)

Following General Procedure II, using **1a** (506 mg, 4.64 mmol), the title compound was obtained (707 mg, 65% yield) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.52 (d, J = 4.4 Hz, 1H), 7.62-7.57 (m, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.24 (dd, J = 2.0, 6.8 Hz, 2H), 7.20 (dd, J = 2.0, 6.8 Hz, 2H), 7.14 (dd, J = 5.2, 6.8 Hz, 1H), 4.22 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.4, 149.4, 136.8, 134.3, 132.5, 131.1, 129.0, 123.1, 122.3, 40.7. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>11</sub>NSCl 236.0295; Found 236.0297.

#### 2-(((2,6-dichlorophenyl)thio)methyl)pyridine (3e)

Following General Procedure II, using **1a** (506 mg, 4.64 mmol), the title compound was obtained (833 mg, 67% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.46 (d, *J* = 4.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.32-7.29 (m, 2H), 7.16-7.08 (m, 3H), 4.20 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.2, 149.4, 141.9, 136.4, 132.0, 130.2, 128.5, 123.2, 122.1, 41.2. HRMS (+ESI-TOF) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>9</sub>NSCl<sub>2</sub>Na 291.9725; Found 291.9709.

#### 2-(((3-bromophenyl)thio)methyl)pyridine (3f)

Following General Procedure II, using **1a** (500 mg, 4.58 mmol), the title compound was obtained (791 mg, 62% yield) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.54 (d, *J*=4.8 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.46 (s, 1H), 7.31(d, *J* = 7.6 Hz, 1H), 7.27-7.22 (m, 2H), 7.16-7.13 (m, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 4.26 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 157.1, 149.5, 138.4, 136.8, 131.8, 130.2, 129.3, 127.7, 123.0, 122.7, 122.3, 40.2. HRMS





∽<sup>s</sup>

(+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>11</sub>NSBr 279.9790; Found 279.9781.

#### 2-(((2-bromophenyl)thio)methyl)pyridine (3g)

Following General Procedure II, using **1a** (501 mg, 4.59 mmol), the title compound was obtained (968 mg, 75% yield) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.63 (d, J = 1.2 Hz, 1H), 7.61-7.54 (m, 1H), 7.52 (d, J = 0.8 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.31-7.26 (m, 1H), 7.21-7.03 (m, 2H), 7.01-6.99 (m, 1H), 4.31 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.6, 149.0, 137.2, 136.7, 132.7, 128.5, 127.6, 126.7, 123.2, 122.9, 122.1, 39.2. HRMS (+ESI-TOF) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>10</sub>NSBrNa 301.9610; Found 301.9603.

#### 2-(((4-nitrophenyl)thio)methyl)pyridine (3h)



Following General Procedure II, using **1a** (515 mg, 4.72 mmol), the title compound was obtained (135 mg, 12% yield) as a pale yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.56 (d, *J* =4.8 Hz, 1H), 8.09 (dd, *J* = 2.0, 6.8 Hz, 2H), 7.67 (dt, *J* =1.6, 9.2 Hz, 1H), 7.45-7.40 (m, 3H), 7.21 (dd, *J* = 6.0, 7.2 Hz, 1H), 4.39 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.4, 149.6, 146.8, 145.4, 137.2, 126.8, 124.1, 123.0, 122.7, 38.7. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub>S 247.0536; Found 247.0532.

### 2-((pentylthio)methyl)pyridine (3i)

Following General Procedure II, using **1a** (532 mg, 4.87 mmol) and 1-pentanethiol (1.04 g 9.74 mmol), the title compound was obtained (217 mg, 23% yield) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.45 (d, *J* =4.4 Hz, 1H), 7.58 (dt, *J* = 9.2, 1.6 Hz, 1H), 7.30 (d, *J* =7.6 Hz, 1H), 7.08 (dd, *J* = 7.2, 5.6 Hz, 1H), 3.76 (s, 2H), 2.45-2.39 (m, 2H), 1.53-1.45 (m, 2H), 1.29-1.18 (m, 4H), 0.79 (t, *J* =7.2 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.2, 149.3, 136.8, 123.1, 121.9, 38.4, 31.9, 31.1, 29.1, 22.4, 14.1. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>11</sub>H<sub>18</sub>NS 196.1154; Found 196.1145.

#### 2-((benzylthio)methyl)pyridine (3j)

Following General Procedure II, using 1a (501 mg, 4.59 mmol), the title compound was

obtained (313 mg, 32% yield) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.55 (dd, J = 4.8, 0.8 Hz, 1H), 7.62 (dt, J = 9.6, 1.6 Hz, 1H), 7.31-7.21 (m, 6H), 7.16-7.13 (m, 1H), 3.75 (s, 2H), 3.69 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.7, 149.4, 138.1, 136.7, 129.1, 128.6, 127.1, 123.2, 121.9, 37.6, 36.0. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>14</sub>NS 216.0841; Found 216.0850.



#### 2-((pyridin-2-ylmethyl)thio)pyridine (3k)

Following General Procedure II, using **1a** (505 mg, 4.63 mmol), the title compound was obtained (589 mg, 63% yield) as a deep brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.55 (d, J = 4.8 Hz, 1H), 8.45 (d, J = 1.2 Hz, 1H), 7.61-7.57 (m, 1H), 7.48-7.44 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 7.15-7.10 (m, 1H), 7.00-6.96 (m, 1H), 4.59 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.44, 158.39, 149.5, 149.3, 136.8, 136.1, 123.4, 122.2, 122.1, 119.8, 36.1. HRMS (+ESI-TOF) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>SNa 225.0457; Found 225.0448.

#### 2-(((2-methylfuran-3-yl)thio)methyl)pyridine (3l)

Following General Procedure II, using **1a** (503 mg, 4.61 mmol), the title compound was obtained (519 mg, 55% yield) as a brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.52 (d, *J* = 4.0 Hz, 1H), 7.56 (dt, *J* = 9.6, 1.6 Hz, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.16-7.14 (m, 1H), 7.13-7.05 (m, 1H), 6.21 (d, *J* = 1.6 Hz, 1H), 3.90 (s, 2H), 2.02 (s, 3H) .<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.3, 156.1, 149.6, 140.7, 136.4, 123.3, 122.0, 115.2, 109.3, 42.5, 11.5. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>11</sub>H<sub>11</sub>NOSNa 228.0454; Found 228.0443.

#### 2-((pyridin-2-ylmethyl)thio)-1H-benzo[d]imidazole (3m)

Following General Procedure II, using **1a** (500 mg, 4.58 mmol), the title compound was obtained (784 mg, 71% yield) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.54 (d, J = 4.4 Hz, 1H), 7.63-7.59 (m, 1H), 7.55-7.53 (m, 2H), 7.33-7.19 (m, 1H), 7.17 (t, J = 3.2 Hz, 3H), 4.43 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.7, 150.9, 148.9, 139.6, 137.8, 123.6, 122.9, 122.0, 114.3, 38.0. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>12</sub>N<sub>3</sub>S 242.0746; Found 242.0743.

#### 2-((pyridin-2-ylmethyl)thio)benzo[d]oxazole (3n)

Following General Procedure II, using **1a** (510 mg, 4.67 mmol), the title compound was obtained (832 mg, 74% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.60 (d, *J* = 4.0 Hz, 1H), 7.67 (t, *J* = 7.6Hz, 1H), 7.60 (d, *J* = 7.6Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.29-7.18 (m, 3H), 4.74 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  164.5, 156.0, 152.0, 149.4, 141.8, 137.2, 124.4, 124.0, 123.5, 122.8, 118.5, 110.0, 38.0. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>OS 243.0587; Found 243.0580.

#### 5-methoxy-2-((pyridin-2-ylmethyl)thio)-1H-benzo[d]imidazole (30)

Following General Procedure II, using **1a** (501 mg, 4.59 mmol), the title compound was obtained (770 mg, 62% yield) as a brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.64 (d, *J* = 4.8 Hz, 1H), 7.75-7.71 (m, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 5.6, 7.2 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.37 (s, 2H), 3.84 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.2, 155.9, 149.5, 148.7, 139.6, 137.4, 134.4, 123.3, 122.5, 114.9, 111.2, 97.2, 55.6, 38.1. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>3</sub>OS 272.0852; Found 272.0850.



#### 3-bromo-2-((p-tolylthio)methyl)pyridine (3p)

Following General Procedure II, using **1b** (502 mg, 2.67 mmol), the title compound was obtained (393 mg, 50% yield) as a deep brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.42 (dd, J = 4.8, 1.2 Hz, 1H), 7.80 (dd, J = 8.0, 1.2 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H),7.06 (d, J = 7.6 Hz, 1H), 7.01(dd, J = 8.0, 4.4 Hz, 2H), 4.37 (s, 2H), 2.29 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.3, 147.8, 140.6, 137.0, 131.8, 131.5, 129.7, 123.4, 121.4, 41.6, 21.1. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>13</sub>NSBr 293.9947; Found 293.9937.



4-(p-tolylthio)-2-((p-tolylthio)methyl)pyridine (3q)

Following General Procedure II, using **1c** (507 mg, 2.70 mmol) and p-toluenethiol (671 mg 5.40 mmol), the title compound was obtained (473 mg, 52% yield) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.23 (d, *J* = 5.2 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.21-7.15 (m, 4H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 1.2 Hz, 1H), 6.74 (dd, *J* = 5.2, 1.6 Hz 1H), 4.06 (s, 2H), 2.39 (s, 3H), 2.29 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.7, 151.5, 148.9, 140.0, 136.5, 135.3, 131.9, 130.7, 130.6, 129.6, 125.5, 119.6, 118.8, 41.2, 21.4, 21.1. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>20</sub>H<sub>20</sub>NS<sub>2</sub> 338.1032; Found 338.1019.

#### methyl 2-((p-tolylthio)methyl)nicotinate (3r)

Following General Procedure II, using **1d** (481 mg, 2.90 mmol), the title compound was obtained (174 mg, 22% yield) as a brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.59 (dd, J = 4.8, 1.6 Hz, 1H), 8.19 (dd, J = 8.0, 2.0 Hz, 1H), 7.26-7.22 (m, 3H), 7.04 (d, J = 7.6 Hz, 2H), 4.65 (s, 2H), 3.89 (s, 3H), 2.29 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.6, 159.7, 151.7, 138.9, 136.8, 132.0, 131.5, 129.6, 125.4, 122.0, 52.5, 40.8, 21.1. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>16</sub>NO<sub>2</sub>S 274.0896; Found 274.0884.



#### methyl 6-((p-tolylthio)methyl)nicotinate (3s)

Following General Procedure II, using **1e** (506 mg, 3.03 mmol), the title compound was obtained (239 mg, 29% yield) as a pale yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.11 (d, *J* = 1.6 Hz, 1H), 8.17 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 4.23 (s, 2H), 3.93 (s, 3H), 2.29 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  165.8, 162.7, 150.7, 137.8, 137.2, 131.2, 131.1, 129.9, 124.5, 122.7, 52.5, 41.5, 21.2. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>16</sub>NO<sub>2</sub>S 274.0896; Found 274.0890.

#### 3,5-dimethyl-2-((p-tolylthio)methyl)pyridine (3t)

Following General Procedure II, using **1f** (230 mg, 1.26 mmol), the title compound was obtained (283 mg, 70% yield) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.18 (s,

1H), 7.30 (d, J = 8.4 Hz, 2H), 7.24 (s, 1H), 7.07 (d, J = 8.0 Hz, 2H), 4.21 (s, 2H), 2.31 (s, 3H), 2.30 (s, 3H), 2.27 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  152.5, 147.0, 138.7, 136.5, 132.5, 131.7, 131.2, 130.9, 129.5, 39.6, 21.0, 18.4, 17.8. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>18</sub>NS 244.1154; Found 244.1142.

#### 4-methyl-2-((p-tolylthio)methyl)pyridine (3u)

Following General Procedure II, using **1g** (504 mg 4.10 mmol), the title compound was obtained (369 mg, 40% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.38 (d, *J* = 5.2 Hz, 1H), 7.26-7.22 (m, 2H), 7.11 (s, 1H), 7.06 (d, *J* =8.0 Hz, 2H), 6.96 (d, *J* =4.8 Hz, 1H), 4.18 (s, 2H), 2.293 (s, 3H), 2.287 (s, 3H),. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.7, 149.1, 147.9, 136.6, 132.3, 130.4, 129.7, 124.0, 123.2, 41.2, 21.12, 21.11. HRMS (+ESI-TOF) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>14</sub>H<sub>15</sub>NSNa 252.0817; Found 252.0803.

#### 2-methyl-6-((p-tolylthio)methyl)pyridine (3v)

Following General Procedure II, using **1h** (510 mg, 4.14 mmol), the title compound was obtained (504 mg, 53% yield) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.43 (dd, J = 7.6, 6.8 Hz, 1H), 7.23-7.21 (m, 2H), 7.06-7.02 (m, 3H), 6.95 (d, J = 7.6 Hz, 1H), 4.17 (s, 2H), 2.51 (s, 3H), 2.26 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.9, 157.0, 136.7, 136.3, 132.2, 130.2, 129.5, 121.5, 119.8, 41.1, 24.3, 20.9. HRMS (+ESI-TOF) *m/z*: [M+Na]<sup>+</sup>Calcd for C<sub>14</sub>H<sub>15</sub>NSNa 252.0817; Found 252.0812.



#### **3,5-dimethyl-4-nitro-2-((p-tolylthio)methyl)pyridine (3w)**

Following General Procedure II, using **1i** (500 mg, 2.74 mmol), the title compound was obtained (240 mg, 30% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.33 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.67 (s, 2H), 2.35 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  154.6, 146.2, 143.2, 136.0, 136.0, 133.5, 131.9, 130.0, 127.7, 62.0, 20.9, 18.7, 14.6. HRMS (+ESI-TOF) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>SNa 311.0825; Found 311.0825.

#### 3-methyl-4-nitro-2-((p-tolylthio)methyl)pyridine (3x)

Following General Procedure II, using **1j** (513 mg, 3.05 mmol), the title compound was obtained (97 mg, 12% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.08 (d, *J* = 5.6 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 6.53 (d, *J* = 5.6 Hz, 1H), 4.70 (s, 2H), 2.42 (s, 3H) , 2.22 (s, 3H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  155.2, 150.8, 144.7, 140.2, 135.6, 130.9, 126.1, 125.6, 119.0, 61.7, 21.4, 12.9. HRMS (+ESI-TOF) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>SNa 297.0668; Found 297.0655.

#### 4-fluoro-2-((p-tolylthio)methyl)pyridine (3z)

N S

Following General Procedure II, using **11** (400 mg, 3.15 mmol) and *p*-toluenethiol (391 mg 3.15 mmol), **3q** was isolated as the major product (396 mg, 75% yield), and the title compound was obtained (50 mg, 7% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.26 (d, *J* = 5.2 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 2H), 6.88 (s, 1H), 6.84 (d, *J* = 5.2 Hz, 1H), 4.63 (s, 2H), 2.42 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.9, 152.6, 147.9, 140.5, 135.6, 131.0, 125.4, 119.5, 117.2, 64.1, 21.5. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>13</sub>NFS 234.0747; Found 234.0752.

#### 2-(((4-methoxypyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (3aa)

Following General Procedure II without adding any TBAB in the second step, using **1m** (500 mg, 3.59 mmol), the title compound was obtained (595 mg, 61% yield) as a pale yellow oil. The spectroscopic data are consistent with data previously reported.<sup>2</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.45 (d, *J* = 6.0 Hz, 1H), 7.56 (dd, *J* = 3.2, 6.0 Hz, 2H), 7.20 (dd, *J* = 3.2, 6.0 Hz, 2H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, J = 2.4, 6.0 Hz, 1H), 4.31 (s, 2H), 3.86 (s, 3H).

#### ((p-tolylthio)methyl)quinoline (3ab)



Following General Procedure II, using **1n** (500 mg, 3.44 mmol), the title compound was obtained (290 mg, 32% yield) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.05 (dd, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.71-7.67 (m, 1H), 7.52-7.047 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 2H),7.03 (d, *J* = 7.6 Hz, 2H), 4.40 (s, 2H), 2.27 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.5, 147.7, 136.8, 136.7, 132.0, 130.5, 129.8, 129.7, 129.1, 127.6, 127.2, 126.4, 121.2, 42.0, 21.1. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>17</sub>H<sub>16</sub>NS 266.0998; Found 266.0998.



#### 2-((pyrazin-2-ylmethyl)thio)-1H-benzo[d]imidazole (3ac)

Following General Procedure II, using **10** (486 mg 4.42 mmol), the title compound was obtained (283 mg, 26% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  8.65 (s, 1H), 8.51 (s, 1H), 8.44 (d, *J* = 2.4 Hz, 1H), 7.46 (dd, *J* = 3.2, 6.0 Hz, 2H), 7.18 (dd, *J* = 3.2, 6.0 Hz, 2H), 4.62 (s, 2H). <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD)  $\delta$  154.8, 149.9, 145.44, 145.39, 144.3, 140.4, 123.5, 115.1, 36.6. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>11</sub>N<sub>4</sub>S 243.0699; Found 243.0694.

#### 2-(((3-methylpyrazin-2-yl)methyl)thio)-1H-benzo[d]imidazole (3ad)



Following General Procedure II, using **1p** (441 mg 3.56 mmol), the title compound was obtained (531 mg, 58% yield) as a brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.46 (d, *J* = 2.4 Hz, 1H), 8.39 (d, *J* = 2.4 Hz, 1H), 7.54 (dd, J = 3.2, 6.0 Hz, 2H), 7.23-7.18 (m, 2H), 4.56 (s, 2H), 2.69 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  152.9, 150.7, 149.9, 142.9, 141.0, 139.4, 122.3, 114.2, 35.7, 21.6. HRMS (+ESI-TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>13</sub>N<sub>4</sub>S 257.0855; Found 257.0849.

#### 3. Synthesis of Omeprazole Sulfide and Rabeprazole Sulfide



#### **Omeprazole sulfide (3ae)**

To a solution of compound 1q (445 mg, 2.66 mmol) in EA (6.6 ml) was added TFAA (1.4

g, 6.65 mmol). The resulting solution was stirred and heated to reflux for three hours. The solution was cooled down to r.t. and concentrated in vacuo to give compound 2q, which was good enough to go to the next step.

To a solution of compound **2q** in toluene (3.3 ml) was added 5-methoxy-2mercaptobenzimidazole (480 mg, 2.66 mmol). The resulting solution was stirred and heated to reflux for four hours. After cooled down to r.t., sat. aqueous Na<sub>2</sub>CO<sub>3</sub> were added to the reaction mixture and extracted with EA for three times. The combined organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo and the crude product was purified by flash column chromatography using PE/EA (10:1~1:3) to afford product **3ae** (519 mg, 60% yield) as a brown oil, which solidified after a while. The spectroscopic data are consistent with data previously reported.<sup>3</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.27 (s, 1H), 7.41 (d, *J* = 6.4 Hz, 1H), 7.03 (s, 1H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.35 (s, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H).



#### Rabeprazole sulfide (3af)

To a solution of compound 1r (12 g, 56.8 mmol) in EA (142 ml) was added TFAA (29.82 g, 142.0 mmol). The resulting solution was stirred and heated to reflux for three hours. The solution was cooled down to r.t. and concentrated in vacuo to give compound 2r, which was good enough to go to the next step.

To a solution of compound 2r in toluene (71 ml) was added 2-mercaptobenzimidazole (8.53 g, 56.8 mmol). The resulting solution was stirred and heated to reflux for three hours. After cooled down to r.t., sat. aqueous Na<sub>2</sub>CO<sub>3</sub> were added (60 ml) to the reaction mixture to adjust the pH to 8. The water phase was extracted with EA (45 ml  $\times$  2) after separation. The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo to ~60 ml and the resulting solution was cooled to 0°C. The precipitated solid was filtered, washed with ethyl acetate (30 ml) and dried the product under vacuum to obtain 13.5 g title compound as an off white crystalline solid. The mother liquor was washed with aqueous NaOH solution (10 ml  $\times$  2) and concentrated to obtain crude compound, which was further purified by

flash column chromatography (19 g silica gel) using PE/EA (10:1~1:3, ~150 ml PE, ~150 ml EA) to afford product **3af** (2.1 g) as a white solid. Total yield: 15.6 g, 80%. The spectroscopic data are consistent with data previously reported.<sup>4</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.35 (d, *J* = 6.0 Hz, 1H), 7.54 (s, 2H), 7.18 (dd, *J* = 6.0, 3.2 Hz, 2H), 6.77 (d, *J* = 6.0 Hz, 1H), 4.38 (s, 2H), 4.13 (t, *J* = 6.4 Hz, 2H), 3.57 (t, *J* = 6.0 Hz, 2H), 3.36 (s, 3H), 2.26 (s, 3H), 2.10 (t, *J* = 6.0 Hz, 2H).

#### 4. Green Chemistry Metrics Analysis

The following formula were used for calculating Atom Economy (AE), atom efficiency

(AEf), carbon efficiency (CE), reaction mass efficiency (RME), overall efficiency (OE).

$$AE = \frac{Molecular \ weight \ of \ product}{Total \ molecular \ weight \ of \ reactants} X \ 100$$

$$AEf = AE \ X \ yield\%$$

$$CE = \frac{Amount \ of \ carbon \ in \ the \ product}{Total \ carbon \ present \ in \ reactants} X \ 100$$

$$RME = \frac{Mass \ of \ isolated \ product}{Total \ mass \ of \ reactants} X \ 100$$

$$OE = \frac{RME}{AE} X \ 100$$

$$MI = \frac{Total \ mass \ of \ input \ material \ in \ a \ process \ or \ process \ step}{Mass \ of \ product}$$

$$PMI = \frac{Total \ mass \ of \ input \ material \ in \ the \ whole \ process}{Mass \ of \ product}$$

$$E \ Factor = PMI - 1$$

4.1 Process A



(80%, 2 steps)

Step 1-2: Synthesis of 3af



Experimental procedure: See SI-13

$$AE (3af) = \frac{343.45}{211.26 + 210.03 + 150.2} X \ 100 = 60.00$$

$$AEf (3z) = 60 \ X \ 80\% = 48$$

$$CE (3af) = \frac{45.4 \ X18}{56.8 \ X \ 11 + 142 \ X \ 4 + 56.8 \ X \ 7} X \ 100 = 51.38$$

$$RME (3af) = \frac{15.6}{12 + 29.82 + 8.53} X \ 100 = 30.98$$

$$OE (3af) = \frac{30.98}{60} X \ 100 = 51.63$$

$$MI (3af)$$

$$12 + 127.9 + 29.82 + 61.6 + 8.53 + 60 + 108 + 20 + 19$$

15.6

+

E Factor (3af) = 43.64 - 1 = 42.64



#### 4.2 Process B<sup>5</sup>

Step 1-2: Synthesis of 5a



Experimental procedure: 145 g (1.42 mol) of the acetic anhydride was added over 30 minutes to 150 g (0.71 mol) of 4-(3-methoxy propoxy)-2,3-dimethyl pyridine-N-oxide at 0°C. The solution was heated to 90°C and stirred for 6 hrs. After the completion of reaction, it was distilled under reduced pressure to remove acetic anhydride. The obtained residue containing 2-acetoxymethyl-4-(3-methoxy propoxy)-3-methyl pyridine was added in 34.2 g (0.85 mol) of sodium hydroxide & 450 ml of ethanol at room temperature. The reaction mixture was stirred at 55 °C for 2 hrs. After completion of reaction, remove ethanol by distillation under reduced pressure. The obtained residue was diluted with 1500 ml of water & extracted with methylene dichloride (500 ml  $\times$  2 & 100 ml  $\times$  1). The combined organic layer was dried over sodium sulfate. The methylene dichloride layer was concentrated to obtain 98 g (65 %) of 2-hydroxymethyl-4-(3-methoxy propoxy)-3-methyl pyridine as brown oil. (Note: the yield in the patent is 79%, which is wrong. After recalculation, it should be 65%).

$$AE (5a) = \frac{211.26}{211.26 + 102.09 + 40} X \ 100 = 59.79$$

$$AEf (5a) = 59.79 \ X \ 65\% = 38.86$$

$$CE (5a) = \frac{11 \ X \ 0.464}{11 \ X \ 0.71 + 4 \ X \ 1.42} X \ 100 = 37.84$$

$$RME (5a) = \frac{98}{150 + 145 + 34.2} X \ 100 = 29.77$$

$$OE (5a) = \frac{29.77}{59.79} X \ 100 = 49.79$$

$$MI (5a) = \frac{145 + 150 + 34.2 + 355 + 1500 + 1458.6}{98} = 37.17$$

E Factor (5a) = 37.17 - 1 = 36.17

#### Step 3: Synthesis of 6a



Experimental procedure: 70 g of the 2-hydroxymethyl-4-(3-methoxy propoxy)-3-methyl pyridine obtained in example 3 was dissolved in 135 ml of methylene dichloride to obtain a solution. 73.1 g (0.61 mol) of thionyl chloride was drop wise added to this solution at 0°C. The obtained mixture was stirred at room temperature for 2 hrs. After the completion of reaction, the reaction mixture was distilled to remove the methylene dichloride & thionyl chloride under vacuum. The obtained residue was cooled to 5°C and neutralized using saturated sodium bicarbonate solution (*assuming use of 450 ml*) to pH-7.5 and extracted with methylene dichloride (*assuming use of 400 ml*). The methylene dichloride layer dried over sodium sulfate & filtered. The obtained filtrate concentrated to obtain 76 g (99.9%) of 2-chloromethyl-4-(3-methoxy propoxy)-3-methylpyridine as a brown oil.

$$AE (6a) = \frac{229.70}{211.26 + 118.96} X \ 100 = 69.56$$

$$AEf (5a) = 69.56 \ X \ 99.9\% = 69.49$$

$$CE (6a) = \frac{11 \ X \ 0.33}{11 \ X \ 0.33} X \ 100 = 100$$

$$RME (6a) = \frac{76}{70 + 73.1} X \ 100 = 53.11$$

$$OE (6a) = \frac{53.11}{69.56} X \ 100 = 76.35$$

$$MI (6a) = \frac{70 + 179 + 73.1 + 450 + 530.4}{76} = 17.14$$

E Factor (6a) = 17.14 - 1 = 16.14

**Cumulative Metrics for 6a:** 



Step 4: Synthesis of 3af



Experimental procedure: 11 g (0.27mol) of sodium hydroxide was added in 350 ml of ethanol at room temperature. The mixture was stirred at 55°C for 30 minutes and cooled. 30 g (0.2mol) of 2-mercapto benzimidazole and 50 g (0.21 mol) of 2-chloromethyl-4-(3-methoxy propoxy)-3-methylpyridine was added in above mixture. The obtained reaction mixture was stirred at 55°C for 2 hrs. After completion of the reaction, the reaction mixture was distilled to remove ethanol. 500 ml of ethyl acetate was added in residue. The ethyl acetate layer was extracted with 5 % sodium hydroxide aqueous solution (*assuming use of 200 ml*). The ethyl acetate layer was dried over sodium sulfate & distilled out ethyl acetate under reduced pressure. The obtained residue was dissolved in methylene dichloride (*assuming use of 500 ml*) & filtered the suspended particles. Distilled out the methylene dichloride, residue dissolved in 500 ml of ethyl acetate and cooled the mixture to 0 °C. The

precipitated solid was filtered, wash with ethyl acetate (*assuming use of 100 ml*) and dried the product under vacuum to obtain 50.4 g (67.8 %) crude title compound as an off white crystalline solid. The obtained crude compound was further purified in ethyl acetate (*assuming use of 500 ml*) to obtain pure 2-[4-(3-methoxy propoxy-3-methylpyridine-2-yl) methylthio]-1H-benzimidazole. (Note: the yield in the patent is 67.8%, which is wrong. After recalculation, it should be 73.5%).

$$AE (3af) = \frac{343.45}{229.70 + 150.20} X \ 100 = 90.41$$

$$AEf (3af) = 90.41 X \ 73.5\% = 66.45$$

$$CE (3af) = \frac{18 X \ 0.147}{11 X \ 0.218 + 7X0.2} X \ 100 = 69.67$$

$$RME (3af) = \frac{50.4}{50 + 30} X \ 100 = 63$$

$$OE (3af) = \frac{63}{90.41} X \ 100 = 69.68$$

$$MI (3af) = \frac{11 + 276.2 + 30 + 50 + 450.5 + 200 + 663 + 991}{50.4} = 53.00$$

E Factor (3af) = 53.00 - 1 = 52.00

#### **Cumulative Metrics for 3af:**



$$AE (3af \ cumulative) = \frac{343.45}{211.26 + 102.09 + 40 + 118.96 + 150.2} X \ 100 = 55.17$$

$$AEf (3af \ cumulative) = 55.17 \ X \ 65\% \ X \ 99.9\% \ X73.5\% = 26.33$$

$$CE (3af \ cumulative) = \frac{18 \ X \ 0.147}{11 \ X \ 0.33 + 4 \ X \ 0.668 + 7 \ X0.2} X \ 100 = 34.35$$

$$RME (3af \ cumulative) = \frac{50.4}{70.56 + 68.21 + 16.1 + 48.1 + 30} X \ 100 = 21.63$$

$$OE (3af \ cumulative) = \frac{21.63}{55.17} X \ 100 = 39.21$$

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PMI (3af cumulative)
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 $= \frac{50 \times 50.45 + 11 + 276.2 + 30 + 450.5 + 200 + 663 + 991}{50.4} = 102.07$ 

*E* Factor  $(3af \ cumulative) = 102.07 - 1 = 101.07$ 

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#### 6. Spectra Data

Spectra data are shown from the next page.







SI-26

















































![](_page_50_Figure_0.jpeg)

SI-51

![](_page_51_Figure_1.jpeg)

SI-52

![](_page_52_Figure_0.jpeg)

![](_page_53_Figure_1.jpeg)

![](_page_54_Figure_1.jpeg)

![](_page_55_Figure_1.jpeg)

![](_page_56_Figure_1.jpeg)

![](_page_57_Figure_1.jpeg)

![](_page_58_Figure_1.jpeg)

![](_page_59_Figure_1.jpeg)