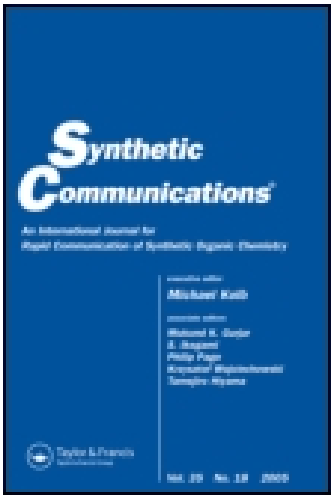

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# Synthesis and Characterization of Metabolites and Potential Impurities of Lansoprazole, an Antiulcerative Drug

**Ganta Madhusudhan Reddy,[1,2] K. Mukkanti,[2] T. Laxmi Kumar,[1] J. Moses Babu,[1] and Padi Pratap Reddy[1]**

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**Abstract:** Lansoprazole (Prevacid) is an antiulcerative drug used for the treatment of duodenal and gastric ulcers, reflux oesophagitis, and Zollinger–Ellison syndrome. During the bulk synthesis of lansoprazole, we have observed five impurities: lansoprazole *N*-oxide, lansoprazole sulfone *N*-oxide, lansoprazole sulfide, lansoprazole sulfone and *N*-aralkyl lansoprazole. The present work describes the synthesis and characterization of these impurities.

**Keywords:** HR-MS, impurities, lansoprazole, spectral characterization, synthesis

## INTRODUCTION

[(Pyridylmethyl)sulfinyl]benzimidazoles (PSBs) are highly active inhibitors of the gastric ($H^+$, $K^+$)-ATPase both *in vitro* and *in vivo* with high and long-lasting antisecretory activity.[1,2] Lansoprazole is the generic

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name of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole (**1**). It has been demonstrated to be effective in the treatment of duodenal and gastric ulcers, reflux oesophagitis, and Zollinger–Ellison syndrome.[3,4] Current evidence indicates that lansoprazole **1** is an alternative to omeprazole and $H_2$-receptor antagonists in the short-term treatment of duodenal and gastric ulcer and reflux oesophagitis, particularly in the light of the potential of lansoprazole for faster healing and more rapid symptom resolution.[5]

The presence of impurities in an active pharmaceutical ingredient (API) can have a significant impact on the quality and safety of the drug products. Therefore, it is necessary to study the impurity profile of the API to be used in the manufacturing of a drug product. International conference on Harmonization (ICH) guidelines recommend identifying and characterizing all impurities that are present at a level of $\geq$0.10%.[6] In this context, a comprehensive study was undertaken to synthesize and characterize the following five impurities:[7] 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-1-oxide-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole (*N*-oxide, **2**); 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-1-oxide-2-pyridyl]-methyl]sulfonyl]-1*H*-benzimidazole (sulfone *N*-oxide, **3**); 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]-1*H*-benzimidazole (sulfide, **4**); 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfonyl]-1*H*-benzimidazole (sulfone, **5**), and 1-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]-sulfinyl]-1*H*-benzimidazole (*N*-aralkyl lansoprazole, **6**).

Several analytical methods have been reported for the determination of lansoprazole and pantoprazole in biological fluids and pharmaceutical formulations.[8] Two of the lansoprazole impurities, lansoprazole sulfide **4** and sulfone **5**, were earlier reported as metabolites.[9] However, except for sulfide impurity **4**, a detailed synthetic procedure is not reported for other impurities. Among these five impurities, sulfone *N*-oxide **3** and *N*-aralkyl **6** impurities are reported here for the first time.

## RESULTS AND DISCUSSION

Lansoprazole **1** has been synthesized (Fig. 1) by an oxidation of sulfide **4**, which is produced from a condensation reaction between 2-mercaptobenzimidazole **8** and 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)-pyridine (**7**). The transformation of sulfide **4** into lansoprazole **1** was conducted using peroxy acid such as *m*-chloroperbenzoic acid (*m*-CPBA) or hydrogen peroxide.[10]

Lansoprazole-*N*-oxide **2** was prepared from 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy) pyridine hydrochloride (**7**). Reaction of **7** with

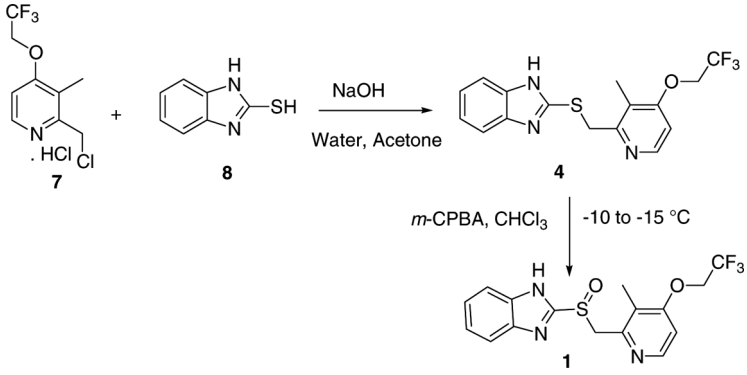


*Figure 1.* Synthesis of lansoprazole.

alkali and subsequent oxidation using *m*-CPBA gave the corresponding *N*-oxide **10**. Condensation of **10** with mercapto benzimidazole derivative **8** in aqueous alkali followed by *m*-CPBA oxidation of resulting sulfide **11** furnished the desired *N*-oxide impurity **2** (Fig. 2). High-resolution mass spectrometry (HRMS): $m/z$ calcd. for $C_{16}H_{15}N_3O_3F_3S$ $(M^+ + H)$: 386.0786; found: 386.0792; calcd. for $C_{16}H_{14}N_3O_3F_3NaS$ $(M^+ + Na)$: 408.0606; found: 408.0615; $m/z$ calcd. for $C_{16}H_{13}N_3O_3F_3S$ $(M^- - H)$: 384.0630; found: 384.0638. IR (NH)3436 $cm^{-1}$, Ar-H 3066 $cm^{-1}$, aromatic C = C 1585, 1480, 1449 $cm^{-1}$, S = O 1069 $cm^{-1}$. $^1$HNMR ($\delta$

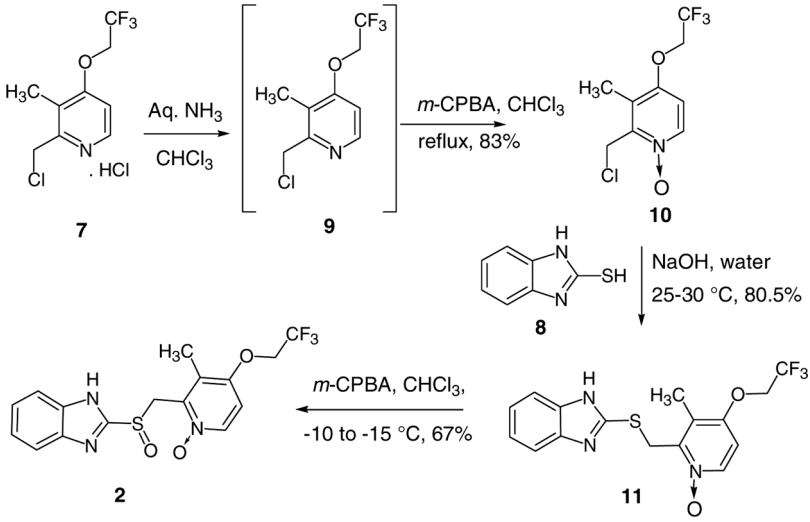


*Figure 2.* Synthesis of lansoprazole *N*-oxide.

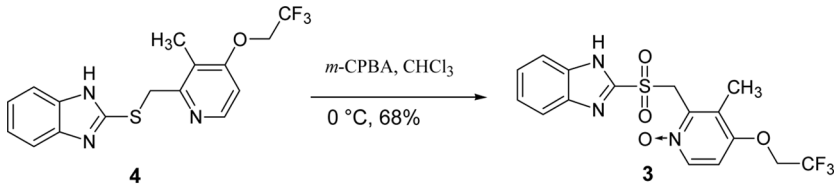


***Figure 3.*** Synthesis of lansoprazole sulfone *N*-oxide.



ppm) 13.68 (br, NH), 8.34 (d, $J = 7.2$, 1H, Py-H), 7.66 (m, 2H), 7.32 (m, 2H, Ar-H), 7.27 (d, $J = 7.2$, 1H, Py-H), 4.92 (m, 2H, Py-$CH_2$), 4.92 (m, 2H, $OCH_2$–$CF_3$), 2.05 (s, 3H, Py-$CH_3$).

Lansoprazole sulfone *N*-oxide **3** is the overoxidized by-product formed in the synthesis of lansoprazole. Lansoprazole sulfide **4**, on treatment with *m*-CPBA in chloroform, smoothly afforded lansoprazole sulfone *N*-oxide **3** (Fig. 3). The protonated molecular ion of **3** appeared at 402.0, and the sodium adduct appeared as the base peak at 424.1 in the EI spectrum. HRMS $m/z$ calcd. for $C_{16}H_{14}N_3O_4F_3NaS$ ($M^+ + Na$): 424.0555; found: 424.0558; $m/z$ calcd. for $C_{16}H_{13}N_3O_4F_3S$ ($M^- - H$): 400.0579; found: 400.0579. This is consistent with the assigned structure of **3**. IR spectrum of **3** showed the presence of O = S = O stretching (1335 $cm^{-1}$), C–N stretching (1109 $cm^{-1}$), and C–O aryl alkyl stretching (1016 $cm^{-1}$). The $^1$HNMR spectral data of compound **3** are similar to that of compound **2**.

Lansoprazole sulfide **4** was obtained using the synthetic sequence followed for lansoprazole (Fig. 1). HRMS $m/z$ calcd. for $C_{16}H_{15}N_3OF_3S$ ($M^+ + H$): 354.0888; found: 354.0894; $m/z$ calcd. for $C_{16}H_{13}N_3OF_3S$ ($M^- - H$) 352.0731; found: 352.0726. Data of **4** are consistent with that of sulfide. IR, mass, and $^1$HNMR spectral data of **4** are identical with that of the reference sample.[10]

Lansoprazole sulfone **5** was prepared by the controlled oxidation of lansoprazole sulfide **4**, using an optimal amount of *m*-CPBA (Fig. 4). The protonated molecular ion appeared at 386.0 and a sodium adduct

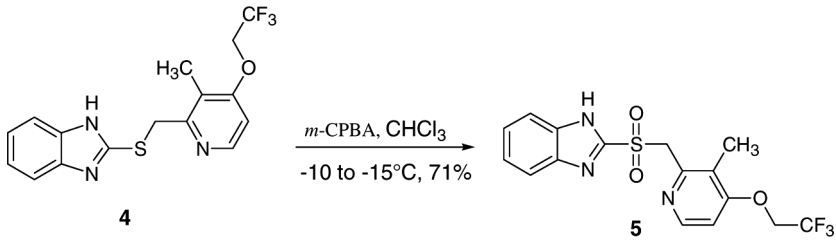


***Figure 4.*** Synthesis of lansoprazole sulfone.

appeared as the base peak at 408.0 in the EI spectrum. HRMS (EI), $m/z$ calcd. for $C_{16}H_{15}N_3O_3F_3S$ ($M^+ + H$): 386.0786; found: 386.0791; calcd. for $C_{16}H_{14}N_3O_3F_3NaS$ ($M^+ + Na$): 408.0606; found: 408.0626; $m/z$ calcd. for $C_{16}H_{13}N_3O_3F_3S$ ($M^- - H$): 384.0630; found: 384.0628). IR O = S = O stretching (1329 $cm^{-1}$), C–O stretching (1227, 1086 $cm^{-1}$), C–N stretching (1165 $cm^{-1}$). The $^1$HNMR spectral data of compound **5** is similar to that of compound **2**.

Synthesis of lansoprazole *N*-aralkyl impurity commenced from 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride (**7**). Condensation of **7** with mercapto derivative **8** in the presence of alkali and subsequent oxidation using *m*-CPBA gave the corresponding lansoprazole *N*-aralkyl impurity **6** in poor yield but better yield was obtained from the reaction of lansoprazole **1** with chloro compound **7** (Fig. 5). HRMS $m/z$ calcd. for $C_{25}H_{23}N_4O_3F_6S$ ($M^+ + H$): 573.1395; found: 573.1399; calcd. for $C_{25}H_{22}N_4O_3F_6NaS$ ($M^+ + Na$): 595.1215; found: 595.1243. IR spectrum with S = O absorption (1040 $cm^{-1}$) $^1$HNMR $\delta$ ppm: 8.28 (d, $J = 5.6$, 1H, Py-H), 8.09 (d, $J = 5.6$, 1H, Py-H), 7.78 (m, 1H, Ar-H), 7.56 (m, 1H, Ar-H), 7.30 (m, 2H, Ar-H), 7.07 (d, $J = 5.6$, 1H, Py-H), 7.03 (d, $J = 5.6$, 1H, Py-H), 5.91 (d,

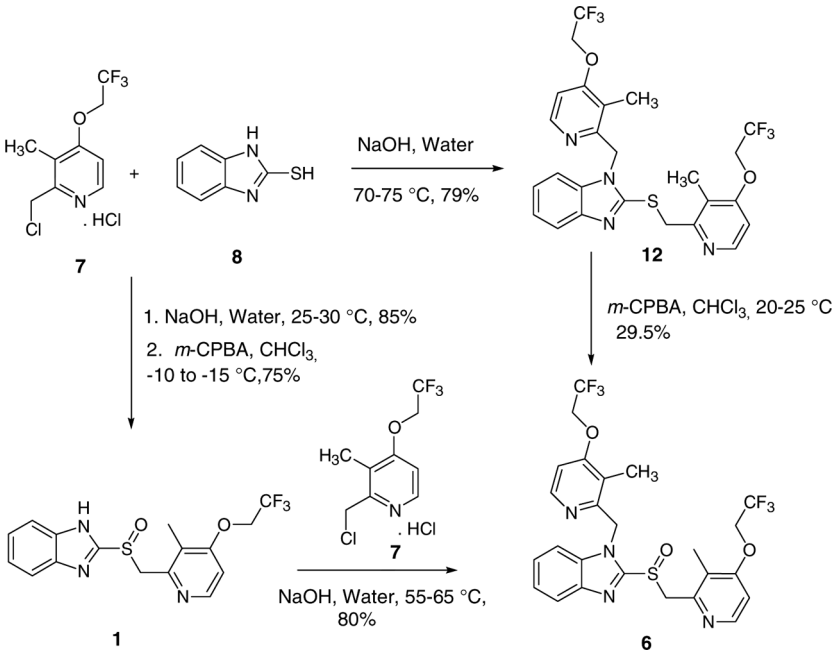


***Figure 5.*** Synthesis of *N*-aralkyl lansoprazole.

$J = 17.2$, 1H, Py-$CH_2$), 5.80 (d, $J = 17.2$, 1H, Py-$CH_2$), 5.00 (d, $J = 13.6$, 1H, Py-$CH_2$), 4.88 (m, 4H, $OCH_2CF_3$), 4.71 (d, $J = 13.6$, 1H, Py-$CH_2$), 2.30 (s, 3H, Py-$CH_3$), 2.08 (s, 3H, Py-$CH_3$). This further supports the assigned structure **6**.

## CONCLUSION

Information about the different possible impurities, metabolites, and their synthetic routes is a prerequisite for a thorough understanding of the impurity formation pathway of the antiulcerative drug lansoprazole. Keeping in view this regulatory importance of lansoprazole impurities, the process-related impurities and metabolites in bulk lansoprazole were identified, synthesized and characterized using mass, HRMS, IR, and NMR techniques.

## EXPERIMENTAL

The $^1$HNMR spectra data were recorded at 200 MHz on Varian and 400 MHz on Varian, Gemini-2000, FT NMR spectrometers; the chemical shifts were reported in $\delta$ ppm relative to TMS. The infrared spectra were obtained using a Perkin-Elmer, Spectrum One Fourier transform infrared (FT-IR) spectrophotometer, with substances being pressed in KBr pellets. The mass analysis was performed on a AB-4000 Q-trap LC-MS/MS mass spectrometer. The high resolution mass spectroscopy (HRMS) analysis was performed on the Micromass LCT Premier XE mass spectrometer equipped with an ESI Lock spray source for accurate mass values (Water Corporation, Milford, MA, USA). Solvent removal was accomplished by a rotary evaporator operating at house vacuum (40–50 Torr). The solvents and reagents were used without further purification. *m*-CPBA was used in the reaction, having the assay of 70% w/w.

### 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-1-oxide-2-pyridyl]methyl] sulfinyl]-1*H*-benzimida-zole (Lansoprazole-*N*-Oxide, 2)

### 2-Chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine-1-oxide (10)

In the solution of 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride (20.0 g, 72 mmol, **7**) in $CHCl_3$ (100.0 mL) and $H_2O$ (100.0 mL), pH was adjusted to 8.0 with aq. ammonia and stirred for 10 min. The chloroform layer was separated and washed with $H_2O$ ($2 \times 100$ mL). To this solution of free base 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine (**9**), a solution of *m*-CPBA (43.0 g,

175 mmol) in $CHCl_3$ (250.0 mL) was added at reflux temperature for 1 h and stirred for 1.5 h for reaction completion. pH was adjusted to 8.5 with aq. ammonia at 15–20 °C. The organic and aqueous layers were separated, and the organic layer was washed with water (2 × 50.0 mL). The organic layer was concentrated under reduced pressure at less than 45 °C; the solid was isolated in *n*-hexane and dried to get the brown solid **10**. Yield 17.4 g, 83%); IR (KBr, $cm^{-1}$): 3027 (Ar-H), 1572, 1473 (aromatic C = C), 1246 (C−O aryl alkylether), 1170 (C–N), 780 (Ar-H bending); $^1$HNMR (DMSO-$d_6$, 400 MHz, $\delta$ ppm): 8.30 (d, $J = 7.6$, 1H, Py-H) 7.27 (d, $J = 7.2$, 1H, Py-H), 5.0 (s, 2H, $-CH_2Cl$), 4.96–4.79 (m, 2H, $OCH_2CF_3$), 2.27 (s, 3H, Py-$CH_3$); MS $m/z$ (EI): 256.0 ($M^+ + H$).

### 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-1-oxide-2-pyridyl]methyl]thio]-1*H*-benzimidazole (11)

To the solution of 2-mercapto-1*H*-benzimidazole (10.3 g, 68 mmol, **8**) in water (50.0 mL) and NaOH (4 g, 100 mmol), a solution of 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine-1-oxide (16 g, 62 mmol, **10**) in acetone (50.0 mL) was added and stirred for 1 h to reaction completion. The isolated solid was filtered, washed with a 1:1 mixture of water and acetone (20.0 mL), and dried at 40–45 °C to get a white solid. Yield 18.6 g, 80.5%; IR (KBr, $cm^{-1}$): 3037 (Py-H), 2958, 2938 (Ali-H), 1613 (C = N), 1574, 1442 (aromatic C = C), 1270, 1049 (arylalkylether), 1174 (C–N), 762 (Ar-H bending); $^1$HNMR (DMSO-$d_6$ + $CHCl_3$-d, 400 MHz, $\delta$ ppm): 13.24 (s, benzimidazole-NH), 8.24 (d, $J = 7.2$, 1H, Py-H), 7.48–7.50 (m, 1H, Ar-H), 7.33–7.36 (m, 1H, Ar-H), 7.14 (d, $J = 7.2$, 1H, Py-H), 7.08–7.15 (m, 2H, Ar-H), 4.86 (s, 2H, $PyCH_2Cl$), 2.39 (s, 3H, $PyCH_3$), 4.63–4.69 (m, 2H, $OCH_2CF_3$); MS $m/z$ (EI): 370.0 ($M^+ + H$), 392.1 ($M^+ + Na$).

### 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-1-oxide-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole (Lansoprazole *N*-Oxide, 2)

To a cooled solution of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-1-oxide-2-pyridyl]methyl]thio]-1*H*-benzimidazole (6.0 g, 16 mmol, **11**) in chloroform (30.0 mL), a solution of *m*-CPBA (4.0 g, 16 mmol) in chloroform (30.0 mL) was added slowly at −10 to −15 °C over a period of 30 min. The reaction mass was poured into the solution of NaOH (2.0 g, 50 mmol) in water (50.0 mL), and pH was adjusted to 8–8.5 using acetic acid. The organic and aqueous layers were separated. The organic layer was extracted with aq. NaOH solution (1.5 g in 30.0 mL water), and the resulting aq. layer was washed with chloroform (2 × 15.0 mL) to remove unreacted sulfide **11.** Methanol (15.0 mL) was added, and then

pH was adjusted with acetic acid to 7–7.5. The isolated product was filtered and dried at 50 °C to yield a white solid **2**. Yield 6.2 g, 67%; mp 196–200 °C (dec.). IR (KBr, $cm^{-1}$): 3436 (moisture O–H), 3066 (Ar–H), 2941, 2864 (Ali–H), 1615 (C = N), 1585, 1470, 1449, 1408 (Ar C = C), 1255 (arylalkylether), 1174 (C–N), 1155 (C–F), 1069 (S = O); $^1$HNMR (DMSO-$d_6$, 400 MHz, $\delta$ ppm): 13.68 (br, benzimidazole-NH), 8.34 (d, $J = 7.2$, 1H, Py-H), 7.66 (m, 2H, Ar-H), 7.32 (m, 2H, Ar-H), 7.27 (d, $J = 7.2$, 1H, Py-H), 4.92 (s, 2H, Py-$CH_2$–Cl), 2.05 (s, 3H, Py-$CH_3$), 4.92 (m, 2H, –$CH_2CF_3$); $^{13}$CNMR (DMSO-$d_6$, 400 MHz, $\delta$ ppm) 154.71, 136.78, 123.59 (q, 275.7, splitting due to coupling between $^{19}$F and $^{13}$C), 123.30, 117.35, 109.98, 65.33 (q, 34.4, splitting due to coupling between $^{19}$F and $^{13}$C), 54.30, 11.55; MS: +ve. HRMS: $m/z$ calcd. for $(M^+ + H)$ $C_{16}H_{15}N_3O_3F_3S$: 386.0786; found: 386.0792 (1.6 ppm); calcd. for$(M^+ + Na)C_{16}H_{14}N_3O_3F_3Na$ S: 408.0606; found: 408.0615 (2.2 ppm). –ve HRMS: $m/z$ calcd. for $(M^- - H)$. $C_{16}H_{13}N_3O_3F_3S$: 384.0630; found: 384.0638 (2.1 ppm).

### 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-1-oxide-2-pyridyl]methyl] sulfonyl]-1*H*-benzimidazole (3)

To a solution of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]-thio]-1*H*-benzimidazole (10.0 g, 28.3 mmol, **4**) in $CHCl_3$ (50.0 mL) at − 20 to − 25 °C, a solution of *m*-CPBA (40.0 g, 162 mmol) in $CHCl_3$ (60.0 mL) was added slowly for 45 min. The reaction was maintained for 1 h, and then the temperature was raised to 0 °C and maintained for 1 h. The reaction mass was poured into the aq. NaOH solution (12.0 g NaOH in 100.0 mL of water), pH was adjusted to 8.0 with AcOH, and the organic layer was separated. This $CHCl_3$ layer was extracted with basic water (1.5 g of NaOH in 50.0 mL of water) and washed with $CHCl_3$ ($2 \times 20.0$ mL). Methanol (25.0 mL) was added, and the solution was cooled to 10 °C. pH was adjusted to 7.0 with AcOH, temperature cooled to 5°C, and the isolated solid was filtered. The solid was washed with the 1:1 mixture of $H_2O$ and methanol (10.0 mL) and purified from the acetone to yield white solid **3,** 7.4 g, 68%; mp: 239–244 °C. IR (KBr, $cm^{-1}$): 3415 (moisture O–H), 3079 (Ar–H), 2954 (Ali–H), 1612, 1456 (aromatic C = C), 1397 (Ali-H bending), 1335 (O = S = O), 1135 (C–F), 1109 (C–N), 1016 (C–O aryl alkyl ether), 750 (Ar-H bending); $^1$HNMR (DMSO-$d_6$, 400 M Hz, $\delta$ ppm): 13.85 (br, benzimidazole-NH), 8.12 (d, $J = 7.2$, 1H, Py-H), 7.74 (br, 1H, Ar-H), 7.61 (br, 1H, Ar-H), 7.38 (br, 2H, Ar-H), 7.22 (d, $J = 7.2$, 1H, Py-H), 5.44 (s, 2H, Py$CH_2$), 4.93 (q, $J = 8.8$, 2H, $OCH_2$–$CF_3$), 2.25 (s, 3H, Py$CH_3$); $^{13}$CNMR (DMSO-$d_6$, 400 MHz, $\delta$ ppm) 151.79, 148.41, 142.14, 139.45, 136.68, 134.21, 126.81, 125.26,

123.61 (q, 276.5, splitting due to coupling between $^{19}F$ and $^{13}C$), 123.43, 120.63, 113.13, 110.19, 65.29 (q, 34.4, splitting due to coupling between $^{19}F$ and $^{13}C$), 54.05, 11.97. Mass ($M^+ + H$) 402.0, ($M^+ + Na$) 424.1, (EI): + ve HRMS: $m/z$ calcd. for ($M^+ + Na$) $C_{16}H_{14}N_3O_4F_3NaS$: 424.0555; found: 424.0558 (0.7 ppm); −ve HRMS: $m/z$ calcd. for ($M^- - H$). $C_{16}H_{13}N_3O_4F_3S$: 400.0579; found: 400.0579 (0.0 ppm).



**2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]-1*H*-benzimidazole (4)**

To the solution of 2-mercapto-1*H*-benzimidazole (7.8 g, 52 mmol, **8**) and sodium hydroxide (3.8 g, 95 mmol) in water (60.0 mL) and acetone (60.0 mL) at 15–20 °C, a solution of 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride (12.0 g, 43 mmol, **7**) in water (30.0 mL) was added slowly for 45 min. The precipitated solid was filtered at 25–30 °C, washed with a 1:1 mixture (20.0 mL) of acetone and water, and dried to a constant weight at 60 °C to yield off-white solid **4**. Yield 12.3 g, 80%; mp 111–116 °C; IR (KBr, $cm^{-1}$) 3551 (moisture O–H), 3054 (Ar–H), 2984, 2898 (Ali–H), 1662 (C = N), 1590, 1509, 1445 (aromatic C = C), 1380, 1363 (Ali-H bending), 1256, 1175 (C–N), 1163 (C-F), 1009 (arylalkylether), 762, 746 (Ar-H bending). Mass (EI) + ve HRMS: $m/z$ calcd. for ($M^+ + H$) $C_{16}H_{15}N_3OF_3S$: 354.0888; found: 354.0894 (1.7 ppm); −ve HRMS: $m/z$ calcd. for ($M^- - H$) $C_{16}H_{13}N_3OF_3S$: 352.0731; found: 352.0726 (−1.4 ppm); $^1$HNMR (DMSO-$d_6$, 200 MHz, $\delta$ ppm]: 12.59 (s, benzimidazole-NH), 8.31 (d, $J = 5.6$, 1H, Py-H), 7.53 (m, 1H, Ar-H), 7.38 (m, 1H, Ar-H), 7.13 (m, 2H, Ar-H), 7.09 (d, $J = 5.6$, 1H, Py-H), 4.90 (q, $J = 8.8$, 2H, splitting due to coupling between $^1$H and $^{19}$F), 4.73 (s, 2H, Py-$CH_2$), 2.25 (s, 3H, Py-$CH_3$); $^{13}$CNMR (DMSO-$d_6$, 200 M Hz, $\delta$ ppm) 161.19, 155.55, 150.05, 147.78, 142.65, 136.33, 123.76 (q, 275.7, splitting due to coupling between $^{19}F$ and $^{13}C$), 121.40, 120.12, 117.05, 110.12, 106.86, 64.70 (q, 34.4, splitting due to coupling between $^{19}F$ and $^{13}C$), 36.19, 10.23.

**2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfonyl]-1*H*-benzimidazole (5)**

To the solution of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]-methyl]thio]-1*H*-benzimi-dazole (8.0 g, 22.6 mmol, **4**) in $CHCl_3$ (40.0 mL) and MeOH (15.0 mL), a solution of *meta* chloroperbenzoic acid (*m*-CPBA) (11.5 g, 46.9 mmol) in $CHCl_3$ (50.0 mL) was added for 45 min to 1 h at −10 to −15 °C. The reaction mass was poured into the

solution of aq. NaOH (5.0 g of NaOH in 100.0 mL of water). pH was adjusted to 8 with AcOH, and then the organic layer was separated. It was extracted with basic water (2.0 g of NaOH in 60.0 mL of water) and washed with $CHCl_3$ ($2 \times 20.0$ mL). Acetone (20.0 mL) was charged to the aqueous layer and cooled to 5–10 °C. pH was adjusted with AcOH to 8, and the isolated solid was filtered and washed with the 1:1 mixture of water and acetone (20.0 mL), then purified from methanol and dried to a constant weight at 60–65 °C to yield white solid **5**. Yield 6.2 g, 71%; mp 206–210 °C; IR (KBr, $cm^{-1}$): 3437 (moisture O–H), 3091 (Ar–H), 2964, (Ali–H), 1586, 1480, 1456 (aromatic C = C), 1442, 1386 (Ali-H bending), 1329 (O = S = O), 1227, 1086 (arylalkylether), 1165 (C–N), 1143 (C–F), 744 (Ar–H bending); $^1$H NMR (DMSO-$d_6$, 400 M Hz, $\delta$ ppm]: 12.00 (br, benzimidazole-NH), 8.14 (d, $J = 5.6$, 1H, Py-H), 7.68 (m, 2H, Ar-H), 7.35 (m, 2H, Ar-H), 7.08 (d, $J = 5.6$, 1H, Py-H), 5.10 (s, 2H, Py-$CH_2$), 4.90 (q, $J = 8.4$, 2H, $OCH_2CF_3$), 2.23 (s, 3H, Py-$CH_3$); $^{13}$CNMR (DMSO-$d_6$, 400 MHz, $\delta$ ppm) 161.47, 148.77, 148.04, 138.94, 123.98, 123.72 (q, 275.7, splitting due to coupling between $^{19}$F and $^{13}$C), 123.32, 117.04, 107.41, 64.70 (q, 33.8, splitting due to coupling between $^{19}$F and $^{13}$C), 60.39, 10.90. Mass (EI) +ve HRMS: $m/z$ calcd. for ($M^+ + H$) $C_{16}H_{15}N_3O_3F_3S$: 386.0786; found: 386.0791 (1.3 ppm); calcd. for ($M^+ + Na$) $C_{16}H_{14}N_3O_3F_3NaS$: 408.0606; found: 408.0626 (4.9 ppm); −ve HRMS: $m/z$ calcd. for ($M^- - H$) $C_{16}H_{13}N_3O_3F_3S$: 384.0630; found: 384.0628 (− 0.5 ppm).

### 1-[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole (6)

### 1-[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]-1*H*-benzimidazole (12)

To a solution of 2-mercapto-1*H*-benzimidazole (6.0 g, 40 mmol, **8**) and NaOH (12.75 g, 318 mmol) in $H_2O$ (30.0 mL) at 25–30 °C, a solution of 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine HCl (22.0 g, 80 mmol, **7**) in $H_2O$ (65.0 mL) was added for 30–45 min. Reaction mass was heated to 70–75 °C and maintained at 70–75 °C for 4 h. The precipitated solid was filtered at 25–30 °C and washed with a 1:1 mixture of MeOH and $H_2O$ (20.0 mL), the recrystallized from ethyl acetate and dried to a constant weight at 55 °C to yield **12**. Yield 17.5 g, 79%. MS m/z ($M^+ + H$) 557.2, ($M^+ + Na$) 579.2; $^1$HNMR (DMSO-$d_6$, 400 MHz, $\delta$ ppm): 8.28 (dd, $J = 8$, 20, 1H, Py-H), 8.10 (d, $J = 6$, 1H, Py′-H), 7.58–7.60 (m, 1H, Ar-H), 7.29–7.38 (m, 1H, Ar-H), 7.01–7.17 (m, 2H, Ar-H), 7.02 (d, $J = 6$, 2H, Py-H), 5.48 (s, 2H, Py'-$CH_2$), 4.70–4.92 (m,

4H, Py-$CH_2$), 4.71 (d, $J = 6.8$, 2H, Py-$CH_2$), 2.25 (s, 3H, Py-$CH_3$), 2.20 (s, 3H, Py′-$CH_3$).

### 1-[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole (6)

To the solution of 1-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]-methyl]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]-1*H*-benzimidazole (12.0 g, 21.5 mmol, **12**) in $CHCl_3$ (60.0 mL) and MeOH (30.0 mL) at 20–25°C, a solution of *m*-CPBA (6.0 g, 24.4 mmol) in $CHCl_3$ (50.0 mL) was added slowly for 30 min. The reaction was maintained for 4 h, and the reaction mass was poured into the solution of NaOH (2.0 g of NaOH in 100.0 mL of water). pH was adjusted to 8.5 with AcOH, and then the both layers were separated. Aq. layer was extracted with $CHCl_3$ ($2 \times 50.0$ mL), and the combined organics were concentrated under reduced pressure. A solid was recrystallized from MeOH (30.0 mL) and dried to a constant weight at 50 °C to yield a white solid **6**. Yield 3.64 g, 29.5%; mp 155–160 °C. IR (KBr, $cm^{-1}$): 3411 (moisture O–H), 3086 (Ar–H), 2949, 2805 (Ali–H), 1583, 1476, 1459 (aromatic C = C), 1382 (Ali–H bending), 1040 (S = O), 1263 (arylalkylether), 1165 (C–N), 748 (Ar–H bending); mass (EI): +ve HRMS: $m/z$ calcd. for ($M^+ + H$) $C_{25}H_{23}N_4O_3F_6S$: 573.1395; found: 573.1399 (0.7 ppm); calcd. for ($M^+ + Na$) $C_{25}H_{22}N_4O_3F_6NaS$: 595.1215; found: 595.1243, (4.7 ppm); $^1$HNMR (DMSO-$d_6$, 400 MHz, $\delta$ ppm): 8.28 (d, $J = 5.6$, 1H, Py-H), 8.09 (d, $J = 5.6$, 1H, Py′-H), 7.75–7.80 (m, 1H, Ar-H), 7.70–7.60 (m, 1H, Ar-H), 7.25–38 (m, 2H, Ar-H), 7.07 (d, $J = 5.6$, 1H, Py-H), 7.03 (d, $J = 5.6$, 1H, Py′-H), 5.80 (dd, $J = 8$, 17.2, 1H, Py'-$CH_2$), 5.00 (d, $J = 13.6$, 1H, Py-$CH_2$), 4.82–4.90 (m, 4H, Py-$CH_2$), 4.71 (d, $J = 13.6$, 1H, Py-$CH_2$), 2.30 (s, 3H, Py-$CH_3$), 2.08 (s, 3H, Py'-$CH_3$); $^{13}$CNMR (DMSO-$d_6$, 400 MHz, $\delta$ ppm) 161.30, 161.11, 154.08, 153.98, 151.51, 148.03, 147.77, 141.71, 136.16, 124.00, 123.76 (q, 277.0, splitting due to coupling between $^{19}$F and $^{13}$C), 123.71 (q, 277.4, splitting due to coupling between $^{19}$F and $^{13}$C), 122.82, 121.96, 120.08, 118.86, 111.21, 106.94, 64.62 (q, 32.4, splitting due to coupling between $^{19}$F and $^{13}$C), 59.33, 45.85, 10.31, 9.31.

### Alternative Procedure to Prepare 6

To a solution of lansoprazole (5.0 g, 13.5 mmol, **1**) and NaOH (1.2 g, 30 mmol) in $H_2O$ (30.0 mL) at 25–30 °C, a solution of 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine HCl (3.73 g, 13.5 mmol, **7**) in

$H_2O$ (15.0 mL) was added. The reaction mass was heated to 70–75 °C and maintained at 70–75 °C with the completion of the reaction. The precipitated solid was filtered at 25 °C, washed with a 1:1 mixture of MeOH and $H_2O$ (20.0 mL), then purified in ethyl acetate and dried to a constant weight at 50–55 °C to yield, **6**. Yield 6.2 g, 80%.



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