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Synthesis and Characterization of Metabolites and Potential Impurities of the Antiulcerative Drug Tenatoprazole

Ganta Madhusudhan Reddy,[1,2] V. V. N. K. V. Prasada Raju,[1] J. Moses Babu,[1] Ch. Praveen,[1] Mayur Khunt,[1] K. Mukkanti,[2] and Padi Pratap Reddy[1]

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Abstract: Tenatoprazole (Ulsacare®) is a recently developed antiulcerative drug used for the treatment of both erosive and nonerosive gastroesophageal reflux disease. During the bulk synthesis of tenatoprazole, we have observed four impurities (tenatoprazole N-oxide, tenatoprazole sulfone N-oxide, N-methyl tenatoprazole, and desmethoxy tenatoprazole) and two metabolites (tenatoprazole sulfide and tenatoprazole sulfone). The present work describes the synthesis and characterization of these impurities.

Keywords: Impurities, metabolites, sulfide and sulfone, synthesis, tenatoprazole

INTRODUCTION

Proton pump inhibitors (PPIs) are now widely used for the treatment of both erosive and nonerosive gastro-esophageal reflux disease.[1] Current PPIs used clinically are substituted pyridylmethylsulfinyl benzimidazole

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prodrugs. Tenatoprazole, 5-methoxy-2-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethanesulfinyl)-1*H*-imidazo[4,5-*b*]pyridine (**1**), is a novel proton pump inhibitor, which structurally resembles omeprazole. Tenatoprazole belongs to the class of covalent proton pump inhibitors and inhibits gastric (H^+, K^+)-ATPase with potency similar to that of omeprazole. However, the antisecretary and antiulcer effects of tenatoprazole were reported to be two to four times more potent than those of omeprazole with long-lasting effects on gastric acid secretion.[1–3] In human studies, tenatoprazole was more potent than esomeprazole. Particularly, the $pH > 4$ holding time was higher during the night for tenatoprazole than for esomeprazole.[4]

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 0.10% or more.[5,6] In this context, a comprehensive study was undertaken to synthesize and characterize the following four impurities:[7] 5-methoxy-2-(4-methoxy-3,5-dimethyl-1-oxide-2-pyridinylmethanesulfinyl)-1*H*–imidazo [4, 5-*b*]pyridine (tenatoprazole *N*-oxide, **2**); 5-methoxy-2-(4-methoxy-3,5-dimethyl-1-oxide-2-pyridinylmethanesulfonyl)-1*H*-imidazo[4,5-*b*]pyridine (tenatoprazole sulfone *N*-oxide, **3**); 5-methoxy-2-(3,5-dimethylpyridin-2-ylmethanesulfinyl-1*H*-imidazo[4,5-*b*]pyridine (desmethoxy tenatoprazole, **4**); and 5-methoxy-2-(4-methoxy-3,5-dimethylpyridin-2-ylmethanesulfinyl-1-methyl-1*H*-imidazo[4,5-*b*]pyridine (*N*-methyl tenatoprazole, **5**); and two metabolites, 5-methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridinylmethanethio)-1*H*–imidazo[4,5-*b*]pyridine (tenatoprazole sulfide, **6**) and 5-methoxy-2-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethanesulfonyl)-1*H*-imidazo[4,5-*b*]pyridine (tenatoprazole sulfone, **7**). Results are presented in this article. Except for sulfide **6** and sulfone **7**, which were earlier reported as metabolites,[8] other impurities **2**, **3**, **4**, and **5** are hitherto not known.

RESULTS AND DISCUSSION

Synthesis of tenatoprazole **1** involves condensation of chloro methyl pyridine derivative **8** with the mercapto compound **9** in the presence of NaOH and oxidation of the resulting compound **6** with *m*-CPBA (Fig. 1).

5-Methoxy-2-(4-methoxy-3,5-dimethyl-1-oxide-2-pyridinylmethane sulfinyl)-1*H*-imidazo[4,5-*b*]pyridine (Tenatoprazole-*N*-oxide, 2)

Preparation of tenatoprazole-*N*-oxide commenced from 3,5-dimehtyl-2-chloromethyl pyridine hydrochloride (**8**). Treatment of **8** with alkali and

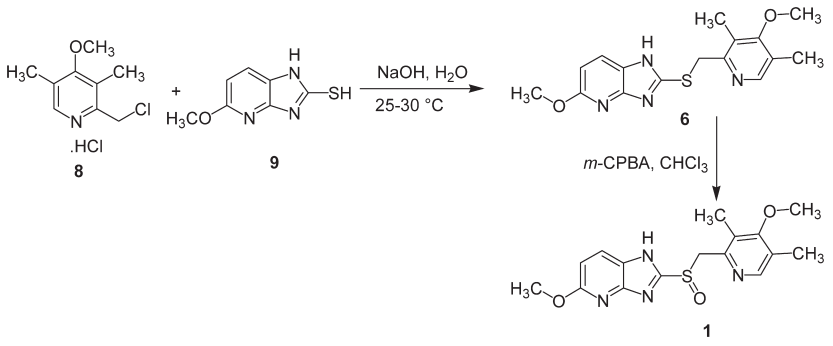

Figure 1. Synthesis of tenatoprazole.

subsequent oxidation using meta-chloro perbenzoic acid (*m*-CPBA) gave the corresponding N-oxide **11**. Condensation of **11** with mercapto derivative **9** in aqueous alkali followed by *m*-CPBA oxidation of resulting sulfide **12** furnished the desired N-oxide impurity **2** in 72% yield (Fig. 2). The protonated molecular ion of **2** appeared as the base peak at m/z 363.1 and sodium adduct at 385.0 in the EI spectrum. High-resolution mass spectrometry (m/z calcd. for $C_{16}H_{18}N_4O_4SNa$ ($M^+ + Na$): 385.0946; found: 385.0943), IR (NH 3448 cm^{-1}, S═O 1064 cm^{-1}, arylalkylether 1030 cm^{-1}), and ^1H NMR (δ ppm, 13.8, s, NH; 3.66, s, 3H, 3.92, s, 3H, O-CH_3, 2.09, s, 3H, py-CH_3 and 2.21, s, 3H, py-CH_3) further support the assigned structure of **2**.

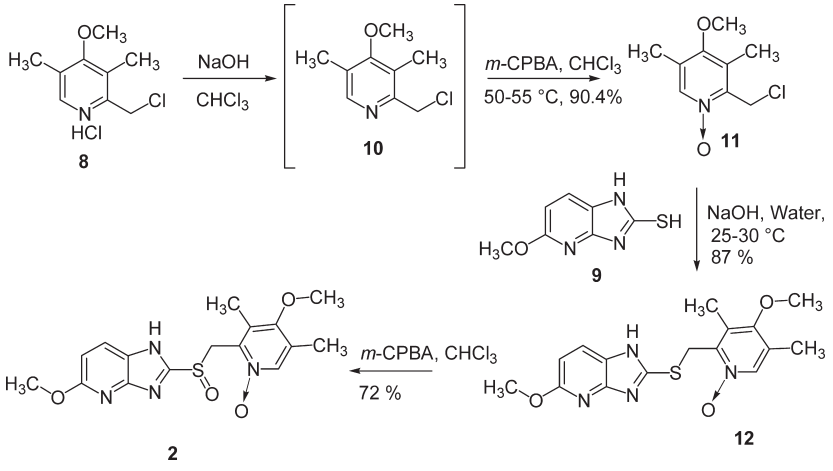

Figure 2. Synthesis of tenatoprazole-*N*-oxide.

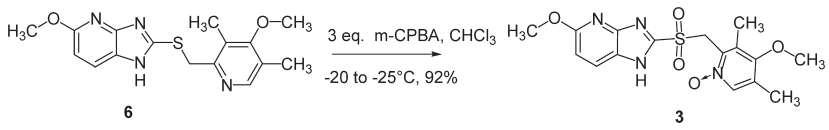

Figure 3. Synthesis of tenatoprazole sulfone N-oxide.

5-Methoxy-2-(4-methoxy-3,5-dimethyl-1-oxide-2-pyridinmethane sulfonyl)-1*H*-imidazo[4,5-*b*]pyridine (Tenatoprazole Sulfone *N*-oxide, 3)

Tenatoprazole sulfide **6** on treatment with 3 equiv. of *m*-CPBA in chloroform smoothly afforded tenatoprazole sulfone *N*-oxide **4** (Fig. 3). The sodium adduct appeared as the base peak at m/z 401.0. HRMS (m/z calcd. for $C_{16}H_{19}N_4O_5S$ ($M^+ + H$): 379.1076; found: 379.1062) is consistent with the assigned structure of **1**. IR spectrum showed the presence of NH (3429 cm^{-1}), O═S═O (1330 cm^{-1}), and arylalkylether (1136 cm^{-1}) stretchings. In the ^1H NMR spectrum, a deuterium exchangeable singlet at 14.28 corresponds to NH function. The O-CH_3 protons appeared as singlets at 3.71 and 3.92. Singlets at 2.16 and 2.26, each integrating for three protons, are due to two methyl groups of pyridine ring.

5-Methoxy-2-(3,5-dimethylpyridin-2-ylmethanesulfinyl-1*H*-imidazo[4,5-*b*]pyridine (Desmethoxy Tenatoprazole, 4)

2,3,5-Trimethyl pyridine (**13**) was chosen as the starting material for the synthesis of **4**. Hydrogen peroxide–mediated oxidation of **13** and subsequent transformation of the resulting **14** into 2-hydroxy methyl pyridine derivative **15** in the presence of acetic anhydride, followed by reaction with thionyl chloride, provided the required key intermediate **16**. Condensation of **16** with 2-mercapto derivative **9** in the presence of alkali in methanolic medium and concomitant oxidation with *m*-CPBA yielded the desmethoxy tenatoprazole **4** (Fig. 4). HRMS (EI) (m/z calcd for $C_{15}H_{17}N_4O_2S$ ($M^+ + H$): 317.1072; found: 317.1081), IR (NH 3445 cm^{-1}, S═O 1060 cm^{-1} and arylalkylether 1257, 1060 cm^{-1}), and ^1H NMR (δ ppm, 14.00, s, NH; 3.90, s, 3H O-CH_3, 2.24, s, 3H and 2.29, s, 3H py-CH_3) spectral data of **4** are in conformity with the assigned structure (Figure 5).

5-Methoxy-2-(4-methoxy-3,5-dimethylpyridin-2-ylmethanesulfinyl-1-methyl-1*H*-imidazo[4,5-*b*]pyridine (*N*-Methyltenatoprazole, 5)

Methylation of tenatoprazole **1** using 1.2 equiv of methyl iodide in the presence of potassium carbonate in dichloromethane yielded *N*-methyl

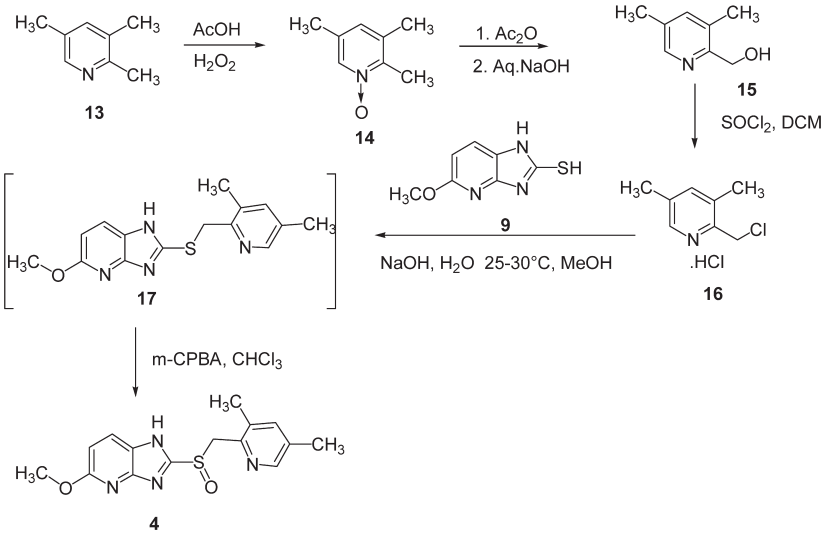

Figure 4. Synthesis of desmethoxy tenatoprazole.

tenatoprazole, whose molecular formula in high resolution mass spectra (HRMS) corresponds to $C_{17}H_{21}N_4O_3S$ with $M^+ + H$ at 361.1332 (Calculated 361.1334). ^{1}H-NMR spectrum of **5** is characterized by the presence of five singlets corresponding to five methyl groups (δ ppm = 3.90, 3.89, 3.67, 2.19, and 2.16).

5-Methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridinylmethanethio)-1*H*-imidazo[4,5-*b*]pyridine (Tenatoprazole Sulfide, 6)

Tenatoprazole sulfide **6** was obtained using the synthetic sequence followed for tenatoprazole (Fig. 1). In the EI mass spectrum of **6**, the potassium adduct ion appeared as the base peak at m/z 369.1, HRMS (EI) (m/z calcd. for $C_{16}H_{19}N_4O_2S$ ($M^+ + H$): 331.1229; found: 331.1227) data of **6** is consistent with that of sulfide. IR and spectral data of **6** are identical with those of reference sample.

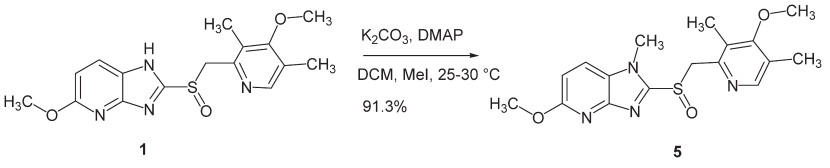

Figure 5. Synthesis of *N*-methyl tenatoprazole.

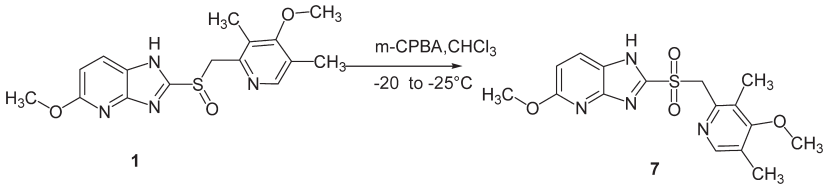

Figure 6. Synthesis of tenatoprazole sulfone.

5-Methoxy-2-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethanesulfonyl) -1*H*-imidazo[4,5-*b*] pyridine (Tenatoprazole Sulfone, 7)

Tenatoprazole sulfone **7** was prepared by the controlled oxidation of tenatoprazole **1**, using an optimal amount of *m*-CPBA (Fig. 6). The protonated molecular ion of **7** appeared as the base peak at m/z 363.1, in HRMS (EI, m/z calcd. for $C_{16}H_{19}N_4O_4S$ ($M^+ + H$): 363.1127; found: 363.1132). IR [NH (3435 cm^{-1}), O═S═O (1328 cm^{-1}), arylalkylether (1080 cm^{-1})] and ^1H NMR spectral data (δ ppm, 13.0, s, NH; 3.92, s, 3H, O-CH_3; 3.69, s, 3H, O-CH_3; 2.23, s, 3H, CH_3; 2.16, s, 3H, CH_3) of **7** are similar to those of tenatoprazole **1** (Figure 6).

CONCLUSION

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

EXPERIMENTAL

The ^1H NMR spectra data were recorded at 200 MHz on a Varian Gemini-2000 FT NMR spectrometer; the chemical shifts were reported on δ parts per million (ppm) relative to TMS. The infrared spectra were obtained using a Perkin-Elmer Spectrum One FT IR spectrophotometer, with substances being pressed in a KBr pellet. The mass analysis has been performed on AB-4000 Q-trap LC-MS/MS mass spectrometer (MDS SCIEX, Applied Bio systems, California, USA). The HRMS analysis has been 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.

5-Methoxy-2-(4-methoxy-3,5-dimethyl-1-oxide-2-pyridinylmethane sulfinyl)-1*H*-imidazo[4,5-*b*]pyridine (Tenatoprazole-*N*-oxide, 2)

4-Methoxy-3,5-dimehtyl-2-chloromethylpyridine-1-oxide (11)

Aq. NaOH (2.0 g, 0.050 mol) was added to a solution of 4-methoxy-3,5-dimethyl-2-chloromethylpyridine hydrochloride (10.0 g, 0.045 mol, **8**) in $CHCl_3$ (50.0 mL) and H_2O (50.0 mL) for pH adjustment and stirred for 30 min. The chloroform layer was separated and washed with water (50.0 mL). *m*-CPBA (13.0 g, 0.052 mol, 70%) in $CHCl_3$ (50.0 mL) was added to this solution at 55–60 °C for 1 h and stirred for 30 min for reaction completion. Water (50.0 mL) was added to the reaction mass, and pH was adjusted to 8.5–9.0 with aq. NaOH solution. The organic and aqueous layers were separated. The organic layer was washed with H_2O (2×25.0 mL) and concentrated under reduced pressure at less than 45 °C to get the residue. To the residue, Ethyl acetate (25.0 mL) was added and stirred for 30 min. The isolated solid was filtered, washed with chilled ethyl acetate (10.0 mL), and dried at 40–45 °C to yield **11** (yield 8.2 g, 90.4%). IR (KBr, cm^{-1}): 3050 (Py-H), 2943 (Ali-H), 1247, 1054 (arylalkylether), 1460 (aromatic C═C); ^{1}H NMR ($CDCl_3$, δ ppm): 2.2 (s, 3H, Py-CH_3), 2.3 (s, 3H, Py-CH_3), 3.71 (s, 3H, O-CH_3), 4.94 (s, 2H, -CH_2Cl), 8.17 (s, 1H, Py-H); MS m/z (EI): 201.9 (M^++ H), 223.9 ($M^+ + Na$), 425 ($2M^+ + Na$).

5-Methoxy-2-(4-methoxy-3,5-dimethyl-1-oxide-2-pyridinylmethanethio)-1*H*-imidazo [4,5-*b*]pyridine (12)

4-Methoxy-3,5-dimehtyl-2-chloromethyl-pyridine-1-oxide (5 g, 0.026 mol, **11**) in MeOH (50 mL) was added slowly to a solution of 2-mercapto-5-methoxypyridine imidazole (5 g, 0.027 mol, **9**) and NaOH (2 g, 0.05 mol) in H_2O (100 mL) and stirred for 1 h. After completion of the reaction, the reaction mixture was extracted with $CHCl_3$ (2×30 mL) and washed with water (50 mL). The organic layer was distilled off completely and charged with n-hexane (10 mL). The isolated solid was filtered, washed with n-hexane (10 mL), and dried at 35–40 °C to get a white solid **12** (yield 8.1 g, 87%). IR (KBr, cm^{-1}): 2941 (Ali-H), 1227, 1031 (arylalkylether), 1608, 1590 (C═C); ^{1}H NMR (DMSO-d_6, 200 MHz, δ ppm): 2.17 (s, 3H, Py-CH_3), 2.28 (s, 3H, Py-CH_3), 3.71 (s, 3H, O-CH_3), 4.94 (s, 2H, Py-CH_2Cl), 8.17 (s, 1H, Py-H); MS m/z (EI): ($M^+ + H$) 347.1, ($M^+ + Na$) 369.1, ($M^+ + K$) 385.0.

5-Methoxy-2-(4-methoxy-3,5-dimethyl-1-oxide-2-pyridinylmethanesulfinyl)-1*H*-imidazo [4,5-*b*]pyridine (2)

m-CPBA (1.1 g, 4.4 mmol) in $CHCl_3$ (15 mL) at -10 to -15 °C was added slowly to a cooled solution of 5-methoxy-2-(4-methoxy-3,5-dimethyl-1-oxide-2-pyridinylmethanethio)-1*H*−imidazo[4,5-b]pyridine (2 g, 5.5 mmol, **12**) in $CHCl_3$ (15 mL) over a period of 30 min. Reaction mass was decomposed with the solution of NaOH (1 g, 0.025 mol) in water (25 mL), and pH was adjusted to 8−8.5 using AcOH. The organic and aqueous layers were separated. Compounds were extracted into the aq. NaOH solution (0.5 g in 25 mL of water) from the organic layer, the resulting aq. layer was washed with $CHCl_3$ (2 × 15 mL) to remove unreacted sulfide, and pH was adjusted with acetic acid to 8.5−9.0. It was washed with $CHCl_3$ (2 × 15 mL) and the aq. layer pH was adjusted to 7.0 with AcOH and then extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were concentrated under reduced pressure. The product was isolated from MeOH (10 mL) and dried at 45−50 °C to yield a white solid **3** (yield 1.5 g, 72%). IR (KBr, cm^{-1}): 3448 (N-H), 3057 (Py-H), 2993, 2938 (Ali-H), 1274, 1030 (arylalkylether), 1609, 1586 (C═C), 1064 (S═O); ^{1}H NMR (DMSO-d_6, 200 MHz, δ ppm): 2.09 (s, 3H, Py-CH_3), 2.21 (s, 3H, Py-CH_3), 3.66 (s, 3H, O-CH_3), 3.92 (s, 3H, O-CH_3), 4.85 (s, 2H, Py-CH_2), 6.79 (d, $J = 8.6$, 1H, Py-H), 7.97 (d, $J = 8.8$, 1H, Py-H), 8.21 (s, 1H, Py-H), 8.26 (s, 1H, Py-H); HRMS (EI); m/z calcd. for ($M^+ + Na$) $C_{16}H_{18}N_4O_4SNa$: 385.0946; found: 385.0943 (−0.8 ppm).

5-Methoxy-2-(4-methoxy-3,5-dimethyl-1-oxide-2-pyridinmethane sulfonyl)-1*H*-imidazo[4,5-*b*]pyridine (Tenatoprazole Sulfone *N*-Oxide, 3)

m-CPBA (2.3 g, 9.3 mmol, 70%) in $CHCl_3$ (10 mL) was added to a cooled solution of 5-methoxy-2-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethanethio)-1*H*-imidazo[4,5-*b*]pyridine (1 g, 3 mmol, **1**) in $CHCl_3$ (15 mL) and MeOH (5 mL) slowly at -10 to -15 °C over a period of 20 min. The reaction was maintained for 30 min for the completion of the reaction. The reaction mass was decomposed into the solution of NaOH (1 g, 0.025 mol) in H_2O (25 mL), and pH was adjusted to 8−8.5 using AcOH (1.4 mL). The organic and aqueous layers were separated. Compounds were extracted into the aq. NaOH solution (0.3 g in 25 mL of H_2O) from the organic layer. MeOH (5 mL) was charged to the aq. layer, and pH was adjusted to 8.5−9 with AcOH (0.4 mL). The isolated solid was filtered, washed with mixture of H_2O and MeOH (1:1, 3 mL), and dried at 45−50 °C to yield a white solid **4** (yield 1.05 g, 92%). IR (KBr, cm^{-1}): 3106 (Py-H), 2989 (Ali-H), 1276, 1027 (arylalkylether), 1610, 1585 (C═C), 1330 (O═S═O); ^{1} H NMR (DMSO, 200 MHz, δ ppm): 2.16 (s, 3H, Py-CH_3), 2.26 (s, 3H, Py-CH_3), 3.71 (s, 3H, O-CH_3), 3.92 (s, 3H, O-CH_3), 5.32 (s, 2H, Py-CH_2), 8.03

(s, 1H, Py-H), 14.28 (s, 1H, benzimidazole-NH); MS: +ve ESI: ($M^+ + 1$) 379, ($M^+ + Na$) 401, −ve ESI: (M^- −H) 377; HRMS (EI): m/z calcd. for ($M^+ + H$) $C_{16}H_{19}N_4O_5S$: 379.1076; found: 379.1062. (−3.7 ppm).

5-Methoxy-2-(3, 5-dimethyl-2-pyridinylmethanesulfinyl)-1*H*-imidazo[4,5-*b*]pyridine (Desmethoxy Tenatoprazole, 4)

2,3,5-Trimethylpyridine-1-oxide (14)

H_2O_2 (9 g, 264 mmol) was added to a solution of 2,3,5-trimethylpyridine (10 g, 55 mmol, **13**) in AcOH (15 mL) at 90–95 °C, for 10–15 min. Reaction was maintained at 90–95 °C for 8–9 h, and aq. HCl (10 mL) was added to the reaction mass at 90–95 °C for 10 min. The reaction mass was distilled off completely under vacuum at less than 90–95 °C, and the solid was isolated in pet. ether (30 mL). The solid was dried at 40–45 °C to constant weight to yield **14** (9.7 g, 85%). IR: (KBr, cm^{-1}): 3051 (Py-H), 1255 (N-O); ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 2.22 (s, 3H, Py-CH_3), 2.29 (s, 3H, Py-CH_3), 2.46 (s, 3H, Py-CH_3), 6.89 (s, 1H, Py-H), 8.02 (s, 1H, Py-H); MS m/z: ($M^+ + H$) 138.0.

2-Hydroxymethyl-3,5-dimethylpyridine (15)

2,3,5-Trimethylpyridine-1-oxide (10 g, 50 mmol, **14**) was added slowly to liquid Ac_2O (40 mL) at 25–30 °C. The reaction mass was heated to 90–95 °C and maintained at 90–95 °C for 3 h. Ac_2O was distilled off completely to obtain the crude product. To the reaction mixture, a solution of caustic lye (4 mL) in water (70 mL) at 15–20 °C was added, and the reaction mass was maintained for 1 h. The reaction mass was extracted with DCM (3 × 20 mL), and combined neat organic layers were distilled off completely under vacuum to obtain the crude material **15** (8.6 g, 85%). IR (neat, cm^{-1}): 3391 (O-H), 3019 (Py-H), 2952 (Ali-H), 1606, 1575 (aromatic C=C); ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 2.17 (s, 3H, Py-CH_3), 2.30 (s, 3H, Py-CH_3), 4.64 (s, 2H, Py-CH_2-O), 4.78 (broad s, 1H, CH_2-OH), 7.28 (s, 1H, Py-H), 8.21 (s, 1H, Py-H); MS m/z: ($M^+ + H$) 138.0.

2-Chloromethyl-3,5-dimethylpyridine hydrochloride (16)

$SOCl_2$ (9.5 mL, 130 mmol) was added slowly to a solution of 2-hydroxymethyl-3,5-dimethylpyridine (15 g, 76 mmol, **15**) in DCM (45 mL) at 0–5 °C for 45 min. The reaction was maintained at 0–5 °C for 1 h. The reaction mass was distilled off completely under reduced pressure, and a solid was isolated from ethyl acetate (45 mL). The solid was dried at 45 °C to yield **16** (16.3 g, 85%). IR (KBr, cm^{-1}): 3005 (Py-H), 2968 (Ali-H), 1594, 1503, 1450 (aromatic C=C); ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm):

2.55 (s, 3H, Py-CH_3), 2.61 (s, 3H, Py-CH_3), 5.15 (s, 2H, Py-CH_2-Cl), 8.03 (s, 1H, Py-H), 8.42 (s, 1H, Py-H); MS m/z: ($M^+ + H$) 156.0.

5-Methoxy-2-(3,5-dimethyl-2-pyridinylmethanesulfinyl)-1*H*-imidazo [4,5-*b*]pyridine (Desmethoxy Tenatoprazole, 4)

A solution of 2-chloromethyl-3,5-dimethylpyridine hydrochloride (17.2 g, 95 mmol, **16**) in H_2O (60 mL) was added slowly to the solution of 2-mercapto-5-methoxypyridineimidazole (20 g, 104 mmol, **9**) in H_2O (100 mL), acetone (60 mL), and NaOH (10 g, 250 mmol) at 25–30 °C for 45 min. The reaction was maintained at the same temperature for 30 min and then extracted with $CHCl_3$ (2 × 50 mL), and the combined organic layers were washed with water (2 × 50 mL).

Per acetic acid (45 mL, 88.8 mmol, assay: 15%) was added slowly to the cooled solution (110 mL) at −25 to −30 °C for 1 h. The reaction mass was decomposed into a basic aqueous solution (15 g of NaOH in water 100 mL of water), pH was adjusted with AcOH to 8.0, and the layers were separated. The $CHCl_3$ layer was extracted with alkaline solution (5 g of NaOH in 100 mL of H_2O) and then given $CHCl_3$ washings (2 × 25 mL) to the aq. layer. To the aq. layer, acetone (60 mL) was added, and pH was adjusted to 8.0 with AcOH. The separated solid was filtered, washed with acetone (15 mL), and dried at 45–50 °C for 5 h to yield **5** as a white solid (yield 23.7 g, 72%). IR (KBr, cm^{-1}): 3445 (N-H) 2982 (Ali-H), 1257 (arylalkylether), 1611, 1585, 1466 (aromatic C═C), 1060 (S═O); ^{1}HNMR (DMSO-d_6, 200 MHz, δ ppm): 2.24 (s, 3H, Py-CH_3), 2.29 (s, 3H, Py-CH_3), 3.90 (s, 3H, O-CH_3), 4.74 (dd, $J = 14$, $J' = 24$, 2H, Py-CH_2), 6.79 (d, $J = 8$, 1H, Py-H), 7.45 (s, 1H, Py-H), 7.98 (d, $J = 8$, 1H, Py-H), 8.16 (s, 1H, Py-H), 13.9 (broad s, 1H, benzimidazole N-H); MS m/z: ($M^+ + 1$) 317.0, ($2M^+ + 1$) 655.2; HRMS (EI) m/z calcd. for $C_{15}H_{17}N_4O_2S$ ($M^+ + H$): 317.1072; found: 317.1081 (2.8 ppm).

1-Methyl-5-methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridinmethane sulfinyl)-1*H*-imidazo[4,5-*b*]pyridine (*N*-Methyltenatoprazole, 5)

To a mixture of 5-methoxy-2-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethane-sulfinyl)-1*H*-imidazo[4,5-*b*]pyridine (10 g, 28.9 mmol, **2**), K_2CO_3 (30 g, 217 mmol), and a catalytic amount of *N,N*-(dimethylamino)pyridine (DMAP) in DCM (100 mL) at 25–30 °C, MeI (4.92 g, 34.6 mmol) was slowly added over a period of 20 min. The reaction was maintained for 10 h for the completion of reaction. The reaction mass was filtered through the hyflow bed and washed with DCM (25 mL); the filtrate was washed with H_2O (3 × 100 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure, isolated from ethyl acetate (25 mL), and dried at 45–50 °C to yield **6** as a white solid (yield 9.5 g, 91.3%). IR

(KBr, cm^{-1}): 2929 (Ali-H), 1269 (arylalkylether), 1603, 1588 (C═C), 1048 (S═O); ^{1}H NMR (DMSO, 200 MHz, δ ppm): 2.16 (s, 3H, Py-CH_3), 2.19 (s, 3H, Py-CH_3), 6.67 (s, 3H, N-CH_3), 3.89 (s, 3H, O-CH_3), 3.90 (s, 3H, O-CH_3), 4.91 (dd, $J = 13.8$, $J' = 19.6$, 2H, Py-CH_2), 6.84 (dd, $J = 10$, $J' = 12$, 1H, Py-H), 8.10 (d, $J = 8$,1H, Py-H), 8.10 (s, 1H, Py-H). MS m/z: ($M^+ + H$) 361.2, ($M^+ + Na$) 383.1, ($2M^+ + Na$) 743.3; HRMS (EI) m/z calcd. for $C_{17}H_{21}N_4O_3S$ ($M^+ + H$): 361.1334; found: 361.1332. (-0.6 ppm).

5-Methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridinylmethanethio)-1*H*-imidazo[4,5-*b*]pyridine (Tenatoprazole sulfide, 6)

A solution of 3,5-dimehtyl-2-chloromethyl pyridine hydrochloride (10 g, 45 mmol, **8**) in H_2O (50 mL) was added to a solution of 2-mercapto-5-methoxypyridine imidazole (9.72 g, 54 mmol, **9**), NaOH (4.5 g, 112 mmol) in H_2O (100 mL) and MeOH (25 mL) at 25–30 °C over a period of 30–45 min. The isolated solid was filtered, washed with a 1:1 mixture of H_2O and MeOH (30 mL), and dried at 45–50 °C to yield **6** (yield 13.2 g, 88.8%). IR (KBr, cm^{-1}): 3218 (NH), 2942 (Ali-H), 1265, 1042 (arylalkylether), 1598, 1481 (aromatic C═C). ^{1}H NMR (DMSO, 200 MHz, δ ppm): 2.20 (s, 3H, Py-CH_3), 2.27 (s, 3H, Py-CH_3), 3.72 (s, 3H, O-CH_3), 3.86 (s, 3H, O-CH_3), 4.66 (s, 2H, Py-CH_2), 6.60 (d, $J = 8.4$, 1H, Py-H), 7.78 (broad s, 1H, Py-H), 8.17 (s, 1H, Py-H), 13.01 (broad s, 1H, NH); MS m/z: ($M^+ + H$) 331.0, ($M^+ + Na$) 353.1, ($M^+ + K$) 369.1; HRMS (EI) m/z calcd. for ($M^+ + H$) $C_{16}H_{19}N_4O_2S$ 331.1229; found: 331.1227 (-0.6 ppm).

5-Methoxy-2-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethane sulfonyl)-1*H*-imidazo[4,5-*b*]pyridine (Tenatoprazole Sulfone, 7)

m-CPBA (6.5 g, 0.026 mol, 70%) in $CHCl_3$ (25 mL) was added slowly to a cooled solution of 5-methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridinylmethanethio)-1*H*-imidazo[4,5-*b*]pyridine (5 g, 0.015 mol, **6**) in $CHCl_3$ (25 mL), at -10 to -15 °C over a period of 30 min. The reaction was maintained for 30 min for the maximum completion of reaction. The reaction mass was decomposed into the solution of NaOH (5 g, 0.125 mol) in H_2O (25 mL), and pH was adjusted to 8–8.5 using AcOH. The organic and aqueous layers were separated. Compounds were extracted into the aq. NaOH solution (2.5 g in 25 mL of water) from the organic layer. $CHCl_3$ (20 mL) was charged to the aq. layer, pH was adjusted to 8.5–9 with AcOH, and organic and aqueous layers were separated. pH was adjusted to 7.0 with AcOH, and then aq. layer was extracted with $CHCl_3$ (2×20 mL), dried over anhydrous Na_2SO_4, and distilled off completely under reduced pressure. The isolated solid in MeOH (10 mL) was filtered, washed with MeOH (5 mL), and dried at 45–50 °C to yield a white solid **7** (yield 3.9 g, 71%). IR (KBr, cm^{-1}): 3021 (Py-H), 2939

(Ali-H), 1233, 1020 (arylalkylether), 1612, 1510, 1575 (aromatic C═C), 1328, 1142 (O═S═O in sulfone); ^{1}H NMR (DMSO, 200 MHz, δ ppm): 2.16 (s, 3H, Py-CH_3), 2.23 (s, 3H, Py-CH_3), 3.69 (s, 3H, O-CH_3), 3.92 (s, 3H, O-CH_3), 5.01 (s, 2H, Py-CH_2), 6.87 (d, $J = 10$, 1H, Py-H), 8.00 (s, 1H, Py-H), 8.03 (d, $J = 11.6$, 1H, Py-H), 13.00 (broad s, 1H, NH); MS m/z: ($M^+ + H$) 363.1, ($M^+ + Na$) 385.0, ($M^+ + K$) 401.0, ($2M^+ + Na$) 747.1; HRMS (EI) m/z calcd. for $C_{16}H_{19}N_4O_4S$ ($M^+ + H$) 363.1127; found: 363.1132 (1.4 ppm).

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