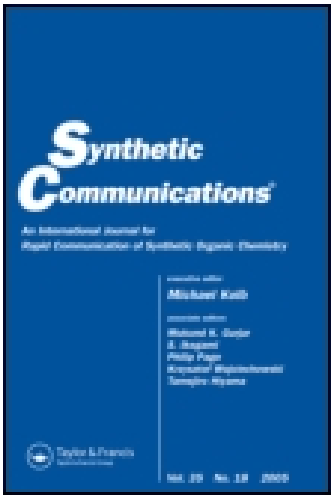

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 22 Dec 2008.

To cite this article: Ganta Madhusudhan Reddy, Kaga Mukkanti, Boluggodu Vijaya Bhaskar & Padi Pratap Reddy (2008) Synthesis of Metabolites and Related Substances of Rabeprazole, an Anti-Ulcerative Drug, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:2, 278-290, DOI: 10.1080/00397910802372541

To link to this article: http://dx.doi.org/10.1080/00397910802372541

Synthetic Communications®, 39: 278–290, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802372541

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Synthesis of Metabolites and Related Substances of Rabeprazole, an Anti-Ulcerative Drug

Ganta Madhusudhan Reddy,[1,2] Kaga Mukkanti,[2] Boluggodu Vijaya Bhaskar,[1] and Padi Pratap Reddy[1]
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Abstract: Rabeprazole sodium (Aciphex®) is a gastric proton pump inhibitor used for the prevention and treatment of gastric acid–related diseases. During the synthesis of bulk drug of rabeprazole sodium, we have observed metabolites rabeprazole sulfide and rabeprazole sulfone and related substances rabeprazole-*N*-oxide, rabeprazole sulfone-*N*-oxide, *N*-aralkyl rabeprazole, chloro rabeprazole, and methoxy rabeprazole as impurities in the drug substance. The present work describes the synthesis and characterization of these compounds.

Keywords: Impurities, metabolites, rabeprazole Na, spectral characterization, synthesis

INTRODUCTION

Rabeprazole sodium, 2-[([4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl)sulfinyl]-1*H*-benzimidazole sodium (**1**), is a proton pump inhibitor, inhibits the action of H^+-K^+ ATPase in parietal cells,[1–5] and is

Received April 29, 2008.
DRL Communication No. IPDO-IPM-00022
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used for the prevention and treatment of gastric acid–related diseases. It has also demonstrated efficacy in healing and symptom relief of gastric and duodenal ulcers and has shown a high eradication rate of the microorganism *Helicobacter pylori* when associated with antimicrobial therapy.[6,7]

The presence of impurities (related substances) in an active pharmaceutical ingredient (API) can have a significant impact on the quality and safety of the drug products. International conference on harmonization (ICH) guidelines recommend identifying and characterizing all impurities present in API at a level of $\geq$0.10%.[8] These impurities are required in pure form to check the analytical performance characteristics such as specificity, linearity, range, accuracy, precision, limit of detection (LOD), limit of quantification (LOQ), robustness, system suitability testing, and relative retention factor.[9] These related substances are also used to check the accuracy of the analytical method of API.

In our manufacturing process of rabeprazole sodium (**1**), we have identified following seven impurities: 2-[([4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl)thio]-1*H*-benzimidazole (sulfide, **2**), 2-[([4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl)sulfonyl]-1*H*-benzimidazole (sulfone, **3**), [([4-chloro-3-methylpyridine-2-yl]methyl)thio]-1*H*-benzimidazole (chloro rabeprazole, **4**), 2-[([4-methoxy-3-methyl-2-pyridinyl]methyl)sulfinyl]-1*H*-benzimidazole (methoxy rabeprazole, **5**), 2-[([4-(3-methoxypropoxy)-3-methyl-2-pyridinyl-1-oxide]methyl)sulfonyl)-1*H*-benzimidazole (sulfone-*N*-oxide, **6**), 2-[([4-(3-methoxypropoxy)-3-methyl-2-pyridine-1-oxide]-methyl)sulfinyl]-1*H*-benzimidazole (*N*-oxide, **7**) and 2-[([4-(3-methoxypropoxy)-3-methyl]pyridin-2-yl)methanesulfinyl]-1-([4-(3-methoxypropoxy)-3-methyl]pyridin-2-ylmethyl)-1*H*-benzimidazole (*N*-aralkyl rabeprazole, **8**) (Fig. 1). Although rabeprazole sulfide **2** and sulfone **3** were known as metabolites,[2,10] synthesis and characterization of chloro rabeprazole **4** and methoxy rabeprazole **5** were reported.[11,12] An increasing number of publications on development of analytical methods for rabeprazole bulk drug analysis indicated the significance of impurities of rabeprazole.[12–26] Except for chloro rabeprazole **4** and methoxy rabeprazole **5**, a detailed synthetic procedure has not been reported for rest of the related substances. In our present investigation, we have taken up the synthesis and characterization of these impurities.

RESULTS AND DISCUSSION

Synthesis of rabeprazole sodium **1** involved condensation of chloromethylpyridine derivative **9** with the 2-mercapto benzimidazole **10** in the presence of NaOH and oxidation of the resulting compound **2** using

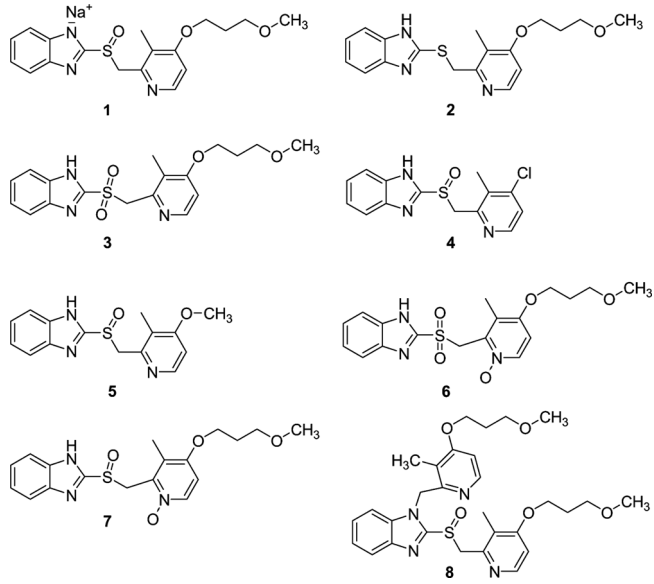
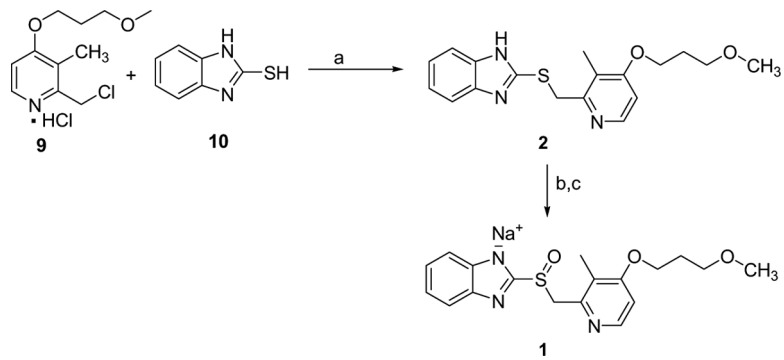
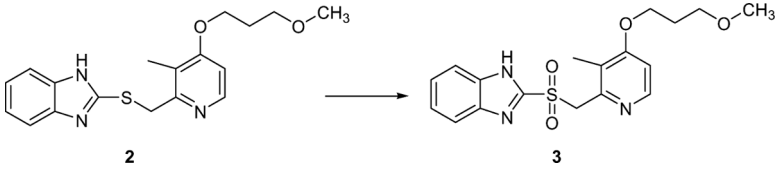


Figure 1. Structure of rabeprazole and its related substances Structural framework of rabeprazole sodium **(1)**, rabeprazole sulfide **(2)**, rabeprazole sulfone **(3)**, chloro rabeprazole **(4)**, methoxy rabeprazole **(5)**, rabeprazole sulfone-*N*-oxide **(6)**, rabeprazole *N*-oxide **(7)**, and *N*-aralkyl rabeprazole **(8)**.

meta chloro perbenzoic acid (*m*-CPBA).[27] Rabeprazole free base **1a** was converted into its sodium salt **1** (Scheme 1) and was purified from methanol and methyl *tert*-butylether (MTBE).



Scheme 1. Synthetic scheme of rabeprazole sodium **(1)**). Reagents and conditions: (a) NaOH, water–acetone (2:1), 25–30 °C; (b) *m*-CPBA, $CHCl_3$, −10 to −15 °C, 3 h; (c) NaOH, MeOH–MTBE (1:10), 25–30 °C, 8 h.



2 3

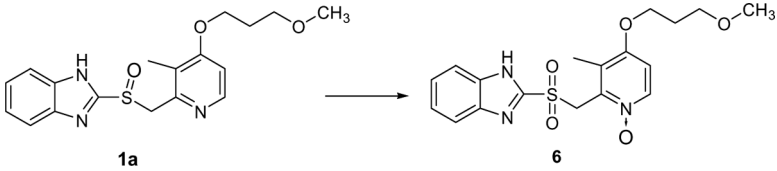
Scheme 2. Synthetic scheme of rabeprazole sulfone **(3)**. Reagents and conditions: *m*-CPBA, $CHCl_3$–MeOH (2:1), −20 to −25 °C, 45 min, 80%.

Rabeprazole sulfide **2** was obtained from the synthetic sequence followed for rabeprazole (Scheme 1). Infrared (IR), ^{1}H NMR, and mass spectral data of compound **2** are identical with those of reference sample.[27]

Rabeprazole sulfone **3** was prepared by the controlled oxidation of rabeprazole sulfide **2**, using an optimal amount of *m*-CPBA (Scheme 2). The protonated molecular ion appeared at 376.0, and sodium adduct appeared as the base peak at 398.1 in the mass spectra. In the ^{1}H NMR, a deuterium-exchangeable singlet at δ 13.80 corresponded to benzimidazole-NH proton. Two singlets due to *O*-methyl and 3-methyl group of pyridine ring are displayed at δ 3.25 and δ 2.18, respectively. Aromatic protons of benzimidazole moiety appeared as multiplets at δ 7.36–7.41 and 7.66–7.71, while those of pyridine ring are seen as two doublets at δ 8.0 and 6.90. Two triplets and one quintet at δ 4.10, 3.48, and 1.97 corresponded to *O*-propyloxy group protons.

Rabeprazole sulfone-*N*-oxide **6** is the overoxidized by-product formed in the synthesis of rabeprazole. We have prepared this compound by the oxidation of rabeprazole **1a** using excess of *m*-CPBA (2.2 equiv) in chloroform (Scheme 3). The protonated molecular ion of **6** appeared at 391.9, and sodium adduct appeared as the base peak at 414.3 in the mass spectrum. IR spectrum of **6** showed the presence of O=S=O stretching (1324 cm^{-1}), C−N stretching (1301 cm^{-1}), and C–O arylalkyl stretching (1094 cm^{-1}). ^{1}H NMR spectral data of compound **6** is similar to that of compound **3**.

Rabeprazole-*N*-oxide **7** was prepared starting from 2-chloromethyl-3-methyl-4-(3-methoxy propoxy)pyridine hydrochloride (**9**). Conversion of hydrochloride **9** into its free base by reacting with ammonia and

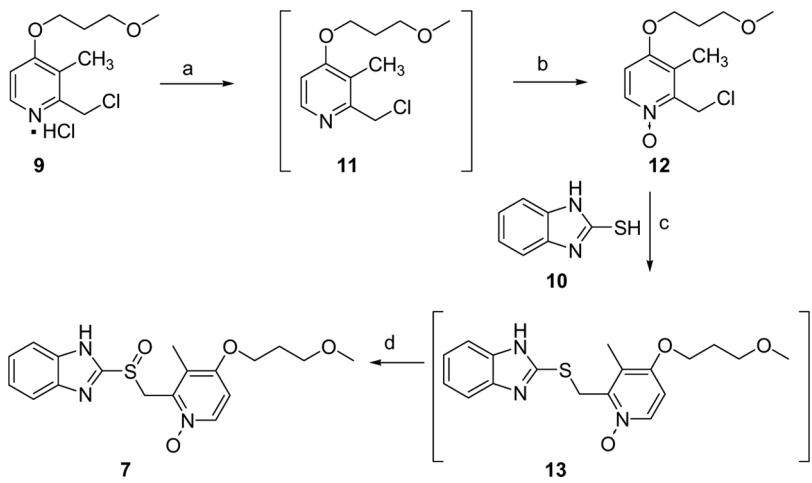


1a 6

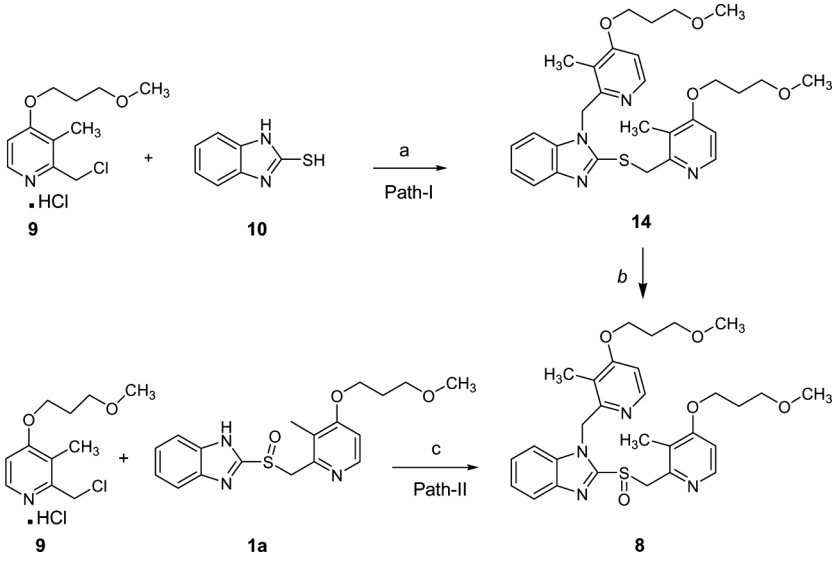
Scheme 3. Synthetic scheme of rabeprazole sulfone-*N*-oxide **(6)**. Reagents and conditions: *m*-CPBA, MeOH–$CHCl_3$ (1:3), −5 to −10 °C, 45 min, 80%.

subsequent oxidation using *m*-CPBA gave the corresponding *N*-oxide **12.** Condensation of **12** with mercapto derivative **10** in aqueous alkali followed by *m*-CPBA oxidation of resulted sulfide **13** furnished the desired *N*-oxide impurity **7** (Scheme 4). Mass spectrum of the *N*-oxide showed peaks at m/z 376.2 and 398.0 corresponding to the adduct ions ($M^+ + H$) and ($M^+ + Na$), respectively. IR spectrum displayed characteristic absorptions at 1098 and 1059 cm^{-1} corresponding to C–O stretching and S=O stretching, respectively. ^1H NMR spectrum of rabeprazole-*N*-oxide **7** is similar to that of rabeprazole sulfone-*N*-oxide **6**.

N-Aralkyl rabeprazole **8** was prepared following the rabeprazole synthetic pathway with a slight modification of reaction conditions. Thus, condensation of two equivalents of **9** with mercapto benzimidazole **10** in aqueous alkali at 70–75 °C, followed by oxidation of resulted sulfide **14** with *m*-CPBA, yielded the desired *N*-aralkyl rabeprazole **8** in 23% yield (Scheme 5, path I). Compound **8** was obtained in a better yield by the direct aralkylation of rabeprazole **1a** using 2-chloromehtylpyridine derivative **9** (Scheme 5, path II). Assigned structure of compound **8** was confirmed from its mass, IR, and ^1H NMR spectra. The protonated molecular ion of **8** appeared at 553.6 in the mass spectrum. IR spectrum of **8** showed the presence of S=O stretching at 1046 cm^{-1}. ^1H NMR spectrum is devoid of benzimidazole NH signal. It is evidenced the presence of two methoxy groups (δ 3.17, s, 3H; δ 3.3, s, 3H), two methyl groups (δ 2.27, s, 6H), eight aromatic protons (δ 7.76–7.81, m, 2H; δ 7.28–7.38, m,



Scheme 4. Synthetic scheme of rabeprazole N-oxide **(7)**. Reagents and conditions: (a) NaOH, water–$CHCl_3$ (2:3), 25 °C; (b) *m*-CPBA, $CHCl_3$, 35 °C, 2.5 h, 71% (c) NaOH, water–Acetone (1:1), 25 °C, 1 h; (d) *m*-CPBA, $CHCl_3$, −10 °C, 45 min, 72%.



Scheme 5. Synthetic scheme of rabeprazole *N*-aralkyl impurity **(8)**. Reagents and conditions: (a) NaOH, water 70–75 °C, 4 h, 79% (b) *m*-CPBA, MeOH–$CHCl_3$ (1:2), 0–5 °C, 45 min, 23% (c) NaOH, water, 70–75 °C, 4 h, 78%.

2H; δ 8.22, d, 1H; δ 8.03, d, 1H; δ 6.90, d, 1H; δ 6.94, d, 1H), S-CH_2 group (δ 4.67, d, 1H; δ 4.98, d, 1H), N-CH_2 group (δ 5.81, q, 2H), and three multiplets at δ 4.08–4.09, 3.43–3.53 and 1.66–2.02 corresponding to *O*-propyloxy group protons.

CONCLUSION

Information of the different possible impurities, metabolites, and their synthetic routes is a prerequisite for thorough understanding of impurity profile in the manufacturing of the anti-ulcerative drug rabeprazole. Keeping in view this regulatory requirement of rabeprazole impurities, the process-related impurities and metabolites in rabeprazole bulk drug were identified, synthesized, and characterized using mass, IR and NMR spectral data.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Varian Mercury plus and Gemini-2000 at 400 MHz and 200 MHz, respectively. The infrared spectra were recorded in the solid sate as KBr dispersion medium

using a Perkin-Elmer Spectrum One Fourier transform infrared (FT-IR) spectrophotometer. The mass analysis was performed on AB-4000 Q-trap LC-MS/MS mass spectrometer MDS SCIEX, Applied Bio Systems, California, USA. Melting points were determined on a Polmon digital capillary melting-point apparatus MP96 and are uncorrected. The solvents and reagents were used without further purification.

2-[([4-(3-Methoxypropoxy)-3-methyl-2-pyridinyl]methyl)thio]-1*H*-benzimidazole (Rabeprazole Sulfide, 2)

To a stirred solution of **10** (6.7 g, 44.6 mmol), sodium hydroxide (3.75 g, 93.7 mmol) in acetone (50.0 mL), and water (50.0 mL), a solution of **9** (10.0 g, 37.6 mmol) in water (50.0 mL) was added dropwise over a period of 45 min at 15–20 °C. The precipitated solid was filtered at 25–30 °C, washed with 1:1 mixture of acetone and water (20.0 mL), and dried to a constant weight at 55 °C to provide compound **2** (11.0 g, 85% yield). Mp: 116–118 °C; IR (KBr, cm^{-1}) 3049 (Ar-H), 2888 (Ali-H), 1585 (aromatic C = C), 1303 (C–N), 1092 (C–O arylalkylether), 746 (Ar-H bending); mass (EI) +ve ES-MS: 344 ($M^+ + H$), 687 ($2M^+ + H$), −ve ES-MS: 342 ($M^- - H$) 378.1 ($M^- + Cl$); ^1H NMR (200 MHz, DMSO-d_6): δ 12.61 (s, NH), 8.23 (d, $J = 5.6$ Hz, 1H), 7.39–7.52 (m, 2H), 7.11–7.16 (m, 2H), 6.95 (d, $J = 5.6$ Hz, 1H), 4.70 (s, 2H), 4.10 (t, $J = 6.2$ Hz, 2H), 3.49 (t, $J = 6.4$ Hz, Hz, 2H), 3.25 (s, 3H), 2.22 (s, 3H), 1.98 (qn,$J = 6$, 2H); ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.68, 154.68, 150.29, 147.74, 121.35, 119.75, 117.39, 110.51, 106.22, 68.28, 65.04, 57.92, 36.28, 28.66, 10.35.

2-[([4-(3-Methoxypropoxy)-3-methyl-2-pyridinyl]methyl)sulfonyl]-1*H*-benzimidazole (Rabeprazole Sulfone, 3)

A solution of *m*-CPBA (15.0 g, 60.8 mmol, 70% w/w) in $CHCl_3$ (50.0 mL) was added to a solution of **2** (10.0 g, 29.1 mmol) in $CHCl_3$ (50.0 mL) and MeOH (25.0 mL) dropwise over a period of 45 min at −20 to − 25 °C. On completion of reaction (vide Thin Layer Chromatography, TLC), reaction mass was poured in to the NaOH solution (5.0 g of NaOH in 100.0 mL of water), pH was adjusted to 7–7.5 with AcOH, chloroform layer was separated, and product was extracted into basic water (2.0 g of NaOH in 70.0 mL of water). This alkaline solution containing the product was given $CHCl_3$ washings (3 × 25 mL). Acetone (25.0 mL) was charged to the aqueous phase and cooled to 5–10 °C. pH was adjusted to 8–8.5 with AcOH; the isolated solid was filtered, washed with 1:1 mixture of water and acetone (20.0 mL), and dried to a constant weight at 50 °C to provide compound **3** (8.3 g, 80% yield). Mp: 138–142 °C; IR (KBr, cm^{-1}): 3063 (Ar-H),

2933 (Ali-H), 1339 (O=S=O), 1301 (C–N), 1095 (C–O), 756 (Ar-H bending); mass (EI): +ve ES-MS: 376.0 ($M^+ + H$), 398.1 ($M^+ + Na$). −ve ES-MS: 373.9 ($M^- - H$);^{1}H NMR (200 MHz, DMSO-d_6]: δ 13.80 (s, NH), 8.00 (d, $J = 5.6$ Hz, 1H), 7.66–7.71 (m, 2H), 7.36–7.41 (m, 2H), 6.90 (d, $J = 5.6$ Hz, 1H), 5.07 (s, 2H), 4.10 (t, $J = 6.2$ Hz, 2H), 3.48 (t, $J = 6.2$ Hz, 2H), 3.25 (s, 3H), 2.18 (s, 3H), 1.97 (qn, $J = 6$, 2H); ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.95, 148.04, 147.91, 147.09, 138.04, 124.40, 123.14, 116.84, 106.83, 68.24, 65.12, 60.51, 57.93, 28.59, 11.02.

2-[([4-(3-Methoxypropoxy)-3-methyl-2-pyridinyl-1-oxide]methyl)sulfonyl]-1*H*-benzimidazole (Rabeprazole Sulfone-*N*-oxide, 6)

A solution of *m*-CPBA (30.0 g, 121.7 mmol, 70% w/w) in $CHCl_3$ (110.0 mL) was added to a solution of **1a** (20.0 g, 55.7 mmol) in $CHCl_3$ (120.0 mL) and MeOH (40.0 mL) over a period of 45 min at −5 to −10 °C. On completion of reaction (vide TLC), reaction mass was poured into the NaOH solution (15.0 g NaOH in 200.0 mL of water), pH was adjusted to 7–7.5 with AcOH, and two layers were separated. Product was extracted from the $CHCl_3$ phase into basic water (5.0 g of NaOH in 150.0 mL of water), and this alkaline solution was given $CHCl_3$ washings (2 × 30 mL). Acetone (50.0 mL) was charged to the water phase, solution was cooled to 5–10 °C, and pH was adjusted to 8–8.5 using AcOH. Isolated solid was filtered, washed with 1:1 mixture of H_2O and acetone (20.0 mL), and purified from the acetone to give compound **6** as a white solid (17.4 g, 80% yield). Mp: 170–174 °C; IR (KBr, cm^{-1}): 3058 (Ar-H), 2927 (Ali-H), 1324 (O=S=O), 1301 (C–N), 1094 (C–O arylalkyl ether), 747 (Ar-H bending); mass (EI): +ve ES-MS: 391.9 ($M^+ + H$), 783.8 ($2M^+ + H$), 414.3 ($M^+ + Na$), 805.8 ($2M^+ + Na$), 430.9 ($M^+ + K$), −ve ES-MS: 390.2 ($M^- - H$); ^{1}H NMR (200 MHz, DMSO-d_6]: δ 13.9 0 (s, NH), 8.03 (d, $J = 7.2$ Hz, 1H), 7.67–7.68 (br, 2H), 7.35–7.41 (m, 2H), 7.08 (d, $J = 7.6$ Hz, 1H), 5.44 (s, 2H), 4.12 (t, $J = 6.2$ Hz, 2H), 3.49 (t, $J = 6.2$ Hz, 2H), 3.25 (s, 3H), 2.20 (s, 3H), 1.98 (qn, $J = 5.8$, 2H); ^{13}C NMR (200 MHz, DMSO-d_6) δ 153.89, 148.52, 138.86, 138.32, 136.61, 126.45, 124.27, 116.96, 108.94, 68.22, 65.88, 57.95, 54.09, 28.62, 12.12.

2-[([4-(3-Methoxypropoxy)-3-methyl-2-pyridinyl-1-oxide]methyl)sulfinyl]-1*H*-benzimidazole (Rabeprazole-*N*-oxide, 7)

2-Chloromethyl-3-methyl-4-(3-methoxypropoxy)pyridine-1-oxide (**12**)

The pH of a stirred solution of **9** (15.0 g, 56.3 mmol) in $CHCl_3$ (75.0 mL) and H_2O (50.0 mL) was adjusted to 7.5 using aq. NH_3, and solution

was stirred for 10 min. Organic layer was separated and washed with water (50.0 mL), and to this solution was added a solution of *m*-CPBA (15.0 g, 60.8 mmol, 70% w/w) in $CHCl_3$ (80.0 mL) over a period of 2 h at 35 °C and stirred for 30 min. Progress of the reaction was monitored by (TLC), and on completion of reaction, reaction mass was cooled to 25 °C, water (100.0 mL) was added, and pH adjusted to 7.5–8.0 with aq. NH_3 solution. The organic phase was separated and washed with water (2 × 50.0 mL) and concentrated under reduced pressure at less then 40 °C to give compound **12** as a semisolid (9.8 g, 71% yield). IR (KBr, cm^{-1}): 2959 (Ali-H), 1103 (C–O arylalkylether), 1304 (N-O); mass (EI): 246.2 ($M^+ + H$), 230 (245-Cl); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, $J = 7.2$ Hz, 1H), 6.80 (d, $J = 7.6$ Hz, 1H), 4.96 (s, 2H), 4.12 (t, $J = 6.4$ Hz, 2H), 3.54 (t, $J = 6.0$ Hz, 2H), 3.34 (s, 3H), 2.30 (s, 3H), 2.06–2.15 (m, 2H).

2-[([4-(3-Methoxypropoxy)-3-methyl-2-pyridinyl-1-oxide]methyl)-sulfinyl]-1*H*-benzimidazole (**7**)

To a stirred solution of **10** (10.0 g, 66.6 mmol) in water (50.0 mL) and NaOH (5.9 g, 147.5 mmol), a solution of 2-chloromethyl-3-methyl-4-(3-methoxypropoxy)pyridine-1-oxide (**12**, 15.5 g, 63.1 mmol) in acetone (50.0 mL) was added and the reaction mixture was stirred over a period of 1 h. On completion of reaction (vide TLC), product **13** was extracted with chloroform (40 mL), and the solution was used as such in the next step.

To the stirred and cooled solution of **13** in chloroform, a solution of *m*-CPBA (8.20 g, 33.4 mmol, 70% w/w) in chloroform (30.0 mL) was added drop by drop at −10 °C over a period of 30 min. On completion of the reaction (vide TLC), the reaction mass was poured into the solution of NaOH (8.24 g, 206.0 mmol) in water (100.0 mL), and pH was adjusted to 8–8.5 using acetic acid. The chloroform layer was separated, and the product was extracted into the aq. NaOH solution (2.75 g in 100.0 mL water). This alkali solution containing the product was washed with chloroform (2 × 30 mL) to remove unreacted sulfide **13**. pH was adjusted to 8.5–9.0 using acetic acid and then extracted with chloroform (3 × 20 mL). The chloroform layer was concentrated under reduced pressure; the product was isolated from methanol (30 mL) and dried at 50 °C to yield compound **7** as a white solid (11.10 g, 72% yield). Mp: 158–164 °C; IR (KBr, cm^{-1}): 3035 (Ar-H), 2984 (Ali-H), 1098 (C–O arylalkylether), 1059 (S=O), 742 (Ar-H bending); mass: + ve ES-MS: 376.2 ($M^+ + H$), 398 ($M^+ + Na$), 1148.7 ($3M^+ + Na$), 414.2 ($M^+ + K$); ^1H NMR (200 MHz, DMSO-d_6]: δ 8.21 (d, $J = 7.0$ Hz, 1H), 7.67–7.71 (m, 2H), 7.30–7.35 (m, 2H), 6.75 (d, $J = 7.2$ Hz, 1H), 5.21 (d, $J = 12.8$ Hz,

Hz, 1H), 4.97 (d, $J = 12.6$ Hz, 1H), 4.08 (t, $J = 6.2$ Hz, 2H), 3.51 (t, $J = 6$ Hz, 2H), 3.33 (s, 3H), 2.24 (s, 3H), 2.06 (qn, $J = 6$ Hz, 2H); ^{13}C NMR (200 MHz, DMSO-d_6) δ156.23, 153.93, 141.47, 139.23, 137.35, 126.91, 123.40, 116.32, 107.44, 65.89, 58.58, 54.23, 28.96, 12.01.

2-[([4-(3-Methoxypropoxy)-3-methyl]pyridinyl)methyl]sulfinyl-1-[([4-(3-methoxypropoxy)-3-methyl]pyridinyl)methyl]-1*H*-benzimidazole (*N*-Aralkyl Rabeprazole, 8)

2-[([4-(3-Methoxypropoxy)-3-methyl-2-pyridinyl]methyl)thio]-1-([4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl)-1*H*-benzimidazole (**14**)

A solution of **9** (28.2 g, 106.0 mmol) in water (100.0 mL) was added to a stirred solution of **10** (8.0 g, 53.3 mmol) and NaOH (5.3 g, 132.5 mmol) in water (50.0 mL) over a period of 45 min at 15–20 °C. The resulting solution was then heated to 70–75 °C, and after being stirred at 70–75 °C for 4 h, the precipitated solid was filtered at 25–30 °C, washed with 1:1 mixture of MeOH and H_2O (20.0 mL), and dried to a constant weight at 50 °C to yield **14** (23.4 g, 79% yield). IR (KBr, cm^{-1}): 2927 (Ali-H), 1290 (C–N), 1083 (C–O), 743 (Ar-H bending); mass (EI): +ve ES-MS: 537.0 ($M^+ + H$), 559.2 ($M^+ + Na$), 575.2 ($M^+ + K$);^{1}H NMR (400 MHz, $CDCl_3$]: δ 8.29 (d, $J = 6.0$ Hz, 1H), 8.23 (d, $J = 5.6$ Hz, 1H), 7.69 (d, $J = 8$ Hz, 1H), 7.14–7.18 (m, 2H), 7.06 (d, $J = 4$ Hz, 1H), 6.67–6.70 (m, 2H), 5.40 (s, 2H), 4.84 (s, 2H), 4.04–4.11 (m, 4H), 3.50–3.57 (m, 4H), 3.35 (s, 6H), 2.28 (s, 6H), 2.01–2.10 (m, 4H).

2-[([4-(3-Methoxypropoxy)-3-methyl]pyridinyl)methyl]sulfinyl-1-[([4-(3-methoxypropoxy)-3-methyl]pyridinyl)methyl]-1*H*-benzimidazole **(8)**

A solution of *m*-CPBA (5.0 g, 20.2 mmol, 70% w/w) in $CHCl_3$ (110.0 mL) was added to a stirred solution of **14** (10.0 g, 18.6 mmol) in $CHCl_3$ (50.0 mL) and MeOH (25.0 mL) dropwise over a period of 45 min at 0–5 °C. On completion of reaction (vide TLC), reaction mass was poured into NaOH solution (2.0 g of NaOH in 100.0 mL of water), pH was adjusted to 8–8.5 using AcOH and the aqueous phase was separated and extracted with $CHCl_3$ (2×50.0 mL). Combined organics were concentrated under reduced pressure to yield a brown color liquid **8** (2.4 g, 23% yield). IR (neat, cm^{-1}): 3057 (Ar-H), 2923 (Ali-H), 1291 (C–N), 1065 (C–O), 1046 (S=O), 743 (Ar-H bending); mass (EI): +ve ES-MS: 553.6 ($M^+ + H$); ^{1}H NMR (200 MHz, DMSO-d_6]: δ 8.22 (d, $J = 6.0$, 1H), 8.03 (d, $J = 5.6$ Hz, 1H), 7.76–7.81 (m, 2H), 7.28–7.38 (m,

2H), 5.81 (q, $J = 6$, 17.2 Hz, 2H), 6.94 (d, $J = 5.6$ Hz, 1H), 6.90 (d, $J = 5.6$ Hz, 1H), 4.98 (d, $J = 13.6$ Hz, 1H), 4.67 (d, 13.6, 1H), 4.08–4.09 (m, 4H), 3.43–3.53 (m, 4H), 3.3 (s, 3H), 3.17 (s, 3H), 2.27 (s, 6H), 1.66–2.02 (m, 4H);^{13}C NMR (200 MHz, DMSO-d_6) δ 162.89, 162.70, 154.19, 153.27, 150.72, 148.06, 147.79, 141.84, 136.25, 123.99, 122.81, 121.85, 120.10, 111.20, 106.30, 68.39, 65.14, 57.94, 56.58, 48.67, 45.95, 28.78, 10.45, 9.47.

Alternative Procedure for **8**

A solution of **9** (5.92 g, 22.2 mmol) in water (30.0 mL) was added to a stirred solution of **1a** (8.0 g, 22.2 mmol) and NaOH (2.0 g, 50.0 mmol) in water (40.0 mL) at 25–30 °C. The resulting solution was then heated to 70–75 °C and maintained for 5 h. On completion of reaction (vide TLC), solution was extracted with chloroform (2×25 mL), and the chloroform layer was concentrated under reduced pressure to yield a brown liquid **8** (9.6 g, 78% yield).

ACKNOWLEDGMENTS

The authors are grateful to colleagues of the Analytical Research Department of Integrated Product Development Operations, Discovery Research, and the management of Dr. Reddy's Laboratories Ltd. for providing necessary support.

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