Synthetic Studies Connected with The Preparation of H^+/K^+-ATPase Inhibitors Rabeprazole and Lansoprazole

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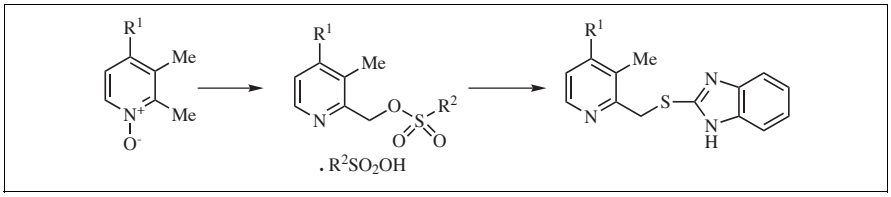

Synthesis of lansoprazole and rabeprazole using common intermediates is devised. The common intermediates, 2-[(4-nitro-3-methylpyridin-2-yl)methanesulfanyl]-1*H*-benzoimidazole and 2-[(4-chloro-3-methyl-pyridin-2-yl)methanesulfanyl]-1*H*-benzoimidazole, were prepared in several ways.

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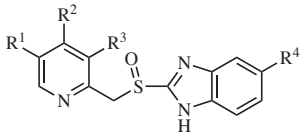
Introduction.

Modern antiulcer drugs of the 2-(pyridin-2-ylmethanesulfinyl)-1*H*-benzimidazole group, such as omeprazole (**1a**), pantoprazole (**1b**), lansoprazole (**1c**), and rabeprazole (**1d**), have been found to be powerful therapeutic agents for treating gastric and duodenal ulcer disease. Their antisecretory activity has been ascribed to a specific inhibition of the gastric proton pump, the H^+/K^+-ATPase, which is responsible for the transport of gastric acid into lumen of the stomach. This transport is the final step of the gastric acid secretion and therefore these drugs are active despite the different kinds of stimulation of the gastric secretion [1-3].

Lansoprazole and rabeprazole seem to have great potential as generic drugs for this decade and many generic companies are focused on their development. The present paper describes our synthetic activity during the development of these two generic substances.



1	Drug	R^1	R^2	R^3	R^4
a	omeprazole	Me	MeO	Me	MeO
b	pantoprazole	H	MeO	MeO	CHF_2O
c	lansoprazole	H	CF_3CH_2O	Me	H
d	rabeprazole	H	$MeO(CH_2)_3O$	Me	H

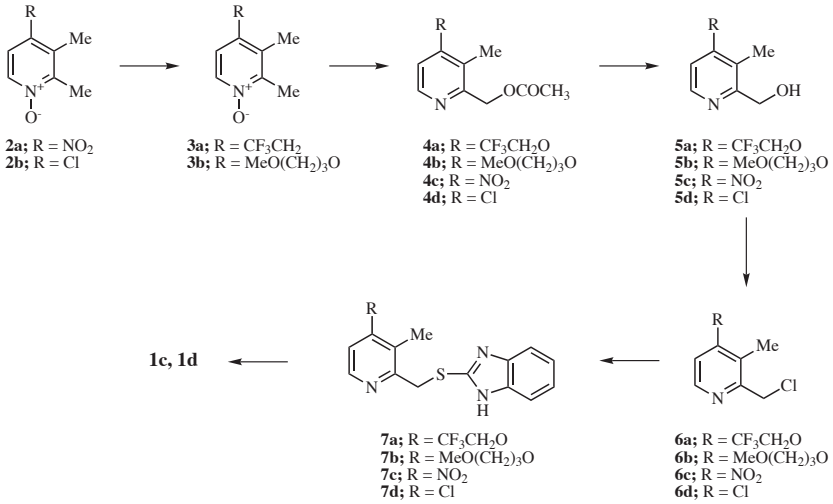
Results and Discussion.

The original method of preparation of these two drugs [4-6] started from 2,3-dimethyl-4-nitropyridine-1-oxide (**2a**). Nucleophilic substitution of the nitro group with the 2,2,2-trifluoroethoxy group provided compound **3a**. Compound **3b** was prepared from the corresponding 4-chloro derivative **2b**, which can be prepared from **2a** by several methods [7,8], and 3-methoxypropanol. Compounds **3a** and **3b** were converted to the corresponding 2-acetoxymethyl derivatives **4** by a classical procedure using acetic anhydride [9,10]. These acetoxymethyl intermediates after hydrolysis provided the corresponding 2-hydroxymethyl derivatives **5a** and **5b** and their treatment with thionyl chloride provided chloromethyl derivatives **6a** and **6b**, respectively. Their treatment with 2-mercaptobenzimidazole under various conditions gave **7a** and **7b**, the key intermediates of synthesis of compounds **1c**, **1d** (Scheme I).

These two drugs differ only at position 4 of the pyridine nucleus and therefore we decided to develop a procedure, where these two substituents would be introduced at a more advanced stage of the synthesis, preferably after the introduction of the benzimidazole moiety. The simplest procedure uses the protocol shown in Scheme I starting from *N*-oxides **2a** and **2b**, *via* 2-acetoxymethyl derivatives **4c, 4d**, to get the corresponding intermediates **6**. The relative reactivity of the 2-chloromethyl substituent *vs* 4-nitro and 4-chloro substituent of compounds **6c** and **6d**, respectively, should enable selective nucleophilic displacement of the chloro atom of the 2-chloromethyl group by thiolate anion to provide intermediates **7**. It is a well known fact that reactivity of 4-nitro or 4-chloro group in 4-nitro or 4-chloro pyridine-1-oxides towards nucleophiles is higher than in corresponding pyridine derivatives [11]. Consequently, conversion of compounds **7c** or **7d** into 4-alkoxy derivatives **7a** or **7c** could present trouble for this approach.

The first approach to these compounds was outlined above. Starting *N*-oxides **2a** and **2b** treated with acetic anhydride provided after flash chromatography good

Scheme I

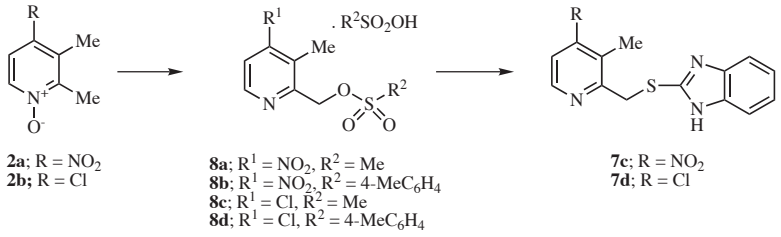


yields of **4c** and **4d**, respectively. Their alkaline hydrolysis gave the corresponding 2-hydroxymethyl derivatives **5c** and **5d**. Thionyl chloride was used to convert these compounds to the corresponding chloromethyl derivatives **6c** and **6d**, respectively. While compound **5d** was converted into **6d** as expected; a mixture of nitro derivative **6c** and the corresponding chloro derivative **6d** was obtained from **5c**. Similar treatment of 2-hydroxymethyl-4-nitropyridine is reported to provide the corresponding 2-chloromethyl-4-nitropyridine [12]. Medium yields of compound **6d** were obtained directly from **2b** by its treatment with phosphorus oxychloride in the presence of triethylamine. This methodology had been described for the synthesis of 2-chloromethylpyridine from 2-methylpyridin 1-oxide [13]. When the methodology was used for nitro derivative **2a**, low yields of **6d** was obtained, *i.e.*, the nitro group was also substituted for chlorine atom. Compound **6d** is a very strong lachrymator. Treatment of compound **6d** with 2-mercaptobenzimidazole provided compound **7d**.

A different possibility to obtain compounds **7c** and **7d** is to substitute the 2-chloromethyl derivatives **6** by other reactive intermediates. Such intermediates could be the corresponding 2-trifluoromethyl derivatives. Preparation of such compounds by treatment of 2-methylpyridine *N*-oxides with trifluoroacetic anhydride has already been described [14,15]. However, relatively low yield and cost of this reagent discouraged us from its use. Recently, this approach has been claimed in a patent application [16].

Though we were not aware of any literature precedent, we anticipated that *N*-oxides **2a** and **2b** could react with methanesulfonic anhydride and/or 4-toluenesulfonic anhydride similarly as with acetic anhydride to provide compounds **8a** – **8d**, respectively. In fact, the reaction provided the corresponding crystalline salts, which were directly separated from the reaction mixtures. The ^{1}H nmr spectra proved the structures of these salts though the elemental analysis of compounds **8a** and **8b** were not quite satisfactory and our attempts to purify the compounds by crystallization failed and therefore the salts were used for further step without purification. In case of compound **8d**, we obtained a mixture with starting compounds and we were not able to purify it due to decomposition. These reactive intermediates **8a-c** when treated with 2-mercaptobenzimidazole in the presence of triethylamine provided good yields of intermediates **7c** and **7d**, respectively (Scheme II). During our work we found a patent application describing the same approach

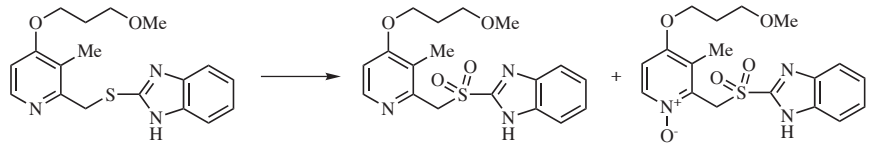
SCHEME II



[16]. Though the patent claimed an easy substitution of the nitro or chloro substituents for the respective alkoxy groups, in our hands the reaction was very sluggish and the yields low.

One of the principal parts of documentation of any drug is identification of its impurities. Since the last step of the synthesis of prazoles is oxidation of the corresponding thioethers, it is not surprising that the main impurities are the corresponding products of overoxidation. To the best of our knowledge, no data concerning impurities of rabeprazole has been published. We have prepared all possible rabeprazole impurities as hplc standards. Oxidation of compound **7b** with excess of peracetic acid provided a mixture of sulfone **9** and its *N*-oxide **10**, which were separated by flash chromatography on silica (Scheme III).

SCHEME III



Similar oxidation of *N*-oxide **13** provided either rabeprazole-*N*-oxide **11**, or the corresponding sulfone **10**, depending on the equivalents of the oxidation agent and the conditions used (Scheme IV). The required compound **13** was prepared from compound **6b** in several steps [17]. Compound **6b** was oxidized by MCPBA and the formed *N*-oxide **12** was used without further purification and treated with 2-mercaptobenzimidazole in acetonitrile in the presence of triethylamine to give **13**.

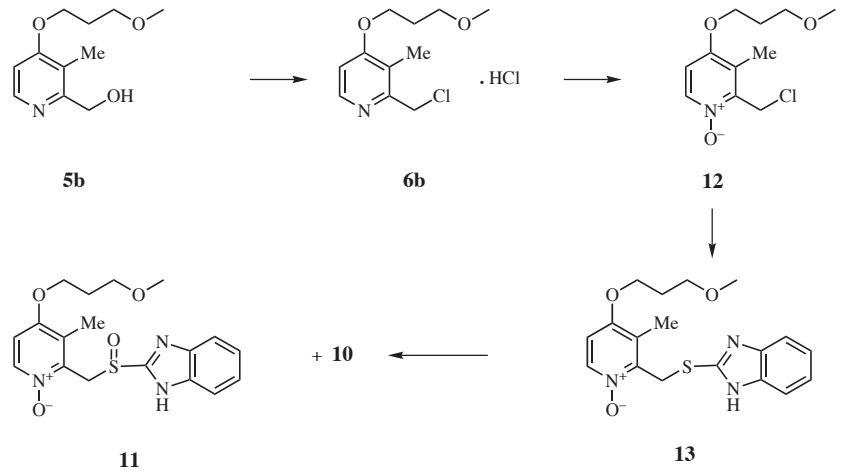
EXPERIMENTAL

Melting points were measured on a Kofler block and are uncorrected. ^1H and ^{13}C nmr spectra were recorded on a Bruker instrument (250 MHz). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. IR spectra were measured on an FTIR Perkin-Elmer Spectrum BX apparatus, using a diffusion reflectance method. Wavenumbers are given in cm^{-1}. UV spectra were recorded on a Shimadzu UV 261, the samples were dissolved in methanol. Mass spectra were recorded on a PE Sciex – Applied Biosystems spectrometer API 3000, using atmospheric pressure chemical ionization. Purity of the substances prepared was evaluated by tlc on silica gel (FP KG F 254, Merck). Flash chromatography was performed on silica gel Merck, particle size 0.04-0.063 mm.

4-Chloro-2,3-dimethylpyridine *N*-oxide (**2b**).

Phosphorus oxychloride (35 mL) was added during 1 h to a stirred ice-cooled solution of 4-nitro-2,3-dimethyl-pyridine *N*-oxide (**2a**) (20 g, 0.12 mol) in dichloromethane (250 mL) and the mixture was stirred at room temperature overnight. Then the mixture was poured on ice (320 g) and basified with 40 % solution of sodium hydroxide. The aqueous layer was extracted with dichloromethane (3 x 100 mL), the combined organic extracts were washed with brine and dried with magnesium sulfate. The residue after evaporation was crystallized from cyclohexane to give 14.0 g (75 %) yellowish crystals of **2b**, mp 104-106 °C. ^1H nmr ($CDCl_3$): δ 2.40 s, 3 H (3-CH_3), 2.57 s, 3 H (2-CH_3), 7.18 d, *J* = 6.9, 1H (H-5), 8.10 d, *J* = 6.9, 1H (H-6).

SCHEME IV



(3-Methyl-4-nitropyridin-2-yl)methyl acetate (**4c**).

A mixture of **2a** (4.2 g, 25 mmol) and acetic anhydride (40 mL) was stirred at 100 °C for 3 h, excess acetic anhydride was evaporated and the residue purified by flash chromatography (hexane – acetone, 10:1) to give 2.55 g (49 %) of **4c** as colorless liquid; ^{1}H nmr ($CDCl_3$): δ 2.16 (s, 3H, CH_3CO), 2.47 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 7.58 (d, 1H, H-5, *J* = 5.3), 8.64 (d, 1H, H-6, *J* = 5.3).

(4-Chloro-3-methylpyridin-2-yl)methyl acetate (**4d**).

By the same procedure as described for the preparation of **4c** starting from **2b**, **4d** was obtained in 63 % yield as slightly yellowish liquid. ^{1}H nmr ($CDCl_3$): δ 2.12 (s, 3H, CH_3CO), 2.48 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 7.20 (d, 1H, H-5, *J* = 5.3), 8.22 (d, 1H, H-6, *J* = 5.3).

(3-Methyl-4-nitropyridin-2-yl)methanol (**5c**).

Compound **4c** (5.75 g, 27 mmol) was added to a solution of sodium hydroxide (5 g, mmol) in water (125 mL) and the mixture was stirred at room temperature for 1 h. The mixture was extracted with dichloromethane, the extract was washed with brine and dried with magnesium sulfate to give, after evaporation, a brownish residue (3.6 g). Flash chromatography (hexane – acetone, 7 : 3) provided 3.2 g (70 %) of pure **5c** as yellowish crystals, m. p. 56-58 °C; ^{1}H nmr ($CDCl_3$): δ 2.36 (s, 3H, CH_3), 4.58 (bs, 1H, OH), 4.81 (s, 2 H CH_2), 7.58 (d, 1H, H-5, *J* = 5.4), 8.63 (d, 1H, H-6, *J* = 5.4).

Anal Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.38; H, 5.07; N, 16.32.

(4-Chloro-3-methyl-pyridin-2-yl)methanol (**5d**).

Method A) A mixture of **4d** (0.5 g, 2.5 mmol) and concentrated hydrochloric acid (5 mL) was stirred at room temperature for 24 h. Residue after evaporation of the reaction mixture was re-evaporated with toluene (5 mL) and then the residue was triturated with acetone to give 0.38 g of **5d** hydrochloride (78 %), m. p. 147-149 °C. ^{1}H nmr (DMSO-*d6*): δ 2.42 (s, 3H, CH_3), 4.93 (s, 2H, CH_2), 8.08 (d, 1H, H-5, *J* = 5.4), 8.62 (d, 1H, H-6, *J* = 5.4).

Anal Cald. for $C_7H_9Cl_2NO$: C, 43.32; H, 4.67; Cl, 36.54; N, 7.22. Found: C, 43.44; H, 4.34; Cl, 36.89; N, 6,87.

Method B) A mixture of **2b** (5.0 g, 32 mmol) and acetic anhydride (50 mL) was stirred at 80 °C for 2 h and excess acetic anhydride was evaporated. Concentrated hydrochloric acid (50 mL) was added to the residue and the mixture was stirred for 14 h. The mixture was evaporated, the residue was dissolved in water, the solution was basified with saturated solution of sodium carbonate, extracted with diethyl ether and dried with magnesium sulfate. The residue was purified by flash chromatography (hexane – ethyl acetate, 9 : 1) to give 2.28 g (45 %) of **5d** as colorless liquid. ^{1}H nmr ($CDCl_3$): δ 2.26 (s, 3H, CH_3), 4.70 (s, 2H, CH_2), 7.26 (d, 1H, H-5, *J* = 5.3), 8.30 (d, 1H, H-6, *J* = 5.3).

2-Chloromethyl-3-methyl-4-nitropyridine (**6c**).

Thionyl chloride (30 g, 25 mmol) was added dropwise to a solution of **5c** (16.8 g, 10 mmol) in dichloromethane (300 mL) at 0 °C and the mixture was stirred for 1 h at this temperature. The mixture was evaporated, the residue was dissolved in dichloromethane (250 mL), and the solution was washed with saturated sodium hydrogencarbonate and dried with magnesium sulfate to give, after evaporation, 2.28 g (49 %) of **6c** as yellow liquid.

4-Chloro-2-chloromethyl-3-methylpyridine (**6d**).

Method A) Thionyl chloride (30 g, 25 mmol) was added dropwise to a solution of **5d** hydrochloride (19.4 g, 10 mmol) in dichloromethane (300 mL) at ambient temperature and the mixture was refluxed for 1 h. The mixture was evaporated, dissolved in small amount of water, basified with saturated sodium hydrogencarbonate and extracted with dichloromethane. Combined organic extracts were washed with brine and dried with magnesium sulfate and evaporated. Flash chromatography (hexane – ethyl acetate, 9:1) provided 7.5 g (43 %) of **6d** as yellowish oil, which was dissolved in methanol, treated with methanolic solution of hydrogen chloride, evaporated and crystallized from 2-propanol to give 8,7 g (41 %) of **6d** hydrochloride. ^{1}H nmr ($CDCl_3$): δ 2.49 (s, 3H, CH_3), 5.06 (s, 2H, CH_2), 7.82 (d, 1H, H-5, *J* = 5.4), 8.53 (d, 1H, H-6, *J* = 5.4).

Anal Calcd. for $C_7H_8Cl_3N$: C, 39.56; H, 3.79; Cl, 50.05; N, 6.59; Found: C, 39.22; H, 3.52; Cl, 49.78; N, 6.44.

Method B) A solution of phosphorus oxychloride (2 g, 13.1 mmol) in dichloromethane (5 mL) was added dropwise at 0 °C to a stirred solution of **2b** (1.6 g, 10 mmol) in dichloromethane (10 mL) and then a solution of triethylamine (1.25 g, 12.4 mmol) in dichloromethane (5 mL) was added and the formed mixture was stirred at room temperature for 2 h. The formed dark mixture was washed with several portions of saturated aqueous sodium carbonate till the washing was basic. The aqueous layer was extracted with dichloromethane, the combined organic extracts were washed with brine and dried with magnesium sulfate and evaporated to give 1.2 g of dark oil. Flash chromatography (hexane – ethyl acetate, 9:1) provided 0.65 g (37 %) of **6d** as yellowish oil.

Method C) Phosphorus oxychloride (5 g, 32.6 mmol) was added dropwise at 0 °C to a stirred solution of **2a** (1.7 g, 10 mmol) in dichloromethane (15 mL) and the mixture was stirred at room temperature for 24 h. Then the mixture was cooled to 0 °C and triethylamine (10 mL) was added dropwise. The formed dark mixture was stirred for 30 min, poured onto ice and basified with saturated aqueous sodium carbonate. The mixture was extracted with dichloromethane, dried with magnesium sulfate and evaporated to give 1.1 g of dark oil. Flash chromatography (hexane – ethyl acetate, 9:1) provided 0.35 g (20 %) of **6d** as yellowish oil.

General Procedure of the Synthesis of 2-Sulfonyloxymethyl-pyridine salts **8a-8c**.

12 Mmol of methanesulfonic anhydride (compounds **8a**, **8c**) or 4-toluenesulfonic anhydride (compounds **8b**) was added to a solution of 10 mmol of **2a** (compounds **8a**, **8b**) or **2b** (compounds **8c**) in dichloromethane (20 mL) and the mixture was refluxed for 6 h, then additional 3 mmol of the respective anhydride was added and the mixture was refluxed for additional 6 h. The mixture was cooled and the insoluble portion was filtered off to give **8**.

2-Methanesulfonyloxymethyl-3-methyl-4-nitropyridinemethane-sulfonate (**8a**).

This compound was obtained in 54 % yield as colorless crystals, mp 118-120 °C; For $C_9H_{14}N_2O_8S_2$ (342.35) C, 31.57; H 4.12; N 8.18% N, 18.73% S; found: 31.12; H 3.88; N 7.86% N, 19.55% S. ^{1}H nmr (DMSO-*d6*): δ 2.46 (s, 3H, CH_3-3), 2.59 (s,

3H, C**H**$_3$SO$_2$OH), 3.32 (s, 3H, CH_3SO_2), 5.53 (s, 2H, CH_2), 7.94 (d, 1H, H-5, *J* = 5.3), 8.76 (d, 1H, H-6, *J* = 5.3).

Anal Calcd. for $C_9H_{14}N_2O_8S_2$: C, 31.57; H, 4.12; N, 8.18; S, 18.73. Found: C, 31.33; H, 3.88; N, 7.86% N; S, 19.07.

3-Methyl-4-nitro-2-(4-toluenesulfonyloxymethyl)pyridine 4-toluenesulfonate (**8b**).

This compound was obtained in 37 % yield as colorless crystals, mp 145-147 °C; ^{1}H nmr (DMSO-*d6*): δ 2.32 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.46 (s, 3H, CH_3-3), 5.41 (s, 2H, CH_2), 7.22 (d, 2H, H-3',5' of toluenesulfonyl, *J* = 8.0), 7.46 (d, 2H, H-3',5' of toluenesulfonyl, *J* = 8.0), 7.54 (d, 2H, H-2',6' of toluenesulfonyl, *J* = 8.0), 7.74 (d, 2H, H-2',6' of toluenesulfonyl, *J* = 8.0), 7.86 (d, 1H, H-5, *J* = 5.3), 8.70 (d, 1H, H-6, *J* = 5.3).

Anal Calcd. for $C_{21}H_{22}N_2O_8S_2$: C, 51.00; H, 4.48; N, 5.66; S, 12.97. Found: C, 49.62; H, 4.44; N, 5.37; S, 13.24.

4-Chloro-2-methanesulfonyloxymethyl-3-methylpyridine methanesulfonate (**8c**).

This compound was obtained in 52 % yield as colorless crystals, mp 138-142 °C; ^{1}H nmr (DMSO-*d6*): δ 2.50 (s, 3H, CH_3-3), 2.68 (s, 3H, C**H**$_3$SO$_2$OH), 3.24 (s, 3H, CH_3SO_2), 5.53 (s, 2H, CH_2), 7.74 (d, 1H, H-5, *J* = 5.3), 8.54 (d, 1H, H-6, *J* = 5.3), 9.74 (s, 1H, SO_3H).

Anal Calcd. for $C_9H_{14}ClNO_6S_2$: C, 32.58; H, 4.25; Cl, 10.69; N, 4.22; S, 19.33. Found: C, 32.21; H, 4.03; Cl, 10.34; N, 3.87; S, 19.02.

2-[(4-Nitro-3-methylpyridin-2-yl)methylsulfanyl]-1*H*-benzoimidazole (**7c**).

Method A) Triethylamine (1.25 g, 12.5 mmol) was added to a stirred suspension of 2-mercaptobenzimidazole (0.75 g, 5 mmol) in acetonitrile (25 mL) and then compound **8a** (1.7g, 5 mmol) was added in several portions. The mixture became clear and the solution was stirred at room temperature for 12 h. Residue after evaporation was triturated with water, the insoluble portion was filtered, washed with water and crystallized from ethanol to give 1.23 g of **7c** (82 %), mp 88-93 °C; ^{1}H nmr (DMSO-*d6*): δ 2.46 (s, 3H, CH_3), 4.51 (s, 2H, CH_2), 7.18 and 7.53 (m, 4H, aromat. H), 7.30 (d, 1H, H-5, *J* = 5.4), 8.31 (d, 1H, H-6, *J* = 5.4), 12.5 (bs, 1H, NH)); ^{13}C nmr (DMSO-d6, 120 °C): δ 12.70, 36.77, 113.59, 114.98, 121.11, 122.83, 139.29, 147.61, 148.66, 156.09, 158.47.

Anal Calcd. for $C_{14}H_{12}N_4O_2S$: C, 55.99; H, 4.03; N, 18.65; S, 10.68. Found: C, 55.67; H, 4.31; N, 18.17; S, 10.38.

Method B) The same procedure described for Method A) using **8b** provided 74 % yield of **7c** of the same properties given above.

2-[(4-Chloro-3-methyl-pyridin-2-yl)methylsulfanyl]-1*H*-benzoimidazole (**7d**).

Method A) Triethylamine (0.2 g, 2 mmol) was added to a stirred suspension of 2-mercaptobenzimidazole (0.15 g, 1 mmol) in acetonitrile (5 mL) and then **6d** hydrochloride (0.21 g, 1 mmol) was added in several portions. The mixture was stirred overnight at room temperature, evaporated and the residue was triturated with water (10 mL) to give 0.24 g of off-white solid which after crystallization from ethanol provided 0.15 g (52 %) of **7d**; mp 155-160 °C; ^{1}H nmr ($CDCl_3$): δ 2.46 (s, 3H, CH_3), 4.51 (s, 2H, CH_2), 7.18 and 7.53 (m, 4H, aromat. H), 7.30 (d, 1H, H-5, *J* = 5.4), 8.31 (d, 1H, H-6, *J* = 5.4).

Anal Calcd. for $C_{14}H_{12}ClN_3S$: C, 58.03; H, 4.17; Cl, 12.23; N, 14.50; S, 11.07. Found: C, 57.67; H, 4.33; Cl, 12.01; N, 14.41; S, 11.12.

Method B) A mixture of **2b** (20 g, 0.127 mol) and acetic anhydride (150 g) was stirred at 80 °C under nitrogen atmosphere for 1 h. The residue after evaporation was stirred at room temperature with concentrated hydrochloric acid (100 mL) for 20 h, the mixture was evaporated to dryness. The residue was dissolved in water, the solution was extracted with diethylether (2 x 50 mL) and the water layer was basified with saturated solution of sodium carbonate. The mixture was then extracted with diethyl ether (4 x 50 mL, 4 x 25 mL) and the extract was dried with magnesium sulfate. The residue after evaporation (13 g) was dissolved in dichloromethane (130 mL), thionyl chloride (25 mL) was added and the mixture was stirred at room temperature for 2 h. The mixture was thoroughly evaporated, the residue (13.2 g) was added to a stirred suspension of 2-mercaptoimidazole (9.4 g, 62.6 mmol) and triethylamine (12.6 g, 125 mmol) in acetonitrile (320 mL) and the mixture was stirred overnight. The residue after evaporation was triturated with water, the insoluble portion was filtered, washed with water and crystallized from ethyl acetate (charcoal) to give 12.6 g of off-white crystals (34 %), mp 155-160 °C.

Method C) Triethylamine (0.25 g, 0.25 mmol) was added to a stirred suspension of 2-mercaptobenzimidazole (0.15 g, 1 mmol) in acetonitrile (20 mL) and then compound **8c** (0.33 g, 1 mmol) was added. The mixture was stirred at room temperature for 18 h, the residue after evaporation was triturated with water and the insoluble portion was filtered, washed with water and crystallized from ethanol to give 0.2 g of **7d** (69 %), mp 155-159 °C.

2-[(4-(3-Methoxypropoxy)-3-methylpyridin-2-yl)methylsulfanyl]-1*H*-benzoimidazole (**7b**).

To a stirred slurry of powdered potassium hydroxide (0.07 g, 1.25 mmol) in dimethyl sulfoxide (1 mL) was added a solution of **7d** (0.2 g, 0.69 mmol) and 3-methoxy-1-propanol (0.12 g, 1.38 mmol) in dimethyl sulfoxide (2 mL) and the mixture was stirred at ambient temperature in screw-capped vial under nitrogen for 14 days. The reaction mixture was then poured into water (50 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (2 x 25 mL) and dried with magnesium sulfate. The residue after evaporation was crystallized from acetone to give 0.7 g of **7b** (29.5 %), m. p. 111-112 °C; ^{1}H nmr ($CDCl_3$): δ 2.09 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 3.35 (s, 3H, OCH_3), 3.56 (t, 2H, CH_2, *J* = 6.0), 4.12 (t, 2H, CH_2, *J* = 6.2), 4.38 (s, 2H, CH_2S), 6.75 (d, 1H, aromat. H, *J*= 5.8), 7.14-7.20 (m, 2H, aromat. H), 7.52 (bm, 2H, aromat. H), 8.33 (d, 1H, aromat. H, *J* = 5.8), 13.00 (bs, 1H, NH); ^{13}C nmr (DMSO-d6, 120 °C): δ 9.74, 28.48, 36.13, 57.35, 65.17, 68.16, 105.98, 119.71, 120.83, 124.34, 147.05, 147.23, 149.67, 154.81, 162.65; UV (MeOH), λ_{max} (log ε): 292.0 (4.22), 285.6 (4.19), 204.4 (4.67); ms, *m/e*: 343 (M^+, 100 %), 344 (19 %), 345 (4 %),.

Anal Calcd. for $C_{18}H_{21}N_3O_2S$: C, 62.95; H, 6.16; N, 12.23; S, 9.34. Found: C, 63.05; H, 6.27; N, 12.47; S, 9.12.

2-{[4-(3-Methoxypropoxy)-3-methylpyridin-2-yl]methyl}sulfonyl-1*H*-benzimidazole (**9**) and 2-{[4-(3-Methoxypropoxy)-3-methyl-1-oxidopyridin-2-yl]methyl}sulfonyl-1*H*-benzimidazole (**10**).

To a stirred solution of **7b** (3.43 g, 10 mmol) in dichloromethane (50 mL) was added a solution of sodium carbonate (3 g) in water (25 mL) and the obtained mixture was cooled in an

ice bath. The solution of peracetic acid (40 mmol) in water (10 mL) was added dropwise over 20 min and the mixture was stirred at ambient temperature for 20 h. The organic layer was separated, washed with saturated aqueous potassium hydrogencarbonate and dried with magnesium sulfate. The residue was separated by flash chromatography on silica (dichloromethane – methanol – triethylamine, 100:5:1) afforded 1.26 g (33.5 %) of **9** and 0.72 g (18.4 %) of **10**.

Compound **9**: M. p. = 158-160 °C; ^{1}H nmr ($CDCl_3$): δ 2.06 (m, 2H, CH_2), 2.34 (s, 3H, OCH_3), 3.36 (s, 3H, CH_3), 3.56 (t, 2H, OCH_2, *J* = 6.0), 4.08 (t, 2H, OCH_2, *J* = 6.0), 5.08 (s, 2H, CH_2S), 6.73 (d, 1H, H-5, *J* = 5.9), 7.25 (m, 2H, aromat. H), 7.56 (bs, 2H, aromat. H), 8.18 (d, 1H, H-6, *J* = 5.9), 12.90 (bs, 1H, NH); ^{1}H nmr (DMSO-d6): δ 1.96 (m, 2H, CH_2), 2.36 (s, 3H, OCH_3), 3.22 (s, 3H, CH_3), 3.48 (t, 2H, OCH_2, *J* = 6.0), 4.08 (t, 2H, OCH_2, *J* = 6.0), 5.08 (s, 2H, CH_2S), 6.94 (d, 1H, H-5, *J* = 6.0), 7.38 (m, 2H, aromat. H), 7.70 (m, 2H, aromat. H), 8.04 (d, 1H, H-6, *J* = 5.9); ^{13}C nmr (DMSO-d6, 120 °C): δ 10.71, 17.05, 28.03, 57.42, 67.81, 68.93, 107.80, 107.98, 119.77, 123.41, 124.95, 129.55, 137.21, 143.46, 145.23, 153.27, 162.65; IR: 2990-2855, 1461 (CH_3, CH_2, CH), 3140-3000, 1500-1455, 775-735 (Arom.), 1584, 1365-1266, 1175-1105 (SO_2); UV (MeOH), λ_{max} (log ε): 279.4 (4.11), 205.0 (4.61); MS: m/e 376.1 (M+1) (100%), 312.2 (9%), 258.2 (21%), 210.2 (8%), 119.0 (11%).

Anal Calcd. for $C_{18}H_{21}N_3O_4S$: C, 57.58; H, 5.64; N, 11.19; S, 8.54. Found: C, 57.69; H, 5.34; N, 11.27; S, 8.32.

Compound **10**: Mp = 138-139 °C; ^{1}H nmr ($CDCl_3$): δ 2.10 (m, 2H, CH_2), 2.44 (s, 3H, OCH_3), 3.36 (s, 3H, CH_3), 3.55 (t, 2H, OCH_2, *J* = 5.9), 4.15 (t, 2H, OCH_2, *J* = 6.2), 5.39 (s, 2H, CH_2S), 6.82 (d, 1H, H-5, *J* = 7.3), 7.25 (m, 2H, aromat. H), 7.56 (bs, 2H, aromat. H), 8.20 (d, 1H, H-6, *J* = 7.3), 12.90 (bs, 1H, NH); ^{13}C nmr (DMSO-d6, 120 °C): δ 10.34, 28.41, 57.34, 60.62, 65.25, 68.13, 106.58, 116.38, 122.91, 123.76, 138.02, 147.09, 147.45, 148.16, 162.84; IR: 2990-2855, 1458 (CH_3, CH_2, CH), 3065, 1183, 1093 (Arom.), 1365-1265, 1175-1105 (SO_2); UV (MeOH), λ_{max} (log ε): 278.2 (4.41), 206.2 (4.56); ms: *m/e* 392.3 (M+1) (32 %), 274.1 (100 %), 210.2 (43 %), 119.0 (68 %).

Anal Calcd. for $C_{18}H_{21}N_3O_5S$: C, 55.23; H, 5.41; N, 10.73; S, 8.19. Found: C, 54.98; H, 5.22; N, 11.06; S, 8.17.

2-Chloromethyl-4-(3-methoxypropoxy)-3-methylpyridine 1-oxide (**12**).

The solution of **6b** as the hydrochloride (4.93 g, 18.5 mmol) in dichloromethane (150 mL) was washed with saturated aqueous sodium hydrogencarbonate (200 mL). A solution of 3-chloroperbenzoic acid (37 mmol) in a mixture of dichloromethane (20 mL) and methanol (6 mL) was added over 2 h to the organic solution of **6b** and the mixture stirred for 1 h. Saturated aqueous sodium hydrogencarbonate (100 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried with magnesium sulfate. Dichloromethane was then evaporated under reduced pressure to obtain **12** (4.54 g, >99 %) as oil, which was used for the next step without further purification.

2-{[4-(3-Methoxypropoxy)-3-methyl-1-oxidopyridin-2-yl]-methylsulfanyl}-1*H*-benzoimidazole (**13**).

Triethylamine (9.49 g, 92.5 mmol) was added to a solution of 2-chloromethyl-4-(3-methoxypropoxy)-3-methylpyridine *N*-oxide **12** (4.54 g, 18.5 mmol) and 2-mercaptobenzoimidazole (2.78 g, 8.5 mmol) in acetonitrile (500 mL). After 2 hours of stirring at ambient temperature the solvent was evaporated, the residue was partitioned between dichloromethane and water (100 mL/100 mL), the aqueous layer was extracted with dichloromethane (2 x 50 mL) and the combined organic layers were dried with magnesium sulfate. The residue after evaporation (6.4 g) was crystallized from acetone to give 3.0 g (46 %) of **13**. Mp = 149-150 °C; ^{1}H nmr ($CDCl_3$): δ 2.10 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 3.34 (s, 3H, OCH_3), 3.53 (t, 2H, CH_2, *J* = 5.9), 4.11 (t, 2H, CH_2, *J* = 6.2), 4.76 (s, 2H, CH_2), 6.77 (d, 1H, aromat. H, *J* = 7.3), 7.12-7.17 (m, 2H, aromat. H), 8.22 (d, 1H, aromat. H, *J* = 7.3), 14.20 (bs, 1H, NH); ^{13}C nmr (DMSO-d6, 120 °C): δ 10.79, 27.73, 28.40, 57.34, 66.14, 68.10, 108.23, 113.39, 120.79, 123.67, 136.57, 139.63, 147.14, 149.81, 154.61; ms, *m/e*: 359,13 (M^+, 100.0%), 360.13 (21.5%), 361.13 (5.5%), 361.14 (1,9%); UV (MeOH), λ_{max} (log ε): 274.8 (4.30), 213.8 (4.60).

Anal Calcd. for $C_{18}H_{21}N_3O_3S$: C, 60.15; H, 5.89; N, 11.69; S, 8.92. Found: C, 59.92; H, 6.12; N, 11.43; S, 8.62.

2-{[4-(3-Methoxypropoxy)-3-methyl-1-oxidopyridin-2-yl)methyl-sulfinyl}-1*H*-benzoimidazole (**11**).

A solution of potassium hydrogencarbonate (0.4 g) in water (5 mL) was added to a solution of **13** (0.72 g, 2 mmol) in dichloromethane (20 mL) and the mixture cooled to 0 °C in an ice bath. To the cooled mixture was added a solution of 3-chloroperbenzoic acid (1.8 mmol) in dichloromethane (10 mL) over 2 h and the reaction mixture was stirred in an ice bath for further 2 h. Then 10 ml of water were added and the aqueous layer was separated. The organic layer was dried over magnesium sulfate and evaporated. The residue (0.74 g) was separated by column chromatography on silica gel, dichloromethane – methanol – triethylamine, 90:5:2.5) to give 0.48 g of **11**. This product was recrystallized from ethanol to obtain 0.26 g of pure product **11** (35 %); m. p. 161-163 °C (decomp.). ^{1}H nmr ($CDCl_3$): δ 2.06 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 3.34 (s, 3H, OCH_3), 3.52 (t, 2H, CH_2, *J* = 5.9), 4.11 (t, 2H, CH_2, *J* = 6.2), 6.77 (d, 1H, aromat. H, *J* = 7.3), 7.28-7.35 (m, 2H, aromat. H), 7.69 (br., 2H, pyridine H), 8.21 (d, 1H, aromat. H, *J* = 7.3), 13.90 (bs, 1H, NH); ms, m/e: 375,13 (100,0%), 376,13 (19,9%), 377,12 (4,5%), 377,13 (3,1%), 376,12 (1,9%).); IR: 3080-2850, 1617, 1566, 1429 (Arom.), 2935, 1458 (CH_3, CH_2, CH), 1490-1430, 1100-1060, 835-690 (SO); UV (MeOH), λ_{max} (log ε): 279.2 (4.39), 206.8 (4.62); ms: *m/e* 376.4 (M+1) (7%), 258.2 (100%), 244.1 (21 %), 194.3 (69 %), 164.3 (85%), 119.0 (78%).

Anal Calcd. for $C_{18}H_{21}N_3O_4S$: C, 57.58; H, 5.64; N, 11.19; S, 8.54. Found: C, 57.77; H, 5.72; N, 11.35; S, 8.24.

2-{[4-(3-Methoxypropoxy)-3-methyl-1-oxidopyridin-2-yl]-methyl}sulfonyl-1*H*-benzimidazole (**10**).

To a stirred solution of **13** (0.36 g, 1 mmol) in dichloromethane (10 mL) was added a solution of sodium carbonate (0.3 g) in water (3.0 mL) and the obtained mixture was cooled in an ice bath. The solution of peracetic acid (0.3 g) in water (2 mL) was added dropwise in 30 min and the mixture was stirred at ambient temperature for 24 h. Then, 0.5 mL of peracetic acid was added and the mixture was stirred at ambient temperature. After 8 h 0.5 mL of peracetic acid was added and the mixture was stirred for 20 h. When the presence of **11** was not indicated on TLC, the reaction mixture was separated and the aqueous layer was extracted with 10 mL of dichloromethane. The

combined organic layers were evaporated and the residue (0.36 g) was recrystallized from ethanol to obtain 0.20 g (51 %) of **10**. The isolated product was by all the measured characteristics (Mp, ^{1}H nmr, IR, UV, MS, EA) identical with compound **10** obtained by oxidation of **9**.

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