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A reverse method for diversity introduction of benzimidazole to synthesize H^+/K^+-ATP enzyme inhibitors

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ABSTRACT

A series of 2-[(2-pyridylmethyl)sulfinyl]benzimidazole derivatives were synthesized via a solution phase synthetic route using a reversal method of diversity introduction. Using this synthetic strategy, we obtained two key intermediates (**4-A** and **4-B**) simultaneously, which allows us to introduce diversity points onto the benzimidazole part of the final product under reliable reaction conditions to identify potent H^+/K^+-ATP enzyme inhibitors. Compound **14l** ($IC_{50} = 1.6 \times 10^{-5}$ M) was comparable with H^+/K^+-ATP enzyme inhibitor in vitro.

Proton pump inhibitors (PPIs) belong to a class of therapeutic agents for most acid-related diseases, including gastroesophageal reflux disease, peptic ulcer diseases, and acute gastrointestinal bleeding.[1–3] Benzimidazole-type agents contribute significantly to these agents, such as omeprazole and pantoprazole.[4–7] Current benzimidazole-type PPIs, which consist of two fragments of benzimidazole and pyridine, act as prodrugs owing to protonation of the pyridine ring under a gastrointestinal acid environment, resulting in a chemical rearrangement of the entire molecule (Fig. 1).[8–10] Recently, PPIs have been investigated using various substitutions on the pyridine ring, but there has been less effort on modifying the benzimidazole moiety. Our laboratory has developed a highly efficient method to generate benzimidazoles at four diversity points using 1,5-difluoro-2,4-dinitrobenzene (DFDNB, **1**),[11,12] where the 2,4-dinitro groups were simultaneously reduced. In this Letter, a selective reduction of the dinitro groups is optimized to allow two disparate intermediates to occur simultaneously (**4-A** and **4-B**), which enables us to generate subsequent substituent diversities with anticipated diversification of benzimidazole under reliable reaction conditions.

Briefly, the two fluorine atoms of **1** were selectively and quantitatively replaced first by ammonia and subsequently by alcohols, phenols, or primary or secondary amines to give **3** as described previously.[11,12] A stepwise reduction of the 2,4-dinitro groups is proposed in this Letter using sodium hydrosulfide (NaHS).[13,14] Two disparate intermediates (**4-A** and **4-B**) were successfully obtained at the same time (Scheme 1).

From intermediate **4-A** in Scheme 2, an imidazole ring could be constructed in the next reaction step from the cyclocondensation of **4-A** with a sulfur-bearing reagent, such as potassium ethyl xanthate,[15] sodium ethyl xanthate,[15] di(1*H*-imidazol-1-yl)methanethione,[16] or carbon disulfide (CS_2).[17] In our work, CS_2 was selected to react with intermediate **4-A**, on taking availability and postprocessing into consideration. Crude intermediate 2-mercapto benzimidazole derivative **5** was obtained with a purity >95% determined using HPLC–MS analysis, which was reacted directly with 2-chloromethyl pyridine hydrochloride to obtain **6**. The 2-chloromethyl pyridine hydrochlorides that appeared in the structure of omeprazole and pantoprazole were chosen to investigate the influence of the diverse substituents of benzimidazole pharmacophore on the antiulcer activity.

Various oxidation conditions were tested that did not give the anticipated product **7** from **6**, including UHP (an adduct of peroxide and urea)/anhydride,[18] sodium hypochlorite (NaClO),[19,20] hydrogen peroxide (H_2O_2),[21] AcOOH, Na_2CO_3/*i*PrOH, and DMSO. It was presumed that the oxidative capability of these oxidants was too high. Therefore, the mild oxidant *m*-chloroperbenzoic acid (*m*CPBA) was investigated in a treatment with **6** in a two-phase mixed solution of dichloromethane (DCM) and a weakly alkaline ($KHCO_3$) saturated aqueous solution maintained near to 0 °C[22] that showed the capability to generate **7** in a high yield. The remaining nitro group of **7** was fully reduced by $Na_2S_2O_4/K_2CO_3$[23] to give **8** in both a high yield and a purity as determined by HPLC analysis. The anticipated final product of **9** was attained through the acylation of **8** at the final step. Compound **9** was purified from recrystallization

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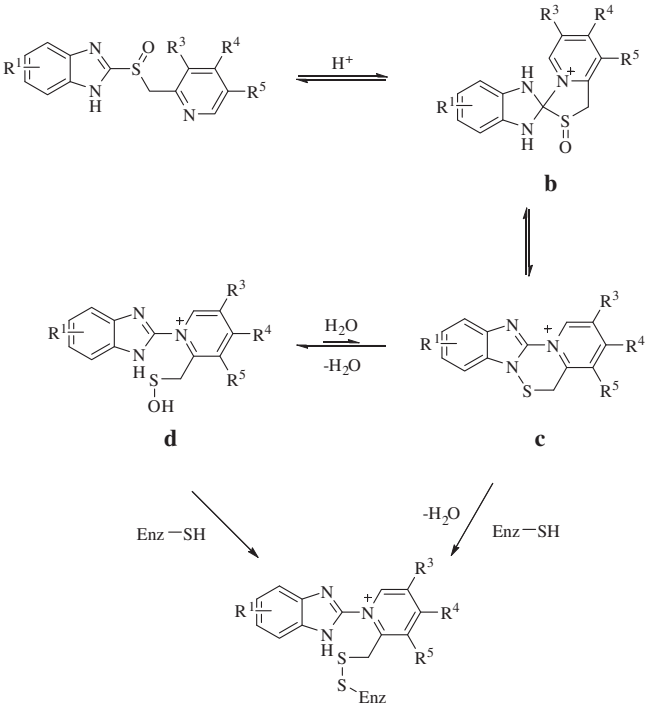


Figure 1. Mechanism of acid transformation of 2-[(2-pyridylmethyl)sulfinyl]benzimidazole derivatives. First, the gastrointestinal acid environment results in the protonation of the pyridine ring to give an intermediate, **b**. Subsequently, the reaction proceeds via a chemical rearrangement, and sulfenic acid **c** is obtained, forming sulfenamide **d** by dehydration. Either the sulfenic acid **c** or the sulfenamide **d** is the active enzyme inhibitor, and this reacts with cysteine from the gastric H^+/K^+-ATP enzyme.[8–10]

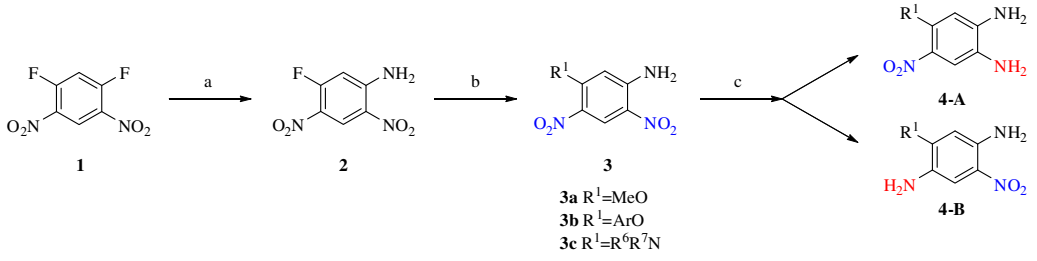
or silica gel column chromatography, and was fully characterized using HRMS (TOF) and ^1H NMR (see Table 1 and Fig. 2).

From **4-B**, a reversal route of R^2 introduction was performed (Scheme 3). The difference between **4-A** and **4-B** allowed us to choose the reaction conditions to introduce the 4-position R^2 group before, or after connection of the pyridine moiety. Interestingly, the acylation of **4-B** only occurred at the 4-NH_2 site rather than at the 1-NH_2 site in the preparation of **10** in the presence of an equivalent amount of the previously mentioned anhydride or acyl chloride. In this route, crude **10**, without any further purification, could be reduced directly using Pd-C/$HCOONH_4$, affording **11** quickly and in high purity. The filtrate of **11** was consequently reacted with CS_2 in the presence of TEA to obtain **12** in 2–3 h at 45 °C with a purity >95% as determined by HPLC–MS analysis. Therefore, the crude product of **12** was further reacted with 2-chloromethyl pyridine hydrochloride under the conditions shown in Scheme 2, to give **13**. Finally, **13** was oxidized by *m*-chloroperbenzoic acid (*m*CPBA) to obtain the final product **14** (Table 1 and Fig. 3).

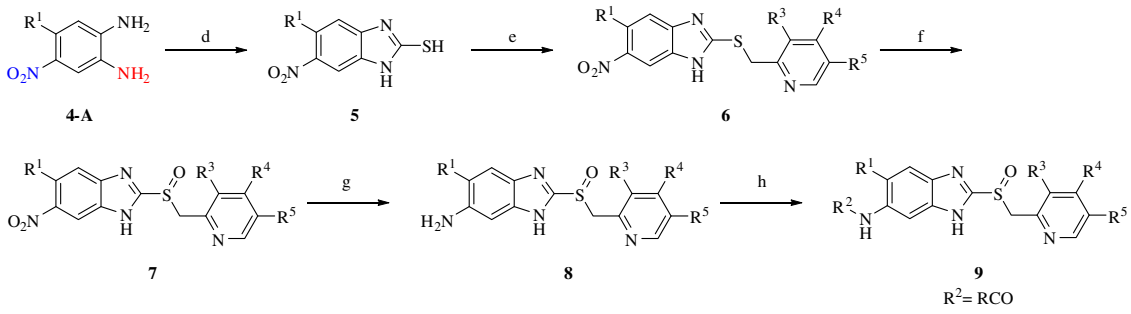
Each synthetic route had an impact on its own sequel. Scheme 2 allowed us to introduce the diversity in the final step, and improved the synthetic throughput of R^2 introduction. Scheme 3 had the advantage of an easy work-up without further purification of the intermediates. Most importantly, the reversal strategy of diversity introduction allowed us to select the reaction conditions to synthesize various molecules.

All the 2-[(2-pyridylmethyl)sulfinyl]benzimidazole derivatives (**9a–r** and **14a–r**) were investigated for in vitro inhibitory activity against the H^+/K^+-ATP enzyme from porcine gastric mucosa. The primary inhibitory rate (in %) on the H^+/K^+-ATP enzyme was determined at a concentration of 10 M, whereas the positive control of omeprazole exhibited an inhibition of 39% (Table 1). Among these compounds, **14g**, **14b**, **14l**, **14n**, and **14d** exhibited an inhibitory percentage of 48%, 58%, 62%, 39%, and 41%, respectively, at the concentration level used. Compound **14l** was tested further to obtain its IC_{50} value at a concentration of 1.6×10^{-5} M (Fig. 4).

From the data shown in Table 1, the variability of benzimidazole moiety provided potent compounds that efficiently inhibited the H^+/K^+-ATP enzymatic activity.



Scheme 1. Synthesis of **4-A** and **4-B**. Reagents and conditions: (a) $NH_3{\cdot}H_2O$, THF, rt, 30 min; (b) CH_3OH, 1 M KOH, THF, rt, 30 min, ArOH, K_2CO_3, acetone, 50 °C, 5–10 h, or R^6R^7NH, DIPEA, THF, 65 °C, 5–10 h; (c) NaHS, CH_3OH, H_2O, reflux, 3–5 h.



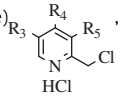
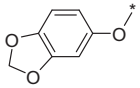
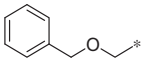
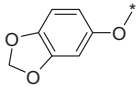
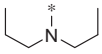
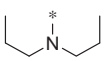
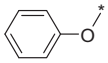
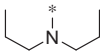
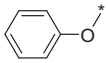
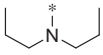
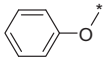
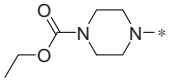
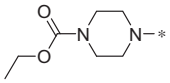
Scheme 2. Synthesis of benzimidazole derivatives using **4-A**. Reagents and conditions: (d) CS_2, Et_3N, CH_3OH, 45 °C, 3 h; (e)  , K_2CO_3, KI, C_2H_5OH and acetone, 45 °C, 4 h; (f) *m*CPBA, $KHCO_3$, DCM and H_2O, 0 °C, 15 min; (g) $Na_2S_2O_4$, K_2CO_3, THF, C_2H_5OH, H_2O, 50 °C, 30 min; (h) $(RCO)_2O$ or RCOCl, Et_3N, DCM, rt, 1–5 h.

Table 1
Structural information and inhibitory rate on the H^+/K^+-ATP enzyme of **9a–r**[a] and **14a–r**[b] at a concentration of 10 M

Compd.	R^1	R^2	Inhibitory rate (%)	Compd.	R^1	R^2	Inhibitory rate (%)
9a			8	**9j**			1
14a		CH_3	10	**14j**		CH_3	35
9b			32	**9k**			0
14b			58	**14k**			10
9c			32	**9l**			28
14c			34	**14l**		CH_3	62
9d			38	**9m**			11
14d			41	**14m**			33
9e			6	**9n**			0
14e		CH_3	37	**14n**			39
9f			2	**9o**			24
14f			18	**14o**			3
9g			9	**9p**			4
14g			48	**14p**	CH_3O	CH_3	4
9h			17	**9q**			16
14h		CH_3	15	**14q**	CH_3O		16
9i			4	**9r**			13
14i			21	**14r**	CH_3O		13
Omeprazole			39	Rabeprazole sodium			90

[a] Compound **9** was synthesized from **4-A**.
[b] Compound **14** was synthesized from **4-B**.

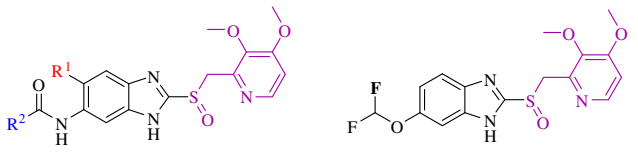


Figure 2. Synthesis of **9a–r**: diversity introduction to benzimidazoles.

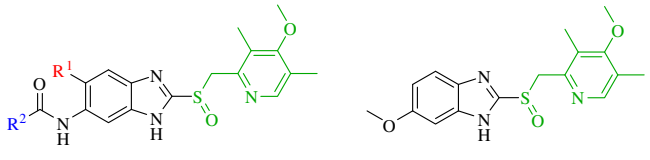
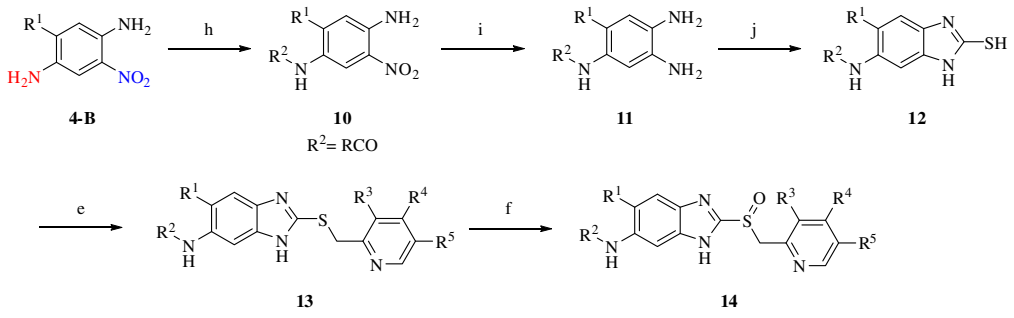
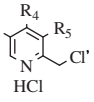


Figure 3. Synthesis of **14a–r**: diversity introduction to benzimidazoles.

In conclusion, we have developed a method for the synthesis of 2-[(2-pyridylmethyl)sulfinyl]benzimidazole derivatives that inhibit H^+/K^+-ATP enzymatic activity as potential proton pump inhibitors. The reversal strategy of the diversity introduction of R^2 on the benzimidazole moiety allows us to select the reaction conditions to make various molecules, and this was helpful in identifying more potent H^+/K^+-ATP enzyme inhibitors. A new compound, **14l** demonstrated an IC_{50} value of 1.6×10^{-5} M, which is comparable with the drug omeprazole.



Scheme 3. Synthesis of benzimidazole derivatives using **4-B**. Reagents and conditions: (h) $(RCO)_2O$ or RCOCl, Et_3N, DCM, rt, 1–5 h; (i) Pd/C, $HCOONH_4$, THF and C_2H_5OH, rt, 15–30 min; (j) CS_2, Et_3N, THF and C_2H_5OH, 45 °C, 3 h; (e)  , K_2CO_3, KI, C_2H_5OH and acetone, 45 °C, 4 h; (f) mCPBA, $KHCO_3$, DCM and H_2O, 0 °C, 15 min.

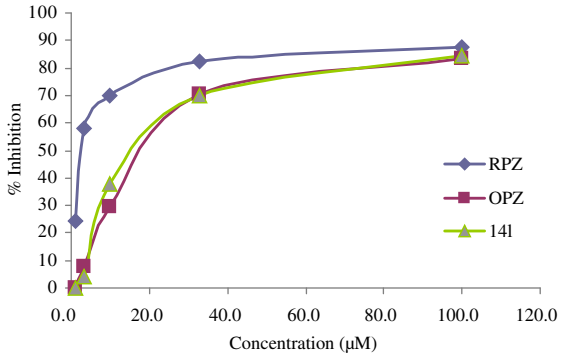


Figure 4. Inhibitory curve of omeprazole, rabeprazole sodium, and **14l**. OPZ and RPZ denote omeprazole and rabeprazole sodium, respectively. The calculated IC_{50} value for omeprazole was 1.8×10^{-5} M, for rabeprazole sodium it was 1.5×10^{-6} M, and for **14l** it was 1.6×10^{-5} M.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.05.080.

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