Synthesis and Antituberculosis Activity of a Novel Series of Optically Active 6-Nitro-2,3-dihydroimidazo[2,1-*b*]oxazoles

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In an effort to develop potent new antituberculosis agents that would be effective against both drug-susceptible and drug-resistant strains of *Mycobacterium tuberculosis*, we prepared a novel series of optically active 6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazoles substituted at the 2-position with various phenoxymethyl groups and a methyl group and investigated the *in vitro* and *in vivo* activity of these compounds. Several of these derivatives showed potent *in vitro* and *in vivo* activity, and compound **19** (OPC-67683) in particular displayed excellent *in vitro* activity against both drug-susceptible and drug-resistant strains of *M. tuberculosis* $H_{37}Rv$ (MIC = 0.006 μg/mL) and dose-dependent and significant *in vivo* efficacy at lower oral doses than rifampicin in mouse models infected with *M. tuberculosis* Kurono. The synthesis and structure−activity relationships of these new compounds are presented.

Introduction

Tuberculosis (TB),[a] an airborne lung infection, still remains a major public health problem worldwide. It is estimated that about 32% of the world population is infected with TB bacillus, and of those, approximately 8.9 million people develop active TB and 1.7 million die as a result annually according to 2004 figures.[1] Human immunodeficiency virus (HIV) infection has been a major contributing factor in the current resurgence of TB.[2,3] HIV-associated TB is widespread, especially in sub-Saharan Africa, and such an infectious process may further accelerate the resurgence of TB. Moreover, the recent emergence of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* that are resistant to two major effective drugs, isonicotinic acid hydrazide (INH)[4] and rifampicin (RFP),[5] has further complicated the world situation.[6] The World Health Organization (WHO) has estimated that if the present conditions remain unchanged, more than 30 million lives will be claimed by TB between 2000 and 2020.[7] As for subsequent drug development, not a single new effective compound has been launched as an antituberculosis agent since the introduction of RFP in 1965, despite the great advances that have been made in drug development technologies.[3] Although many effective vaccine candidates have been developed, more potent vaccines will not become immediately available. The current therapy consists of an intensive phase with four drugs, INH, RFP, pyrazinamide (PZA),[8] and streptomycin (SM)[9] or ethambutol (EB),[10] administered for 2 months followed by a continuous phase with INH and RFP for 4 months.[11] Thus, there exists an urgent need for the development of potent new antituberculosis agents with low-toxicity profiles that are effective against both drug-susceptible and drug-resistant strains of *M. tuberculosis* and that are capable of shortening the current duration of therapy.[12]

Recognizing this serious situation, we initiated a program to screen for new antituberculosis agents. We synthesized and screened various compounds, including a number of dihydrophenazines,[13] indoles, and ureas.[14] One group of compounds on which we focused our attention was 6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazoles because of their inhibitory activity against mycolic acid biosynthesis,[14] which plays an important role in mycobacteria.[15] Nitroimidazoles, such as the nitroimidazole antibiotic metronidazole, are widely used for the treatment of anaerobic bacteria and protozoan infections, but they have had poor potency against *M. tuberculosis*.[16] In 1989, researchers at Ciba-Geigy reported the discovery of a bicyclic nitroimidazooxazole, **1** (CGI 17341)[17] (Figure 1), possessing favorable *in vitro* activity and *in vivo* efficacy. However, further investigation of **1** as an antituberculosis agent had to be discontinued due to the compound's mutagenicity.[18] Later, a research group at PathoGenesis Corporation developed a bicyclic nitroimidazopyran, **2** (PA-824),[19] that exhibited potent bactericidal activity against MDR *M. tuberculosis* and promising oral activity in animal infection models. We speculated that changing the substituents at the 2-position of 6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazoles, which have a structure similar to **1**, might enhance antituberculosis activity and eliminate mutagenicity. In our early experiments, however, no decrease in mutagenicity was achieved by introducing other alkyl substituents into the 2-position. After various experiments with different substituents, we succeeded in discovering a number of derivatives that did not exert mutagenicity from among compounds with heteroatoms in the side chains at the 2-position.[20] Therefore, to identify agents that display increased antituberculosis activity, we prepared a series of novel optically active 6-nitro-2,3-dihydroimidazo[2,1-*b*]-oxazoles having various phenoxymethyl groups and a methyl group at the 2-position. As a result of extensive evaluation, we found a potent, orally active compound that is a promising candidate for the treatment of tuberculosis. We describe herein the synthesis and biological activity of these novel agents.

Chemistry

The first objective of this investigation was to immediately synthesize a variety of (*R*)-form derivatives and evaluate their

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[a] Abbreviations: TB, tuberculosis; HIV, human immunodeficiency virus; MDR, multidrug-resistant; INH, isonicotinic acid hydrazide; RFP, rifampicin; PZA, pyrazinamide; SM, streptomycin; EB, ethambutol; MIC, minimum inhibitory concentration; CFU, colony forming unit; DMSO, dimethylsulfoxide.

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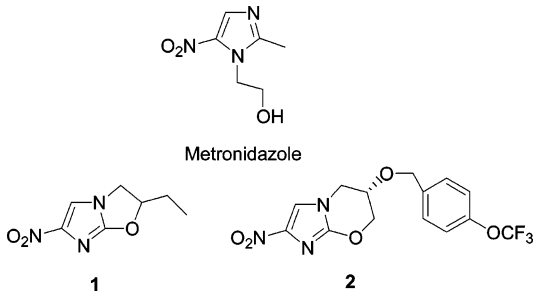
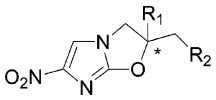


Figure 1. Metronidazole and bicyclic nitroimidazole derivatives **1** and **2**.

Table 1. *In Vitro* MIC Values of **3a**−**g**



compd	R_1	R_2	configuration	MIC (μg/mL)[a]
3a	H	OPh	racemic	0.78
3b	H	OCH_2Ph	racemic	3.13
3c	H	$O(CH_2)_2Ph$	racemic	1.56
3d	H	$OCH_2CH{=}CHPh$	racemic	12.5
3e	Me	OPh	racemic	0.1
3f	Me	OPh	(*R*)	0.05
3g	Me	OPh	(*S*)	3.13

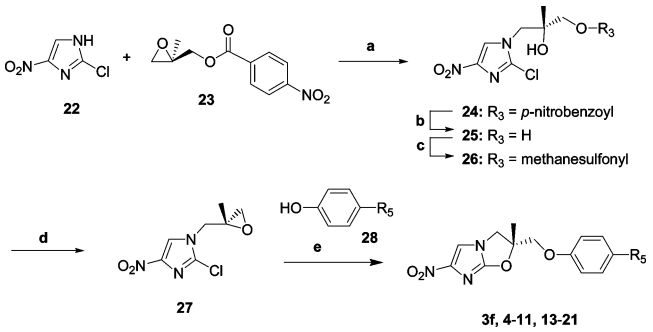
[a] MIC against *M. tuberculosis* $H_{37}Rv$. MIC of RFP = 0.1−0.39 μg/mL.

in vitro and *in vivo* activity. Second, through screening, we intended to identify a potent agent having no mutagenicity as a candidate for the treatment of tuberculosis.

We first synthesized the four racemic compounds **3a**−**d** essentially according to previously reported methods (Table 1).[17,21] Their minimum inhibitory concentration (MIC) values against *M. tuberculosis* $H_{37}Rv$[22] were, respectively, 0.78, 3.13, 1.56, and 12.5 μg/mL, with **3a**, which has a phenoxymethyl group at the 2-position, providing the best result. We then prepared compound **3e**, which has a methyl group at the 2-position of **3a**. Compared with **3a**, **3e** showed increased inhibitory activity (MIC = 0.1 μg/mL). Furthermore, comparison of (*R*)-form **3f** (MIC = 0.05 μg/mL) with (*S*)-form **3g** (MIC = 3.13 μg/mL) showed the (*R*)-form to be the more active form. The synthesis method for these two optically active compounds will be described later. Accordingly, we decided to develop (*R*)-derivatives with various substituted-phenoxymethyl groups and a methyl group at the 2-position to obtain a more potent compound.

Our synthesis strategy for preparation of the optically active 6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazoles with substituted-phenoxymethyl groups **3f** and **4**−**21** ((*R*)-form) involved the utilization of the key intermediate (*R*)-form **27**, an optically active epoxide easily derived from 2-chloro-4-nitro-1*H*-imidazole (**22**)[23] and (*R*)-2-methyl-2,3-epoxypropyl 4-nitrobenzoate (**23**)[24] (Scheme 1). Namely, compound **22** was reacted with the epoxide **23** in the presence of triethylamine in ethyl acetate to afford **24**, followed by de-esterification with methanol and a catalytic amount of potassium carbonate to give the diol **25**. The thus obtained diol was allowed to react with methanesulfonyl chloride in pyridine to afford the mesylate **26**, which was easily converted into the (*R*)-form epoxide **27** with 1,8-diazabicyclo[5.4.0]-7-undecene in ethyl acetate. Finally, the target compounds were synthesized by coupling **27** with various phenol compounds **28**, followed by ring closure in the presence of sodium hydride in *N*,*N*-dimethylformamide.

Scheme 1[a]



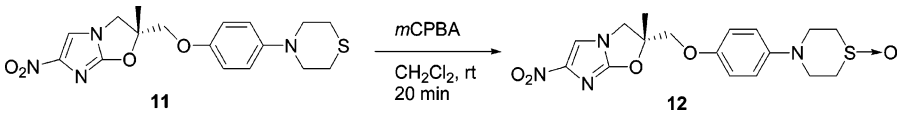
[a] Reagents: (a) Et_3N, AcOEt, 60−65 °C, 6 h; (b) K_2CO_3, MeOH, rt, 2 h; (c) MsCl, pyridine, <15 °C, 2 h; (d) DBU, AcOEt, rt, 2 h; (e) **28**, NaH, DMF, 50 °C, 2 h.

The (*S*)-form **3g** was similarly prepared by using the (*S*)-form epoxide **29** instead of **27** essentially according to the same method. Compound **12** was synthesized by oxidation of **11** with *m*-chloroperbenzoic acid in dichloromethane (Scheme 2). Among the phenol compounds **28**, 4-(piperidin-1-yl)phenol for **9**, 4-(morpholin-4-yl)phenol for **10**, and 4-(thiomorpholin-4-yl)-phenol for **11** were obtained according to the previously reported methods.[25] The synthesis method for the phenol compounds **28a**−**i** for preparing **13**−**21** was as follows: 2-(4-bromophenoxy)tetrahydropyran (**30**)[26] was reacted with various 4-phenoxypiperidine derivatives **31**[27] by the Buchwald palladium-catalyzed amination method[28] to afford **32**. The thus-obtained **32** was deprotected with pyridinium *p*-toluenesulfonate in ethanol to give the desired phenols **28a**−**i** (Scheme 3). All synthesized (*R*)-form compounds are displayed in Tables 2 and 3, and each compound was chemically characterized by melting point and nuclear magnetic resonance (^{1}H NMR), as well as by elemental microanalysis.

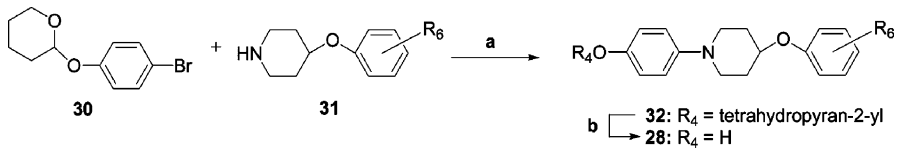
Results and Discussion

All compounds **3f** and **4**−**21** prepared in this investigation were tested for *in vitro* antituberculosis activity against both drug-susceptible and drug-resistant strains of *M. tuberculosis* $H_{37}Rv$[22] and for short-term *in vivo* efficacy at an oral dose of 50 mg/kg for 10 days in mice infected with *M. tuberculosis* Kurono[11] as the primary screening model. The results are summarized in Tables 2 and 3. Among the compounds **3f** and **4**−**8** (Table 2), **3f** (H), **4** (Cl), and **5** (Me) showed high *in vitro* activity and significant *in vivo* efficacy. However, the *in vivo* efficacy of **6** (MeO) was found to be inferior to that of **3f** despite its high *in vitro* activity. Although **7** (CF_3) and **8** (OCF_3) showed only moderate MIC values, they exhibited more potent *in vivo* efficacy than **3f**. Compounds **9**−**12** (Table 2), designed to improve bioavailability by the introduction of hydrophilic substituents into the 4-position of the benzene ring of **3f**, also had moderate MIC values, except for **12**, but unexpectedly their *in vivo* efficacy was generally poor in comparison with **3f**. Because **9** (piperidino) showed the most potent *in vivo* efficacy, (1.9 log CFU reduction in mouse lung) among these four compounds having hydrophilic substituents, we prepared compounds **13**−**21** (Table 3) by introducing lipophilic phenoxy groups to the 4-position of the piperidine ring of **9** to search for more potent agents. Among compounds **13**−**17**, **14** (*p*-Cl) exhibited high *in vitro* activity and **13** (H), **14**, and **15** (*p*-F) showed increased *in vivo* efficacy in comparison with **9**. However, **16** (*p*-Me) and **17** (*p*-MeO) did not show efficacy in *in vivo* screening, contrary to our expectations. In particular, **18** (*p*-CF_3) and **19** (*p*-OCF_3) both showed similar excellent *in*

Scheme 2

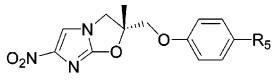


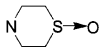
Scheme 3[a]



[a] Reagents: (a) $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, toluene, reflux, 30 min; (b) pyridinium *p*-toluenesulfonate, EtOH, 70 °C, 24 h.

Table 2. *In Vitro* and *in Vivo* Activity of Synthesized Compounds **3f** and **4**−**12**



Compd	R_5	MIC (μg/mL) against *M. tuberculosis* strains			log CFU reduction[b]
		$H_{37}Rv$[a]	$H_{37}Rv$ INH-resistant	$H_{37}Rv$ RFP-resistant	
3f	H	0.05	0.05	0.05	2.0
4	Cl	0.024	0.012	0.006	> 3.1
5	Me	0.012	0.024	0.012	2.9
6	MeO	0.05	0.1	0.05	0.72
7	CF_3	0.2	0.2	0.1	> 4.4
8	OCF_3	0.2	0.39	0.2	> 3.6
9		0.78	0.39	0.39	1.9
10		0.78	0.78	0.39	1.3
11		0.78	0.39	0.2	0.0
12		6.25	6.25	6.25	ND[c]

[a] MIC of RFP against *M. tuberculosis* $H_{37}Rv$ = 0.1−0.39 μg/mL. [b] log CFU reduction in mouse lung relative to untreated controls by once-daily oral administration at 50 mg/kg for 10 days (n = 2) starting on the day after intravenous infection with 10^4 CFU of *M. tuberculosis* Kurono. [c] ND = not determined.

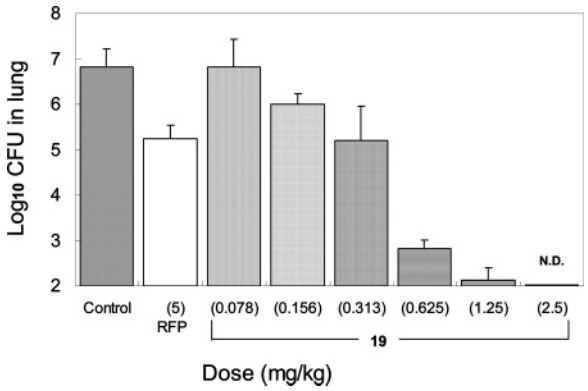


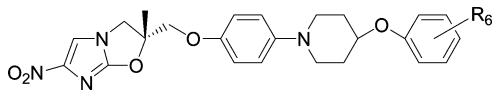
Figure 2. *In vivo* efficacy of compound **19** against *M. tuberculosis* Kurono. Mice were orally dosed once daily for 28 days (n = 6) starting on the day after intravenous infection with 10^4 CFU of mycobacteria.

vitro activity, but **19** was superior to **18** regarding *in vivo* potency (>3.8 log CFU reduction). The excellent *in vitro* activity of **19** was mirrored by its significant *in vivo* efficacy in the mouse acute model. Although **20** (*o*-OCF_3) and **21** (*m*-OCF_3), synthesized by converting the positions of a trifluoromethoxy group of **19** into *ortho* or *meta*, were found to have less potent *in vitro* activity than **19**; the *in vivo* efficacy of **21** was found to be similar to that of **19**.

Next, the compounds **8**, which showed potent *in vivo* efficacy, and **19**, which demonstrated the highest *in vitro* activity among all of the synthesized compounds, were then evaluated *in vivo* at oral doses of 0.5 and 10 mg/kg for 10 days (Table 4). In this *in vivo* test, RFP at 5 mg/kg was used as a reference compound. Compounds **8** and **19** both showed a significant decrease in bacterial load in this evaluation. The oral activity of **8** at a dose of 0.5 mg/kg was similar to that of RFP at 5 mg/kg, and even more notably, oral administration of **19** at a dose of 0.5 mg/kg produced a much better result than RFP at 5 mg/kg. Consequently, based on these evaluation results, compound **19** was selected for further scrutiny.

Finally, **19** was tested for *in vivo* efficacy at lower oral doses of 0.078−2.5 mg/kg once daily for 28 days in mice infected with *M. tuberculosis* Kurono (Figure 2) as a model system. The results for RFP at a dose of 5 mg/kg as a reference drug are

Table 3. *In Vitro* and *in Vivo* Activity of Synthesized Compounds **13**−**21**



compd	R_6	MIC (μg/mL) against *M. tuberculosis* strains: $H_{37}Rv$[a]	$H_{37}Rv$ INH-resistant	$H_{37}Rv$ RFP-resistant	log CFU reduction[b]
13	H	0.39	0.39	0.2	2.8
14	*p*-Cl	0.05	0.05	0.024	2.2
15	*p*-F	0.39	0.39	0.2	2.2
16	*p*-Me	0.78	0.39	0.39	0.6
17	*p*-MeO	0.39	0.39	0.2	0.1
18	*p*-CF_3	0.012	0.012	0.006	2.2
19	*p*-OCF_3	0.006	0.006	0.006	>3.8
20	*o*-OCF_3	0.39	0.39	0.2	3.0
21	*m*-OCF_3	0.024	0.024	0.024	>4.4

[a] MIC of RFP against *M. tuberculosis* $H_{37}Rv$ = 0.1−0.39 μg/mL. [b] log CFU reduction in mouse lung relative to untreated controls by once-daily oral administration at 50 mg/kg for 10 days (n = 2) starting on the day after intravenous infection with 10^4 CFU of *M. tuberculosis* Kurono.

Table 4. *In Vivo* Efficacy of Compounds **8** and **19** as Compared with RFP

compd	**19**		**8**		RFP
dose (mg/kg)	0.5	10	0.5	10	5
log CFU reduction[a]	2.5	>4.4	0.4	3.0	0.5

[a] 10-day treatment of mouse model infection with *M. tuberculosis* Kurono similar to Tables 1 and 2.

also presented. Compound **19** showed a dose-dependent and significant decrease in mouse pulmonary *M. tuberculosis* bacterial counts. In particular, the efficacy of **19** at 0.313 mg/kg was comparable to that of RFP at 5 mg/kg. This potent compound **19** had none of the mutagenicity previously associated with **1**.[20] Therefore, based on the screening results, we selected compound **19** as an orally active candidate for the treatment of tuberculosis.

Conclusions

Screening of this novel series of (*R*)-form optically active 6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole derivatives for *in vitro* antituberculosis activity and *in vivo* oral efficacy indicated that compounds with substituted phenoxymethyl groups and a methyl group at the 2-position are a new class of agents endowed with highly potent antituberculosis activity. Due to its excellent *in vitro* antituberculosis activity against both drug-susceptible and drug-resistant strains of *M. tuberculosis* $H_{37}Rv$ and its potent *in vivo* efficacy in mice infected with *M. tuberculosis* Kurono as a model system, compound **19** was concluded to be a promising orally active candidate for the treatment of tuberculosis. Most notably, compound **19** at an oral dose of 0.313 mg/kg for 28 days showed *in vivo* efficacy comparable to that of RFP at 5 mg/kg. Still more detailed biological data will be presented in a separate paper.[20] Compound **19** (OPC-67683)[20] is now under intensive development.

Experimental Section

General Methods. Reagents were used as supplied unless otherwise noted. All melting points were determined on a Yanaco MP-500D apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker DPX250 instrument operating at 250 MHz. Chemical shifts are shown in parts per million (ppm) on the δ scale downfield relative to tetramethylsilane as an internal standard, and coupling constants are shown in hertz (Hz). Optical rotations were measured on a JASCO DPI-370 digital polarimeter. Satisfactory spectral data were obtained for all of the new compounds. Satisfactory elemental analyses (±0.4%) were obtained for all crystalline derivatives. Chromatographic separations were performed on silica gel columns by gravity column (Kieselgel 60, 0.063−0.200 mm; Merck) chromatography.

Racemic compounds **3b**−**e** were essentially prepared according to the previously reported methods.[17,21] Compound **3a** has been previously reported.[17]

2-Benzyloxymethyl-6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (3b). Mp 125−126 °C. ^{1}H NMR ($CDCl_3$) δ 3.76 (1H, dd, J = 3.5 Hz, 11.2 Hz), 3.87 (1H, dd, J = 4.1 Hz, 11.2 Hz), 4.23−4.34 (2H, m), 4.59 (2H, s), 5.34−5.43 (1H, m), 7.23−7.41 (5H, m), 7.52 (1H, s). MS (DI) m/z 276 (M^+ + 1). Anal. ($C_{13}H_{13}N_3O_4$) C, H, N.

6-Nitro-2-phenethyloxymethyl-2,3-dihydroimidazo[2,1-*b*]oxazole (3c). Mp 115−116 °C. ^{1}H NMR ($CDCl_3$) δ 2.84 (2H, t, J = 6.6 Hz), 3.64−3.86 (4H, m), 4.09 (1H, dd, J = 6.2 Hz, 10.0 Hz), 4.21 (1H, dd, J = 8.6 Hz, 10.0 Hz), 5.25−5.41 (1H, m), 7.07−7.32 (5H, m), 7.46 (1H, s). MS (DI) m/z 289 (M^+). Anal. ($C_{14}H_{15}N_3O_4$) C, H, N.

2-Cinnamyloxymethyl-6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (3d). Mp 145−147 °C. ^{1}H NMR ($CDCl_3$) δ 3.80 (1H, dd, J = 3.6 Hz, 11.3 Hz), 3.90 (1H, dd, J = 4.0 Hz, 11.3 Hz), 4.20−4.34 (4H, m), 5.34−5.50 (1H, m), 6.22 (1H, ddd, J = 6.2 Hz, 12.4 Hz, 16.0 Hz), 6.57 (1H, d, J = 16.0 Hz), 7.20−7.39 (5H, m), 7.54 (1H, s). MS (DI) m/z 302 (M^+). Anal. ($C_{15}H_{15}N_3O_4$) C, H, N.

2-Methyl-6-nitro-2-phenoxymethyl-2,3-dihydroimidazo[2,1-*b*]oxazole (3e). Mp 117−119 °C. ^{1}H NMR ($CDCl_3$) δ 1.79 (3H, s), 4.03 (1H, d, J = 10.2 Hz), 4.09 (1H, d, J = 10.2 Hz), 4.24 (1H, d, J = 10.1 Hz), 4.50 (1H, d, J = 10.1 Hz), 6.84 (2H, dd, J = 2.0 Hz, 8.6 Hz), 7.01 (1H, t, J = 7.4 Hz), 7.20−7.31 (2H, m), 7.56 (1H, s). MS (DI) m/z 275 (M^+). Anal. ($C_{13}H_{13}N_3O_4$) C, H, N.

(*R*)-2-Chloro-1-[2-hydroxy-2-methyl-3-(4-nitrobenzoyloxy)]-propyl-4-nitroimidazole (24). A solution of 2-chloro-4-nitro-1*H*-imidazole (**22**)[23] (3 g, 20.34 mmol), (*R*)-form epoxide **23**[24] (5.31 g, 22.37 mmol), and triethylamine (0.57 mL, 4.07 mmol) in ethyl acetate (10 mL) was heated at 60−65 °C for 6 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. To the residue was added ethyl acetate (3 mL) and toluene (30 mL). The resulting precipitates were collected by filtration and recrystallized from ethyl acetate−isopropylether to give **24** (6.82 g, 87%) as colorless needles. Mp 122−123 °C. ^{1}H NMR (DMSO-d_6) δ 1.23 (3H, s), 4.11−4.33 (4H, m), 5.61 (1H, s), 8.25 (2H, d, J = 8.9 Hz), 8.31−8.45 (3H, m). $[\alpha]_D^{26}$ 54.0° (c 1.04, CH_3CN). MS (DI) m/z 384 (M^+). Anal. ($C_{14}H_{13}ClN_4O_7$) C, H, N.

(*R*)-2-Chloro-1-(2,3-dihydroxy-2-methyl)propyl-4-nitroimidazole (25). To a solution of **24** (6.80 g, 17.67 mmol) in methanol (68 mL) was added potassium carbonate (122 mg, 0.88 mmol). After the solution was stirred at room temperature for 2 h, 6 M hydrochloric acid (0.3 mL) and magnesium sulfate (3 g) were added at 0 °C, and the resulting mixture was stirred for 1 h. The insoluble materials were filtered off through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 20/1) and recrystallized from ethyl acetate−isopropylether to give **25** (4.09 g, 97%) as colorless needles. Mp 110−111 °C. ^{1}H NMR (DMSO-d_6) δ 1.01 (3H, s), 3.25 (2H, d, J = 5.3 Hz), 4.05 (2H, s), 5.01 (1H, s), 5.11 (1H, t, J = 5.4 Hz), 8.32(1H, s). $[\alpha]_D^{27}$ 17.4° (c 1.03, DMSO). MS (DI) m/z 235 (M^+). Anal. ($C_7H_{10}ClN_3O_4$) C, H, N.

(*R*)-2-Chloro-1-(2-methyl-2,3-epoxypropyl)-4-nitroimidazole (27). To a solution of **25** (10 g, 42.44 mmol) in pyridine (20 mL) was added methanesulfonyl chloride (7.29 g, 63.66 mmol) at below 15 °C dropwise over 30 min. After the solution was stirred for 2 h, 6 M hydrochloric acid (63 mL) was added to the reaction mixture at below 30 °C. The resulting mixture was extracted with ethyl acetate (75 mL × 2), and the combined organic layer was washed with brine, dried over magnesium sulfate, and filtered. The

filtrate was concentrated under reduced pressure, and to the residue was added toluene (75 mL). The resulting precipitates were collected by filtration to afford crude **26**. To a solution of this crude **26** in ethyl acetate (100 mL) was added 1,8-diazabicyclo[5.4.0]-7-undecene (7.10 g, 46.68 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethy acetate/hexane = 1/1) to give the (*R*)-form epoxide **27** (6.93 g, 75%) as colorless needles. Mp 72−73 °C. ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, s), 2.62 (1H, d, J = 4.0 Hz), 2.78 (1H, d, J = 4.0 Hz), 4.00 (1H, d, J = 14.9 Hz), 4.38 (1H, d, J = 14.9 Hz), 7.87 (1H, s). $[\alpha]_D^{26}$ 31.1° (*c* 2.02, $CHCl_3$). MS (DI) *m*/*z* 217 (M^+). Anal. ($C_7H_8ClN_3O_3$) C, H, N.

(*S*)-2-Chloro-1-(2-methyl-2,3-epoxypropyl)-4-nitroimidazole (29). This compound was obtained by the same procedure as described for **27** from 2-chloro-4-nitro-1*H*-imidazole (**22**) and (*S*)-2-methyl-2,3-epoxypropyl 4-nitrobenzoate.[24] Mp 72−73 °C. ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, s), 2.63 (1H, d, J = 4.0 Hz), 2.79 (1H, d, J = 4.0 Hz), 4.00 (1H, d, J = 14.9 Hz), 4.38 (1H, d, J = 14.9 Hz), 7.88 (1H, s). $[\alpha]_D^{27}$ −29.2° (*c* 1.18, $CHCl_3$). MS (DI) *m*/*z* 217 (M^+). Anal. ($C_7H_8ClN_3O_3$) C, H, N.

1-[4-(Tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxyphenoxy)piperidine (32g). A mixture of 2-(4-bromophenoxy)-tetrahydropyran (**30**)[26] (30 g, 116.67 mmol) and 4-(4-trifluoromethoxyphenoxy)piperidine (**31g**)[27] (30.30 g, 115.60 mmol) in the presence of palladium acetate (1 g, 4.64 mmol), *rac*-2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (4.30 g, 6.96 mmol), and cesium carbonate (49 g, 150.39 mmol) in toluene (300 mL) was refluxed under a nitrogen atmosphere for 30 min. The reaction mixture was allowed to cool to room temperature, and ethyl acetate (300 mL) and water (200 mL) were added. The thus-obtained mixture was filtered through Celite. The organic layer was separated, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethy acetate/hexane = 1/20) to give **32g** (32.60 g, 64%) as a yellow crystalline powder. ^{1}H NMR ($CDCl_3$) δ 1.55−1.75 (3H, m), 1.81−2.20 (7H, m), 2.95−3.04 (2H, m), 3.38−3.42 (2H, m), 3.55−3.66 (1H, m), 3.87−3.99 (1H, m), 3.56−4.45 (1H, m), 5.29−5.32 (1H, m), 6.89−7.01 (6H, m), 7.11−7.16 (2H, m).

4-[4-(4-Trifluoromethoxyphenoxy)piperidin-1-yl]phenol (28g). A mixture of **32g** (30.10 g, 68.81 mmol) and pyridinium *p*-toluenesulfonate (5.20 g, 20.69 mmol) in ethanol (450 mL) was heated at 70 °C for 24 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. Saturated sodium hydrogen carbonate aqueous solution (100 mL) was added to the residue, which was extracted with dichloromethane (200 mL). The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate = 10/1) to give **28g** (22.90 g, 94%) as a pale yellow crystalline powder. ^{1}H NMR ($CDCl_3$) δ 1.88−2.02 (2H, m), 2.06−2.16 (2H, m), 2.92−3.02 (2H, m), 3.30−3.39 (2H, m), 4.36−4.44 (1H, m), 4.74 (1H, s), 6.71−6.78 (2H, m), 6.85−6.94 (4H, m), 7.10−7.16 (2H, m).

Other phenol derivatives **28a**−**f** and **28h**,**i** were synthesized by the same procedure as described for **28g**. Compounds **28a**−**i** were immediately used for the next reaction.

4-(4-Phenoxypiperidin-1-yl)phenol (28a). ^{1}H NMR ($CDCl_3$) δ 1.89−2.03 (2H, m), 2.04−2.18 (2H, m), 2.92−3.02 (2H, m), 3.31−3.41 (2H, m), 4.39−4.49 (1H, m), 4.92 (1H, s), 6.70−6.78 (2H, m), 6.84−6.98 (5H, m), 7.24−7.33 (2H, m).

4-[4-(4-Chlorophenoxy)piperidin-1-yl]phenol (28b). ^{1}H NMR ($CDCl_3$) δ 1.87−2.01 (2H, m), 2.04−2.16 (2H, m), 2.91−3.02 (2H, m), 3.29−3.39 (2H, m), 4.34−4.44 (1H, m), 4.85 (1H, s), 6.71−6.78 (2H, m), 6.82−6.92 (4H, m), 7.20−7.26 (2H, m).

4-[4-(4-Fluorophenoxy)piperidin-1-yl]phenol (28c). ^{1}H NMR ($CDCl_3$) δ 1.86−2.00 (2H, m), 2.04−2.16 (2H, m), 2.90−3.00 (2H, m), 3.30−3.40 (2H, m), 4.29−4.39 (1H, m), 4.72 (1H, s), 6.71−6.78 (2H, m), 6.83−7.01 (6H, m).

4-[4-(4-Methylphenoxy)piperidin-1-yl]phenol (28d). ^{1}H NMR ($CDCl_3$) δ 1.87−2.01 (2H, m), 2.04−2.16 (2H, m), 2.29 (3H, s), 2.90−3.00 (2H, m), 3.30−3.40 (2H, m), 4.33−4.43 (1H, m), 4.85 (1H, s), 6.71−6.78 (2H, m), 6.80−6.92 (4H, m), 7.06−7.10 (2H, m).

4-[4-(4-Methoxyphenoxy)piperidin-1-yl]phenol (28e). ^{1}H NMR ($CDCl_3$) δ 1.86−2.00 (2H, m), 2.05−2.13 (2H, m), 2.88−2.99 (2H, m), 3.31−3.41 (2H, m), 3.77 (3H, s), 4.25−4.35 (1H, m), 4.72 (1H, s), 6.72−6.77 (2H, m), 6.80−6.92 (6H, m).

4-[4-(4-Trifluoromethylphenoxy)piperidin-1-yl]phenol (28f). ^{1}H NMR ($CDCl_3$) δ 1.90−2.05 (2H, m), 2.08−2.20 (2H, m), 2.94−3.05 (2H, m), 3.30−3.40 (2H, m), 4.46−4.56 (1H, m), 4.64 (1H, s), 6.72−6.80 (2H, m), 6.86−6.93 (2H, m), 6.96−7.00 (2H, m), 7.52−7.56 (2H, m).

4-[4-(2-Trifluoromethoxyphenoxy)piperidin-1-yl]phenol (28h). ^{1}H NMR ($CDCl_3$) δ 1.91−2.16 (4H, m), 2.91−3.07 (2H, m), 3.25−3.40 (2H, m), 4.40−4.53 (1H, m), 4.70 (1H, s), 6.76 (2H, dd, J = 2.3 Hz, 6.7 Hz), 6.81−7.05 (4H, m), 7.12−7.28 (2H, m).

4-[4-(3-Trifluoromethoxyphenoxy)piperidin-1-yl]phenol (28i). ^{1}H NMR ($CDCl_3$) δ 1.89−2.18 (4H, m), 2.94−3.06 (2H, m), 3.27−3.41 (2H, m), 4.35−4.51 (1H, m), 4.71 (1H, s), 6.71−6.96 (7H, m), 7.25−7.35 (1H, m).

(*R*)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-*b*]oxazole (19). To a mixture of **27** (127.56 g, 586.56 mmol) and 4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenol (**28g**) (165.70 g, 468.95 mmol) in *N*,*N*-dimethylformamide (1600 mL) was added 60% sodium hydride (22.51 g, 562.74 mmol) at 0 °C portionwise. After the mixture was stirred at 50 °C for 2 h under a nitrogen atmosphere, the reaction mixture was cooled in an ice bath and carefully quenched with ethyl acetate (230 mL) and ice water (50 mL). The thus-obtained mixture was poured into water (3000 mL) and stirred for 30 min. The resulting precipitates were collected by filtration, washed with water, and dried at 60 °C overnight. This crude product was purified by silica gel column chromatography using a dichloromethane and ethyl acetate mixture (5/1) as solvent. The appropriate fractions were combined and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate (1300 mL)−isopropyl alcohol (150 mL) to afford **19** (119.11 g, 48%) as a pale yellow crystalline powder. Mp 195−196 °C. ^{1}H NMR ($CDCl_3$) δ 1.77 (3H, s), 1.87−2.16 (4H, m), 2.95−3.05 (2H, m), 3.32−3.41 (2H, m), 4.02 (1H, d, J = 10.2 Hz), 4.04 (1H, d, J = 10.2 Hz), 4.18 (1H, J = 10.2 Hz), 4.36−4.45 (1H, m), 4.49 (1H, d, J = 10.2 Hz), 6.76 (2H, d, J = 6.7 Hz), 6.87−6.94 (4H, m), 7.14 (2H, d, J = 8.6 Hz), 7.55 (1H, s). $[\alpha]_D^{28}$ −9.9° (*c* 1.01, $CHCl_3$). MS (DI) *m*/*z* 535 ($M^+ + 1$). Anal. ($C_{25}H_{25}F_3N_4O_6$) C, H, N.

Compounds **3f, 4**−**11**, **13**−**18**, **20**, and **21** were prepared by the same procedure as described for **19**.

(*R*)-2-Methyl-6-nitro-2-phenoxymethyl-2,3-dihydroimidazo-[2,1-*b*]oxazole (3f). Mp 151−153 °C. ^{1}H NMR ($CDCl_3$) δ 1.79 (3H, s), 4.03 (1H, d, J = 10.2 Hz), 4.09 (1H, d, J = 10.2 Hz), 4.24 (1H, d, J = 10.1 Hz), 4.50 (1H, d, J = 10.1 Hz), 6.84 (2H, dd, J = 1.8 Hz, 8.5 Hz), 7.01 (1H, t, J = 7.2 Hz), 7.21−7.31 (2H, m), 7.55 (1H, s). MS (DI) *m*/*z* 275 (M^+). Anal. ($C_{13}H_{13}N_3O_4$) C, H, N.

(*R*)-2-(4-Chlorophenoxymethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (4). Mp 185−187 °C. ^{1}H NMR ($CDCl_3$) δ 1.78 (3H, s), 4.04 (1H, d, J = 3.2 Hz), 4.08 (1H, d, J = 3.2 Hz), 4.21 (1H, d, J = 10.1 Hz), 4.49 (1H, d, J = 10.1 Hz), 6.78 (2H, d, J = 9.0 Hz), 7.19−7.29 (2H, m), 7.56 (1H, s). MS (DI) *m*/*z* 309 (M^+). Anal. ($C_{13}H_{12}ClN_3O_4$) C, H, N.

(*R*)-2-Methyl-2-(4-methylphenoxymethyl)-6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (5). Mp 177−179 °C. ^{1}H NMR ($CDCl_3$) δ 1.78 (3H, s), 2.28 (3H, s), 4.02 (1H, d, J = 7.2 Hz), 4.06 (1H, d, J = 7.2 Hz), 4.20 (1H, d, J = 10.1 Hz), 4.49 (1H, d, J = 10.1 Hz), 6.74 (2H, d, J = 8.3 Hz), 7.08 (2H, d, J = 8.3 Hz), 7.55 (1H, s). MS (DI) *m*/*z* 289 (M^+). Anal. ($C_{14}H_{15}N_3O_4$) C, H, N.

(*R*)-2-(4-Methoxyphenoxymethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (6). Mp 179−180 °C. ^{1}H NMR ($CDCl_3$)

δ 1.77 (3H, s), 3.76 (3H, s), 4.02 (1H, d, J = 2.6 Hz), 4.06 (1H, d, J = 2.6 Hz), 4.17 (1H, d, J = 10.2 Hz), 4.50 (1H, d, J = 10.2 Hz), 6.71−6.86 (4H, m), 7.55 (1H, s). MS (DI) m/z 305 (M^+). Anal. ($C_{14}H_{15}N_3O_5$) C, H, N.

(*R*)-2-Methyl-6-nitro-2-(4-trifluoromethylphenoxymethyl)-2,3-dihydroimidazo[2,1-*b*]oxazole (7). Mp 188−190 °C. ^{1}H NMR ($CDCl_3$) δ 1.81 (3H, s), 4.08 (1H, d, J = 10.3 Hz), 4.18 (1H, d, J = 10.3 Hz), 4.29 (1H, d, J = 10.3 Hz), 4.50 (1H, d, J = 10.3 Hz), 6.93 (2H, d, J = 8.7 Hz), 7.50−7.59 (3H, m). MS (DI) m/z 343 (M^+). Anal. ($C_{14}H_{12}F_3N_3O_4$) C, H, N.

(*R*)-2-Methyl-6-nitro-2-(4-trifluoromethoxyphenoxymethyl)-2,3-dihydroimidazo[2,1-*b*]oxazole (8). Mp 176−178 °C. ^{1}H NMR ($CDCl_3$) δ 1.79 (3H, s), 4.06 (1H, d, J = 6.8 Hz), 4.10 (1H, d, J = 6.8 Hz), 4.23 (1H, d, J = 10.1 Hz), 4.49 (1H, d, J = 10.1 Hz), 6.84 (2H, d, J = 9.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.56 (1H, s). MS (DI) m/z 359 (M^+). Anal. ($C_{14}H_{12}F_3N_3O_5$) C, H, N.

(*R*)-2-Methyl-6-nitro-2-[4-(piperidin-1-yl)phenoxymethyl]-2,3-dihydroimidazo[2,1-*b*]oxazole (9). Mp 217−219 °C. ^{1}H NMR ($CDCl_3$) δ 1.45−1.57 (5H, m), 1.61−1.78 (4H, m), 2.94−3.08 (4H, m), 4.00 (1H, d, J = 7.4 Hz), 4.04 (1H, d, J = 7.4 Hz), 4.17 (1H, d, J = 10.1 Hz), 4.49 (1H, d, J = 10.1 Hz), 6.75 (2H, d, J = 6.8 Hz), 6.89 (2H, d, J = 6.8 Hz), 7.54 (1H, s). MS (DI) m/z 358 (M^+). Anal. ($C_{18}H_{22}N_4O_4$) C, H, N.

(*R*)-2-Methyl-2-[4-(morpholin-4-yl)phenoxymethyl]-6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (10). Mp 233−235 °C. ^{1}H NMR (DMSO-d_6) δ 1.67 (3H, s), 2.92−3.00 (4H, m), 3.61−3.71 (4H, m), 4.08−4.22 (3H, m), 4.36 (1H, d, J = 10.9 Hz), 6.80 (2H, d, J = 6.8 Hz), 6.88 (2H, d, J = 6.8 Hz), 8.15 (1H, s). MS (DI) m/z 360 (M^+). Anal. ($C_{17}H_{20}N_4O_5$) C, H, N.

(*R*)-2-Methyl-6-nitro-2-[4-(thiomorpholin-4-yl)phenoxymethyl]-2,3-dihydroimidazo[2,1-*b*]oxazole (11). Mp 227−229 °C. ^{1}H NMR ($CDCl_3$) δ 1.77 (3H, s), 2.69−2.80 (4H, m), 3.31−3.71 (4H, m), 4.01 (1H, d, J = 5.5 Hz), 4.05 (1H, d, J = 5.5 Hz), 4.18 (1H, d, J = 10.1 Hz), 4.49 (1H, d, J = 10.1 Hz), 6.77 (2H, d, J = 6.7 Hz), 6.86 (2H, d, J = 6.7 Hz), 7.55 (1H, s). MS (DI) m/z 376 (M^+). Anal. ($C_{17}H_{20}N_4O_4S$) C, H, N.

(*R*)-2-Methyl-6-nitro-2-[4-(4-phenoxypiperidin-1-yl)phenoxymethyl]-2,3-dihydroimidazo[2,1-*b*]oxazole (13). Mp 195−197 °C. ^{1}H NMR ($CDCl_3$) δ 1.77 (3H, s), 1.86−2.18 (4H, m), 2.92−3.08 (2H, m), 3.31−3.47 (2H, m), 4.01 (1H, d, J = 5.8 Hz), 4.05 (1H, d, J = 5.8 Hz), 4.18 (1H, d, J = 10.2 Hz), 4.37−4.55 (2H, m), 6.78 (2H, dd, J = 2.2 Hz, 6.8 Hz), 6.84−7.00 (5H, m), 7.20−7.33 (2H, m), 7.55 (1H, s). MS (DI) m/z 450 (M^+). Anal. ($C_{24}H_{26}N_4O_5$) C, H, N.

(*R*)-2-{4-[4-(4-Chlorophenoxy)piperidin-1-yl]phenoxymethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (14). Mp 183−184 °C. ^{1}H NMR ($CDCl_3$) δ 1.77 (3H, s), 1.84−2.14 (4H, m), 2.92−3.04 (2H, m), 3.29−3.43 (2H, m), 4.01 (1H, d, J = 6.5 Hz), 4.05 (1H, d, J = 6.5 Hz), 4.18 (1H, d, J = 10.2 Hz), 4.33−4.45 (1H, m), 4.49 (1H, d, J = 10.2 Hz), 6.71−6.92 (6H, m), 7.16−7.27 (2H, m), 7.55 (1H, s). MS (DI) m/z 484 (M^+). Anal. ($C_{24}H_{25}ClN_4O_5$) C, H, N.

(*R*)-2-{4-[4-(4-Fluorophenoxy)piperidin-1-yl]phenoxymethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (15). Mp 191−193 °C. ^{1}H NMR (DMSO-d_6) δ 1.59−1.76 (5H, m), 1.92−2.10 (2H, m), 2.80−2.98 (2H, m), 3.24−3.41 (2H, m), 4.10−4.20 (3H, m), 4.37−4.51 (2H, m), 6.78 (2H, d, J = 8.6 Hz), 6.90 (2H, d, J = 8.6 Hz), 6.92−7.12 (4H, m), 8.16 (1H, s). MS (DI) m/z 468 (M^+). Anal. ($C_{24}H_{25}FN_4O_5$) C, H, N.

(*R*)-2-Methyl-2-{4-[4-(4-methylphenoxy)piperidin-1-yl]phenoxymethyl}-6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (16). Mp 199−201 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ 1.77 (3H, s), 1.86−2.14 (4H, m), 2.29 (3H, s), 2.88−3.04 (2H, m), 3.29−3.45 (2H, m), 4.00 (1H, d, J = 6.3 Hz), 4.04 (1H, d, J = 6.3 Hz), 4.17 (1H, d, J = 10.1 Hz), 4.33−4.43 (1H, m), 4.49 (1H, d, J = 10.1 Hz), 6.71−6.92 (6H, m), 7.08 (2H, d, J = 8.4 Hz), 7.55 (1H, s). MS (DI) m/z 464 (M^+). Anal. ($C_{25}H_{28}N_4O_5$) C, H, N.

(*R*)-2-{4-[4-(4-Methoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (17). Mp 193−195 °C. ^{1}H NMR ($CDCl_3$) δ 1.77 (3H, s), 1.82−2.14 (4H, m), 2.86−3.02 (2H, m), 3.31−3.45 (2H, m), 3.77 (3H, s), 4.00 (1H, d, J = 6.2 Hz), 4.04 (1H, d, J = 6.2 Hz), 4.18 (1H, d, J = 10.1 Hz), 4.22−4.35 (1H, m), 4.49 (1H, d, J = 10.1 Hz), 6.71−6.92 (8H, m), 7.55 (1H, s). MS (DI) m/z 480 (M^+). Anal. ($C_{25}H_{28}N_4O_6$) C, H, N.

(*R*)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-*b*]oxazole (18). Mp 179−181 °C. ^{1}H NMR ($CDCl_3$) δ 1.77 (3H, s), 1.88−2.20 (4H, m), 2.92−3.10 (2H, m), 3.27−3.43 (2H, m), 4.01 (1H, d, J = 5.8 Hz), 4.05 (1H, d, J = 5.8 Hz), 4.18 (1H, d, J = 10.2 Hz), 4.43−4.57 (2H, m), 6.78 (2H, d, J = 6.8 Hz), 6.90 (2H, d, J = 6.8 Hz), 6.98 (2H, d, J = 8.6 Hz), 7.47−7.60 (3H, m). MS (DI) m/z 518 (M^+). Anal. ($C_{25}H_{25}F_3N_4O_5$) C, H, N.

(*R*)-2-Methyl-6-nitro-2-{4-[4-(2-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-*b*]oxazole (20). Mp 152−153 °C. ^{1}H NMR ($CDCl_3$) δ 1.77 (3H, s), 1.86−2.19 (4H, m), 2.95−3.12 (2H, m), 3.28−3.44 (2H, m), 4.10 (1H, d, J = 10.2 Hz), 4.04 (1H, d, J = 10.2 Hz), 4.18 (1H, d, J = 10.2 Hz), 4.42−4.56 (2H, m), 6.78 (2H, dd, J = 2.3 Hz, 6.9 Hz), 6.83−7.07 (4H, m), 7.14−7.28 (2H, m), 7.55 (1H, s). MS (DI) m/z 534 (M^+). Anal. ($C_{25}H_{25}F_3N_4O_6$) C, H, N.

(*R*)-2-Methyl-6-nitro-2-{4-[4-(3-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-*b*]oxazole (21). Mp 184−186 °C. ^{1}H NMR ($CDCl_3$) δ 1.77 (3H, s), 1.88−2.17 (4H, m), 2.96−3.06 (2H, m), 3.31−3.41 (2H, m), 4.02 (1H, d, J = 10.2 Hz), 4.04 (1H, d, J = 10.2 Hz), 4.18 (1H, d, J = 10.2 Hz), 4.40−4.48 (1H, m), 4.50 (1H, d, J = 10.2 Hz), 6.74−6.94 (7H, m), 7.24−7.31 (1H, m), 7.55 (1H, s). MS (DI) m/z 534 (M^+). Anal. ($C_{25}H_{25}F_3N_4O_6$) C, H, N.

(*S*)-2-Methyl-6-nitro-2-phenoxymethyl-2,3-dihydroimidazo-[2,1-*b*]oxazole (3g). This compound was obtained by the same procedure as described for **19** using (*S*)-form epoxide **29** instead of **27**. Mp 153−155 °C. ^{1}H NMR ($CDCl_3$) δ 1.79 (3H, s), 4.04 (1H, d, J = 10.2 Hz), 4.09 (1H, d, J = 10.2 Hz), 4.24 (1H, d, J = 10.1 Hz), 4.50 (1H, d, J = 10.1 Hz), 6.83 (2H, dd, J = 2.0 Hz, 8.6 Hz), 7.01 (1H, t, J = 7.4 Hz), 7.20−7.31 (2H, m), 7.56 (1H, s). MS (DI) m/z 275 (M^+). Anal. ($C_{13}H_{13}N_3O_4$) C, H, N.

(*R*)-2-Methyl-6-nitro-2-{4-[(1-oxo-thiomorpholin)-4-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-*b*]oxazole (12). To a solution of **11** (85 mg, 0.23 mmol) in dichloromethane (5 mL) was added 70% *m*-chloroperbenzoic acid (59 mg, 0.24 mmol), and the resulting mixture was stirred at room temperature for 20 min. Sodium thiosulfate aqueous solution (10%, 15 mL) was added to the reaction mixture, which was extracted with dichloromethane (20 mL). The organic layer was washed with saturated sodium hydrogen carbonate aqueous solution (15 mL) and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was recrystallized from methanol−isopropylether to afford **12** (59 mg, 67%) as a colorless crystalline powder. Mp 198−200 °C. ^{1}H NMR ($CDCl_3$) δ 1.77 (3H, s), 2.82−2.96 (4H, m), 3.33−3.45 (2H, m), 3.78−3.90 (2H, m), 4.02 (1H, d, J = 5.5 Hz), 4.06 (1H, d, J = 5.5 Hz), 4.20 (1H, d, J = 10.2 Hz), 4.49 (1H, d, J = 10.2 Hz), 6.80 (2H, d, J = 6.8 Hz), 6.91 (2H, d, J = 6.8 Hz), 7.56 (1H, s). MS (DI) m/z 392 (M^+). Anal. ($C_{17}H_{20}N_4O_5S$) C, H, N.

***In Vitro* Antituberculosis Activity.** MICs of test agents against both drug-susceptible and drug-resistant strains of *M. tuberculosis* $H_{37}Rv$ were determined essentially according to the previously reported method.[22] Test drugs were each dissolved in dimethyl sulfoxide (DMSO), and the solutions were diluted serially with DMSO in 2-fold dilutions to the desired concentrations. All strains were grown in Middlebrook 7H9 broth. Stock cultures stored frozen at −80 °C were diluted and adjusted to approximately 10^6 CFU/mL. The bacterial suspension containing about 10^6 CFU/mL was spotted onto 7H11 agar plates containing test drugs using a multipoint inoculator (Sakuma Seisakusho). After cultivation at 37 °C for 14 days, MICs were determined as the minimum concentrations of drugs completely inhibiting visible growth of organism.

***In Vivo* Efficacy for 10 Days.** The basic therapeutic efficacy of test agents was determined in mouse models of acute bacterial infection with *M. tuberculosis* Kurono.[10] In brief, the designated compound was suspended in 5% gum arabic. ICR male mice (Japan

SLC) weighing 20−25 g were infected intravenously with 10^4 CFU of mycobacteria through a caudal tail vein and treated once daily at oral doses of 0.5−50 mg/kg for 10 days ($n = 2$) starting on the day after infection. Animals were sacrificed on day 11, approximately 24 h after administration of the final drug dose. Lungs were aseptically removed and ground in a contained tissue homogenizer. The number of viable organisms was determined by dilution plating on 7H11 agar plate and incubating at 37 °C for 14 days prior to counting. Mean log colony forming units (CFU) reduction values were calculated from mycobacterial counts of test groups relative to untreated controls.

***In Vivo* Efficacy for 28 Days.** The designated compound was suspended in 5% gum arabic. ICR male mice (Japan SLC) weighing 20−25 g were infected intravenously with 10^4 CFU of mycobacteria through a caudal tail vein and treated once daily at various oral doses for 28 days ($n = 6$) starting on the day after infection. Animals were sacrificed on day 29, approximately 24 h after administration of the final drug dose. Lungs were aseptically removed and ground in a contained tissue homogenizer. The number of viable organisms was determined by dilution plating on 7H11 agar plate and incubating at 37 °C for 14 days prior to counting. Bacterial counts of test groups were measured and compared with the counts from untreated controls.

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Supporting Information Available: Result of elemental analysis for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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