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Phenylimidazole derivatives as specific inhibitors of bacterial enoyl-acyl carrier protein reductase FabK

Tomohiro Ozawa,[a] Hideo Kitagawa,[a,*] Yasuo Yamamoto,[a] Sho Takahata,[b] Maiko Iida,[a] Yumi Osaki[b] and Keiko Yamada[b]

[a]*Medicinal Chemistry Research Laboratories, Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd, 760 Morooka-cho, Kohoku-ku, Yokohama 222-8567, Japan*
[b]*Pharmacology Research Laboratories, Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd, 760 Morooka-cho, Kohoku-ku, Yokohama 222-8567, Japan*

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Abstract—Bacterial enoyl-acyl carrier protein (ACP) reductases (FabI and FabK) catalyze the final step in each cycle of bacterial fatty acid biosynthesis and are attractive targets for the development of new antibacterial agents. Here, we report the development of novel FabK inhibitors with antibacterial activity against *Streptococcus pneumoniae*. Based on structure–activity relationship (SAR) studies of our screening hits, we have developed novel phenylimidazole derivatives as potent FabK inhibitors.

1. Introduction

Streptococcus pneumoniae is the main causative pathogen of respiratory tract infections such as community-acquired pneumonia and acute otitis media. The increase of penicillin-resistant *S. pneumoniae* (PRSP) and macrolide-resistant *S. pneumoniae* is of great concern worldwide. In addition, the emergence of quinolone-resistant *S. pneumoniae* has been reported recently.[1–3] A key strategy to overcome drug-resistant pathogens is the discovery of antibacterial agents with novel mechanisms of action.[4]

In this regard, fatty acid biosynthesis is an attractive target.[5–7] Bacterial fatty acid biosynthesis (type II FAS) provides fatty acids which are used in the assembly of essential cellular components of bacteria such as cell envelopes, phospholipids, lipoproteins, lipopolysaccharides or mycolic acids. In bacteria, different monofunctional enzymes catalyze each of the reactions and reaction intermediates are carried through the cytosol as thioesters of the small acyl carrier protein (ACP). On the other hand, mammals synthesize fatty acids on a single large multifunctional protein to which the growing chain remains covalently attached. The difference between bacterial and mammalian fatty acid biosynthesis offers an attractive opportunity for selective inhibition of type II FAS. Therefore, inhibitors of the bacterial enzymes are expected to be candidates antibacterial agents.

FabI (enoyl-ACP reductase) is an enzyme which catalyzes the final and rate-limiting step of bacterial FAS. The reaction involves the conjugate reduction of an enoyl-ACP to the corresponding acyl-ACP using the cofactor NADH or NADPH as a hydride source.[8,9] Various compounds, including isoniazid,[10] diazaborines,[11,12] triclosan,[13–18] indole naphthyridinones **1**, **2**[19–22] and thiopyridine **3**[23] have been reported as inhibitors of bacterial enoyl-ACP reductase FabI. We have also reported a series of 4-pyridone derivatives, such as compound **4**, as small-molecular FabI inhibitors with potent antibacterial activity against *Staphylococcus aureus*.[24–26] A FabI-targeting approach to antibacterial drug therapy appears feasible (Fig. 1).

However, recent studies have shown that other bacterial enoyl-ACP reductases exist in addition to FabI.[27,28] A triclosan-resistant flavoprotein, termed FabK, has been shown to be the sole enoyl-ACP reductase in *S. pneumoniae*. Consequently, a selective inhibitor of FabK is expected to be a novel narrow-spectrum antibacterial

Keywords: FabK; Enoyl-ACP reductase; Phenylimidazole; *Streptococcus pneumoniae*.
* Corresponding author. Tel.: +81 45 541 2521; fax: +81 45 541 0667; e-mail: hideokitagawa@coda.ocn.ne.jp

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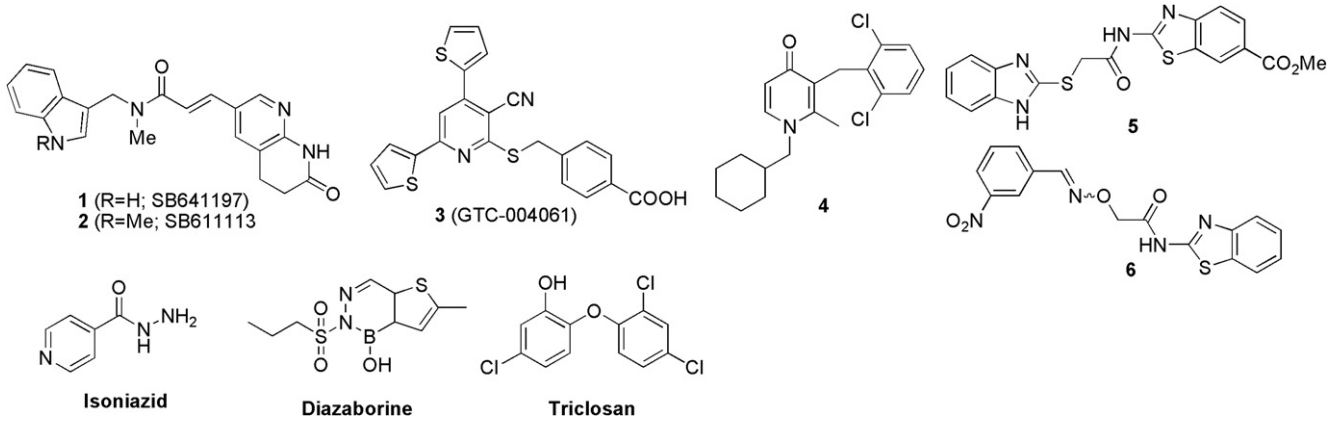


Figure 1. Structures of conventional FabI or FabK inhibitors.

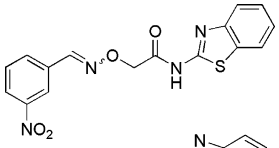
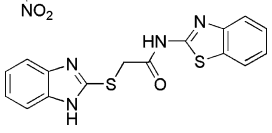
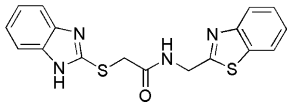
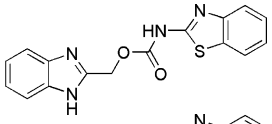
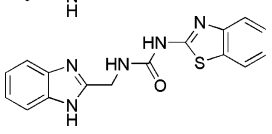
agent against *S. pneumoniae* including PRSP and macrolide-resistant *S. pneumoniae.* Only a few FabK inhibitors have been identified so far. The reported FabK inhibitors **1** and **2** had weak inhibitory activity and failed to show selective inhibition of bacterial FAS.[19,22] Atromentin and leucomelone were also reported as FabK inhibitors, but they did not show any antibacterial activity against *S. pneumoniae*.[29]

To discover small-molecular FabK inhibitors, we screened our compound library for inhibitory activity toward FabK of *S. pneumoniae*. Among the hits, the amide **5** and the oxime **6** were selected as lead compounds because these compounds exhibited moderate and selective inhibitory activity toward FabK of *S. pneumoniae* (compound **5**: *S. pneumoniae* FabK IC_{50} = 1.5 μM, *Escherichia coli* FabI IC_{50} > 32 μM; compound **6**: *S. pneumoniae* FabK IC_{50} = 1.1 μM, *E. coli* FabI IC_{50} > 32 μM).[30] Based on SAR studies of these compounds,[31] we found the ureido compound **47**, which has strong FabK-inhibitory activity (IC_{50} = 0.0024 μM) and potent antibacterial activity against *S. pneumoniae* (MIC = 0.25 μg/ml). In this paper, we would like to report our development of specific inhibitors of enoyl-ACP reductase FabK in detail. All the compounds in Tables 4 and 5 (compounds **41**–**49**) and several compounds in Tables 1–3 (compounds **16**, **33**, **34**, **37**, **40**) are novel compounds which we have never reported before.

2. Chemistry

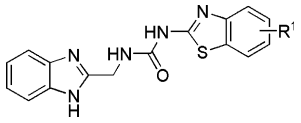
Amide-type derivatives were prepared by means of standard procedures.[32–35] For example, compound **11** was prepared as illustrated in Scheme 1. Commercially available 2-aminobenzo[*d*]thiazole **7** reacted with chloroacetyl chloride **8** in toluene at 60 °C to give the

Table 1. Effects of various structural units on enzyme-inhibitory and antibacterial activities

Compound		FabK IC_{50} (μM) *S. pneumoniae*	MIC (μg/ml) *S. pneumoniae*[a]	FabI IC_{50} (μM) *E. coli*
6		1.1 ± 0.2	>32	>32
11		>32	>32	>32
16		>32	>32	>32
28		>32	>32	>32
29		6.9 ± 1.5	32	>32

[a] *S. pneumoniae* KU197.

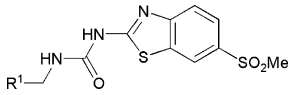
Table 2. Effects of substitution on the benzothiazole ring on enzyme-inhibitory and antibacterial activities

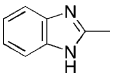
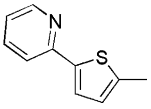
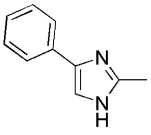
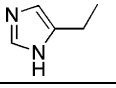


Compound	R^1	FabK IC_{50} (μM) *S. pneumoniae*	MIC (μg/ml) *S. pneumoniae*[a]	FabI IC_{50} (μM) *E. coli*
29	H	6.9 ± 1.5	32	>32
30	4-OMe	>32	NT[b]	>32
31	5-OMe	>32	NT	>32
32	6-OMe	2.0 ± 0.5	16	>32
33	6-Me	2.6 ± 0.4	16	>32
34	6-F	6.4 ± 1.3	NT	>32
35	6-CN	4.5 ± 0.6	8	>32
36	6-SO_2Me	0.74 ± 015	4	>32

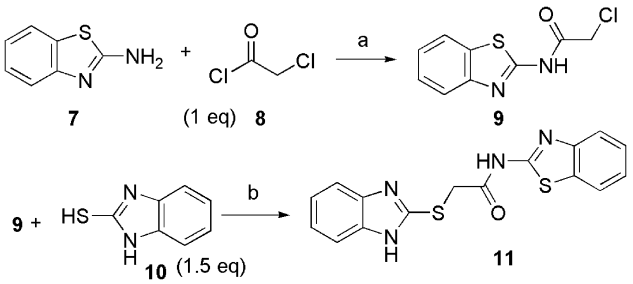
[a] *S. pneumoniae* KU197.
[b] NT, not tested.

Table 3. Effects of other heterocyclic groups on enzyme-inhibitory and antibacterial activities



Compound	R^1	FabK IC_{50} (μM) *S. pneumoniae*	MIC (μg/ml) *S. pneumoniae*[a]	FabI IC_{50} (μM) *E. coli*
36		0.74 ± 0.15	4	>32
37		3.4 ± 0.9	>32	>32
38		23 ± 2	>32	>32
39		30 ± 9	>32	>32
24		0.088 ± 0.014	0.5	>32
40		>32	NT[b]	>32

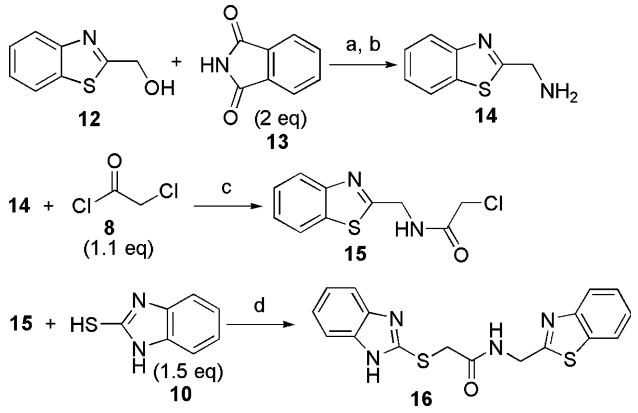
[a] *S. pneumoniae* KU197.
[b] NT, not tested.



Scheme 1. Synthesis of compound **11**. Reagents and conditions: (a) toluene, 60 °C (70%); (b) NaOMe (1.5 equiv), DMF, rt (73%).

chloroacetamide **9** in 70% yield. Compound **9** was treated with 2-mercaptobenzimidazole **10** in the presence of sodium methoxide to give the amide compound **11** in 73% yield.

Compound **16** was prepared as illustrated in Scheme 2. Commercially available 2-hydroxymethylbenzo[*d*]thiazole **12** reacted with phthalimide **13** under Mitsunobu reaction conditions to give the phthalimide derivative, which was converted to the amine **14** by using hydrazine in 46% yield (2 steps).[36,37] The resulting amine **14** reacted with chloroacetyl chloride **8** in toluene at 80 °C



Scheme 2. Synthesis of compound **16**. Reagents and conditions: (a) DEAD (2 equiv), Ph_3P (2 equiv), THF, rt; (b) $NH_2NH_2 \cdot H_2O$ (1.5 equiv), EtOH, reflux (46% for two steps); (c) toluene, 80 °C (68%); (d) NaOMe (1.5 equiv), DMF, rt (19%).

to give the chloroacetamide **15** in 68% yield. Compound **15** was treated with 2-mercaptobenzimidazole **10** in the presence of sodium methoxide to give the amide compound **16** in 19% yield.

The ureido compound **24** was prepared as illustrated in Scheme 3. Commercially available benzyl cyanomethylcarbamate **17** was allowed to react with a catalytic amount of sodium methoxide in MeOH, then converted to the amidine **18** by treatment with ammonium chloride in 97% yield (2 steps).[38] Compound **18** was coupled with bromoacetophenone **19** in the presence of potassium carbonate to give benzyl (4-phenyl-1*H*-imidazol-2-yl)methylcarbamate **20** in 29% yield.[39,40] Deprotection of the benzyloxycarbonyl group under a hydrogen atmosphere at room temperature in MeOH/HCl provided (4-phenyl-1*H*-imidazol-2-yl)methylamine hydrochloride **21** in 76% yield. The resulting methylamine hydrochloride **21** was allowed to react with crude imidazolide **23**, which was prepared from commercially available 2-amino-6-methylsulfonylbenzo[*d*]thiazole **22** and 1,1′-carbonyldiimidazole (CDI), to give the ureido derivative **24** in 33% yield. Other ureido compounds were also obtained according to the procedures illustrated in Scheme 3. Intermediates such as 6-substituted benzo[*d*]thiazoles and 5-substituted thiazoles were prepared according to standard procedures.[41–43]

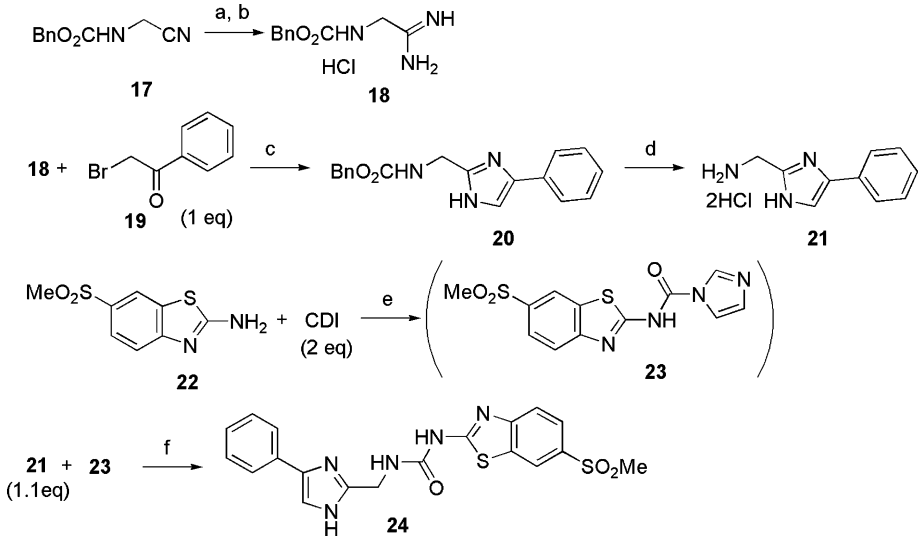
3. Biological methods

3.1. Preparation of *S. pneumoniae* FabK

The *fabK* genes were amplified by PCR from *S. pneumoniae* R6 and cloned into pET-21b(+) expression vector (Novagen). The resulting plasmid was transformed into *E. coli* BL21(DE3). The expression of FabK protein fused with His-tag at C-terminal was induced by 1 mM isopropyl β-D-thiogalactoside and the cells cultivated in LB broth were grown for a further 4 h before collecting by centrifugation. Purification of the His-tagged FabK protein was performed as above. Purified proteins were exchanged into 0.1 M sodium phosphate buffer, pH 7.0, by dialysis and stored at −80 °C until use.

3.2. Preparation of His-tagged FabI

The *fabI* gene from *E. coli* DH5α was amplified by PCR and cloned into pBAD/Myc-His B vector (Invitrogen). The resulting plasmid was transformed into *E. coli* TOP10. The expression of FabI protein fused with a His-tag was induced with 0.2% arabinose. The cell pellets were resuspended in lysis buffer (5 mM Tris–HCl, pH 8.0, 0.3 M NaCl, containing 1 mg/ml of lysozyme) and lysed by sonication. Cell lysates were applied to a Ni-NTA agarose column (QIAGEN), and eluted with 250 mM imidazole. The solvent was exchanged to 20 mM Tris–HCl, pH 7.5, 10 mM EDTA, pH 8.0, 1 mM DTT by dialysis and the purified protein was stored at −80 °C until use.



Scheme 3. Synthesis of compound **24**. Reagents and conditions: (a) NaOMe (0.1 equiv), MeOH, rt; (b) NH_4Cl (1 equiv), MeOH, rt (97% for two steps); (c) K_2CO_3 (1 equiv), DMF, rt (29%); (d) 10 wt% Pd/C (30 w/w%), H_2, MeOH, HClaq (76%); (e) THF, rt; (f) $^iPr_2NEt$ (2.2 equiv), THF, rt (33%).

3.3. Enzyme inhibition assay

Enzymatic activity of FabI and FabK was measured as the reduction of NADH and monitored the change in absorbance at 340 nm. Assays were performed in 96 half-area plates in a final assay volume of 100 μl. For FabI inhibition assay, reaction mixture consisted of 100 mM sodium phosphate (pH 7.4), 0.25 mM crotonoyl-CoA, 0.4 mM NADH, and 50 μg/ml of His-tagged *E. coli* FabI. For FabK inhibition assay, reaction was performed in 100 mM 2-(*N*-morpholino)ethanesulfonic acid (pH 7.0), 100 mM NH_4Cl, 0.2 mM crotonoyl-CoA, 0.4 mM NADH, and 2 μg/ml of purified FabK. The reaction was initiated by addition of the enzyme, and measured absorption at 340 nm for 10 min at room temperature. Concentration giving 50% reduction in the enzymatic activity was determined as IC_{50}.

3.4. MIC testing

Antibacterial activity was determined by the broth microdilution method according to the NCCLS document M7-A6. The minimum inhibitory concentration (MIC) was determined as the lowest concentration of the test compound that prevented the visible growth. *S. pneumoniae* KU197 (PRSP) and *S. pneumoniae* KU197 mutant with FabK (A141S)[30] were used routinely. Twenty-nine clinical isolates of *S. pneumoniae* were used for the MIC testing of compound **47**. They consisted of 11 strains of PRSP, 6 strains of PISP, and 12 strains of PSSP. While 5 out of 29 strains were sensitive to macrolides, remaining 24 strains were resistant to macrolides (ermB positive: 9 strains, mefA: 9 strains, mefA and ermB positive: 6 strains).

3.5. Cytotoxicity

Cytotoxicities of the test compounds were assessed by using human leukemia cells K562. K562 was maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum (Moregate Biotec). The assays were performed in 96-well microtiter plates (Greiner). The cells (5×10^3 cells/150 μl) were suspended in the appropriate assay medium and it was added to each well followed by the testing compounds. The cells were incubated with the drug for 2 days at 37 °C in the presence of 5% CO_2. On day 3, Cell Counting Kit-8 (Dojindo Lab.) was added to each well, and the suspension was reincubated for 4 h under the same conditions. Cell proliferaion was determined by recording the absorbance change at 450 nm. IC_{50} values were defined as the concentration of each test sample that reduced absorbance to 50% of vehicle-treated controls.

4. Results and discussion

Although several of the amide derivatives, including **5**, showed moderate FabK-inhibitory activity, they showed no antibacterial activity against *S. pneumoniae* in standard broth media (cation adjusted Mueller-Hinton broth supplemented with 2% lysed horse blood). Examination of the stability of the compound under the MIC measurement conditions by means of liquid chromatography-mass spectrometry indicated that compound **5** readily decomposed to **26** and **27**, which lack FabK-inhibitory activity (Fig. 2).

To improve the chemical stability of the amide bond, we prepared methylene amide **16**, carbamate **28**, and ureido type **29** derivatives. Compounds **16** and **28** did not show FabK-inhibitory or antibacterial activity, while **29** possessed weak FabK-inhibitory activity (IC_{50} = 6.9 μM). Moreover, compound **29** showed antibacterial activity against *S. pneumoniae*, probably due to its improved chemical stability in the MIC assay medium (MIC = 32 μg/ml). On the other hand, the oxime compound **6** possessing moderate FabK-inhibitory activity did not show any antibacterial activity, presumably due to its poor solubility (Table 1). Compounds **28** and **29** have been reported in our previous paper.[31]

We therefore selected an ureido group as a spacer. The SAR of benzothiazole derivatives is shown in Table 2.

Compounds **32** having a methoxy group at the 6-position of benzothiazole showed greater FabK-inhibitory activity than compound **29** (R^1 = H), while compounds **30** and **31** (R^1 = 4-OMe or 5-OMe) showed no FabK-inhibitory activity. These results indicate that some kind of functional group at the 6-position is essential to improve FabK-inhibitory activity. Next, the substituent effects at the 6-position on the FabK-inhibitory and antibacterial activities were examined. Compounds **33**–**36**, having various functional group at the 6-position of benzothiazole, showed increased FabK-inhibitory activity compared with compound **29**. In particular, compound **36** having a methylsulfonyl group showed good FabK-inhibitory activity (IC_{50} = 0.74 μM). Compounds **30**–**32**, **35**, and **36** have been reported in our previous paper.[31]

Introduction of other heterocyclic rings (compounds **37**, **38**, **39**, and **40**) instead of the benzimidazole ring did not improve either of the activities, but the phenylimidazole derivative (compound **24**) showed strong FabK-inhibitory activity (IC_{50} = 0.088 μM) and antibacterial activity (MIC = 0.5 μg/ml) (Table 3). Thus, we selected the phenylimidazole moiety as a basic structure. Since benzothiazole derivatives tended to show worse solubility in aqueous 5% DMSO, we examined other heterocycles instead of benzothiazoles and found that the substituted thiazoles could be employed (Table 4). Compounds **38**, **39**, and **24** have been reported in our previous paper.[31]

Compound **41**, having a phenyl group at the 5-position of thiazole, showed stronger FabK-inhibitory activity than compound **42** having a phenyl group at the 4-position. This result indicates that substitution at the 5-position is favorable for FabK-inhibitory activity. Next, the substituent effects at the 5-position were examined. Compounds **43**–**46**, having a thiophenyl or thiopyridyl group at the 5-position of thiazole, showed increased FabK-inhibitory activity. In particular, compound **44**, having a thiopyridyl group, showed strong FabK-inhibitory activity (IC_{50} = 0.042 μM) and potent antibacterial

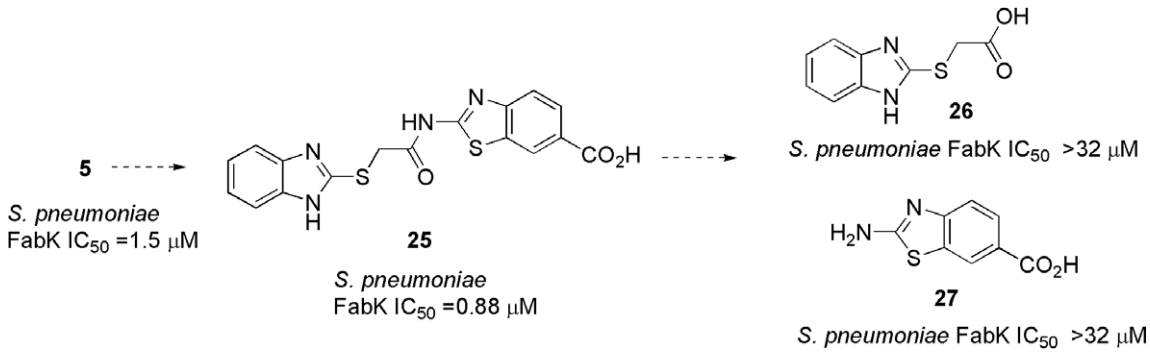
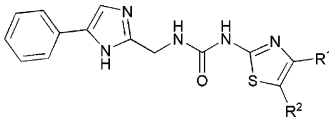
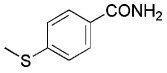
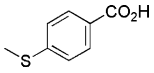


Figure 2. Expected compounds derived from compound **5**.

Table 4. Effects of substituted thiazoles on enzyme-inhibitory and antibacterial activities



Compound	R^1	R^2	FabK IC_{50} (μM) *S. pneumoniae*	MIC (μg/ml) *S. pneumoniae*[a]	Fabl IC_{50} (μM) *E. coli*
41	H	Ph	0.38 ± 0.02	4	>32
42	Ph	H	>32	NT[b]	>32
43	H		0.037 ± 0.006	2	>33
44	H		0.042 ± 0.005	2	>32
45	H		0.037 ± 0.004	2	>32
46	H		0.098 ± 0.015	8	>32

[a] *S. pneumoniae* KU197.
[b] NT, not tested.

activity against *S. pneumoniae* (MIC = 2 μg/ml) with better solubility in aqueous 5% DMSO, as compared with compound **43**.

We therefore selected the thiopyridyl group as a basic structure and the substituent effects of phenylimidazole derivatives were examined (Table 5).

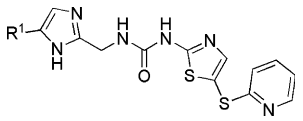
Compounds **47**–**49** having a halogen atom (chlorine or bromine) on the phenyl group of phenylimidazole showed excellent FabK-inhibitory activity (IC_{50} = 0.0024–0.0053 μM). In particular, compound **47** showed potent antibacterial activity against *S. pneumoniae* (MIC = 0.25 μg/ml).

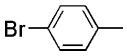
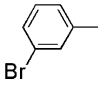
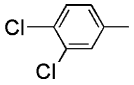
The antibacterial activity of compound **47** was evaluated for 29 clinical isolates of *S. pneumoniae*, including drug-resistant pathogens (11 PRSP strains, 6 penicillin-intermediate *S. pneumoniae* (PISP) strains, and 12 penicillin-susceptible (PSSP) strains). MIC_{50} and MIC_{90} of compound **47** were 1 and 4 μg/ml, respectively (MIC range of 0.125–4 μg/ml). Since compound **47** showed an elevated MIC value (>16-fold) against *S. pneunomiae* KU197 mutant, in which the alanine residue at position 141 of FabK is replaced by serine,[30] its mode of action is considered to involve inhibition of FabK. Moreover, compound **47** showed no significant cytotoxicity (IC_{50} > 20 μM in human erythroleukemia cells K562). These results indicate that FabK inhibitor **47** is a candidate antibacterial agent.

5. Conclusion

We have described the discovery of novel small-molecular inhibitors of bacterial enoyl-ACP reductase FabK. Through the SAR studies of our screening hits, we identified phenylimidazole derivatives as potent FabK-inhibitors. A representative compound **47** showed excellent FabK-inhibitory activity and potent in vitro antibacterial activity against *S. pneumoniae*. An elevated MIC value was observed with a FabK mutant of *S. pneumoniae*. Compound **47** showed no significant cytotoxicity. These results indicate that the phenylimidazole derivative **47** is a specific inhibitor of bacterial enoyl-ACP reductase FabK with antibacterial activity against *S. pneumoniae*, and we consider that it is an interesting candidate drug for the treatment of bacterial infections.

Table 5. Effects of phenylimidazole substitution on enzyme-inhibitory and antibacterial activities



Compound	R^1	FabK IC_{50} (μM) *S. pneumoniae*	MIC (μg/ml) *S. pneumoniae*[a]	FabI IC_{50} (μM) *E. coli*
44	Ph	0.042 ± 0.005	2	>32
47		0.0024 ± 0.0002	0.25	>32
48		0.0053 ± 0.0005	16	>32
49		0.0037 ± 0.0001	1	>32
Triclosan		>32	NT[b]	0.90 ± 0.36

[a] *S. pneumoniae* KU197.
[b] NT, not tested.

6. Experimental

6.1. Chemistry

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz or 125 MHz) spectra were recorded on a JEOL Lambda 400 spectrometer or BRUKER Avance 500 spectrometer. Chemical shifts were reported in δ value (ppm) with tetramethylsilane (TMS) as the internal standard (NMR peak designations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad peak). Mass spectra were recorded with a JEOL JMS-700 spectrometer. High-resolution mass spectra (HRMS) were obtained on a JMS-FABmate spectrometer. LC–MS analyses were performed using the following methods. Method A: Capcellpak C_{18} MG (Shiseido) 3 mm × 150 mm column; linear gradient from 10% to 90% CH_3CN in H_2O over 10 min (0.01% trifluoroacetic acid) at a flow rate 0.4 ml/min. Method B: Capcellpak C_{18} MGII (Shiseido) 3 mm × 150 mm column; linear gradient from 10% to 90% CH_3CN in H_2O over 10 min (5 mM ammonium acetate) at a flow rate 0.4 ml/min. Elemental analyses were performed by Toray Research Center, Inc. Melting points were recorded with a Yanako MICRO MELTINGPOINT APPARATUS. Column chromatography was performed with silica gel (Kanto Chemical: 60N spherical, neutral). Preparative thin layer chromatography (Preparative TLC) was performed with silica gel (Merck: TLC plates Silica gel 60 F254). All the reagents and solvents were from commercial suppliers, and were used without further purification.

6.1.1. *N*-(Benzo[*d*]thiazol-2-yl)-2-chloroacetamide (9).[31] To a solution of 2-amino-benzo[*d*]thiazole **7** (150 mg, 1 mmol) in toluene (3 ml) was added 2-chloroacetyl chloride **8** (112.9 mg, 1 mmol) and stirred at 60 °C for 6 h. It was allowed to cool to room temperature, then it was concentrated under reduced pressure. The residue was diluted with EtOH, then the solid was collected by suction filtration. The filter cake was washed with EtOH. Drying in high vacuum at 50 °C gave the title compound as a white solid (160 mg, 70%). ^{1}H NMR (DMSO-d_6): δ 8.01 (1H, dd, J = 8.0 Hz, J = 0.5 Hz), 7.78 (1H, d, J = 8.0 Hz), 7.46 (1H, dt, J = 8.0 Hz, J = 1.2 Hz), 7.34 (1H, dt, J = 8.1 Hz, J = 1.2 Hz), 4.48 (2H, s). ^{13}C NMR (DMSO-d_6): δ 165.9, 157.5, 148.3, 131.3, 126.2, 123.7, 121.8, 120.6, 42.4. HRMS calcd for $C_9H_7ClN_2OS$ (M+H) 227.0046, found 227.0041.

6.1.2. 2-(1*H*-Benz[*d*]imidazol-2-ylthio)-*N*-(benzo[*d*]thiazol-2-yl)acetamide (11).[31] To a solution of chloroacetamide **9** (113 mg, 0.5 mmol) in DMF (1 ml) was added 1*H*-benz[*d*]imidazole-2-thiol **10** (113 mg, 0.75 mmol), sodium methoxide (40.5 mg, 0.75 mmol) and stirred at room temperature for 24 h. The mixture was diluted with H_2O and CH_2Cl_2, then the solid was collected by suction filtration. The filter cake was washed with H_2O. Drying in high vacuum at 50 °C gave the title compound as a white solid (124.5 mg, 73%). ^{1}H NMR (DMSO-d_6): δ 7.97 (1H, m), 7.77 (1H, m), 7.50 (2H, dd, J = 5.9 Hz, J = 2.7 Hz), 7.45 (1H, m), 7.31 (1H, m), 7.20 (2H, dd, J = 6.1 Hz, J = 2.9 Hz), 4.49 (2H, s). ^{13}C NMR (DMSO-d_6): δ 167.2, 157.7, 149.4, 148.4, 138.0, 131.4, 126.1, 123.6, 122.3, 121.7, 120.6, 113.7, 35.2. HRMS calcd for $C_{16}H_{12}N_4OS_2$ (M+H) 341.0531, found 341.0529.

6.1.3. Benzo[*d*]thiazol-2-ylmethanamine (14). To a solution of 2-hydroxymethylbenzothiazole **12** (ACROS, 800 mg, 4.8 mmol) in THF (45 ml) was added triphenylphosphine (2.5 g, 9.7 mmol), phthalimide **13** (1.4 g, 9.7 mmol) and diethyl azodicarboxylate (1.7 g, 9.7 mmol) and stirred at room temperature for 7 h. The mixture was diluted with H_2O and EtOAc, then extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The

resulting residue was diluted with Et_2O and stirred at room temperature. The generated solid was collected by suction filtration. Drying in high vacuum at 50 °C gave 2-(benzo[*d*]thiazol-2-ylmethyl)isoindoline-1,3-dione as a white solid (953 mg). To a solution of 2-(benzo[*d*]-thiazol-2-ylmethyl)isoindoline-1,3-dione (936 mg, 3.18 mmol) in EtOH (30 ml) was added hydrazine monohydrate (2.39 g, 4.77 mmol) and stirred at reflux for 1.5 h. It was allowed to cool to room temperature, then the generated solid was collected by suction filtration and washed with $CHCl_3$. The filtrated solution was concentrated under reduced pressure, and the resulting residue diluted with H_2O, acidified with 1 N HClaq to pH 1.6. The water layer was washed with EtOAc, and turned into pH8 with 1 N NaOH aq, extracted with EtOAc, washed with H_2O, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The title compound was obtained as a white solid (361 mg, 46% in 2 steps). ^{1}H NMR ($CDCl_3$): δ 7.97 (1H, m), 7.89 (1H, m), 7.47 (1H, m), 7.37 (1H, m), 4.31 (2H, s). MS (FAB+): 165 (M+H).

6.1.4. *N*-(Benzo[*d*]thiazol-2-ylmethyl)2-chloroacetamide (15). To a solution of amine **14** (327 mg, 2 mmol) in toluene (20 ml) was added 2-chloroacetyl chloride **8** (247 mg, 2.19 mmol) and stirred at 80 °C for 2 h. It was allowed to cool to room temperature, then concentrated under reduced pressure. The resulting residue was purified by chromatography ($CHCl_3$/MeOH) to obtain the title compound as a white powder (325 mg, 68%). ^{1}H NMR ($CDCl_3$): δ 8.02 (1H, m), 7.88 (1H, m), 7.50 (1H, m), 7.41 (1H, m), 4.92 (2H, d, J = 5.6 Hz), 4.17 (2H, s). ^{13}C NMR ($CDCl_3$): δ 166.7, 166.2, 152.7, 135.2, 126.3, 125.5, 123.1, 121.8, 42.5, 42.0. MS (FAB+): 241 (M+H).

6.1.5. 2-(1*H*-Benz[*d*]imidazol-2-ylthio)-*N*-(benzo[*d*]thiazol-2-ylmethyl)acetamide (16). To a solution of chloroacetamide **15** (100 mg, 0.42 mmol) in DMF (3 ml) was added 1*H*-benz[*d*]imidazole-2-thiol **10** (93.6 mg, 0.62 mmol) and sodium methoxide (33.7 mg, 0.62 mmol) and the mixture was stirred at room temperature for 5 days. The mixture was diluted with H_2O and CH_2Cl_2, then extracted with CH_2Cl_2, washed with H_2O, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by chromatography ($CHCl_3$/MeOH) to obtain the title compound as a white powder (28.4 mg, 19%). ^{1}H NMR (DMSO-d_6): δ 12.62 (1H, br s), 9.31 (1H, t, J = 5.8 Hz), 7.94 (2H, m), 7.50 (2H, m), 7.39 (2H, m), 7.13 (2H, m), 4.71 (2H, d, J = 6.1 Hz), 4.17 (2H, s). ^{13}C NMR (DMSO-d_6): δ 170.8, 168.1, 152.7, 149.5, 143.5, 135.5, 134.6, 126.1, 125.0, 122.3, 122.1, 121.7, 121.2, 117.4, 110.4, 41.6, 34.8. MS (FAB+): 355 (M+H). HRMS calcd for $C_{17}H_{14}N_4OS_2$ (M+H) 355.0687, found 355.0682. Anal. Calcd for $C_{17}H_{14}N_4OS_2$: C, 57.6; H, 4.0; N, 15.8. Found: C, 57.5; H, 4.0; N, 15.8.

6.1.6. Benzyl 2-amino-2-iminoethylcarbamate hydrochloride (18).[31] To a solution of benzyl cyanomethylcarbamate **17** (Aldrich, 12 g, 63 mmol) in MeOH (240 ml) was added sodium methoxide (0.34 g, 6.3 mmol). The mixture was stirred at room temperature for overnight, then it was added ammonium chloride (3.4 g, 63 mmol). The mixture was stirred at room temperature for 2 more days, then it was cooled in ice-bath, added HCl/EtOAc, and stirred for 2 h more without ice-bath. The mixture was concentrated under reduced pressure, and the resulting solid was dissolved to Hexane/EtOAc = 1/1 (60 ml), stirred at room temperature for 20 min, then it was filtered to obtain the title compound (15 g, 97%) as a dark white powder. ^{1}H NMR (CD_3OD): δ 7.39–7.31 (5H, m), 5.14 (2H, s), 4.10 (2H, s). HRMS calcd for $C_{10}H_{13}N_3O_2$ (M+H) 208.1086, found 208.1084.

6.1.7. Benzyl (4-phenyl-1*H*-imidazol-2-yl)methylcarbamate (20).[31] To a solution of amidine hydrochloride **18** (3.0 g, 12 mmol) in DMF (90 ml) was added phenacylbromide **19** (2.5 g, 12 mmol) and potassium carbonate (1.7 g, 12 mmol). The mixture was stirred at room temperature for 2.5 h, then it was filtered and concentrated under reduced pressure. The resulting residue was dissolved to $CHCl_3$, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by chromatography ($CHCl_3$ to $CHCl_3$/MeOH = 20/1) to obtain the title compound as a brownish white solid (1.1 g, 29%). ^{1}H NMR ($CDCl_3$): δ 7.39–7.34 (8H, m), 7.24–7.22 (3H, m), 5.15 (2H, s), 4.43 (2H, d, J = 6.4 Hz). HRMS calcd for $C_{18}H_{17}N_3O_2$ (M+H) 308.1399, found 308.1394.

6.1.8. 2-Aminomethyl-4-phenyl-1*H*-imidazol hydrochloride (21).[31] To a solution of carbamate **20** (310 mg, 1.0 mmol) in MeOH/HCl (9.9 ml) was added 10 wt% Pd/C (92 mg, 30 wt%). The mixture was stirred at room temperature for 4 h under hydrogen atmosphere, then it was filtered through Celite and concentrated under reduced pressure to obtain the title compound (190 mg, 76%). ^{1}H NMR (CD_3OD): δ 7.70 (2H, d, J = 7.6 Hz), 7.44 (1H, s), 7.37 (2H, dd, J = 8.0 Hz, J = 7.6 Hz), 7.25 (1H, t, J = 7.6 Hz), 4.14 (2H, s). HRMS calcd for $C_{10}H_{11}N_3$ (M+H) 174.1031, found 174.1027.

6.1.9. 1-((4-Phenyl-1*H*-imidazol-2-yl)methyl)-3-(6-(methylsulfonyl)benzo[*d*]thiazol-2-yl)urea (24).[31] To a solution of *N*-(6-(methylsulfonyl)benzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide **23** (113 mg, 0.35 mmol) in THF (4 ml) was added (4-phenyl-1*H*-imidazol-2-yl)methylamine hydrochloride **21** (95 mg, 0.39 mmol) and *N*,*N*′-diisopropylethylamine (149 μl, 0.88 mmol). The mixture was stirred at room temperature for 3 days, then it was poured into brine, extracted with $CHCl_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by chromatography ($CHCl_3$/MeOH) to obtain the title compound. Recrystallization from MeOH afforded completely pure product as a white powder (50 mg, 33%). ^{1}H NMR (DMSO-d_6): δ 8.52–8.51 (1H, m), 7.86 (1H, dd, J = 8.0 Hz, J = 1.6 Hz), 7.80–7.74 (3H, m), 7.55 (1H, br s), 7.44–7.32 (3H, m), 7.19–7.15 (1H, m), 4.46 (2H, d, J = 5.4 Hz), 3.22 (3H, s), 3.17 (1H, d, J = 5.4 Hz). ^{13}C NMR (DMSO-d_6): δ 163.9, 153.9, 152.7, 145.0, 139.7, 134.7, 134.3, 132.0, 128.3, 125.9, 124.5, 124.0, 121.4, 119.6, 112.7, 44.0, 37.4. MS (ESI+): 428 (M+H). HRMS calcd for $C_{19}H_{17}N_5O_3S_2$ (M+H)

428.0851, found 428.0847. Anal. Calcd for $C_{19}H_{17}N_5O_3S_2 \cdot 0.5H_2O$: C, 52.3; H, 4.2; N, 16.0. Found: C, 52.3; H, 4.3; N, 15.8. Mp: 259 °C.

6.1.10. *N*-(Benzo[*d*]thiazol-2-yl)-2-(3-nitrobenzylideneaminoxy)acetamide (6). Purchased from SPECS.

6.1.11. (1*H*-Benz[*d*]imidazol-2-yl)methyl benzo[*d*]thiazol-2-ylcarbamate (28).[31] To a solution of *N*-(benzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide (20 mg, 0.082 mmol) in THF (0.6 ml) was added (1*H*-benz[*d*]imidazol-2-yl)methanol (12 mg, 0.082 mmol). The mixture was stirred at 40 °C for overnight, then it was poured into brine, extracted with $CHCl_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by Preparative TLC (hexane/acetone = 1/1) to obtain the title compound as a white powder (6.8 mg, 26%). ^{1}H NMR (CD_3OD): δ 7.82 (1H, d, J = 8.4 Hz), 7.67 (1H, d, J = 8.0 Hz), 7.59 (2H, dd, J = 5.6 Hz, J = 3.2 Hz), 7.39 (1H, dd, J = 8.4 Hz, J = 8.0 Hz), 7.29–7.25 (3H, m), 5.51 (2H, s). MS (FAB+): 325 (M+H). HRMS calcd for $C_{16}H_{12}N_4O_2S$ (M+H) 325.0759, found 325.0764.

6.1.12. 1-((1*H*-Benz[*d*]imidazol-2-yl)methyl)-3-(benzo[*d*]thiazol-2-yl)urea (29).[31] To a solution of *N*-(benzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide (32 mg, 0.13 mmol) in THF (0.9 ml) was added (1*H*-benz[*d*]imidazol-2-yl)methanamine hydrochloride (29 mg, 0.13 mmol) and *N*,*N*′-diisopropylethylamine (45 μl, 0.26 mmol). The mixture was stirred at room temperature for 1 h, then it was poured into brine, extracted with $CHCl_3$. The generated solid was filtered to obtain the title compound as a white powder (33 mg, 78%). ^{1}H NMR (CD_3OD): δ 7.78 (1H, d, J = 7.2 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.53 (2H, br), 7.38 (1H, dd, J = 8.8 Hz, J = 7.2 Hz), 7.25–7.20 (3H, m), 4.75 (2H, s). MS (ESI+): 324 (M+H). HRMS calcd for $C_{16}H_{13}N_5OS$ (M+H) 324.0919, found 324.0914.

6.1.13. 1-(4-Methoxybenzo[*d*]thiazol-2-yl)-3-((1*H*-benz[*d*]imidazol-2-yl)methyl)urea (30).[31] The title compound was obtained from *N*-(4-methoxybenzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (1*H*-benz[*d*]imidazol-2-yl)methanamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 12.42 (1H, br s), 11.01 (1H, br s), 7.52 (2H, m), 7.44 (1H, d, J = 7.3 Hz), 7.39 (2H, m), 7.17 (1H, m), 7.15 (1H, m), 6.94 (1H, d, J = 7.5 Hz), 4.61 (2H, d, J = 5.6 Hz), 3.89 (3H, s). ^{13}C NMR (DMF-d_6): δ 159.3, 155.2, 153.0, 152.5, 140.0, 134.2, 124.2, 122.1, 113.9, 113.8, 108.9, 59.5, 39.1. HRMS calcd for $C_{17}H_{15}N_5O_2S$ (M+H) 354.1025, found 354.1024.

6.1.14. 1-(5-Methoxybenzo[*d*]thiazol-2-yl)-3-((1*H*-benz[*d*]imidazol-2-yl)methyl)urea (31).[31] The title compound was obtained from *N*-(5-methoxybenzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (1*H*-benz[*d*]imidazol-2-yl)methanamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 7.72–7.70 (2H, m), 7.51 (2H, br), 7.18–7.14 (3H, m), 6.81 (1H, dd, J = 8.8 Hz, J = 2.4 Hz), 4.62 (2H, d, J = 5.6 Hz), 3.78 (3H, s). ^{13}C NMR (DMSO-d_6): δ 161.0, 158.5, 154.0, 152.2, 150.3, 123.0, 121.7, 121.5, 118.4, 111.5, 111.2, 103.7, 55.4, 38.0. HRMS calcd for $C_{17}H_{15}N_5O_2S$ (M+H) 354.1025, found 354.1019.

6.1.15. 1-(6-Methoxybenzo[*d*]thiazol-2-yl)-3-((1*H*-benz[*d*]imidazol-2-yl)methyl)urea (32).[31] The title compound was obtained from *N*-(6-methoxybenzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (1*H*-benz[*d*]imidazol-2-yl)methanamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 7.54–7.49 (5H, m), 7.15 (2H, dd, J = 6.1 Hz, 2.6 Hz), 6.95 (1H, dd, J = 8.9 Hz, J = 2.6 Hz), 4.62 (2H, d, J = 5.6 Hz), 3.78 (3H, s). ^{13}C NMR (DMSO-d_6): δ 157.8, 155.6, 154.1, 152.2, 143.1, 132.6, 121.6, 120.3, 114.7, 114.2, 104.9, 55.6, 38.0. HRMS calcd for $C_{17}H_{15}N_5O_2S$ (M+H) 354.1025, found 354.1019.

6.1.16. 1-(6-Methylbenzo[*d*]thiazol-2-yl)-3-((1*H*-benz[*d*]imidazol-2-yl)methyl)urea (33). The title compound was obtained from *N*-(6-methylbenzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (1*H*-benz[*d*]imidazol-2-yl)methanamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 12.37 (1H, br s), 10.92 (1H, br), 7.67 (1H, s), 7.56–7.47 (4H, m), 7.18–7.15 (3H, m), 4.62 (2H, d, J = 5.3 Hz), 2.38 (3H, s). ^{13}C NMR (DMSO-d_6): δ 158.9, 154.1, 152.2, 147.0, 143.0, 134.3, 132.0, 131.5, 127.0, 121.9, 121.14, 121.09, 119.3, 118.3, 111.2, 38.0, 20.9. MS (FAB+): 338 (M+H). HRMS calcd for $C_{17}H_{15}N_5OS$ (M+H) 338.1076, found 338.1080. Anal. Calcd for $C_{17}H_{15}N_5OS \cdot 0.25H_2O$: C, 59.7; H, 4.6; N, 20.5. Found: C, 59.4; H, 4.5; N, 20.8.

6.1.17. 1-(6-Fluorobenzo[*d*]thiazol-2-yl)-3-((1*H*-benz[*d*]imidazol-2-yl)methyl)urea (34). The title compound was obtained from *N*-(6-fluorobenzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (1*H*-benz[*d*]imidazol-2-yl)methanamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 12.38 (1H, br s), 11.03 (1H, br), 7.81 (1H, dd, J = 8.8 Hz, J = 2.7 Hz), 7.64 (1H, dd, J = 8.8 Hz, J = 4.7 Hz), 7.56 (1H, br) 7.51–7.45 (2H, m), 7.24–7.14 (3H, m), 4.62 (2H, d, J = 5.6 Hz). ^{13}C NMR (DMSO-d_6, 125 Hz): δ 159.6, 158.1 (d, J = 237 Hz), 153.9, 152.0, 145.7, 142.9, 134.2, 132.6 (d, J = 13 Hz), 121.8, 121.1, 120.6, 118.2, 113.5 (d, J = 24 Hz), 111.1, 107.8 (d, J = 27 Hz), 37.9. MS (FAB+): 342 (M+H). HRMS calcd for $C_{16}H_{12}FN_5OS$ (M+H) 342.0825, found 342.0828. Anal. Calcd for $C_{16}H_{12}FN_5OS \cdot 0.5H_2O$: C, 54.9; H, 3.7; N, 20.0. Found: C, 55.3; H, 3.7; N, 20.4.

6.1.18. 1-(6-Cyanobenzo[*d*]thiazol-2-yl)-3-((1*H*-benz[*d*]imidazol-2-yl)methyl)urea (35).[31] The title compound was obtained from *N*-(6-cyanobenzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (1*H*-benz[*d*]imidazol-2-yl)-methanamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR ($CDCl_3$/CD_3OD): δ 8.59 (1H, br s), 7.73 (1H, d, J = 8.3 Hz), 7.63 (1H, dd, J = 8.3 Hz, J = 1.5 Hz), 7.55 (2H, dd, J = 6.0 Hz, J = 3.2 Hz), 7.25 (2H, dd, J = 6.0 Hz, J = 3.2 Hz), 4.72 (2H, s). HRMS calcd for $C_{17}H_{12}N_6OS$ (M+H) 349.0872, found 349.0860.

6.1.19. 1-(6-(Methylsulfonyl)benzo[*d*]thiazol-2-yl)-3-((1*H*-benz[*d*]imidazol-2-yl)methyl)urea (36).[31] The title compound was obtained from *N*-(6-(methylsulfonyl) benzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (1*H*-benz[*d*]imidazol-2-yl)methanamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 8.50 (1H, s), 7.85 (1H, d, J = 8.4 Hz), 7.78 (1H, d, J = 8.4 Hz), 7.57 (2H, br), 7.46 (1H, br), 7.16 (2H, br), 4.64 (2H, d, J = 5.2 Hz), 3.22 (3H, s). ^{13}C NMR (DMSO-d_6): δ 163.7, 153.9, 152.6, 151.9, 142.9, 134.4, 134.2, 131.9, 124.6, 121.8, 121.5, 121.1, 119.7, 118.2, 111.2, 44.0, 38.0. HRMS calcd for $C_{17}H_{15}N_5O_3S_2$ (M+H) 402.0695, found 402.0691.

6.1.20. 1-(6-(Methylsulfonyl)benzo[*d*]thiazol-2-yl)-3-((5-(pyridin-2-yl)thiophen-2-yl)methyl)urea (37). The title compound was obtained from *N*-(6-(methylsulfonyl)-benzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (5-(pyridin-2-yl)thiophen-2-yl)methylamine according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 8.54 (1H, d, J = 1.7 Hz), 8.48 (1H, dd, J = 4.9 Hz, J = 1.7 Hz), 7.88–7.86 (2H, m), 7.82–7.79 (2H, m), 7.64 (1H, dd, J = 3.7 Hz, J = 1.2 Hz), 7.47 (1H, br), 7.24 (1H, m), 7.06 (1H, d, J = 3.7 Hz), 4.55 (2H, d, J = 5.8 Hz), 3.23 (3H, s). ^{13}C NMR (DMSO-d_6): δ 163.9, 153.8, 152.8, 151.8, 149.3, 144.8, 143.4, 137.0, 134.4, 132.1, 126.6, 124.8, 124.6, 122.2, 121.5, 119.8, 118.3, 44.1, 38.5. MS (FAB+): 445 (M+H). HRMS calcd for $C_{19}H_{16}N_4O_3S_3$ 445.0463, found 445.0461. Anal. Calcd for $C_{19}H_{16}N_4O_3S_3 \cdot H_2O$: C, 49.3; H, 3.9; N, 12.1. Found: C, 49.1; H, 3.5; N, 12.3.

6.1.21. 1-(6-(Methylsulfonyl)benzo[*d*]thiazol-2-yl)-3-(pyridin-3-yl)methyl)urea (38).[31] The title compound was obtained from *N*-(6-(methylsulfonyl)benzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (pyridin-3-yl)methylamine according to the similar procedure used to prepare **24**. ^{1}H NMR ($CDCl_3$/CD_3OD): δ 8.52–8.48 (2H, m), 8.35 (1H, d, J = 5.1 Hz), 7.90 (1H, m), 7.79–7.77 (2H, m), 7.36 (1H, m), 7.36 (1H, m), 4.53 (2H, d, J = 6.6 Hz), 3.11 (3H, s). ^{13}C NMR (DMSO-d_6): δ163.9, 154.1, 152.6, 148.8, 148.3, 135.2, 134.9, 134.5, 132.0, 124.7, 123.6, 121.6, 119.8, 44.1, 40.8. HRMS calcd for $C_{15}H_{14}N_4O_3S_2$ (M+H) 363.0586, found 363.0582.

6.1.22. 1-(6-(Methylsulfonyl)benzo[*d*]thiazol-2-yl)-3-(thiophen-2-yl)methyl)urea (39).[31] The title compound was obtained from *N*-(6-(methylsulfonyl)benzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (thiophen-2-yl)methylamine according to the similar procedure used to prepare **24**. ^{1}H NMR ($CDCl_3$/CD_3OD): δ 8.36 (1H, s), 7.90 (1H, m), 7.79–7.77 (1H, m), 7.27 (1H, d, J = 4.9 Hz), 7.05 (1H, m), 6.98 (1H, m), 4.68 (2H, s), 3.14 (3H, s). ^{13}C NMR (DMSO-d_6): δ 163.9, 153.8, 152.7, 142.1, 134.5, 132.0, 126.9, 125.8, 125.3, 124.7, 121.6, 119.8, 44.1, 38.1. HRMS calcd for $C_{14}H_{13}N_3O_3S_3$ (M+H) 368.0197, found 368.0190.

6.1.23. 1-(2-(1*H*-Imidazol-4-yl)ethyl)-3-(6-(methylsulfonyl)benzo[*d*]thiazol-2-yl)urea (40). The title compound was obtained from *N*-(6-(methylsulfonyl)benzo[*d*]thiazol-2-yl)-1*H*-imidazole-1-carboxamide and 2-(1*H*-imidazol-4-yl)ethylamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 11.88 (1H, br), 11.14 (1H, br), 8.52 (1H, d, J = 2.0 Hz), 7.86 (1H, dd, J = 8.5 Hz, J = 2.0 Hz), 7.78 (1H, d, J = 8.5 Hz), 7.57 (1H, br s), 6.90–6.86 (2H, m), 3.46–3.41 (2H, m), 3.22 (3H, s), 2.73–2.70 (2H, m). ^{13}C NMR (DMSO-d_6): δ 163.8, 153.6, 152.7, 134.8, 134.4, 132.0, 124.6, 121.5, 119.7, 44.1, 39.3, 27.2. MS (FAB+): 366 (M+H). HRMS calcd for $C_{14}H_{15}N_5O_3S_2$ (M+H) 366.0695, found 366.0693. LC–MS: Method A; t_R = 6.53 min, 366 (M+H), purity 100%, Method B; t_R = 7.35 min, 366 (M+H), purity 99.8%.

6.1.24. 1-((4-Phenyl-1*H*-imidazol-2-yl)methyl)-3-(5-phenylthiazol-2-yl)urea (41). The title compound was obtained from *N*-(5-phenylthiazol-2-yl)-1*H*-imidazole-1-carboxamide and (4-phenyl-1*H*-imidazol-2-yl)methylamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 12.08 (1H, br s), 10.69 (1H, br s) 7.75–7.73 (3H, m), 7.57–7.55 (3H, m), 7.41–7.32 (4H, m), 7.26 (1H, t, J = 7.1 Hz), 7.18 (1H, t, J = 7.1 Hz), 7.10 (1H, br), 4.42 (2H, d, J = 5.6 Hz). ^{13}C NMR (DMSO-d_6): δ 159.0, 153.6, 145.3, 139.6, 134.7, 133.6, 131.8, 129.5, 129.0, 128.3, 127.0, 125.8, 125.2, 124.1, 112.7, 37.3. MS (FAB+): 376 (M+H). HRMS calcd for $C_{20}H_{17}N_5OS$ 376.1232, found 376.1226. LC–MS: Method A; t_R = 9.07 min, 376 (M+H), purity 99.2%, Method B; t_R = 10.97 min, 376 (M+H), purity 98.8%. Mp: 221 °C.

6.1.25. 1-((4-Phenyl-1*H*-imidazol-2-yl)methyl)-3-(4-phenylthiazol-2-yl)urea (42). The title compound was obtained from *N*-(4-phenylthiazol-2-yl)-1*H*-imidazole-1-carboxamide and (4-phenyl-1*H*-imidazol-2-yl)methylamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 12.08 (1H, br s), 10.78 (1H, br s), 7.87 (2H, d, J = 7.3 Hz), 7.77 (2H, d, J = 7.3 Hz), 7.55 (1H, s), 7.47 (1H, s), 7.42–7.12 (6H, m), 4.42 (2H, d, J = 5.4 Hz). ^{13}C NMR (DMSO-d_6): δ 159.7, 153.8, 148.4, 145.3, 139.6, 134.7, 134.3, 128.5, 128.3, 127.5, 125.8, 125.4, 124.1, 112.7, 106.5, 37.2. MS (FAB+): 376 (M+H). HRMS calcd for $C_{20}H_{17}N_5OS$ (M+H) 376.1232, found 376.1237. LC–MS: Method A; t_R = 9.18 min, 376 (M+H), purity 99.1%, Method B; t_R = 11.23 min, 376 (M+H), purity 99.3%. Mp: 189 °C.

6.1.26. 1-((4-Phenyl-1*H*-imidazol-2-yl)methyl)-3-(5-(phenylthio)thiazol-2-yl)urea (43). The title compound was obtained from *N*-(5-(phenylthio)thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (4-phenyl-1*H*-imidazol-2-yl)methylamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 12.05 (1H, br), 10.97 (1H, br), 7.75 (2H, d, J = 7.6 Hz), 7.62 (1H, s), 7.53 (1H, s), 7.35–7.13 (8H, m), 4.40 (2H, d, J = 5.4 Hz). ^{13}C NMR (DMSO-d_6): δ 163.9, 153.6, 146.2, 145.1, 139.6, 137.5, 134.7, 129.2, 128.3, 126.3, 126.2, 125.8, 124.0, 115.1, 112.6, 37.2. MS (FAB+): 408 (M+H). HRMS calcd for $C_{20}H_{17}N_5OS_2$ (M+H) 408.0953, found 408.0954. LC–MS: Method A; t_R = 9.64 min, 408 (M+H), purity 99.0%, Method B; t_R = 11.77 min, 408 (M+H), purity 98.5%. Mp: 210 °C.

6.1.27. 1-((4-Phenyl-1*H*-imidazol-2-yl)methyl)-3-(5-(pyridin-2-ylthio)thiazol-2-yl)urea (44). The title compound was obtained from *N*-(5-(pyridin-2-ylthio)thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (4-phenyl-1*H*-imidazol-2-yl)methylamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR (DMSO-d_6): δ 8.41 (1H, m), 7.77–7.68 (3H, m), 7.64 (1H, s), 7.55 (1H, br), 7.36–7.32 (2H, m), 7.19–7.10 (3H, m), 7.03 (1H, dd, J = 8.0 Hz, J = 0.7 Hz), 4.41 (2H, d, J = 5.4 Hz). ^{13}C NMR (DMSO-d_6): δ 164.4, 160.0, 153.6, 149.6, 149.3, 146.8, 145.2, 137.6, 128.3, 125.9, 124.0, 120.6, 119.6, 115.5, 112.8, 112.6, 37.2. MS (FAB+): 409 (M+H). HRMS calcd for $C_{19}H_{16}N_6OS_2$ (M+H) 409.0905, found 409.0905. Anal. Calcd for $C_{19}H_{16}N_6OS_2 \cdot 0.25H_2O$: C, 55.3; H, 4.0; N, 20.4. Found: C, 55.4; H, 4.0; N, 20.6. Mp: 219 °C.

6.1.28. 4-(2-(3-((4-Phenyl-1*H*-imidazol-2-yl)methyl)ureido)thiazol-5-ylthio)benzamide (45). To a solution of 4-(2-(3-((4-phenyl-1*H*-imidazol-2-yl)methyl)ureido)thiazol-5-ylthio)benzoic acid **46** (24 mg, 0.053 mmol) in DMF (0.6 ml) was added WSC· HCl (20 mg, 0.11 mmol), 1-hydroxybenzotriazole (14 mg, 0.11 mmol,) and 28% NH_3aq (9.6 μl, 0.16 mmol) under ice cooling. The mixture was stirred at 0 °C for 6 h, then it was poured into water, extracted with $CHCl_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by Preparative TLC ($CHCl_3$/MeOH/NH_3aq = 5/1/0.1) to obtain the title compound as a white powder (12 mg, 51%). ^{1}H NMR ($CDCl_3$/CD_3OD): δ 7.76–7.71 (2H, m), 7.64 (2H, dd, J = 8.6 Hz, J = 1.2 Hz), 7.52 (1H, s), 7.40–7.36 (2H, m), 7.28–7.18 (4H, m), 4.50 (2H, s). MS (FAB+): 451 (M+H). HRMS calcd for $C_{21}H_{18}N_6O_2S_2$ (M+H) 451.1011, found 451.1003. LC–MS: Method A; t_R = 8.03 min, 451 (M+H), purity 100%, Method B; t_R = 9.38 min, 451 (M+H), purity 100%. Mp: 223 °C.

6.1.29. 4-(2-(3-((4-Phenyl-1*H*-imidazol-2-yl)methyl)ureido)thiazol-5-ylthio)benzoic acid (46). To a solution of 1-((4-phenyl-1*H*-imidazol-2-yl)methyl)-3-(5-(4-methoxycarbonylphenylthio)thiazol-2-yl)urea (47 mg, 0.10 mmol) in DMF (1.5 ml) was added 5 N-NaOHaq (200 μl, 1.0 mmol). The mixture was stirred at room temperature for 4 h, then it was acidified by HCl/EtOAc and concentrated under reduced pressure. The resulting solid was filtered and the filter cake was washed with H_2O to obtain the title compound as a white solid (29 mg, 64%). ^{1}H NMR(DMSO-d_6): δ 7.85 (2H, dd, J = 8.3 Hz, J = 1.2 Hz), 7.73 (2H, d, J = 8.0 Hz), 7.67 (1H, m), 7.49–7.48 (2H, m), 7.35–7.31 (2H, m), 7.21–7.15 (4H, m), 4.40 (2H, d, J = 5.4 Hz). ^{13}C NMR (CD_3OD/$CDCl_3$): δ 171.6, 165.3, 155.1, 146.2, 146.1, 143.1, 137.9, 132.4, 132.0, 130.4, 129.0, 127.4, 125.9, 125.0, 116.9, 116.6, 37.3. MS (ESI+): 452 (M+H). HRMS calcd for $C_{21}H_{17}N_5O_3S_2$ (M+H) 452.0851, found 452.0849. LC–MS: Method A; t_R = 8.71 min, 452 (M+H), purity 99.2%, Method B; t_R = 8.07 min, 452 (M+H), purity 98.3%.

6.1.30. 1-((4-(4-Bromophenyl)-1*H*-imidazol-2-yl)methyl)-3-(5-(pyridin-2-ylthio)thiazol-2-yl)urea (47). To a solution of *N*-(5-(pyridin-2-ylthio)thiazol-2-yl)-1*H*-imidazole-1-carboxamide (30 mg, 0.10 mmol) in THF (1 ml) was added (4-(4-bromophenyl)-1*H*-imidazol-2-yl)methylamine hydrochloride (36 mg, 0.11 mmol) and *N*,*N*′-diisopropylethylamine (37 μl, 0.22 mmol). The mixture was stirred at room temperature for overnight, then it was poured into brine, extracted with $CHCl_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting solid was filtered and the filter cake was washed with $CHCl_3$/MeOH to obtain the title compound as a white powder (17 mg, 34%). Recrystallization from $CHCl_3$/MeOH afforded completely pure compound. H NMR ($CDCl_3$/CD_3OD): δ 8.38–8.36 (1H, m), 7.58–7.49 (6H, m), 7.23 (1H, s), 7.09 (1H, ddd, J = 8.2 Hz, J = 7.6 Hz, J = 0.6 Hz), 7.01 (1H, dd, J = 8.2 Hz, J = 0.6 Hz), 4.47 (2H, s). ^{13}C NMR (DMSO-d_6): δ 164.4, 160.0, 153.7, 149.3, 146.8, 145.5, 138.5, 137.6, 134.0, 131.2, 126.0, 120.6, 119.6, 118.5, 113.3, 112.8, 37.2. MS (FAB+): 487 (M+H). HRMS calcd for $C_{19}H_{15}BrN_6OS_2$ (M+H) 487.0010, found 487.0017. Anal. Calcd for $C_{19}H_{15}BrN_6OS_2$: C, 46.8; H, 3.1; N, 17.2. Found: C, 46.6; H, 3.2; N, 16.8. Mp: 246 °C.

6.1.31. 1-((4-(3-Bromophenyl)-1*H*-imidazol-2-yl)methyl)-3-(5-(pyridin-2-ylthio)thiazol-2-yl)urea (48). The title compound was obtained from *N*-(5-(pyridin-2-ylthio)thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (4-(3-bromophenyl)-1*H*-imidazol-2-yl)methylamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR ($CDCl_3$/CD_3OD): δ 8.39–8.37 (1H, m), 7.82 (1H, br s), 7.58–7.52 (3H, m), 7.39–7.37 (1H, m), 7.27–7.23 (2H, m), 7.08–7.06 (1H, m), 7.00 (1H, d, J = 8.3 Hz), 4.46 (2H, s). ^{13}C NMR (DMSO-d_6): δ 164.6, 160.1, 153.9, 149.5, 146.9, 145.8, 138.2, 137.8, 137.3, 130.7, 128.6, 126.6, 123.0, 122.1, 120.8, 119.8, 114.0, 113.0, 37.4. MS (FAB+): 487 (M+H). HRMS calcd for $C_{19}H_{15}BrN_6OS_2$ (M+H) 487.0010, found 487.019. Anal. Calcd for $C_{19}H_{15}BrN_6OS_2 \cdot 0.1H_2O$: C, 46.7; H, 3.1; N, 17.2. Found: C, 46.3; H, 3.3; N, 17.6. Mp: 233 °C.

6.1.32. 1-((4-(3,4-Dichlorophenyl)-1*H*-imidazol-2-yl)methyl)-3-(5-(pyridin-2-ylthio)thiazol-2-yl) urea (49). The title compound was obtained from *N*-(5-(pyridin-2-ylthio)thiazol-2-yl)-1*H*-imidazole-1-carboxamide and (4-(3,4-dichlorophenyl)-1*H*-imidazol-2-yl)methylamine hydrochloride according to the similar procedure used to prepare **24**. ^{1}H NMR ($CDCl_3$/CD_3OD): δ 8.39–8.37 (1H, m), 7.77 (1H, m), 7.57–7.43 (4H, m), 7.24 (1H, s), 7.07 (1H, dd, J = 7.3 Hz, J = 4.9 Hz), 7.00 (1H, d, J = 8.1 Hz), 4.46 (2H, s). ^{13}C NMR (DMSO-*d*6, 125 MHz): δ 164.8, 160.1, 154.1, 149.4, 146.8, 146.0, 137.7, 137.3, 135.6, 131.3, 130.7, 127.8, 125.6, 124.2, 120.7, 119.8, 114.5, 112.8, 37.3. MS (FAB+): 477 (M+H). HRMS calcd for $C_{19}H_{14}Cl_2N_6OS_2$ (M+H) 477.0126, found 477.0126. LC–MS: Method A; t_R = 9.38 min, 477 (M+H), purity 97.2%, Method B; t_R = 11.65 min, 477 (M+H), purity 97.9%. Mp: 246 °C.

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