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Synthesis of New 6-(4-Fluorophenyl)-5-(2-substituted pyrimidin-4-yl)imidazo[2,1-*b*] thiazole Derivatives and their Antiproliferative Activity against Melanoma Cell Line

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Synthesis of a new series of pyrimidinyl-imidazo[2,1-*b*]thiazole derivatives is described. Their antiproliferative activity against A375 human melanoma cell line was tested and the effect of substituents on the pyrimidinyl ring side chain was investigated. The biological results indicated that most of the newly synthesized compounds showed moderate activity against A375, compared with Sorafenib. Among all of these derivatives, the cyclic sulfamide derivatives **IIIa**, **IIIb**, and **IIIe** showed the most potent antiproliferative activity against A375 human melanoma cell line. The IC_{50} values of compounds **IIIa**,**b** were in nanomolar scale. In addition, compound **IIIe** (IC_{50} = 1.9 μM) also demonstrated more potent antiproliferative activity compared with Sorafenib (IC_{50} = 5.6 μM).

Key Words: Antiproliferative activity, Imidazo[2,1-*b*]thiazole, Cyclic sulfamide, A375, Melanoma

Introduction

Much interest has been focused on the chemistry and the biological activity of imidazo[2,1-*b*]thiazole derivatives. Imidazo [2,1-*b*]thiazoles have been reported in the literature as antibacterial,[1] antifungal,[2] anthelmintic,[3,4] and antitumor[5-9] agents. In addition, imidazo[2,1-*b*]thiazole derivatives demonstrated good antiproliferative activity against a variety of human cancer cell lines.[10-14]

Recently, some pyrimidinyl substituted imidazo[2,1-*b*]thiazole derivatives have been reported as RAF kinases inhibitors.[15] It is well known that inhibitors of RAF kinases, such as Sorafenib, have demonstrated antiproliferative activity against different cancer types, such as melanoma.[16]

Melanoma is the most aggressive form of skin cancer and is the fastest growing cancer in the United States.[17,18] Early stage melanoma can be cured surgically. However, melanoma metastasizing to major organs (stage IV) is virtually incurable.[18] Patients with advanced melanoma have a median survival time of less than one year, and the estimated 5-years survival rate is less than 15%.[17,19] With the incidence of melanoma rapidly rising in the United States and other developed countries, there is an urgent need to develop more effective drugs.[20-22]

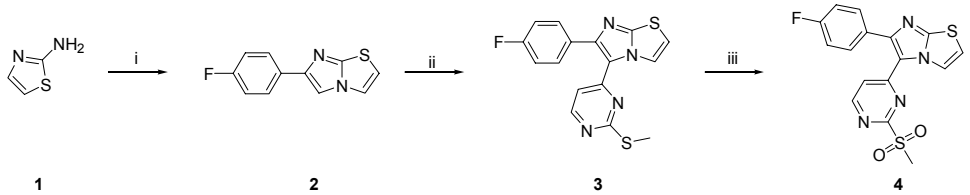
In the present investigation, we synthesized a new series of compounds possessing pyrimidinyl substituted imidazo[2,1-*b*] thiazole scaffold. We tested their antiproliferative activity against A375 human melanoma cell line. The synthetic and screening protocols are discussed in details.

Results and Discussion

Chemistry. For preparation of the target compounds, it was important at the beginning to synthesize the key intermediate compound **4**. It was successfully synthesized as illustrated in Scheme 1. Upon refluxing 2-aminothiazole (**1**) with α-bromo-4-fluoroacetophenone, cyclization to 6-(4-fluorophenyl)imidazo [2,1-*b*]thiazole (**2**) occurred.[23] Heating **2** with 4-iodo-2-(methylthio)pyrimidine in the presence of $Pd(OAc)_2$, Cs_2CO_3, and PPh_3 afforded the corresponding methylthiopyrimidinyl compound **3**. Oxidation of the sulfide moiety of **3** using oxone gave the corresponding sulfonyl compound **4**.

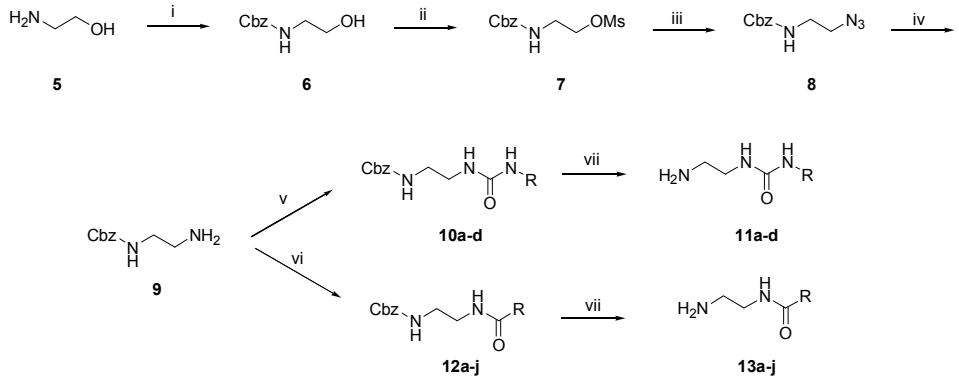
Besides the key intermediate compound **4**, we had to prepare the reagents required for introduction of the side chain of the target compounds. These reagents were prepared according to the sequences of reactions illustrated in Schemes 2 and 3.

Interaction of 2-aminoethanol (**5**) with benzyl chloroformate in the presence of TEA produced the *N*-Boc protected compound **6**.[24] Treatment of **6** with methanesulfonyl chloride in the presence of TEA afforded the corresponding mesyl compound **7**.[25] Replacement of the OMs moiety of **7** with azido group was

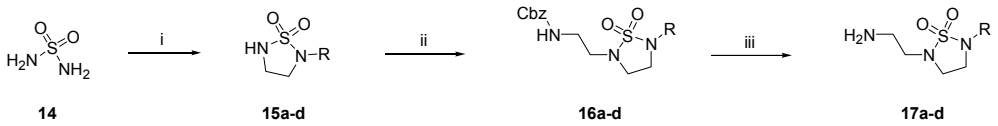


1 2 3 4

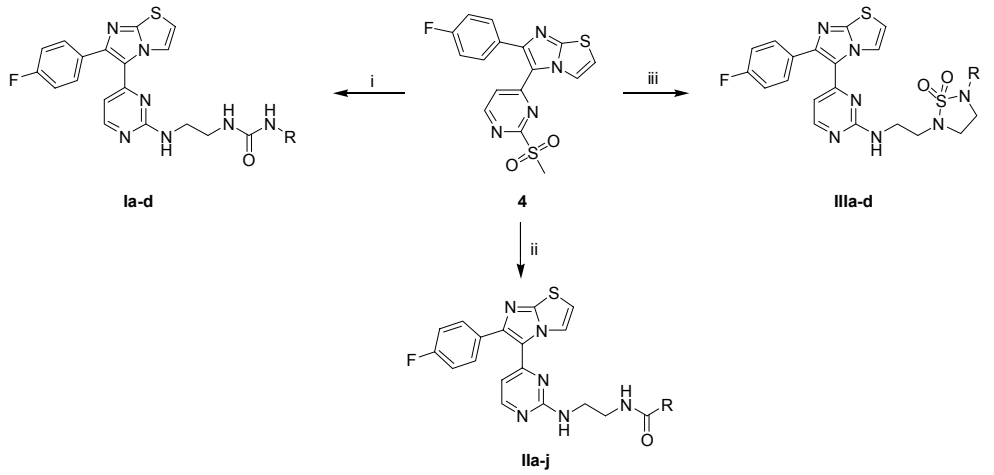
Scheme 1. Reagents and conditions: i) α-bromo-4-fluoroacetophenone, EtOH, reflux, 16 h; ii) 4-iodo-2-(methylthio)pyrimidine, $Pd(OAc)_2$, Cs_2CO_3, PPh_3, DMF, 80 °C, 12 h; iii) oxone, MeOH, H_2O, rt, 16 h



Scheme 2. Reagents and conditions: i) benzyloxycarbonyl chloride, TEA, CH_2Cl_2, 0 °C; ii) methanesulfonyl chloride, TEA, CH_2Cl_2, 0 °C; iii) NaN_3, DMSO, 70 °C, 2 h; iv) PPh_3, MeOH, H_2O, reflux, 2 h; v) appropriate isocyanate, THF, rt, 2 h; vi) appropriate carboxylic acid, HOBt, EDCI, TEA, DMF, 80 °C, 8 h; vii) H_2/Pd-C, MeOH, rt, 1 h



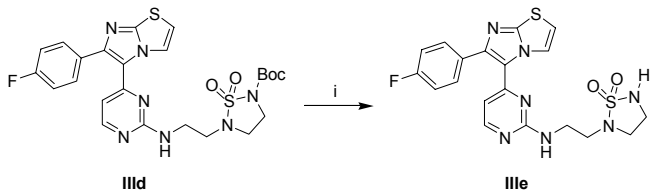
Scheme 3. Reagent and conditions: i) appropriate ethylenediamine, C_5H_5N, reflux, 3 h; ii) **7**, NaH (60%), DMF; iii) H_2/ Pd-C, MeOH, rt, 1 h



Scheme 4. Reagents and conditions: i) **11a-d**, DIPEA, DMSO, 80 °C, 8 h; ii) **13a-j**, DIPEA, DMSO, 80 °C, 8 h; iii) **17a-d**, DIPEA, DMSO, 80 °C, 8 h

carried out by reaction with sodium azide. Reduction of the azido group of **8** using PPh_3/H_2O afforded the corresponding amino compound **9**, which was subsequently treated with the appropriate isocyanates to produce the corresponding urea derivatives **10a-d**. Moreover, the amide derivatives **12a-j** were obtained by condensation of **9** with the appropriate carboxylic acid derivatives using HOBt/EDCI/TEA. Deprotection of compounds **10a-d** and **12a-j** using H_2/Pd-C afforded the corresponding amino compounds **11a-d** and **13a-j**, respectively (Scheme 2).

The cyclic sulfamide reagents were prepared by the sequence of reactions illustrated in Scheme 3. Refluxing sulfamide (**14**) with the appropriate ethylenediamine derivatives in pyridine gave the cyclized products **15a-d**.[26] Treatment of compounds **15a-d** with compound **7** afforded the corresponding Cbz-protected compounds **16a-d**. Deprotection of amino group of **16a-d** using H_2/Pd-C produced the desired *N*-(2-aminoethyl) cyclic sulfamide reagents **17a-d** (Scheme 3).



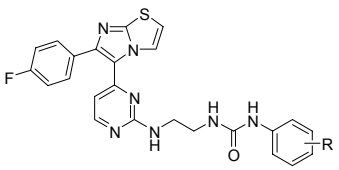
Scheme 5. Reagents and conditions: i) trifluoroacetic acid, CH_2Cl_2, 0 °C, 2 h

Heating compound **4** with the previously prepared reagents **11a-d**, **13a-j**, or **17a-d** in the presence of DIPEA produced the target compounds **Ia-d**, **IIa-j**, and **IIIa-d**, respectively (Scheme 4).

Compound **IIIe** (R = H) was prepared by deprotection of the *N*-Boc protected compound **IIId** using trifluoroacetic acid (Scheme 5).

***In vitro* activity.** The antiproliferative activity of the newly

Table 1. Antiproliferative activity of urea derivatives **Ia-d** against A375P cell line

Structure	Comp. No.	R	IC_{50} (μM)
	**Ia**	H	9.3
	Ib	3-OCH_3	7.8
	Ic	3-CF_3	> 10
	Id	3,5-bis(CF_3)	9.1
Sorafenib			5.6

synthesized compounds against A375P human melanoma cell line was examined. The ability of these compounds to inhibit the growth of A375 cell line is summarized in Tables 1-3. Sorafenib was selected as a reference standard, because it has been extensively used in clinical trials for melanoma.[20,27]

As listed in Tables 1-3, most of the compounds showed moderate activity, while compounds **IIIa**, **IIIb**, and **IIIe** exhibited the most potent antiproliferative activity against A375P human melanoma cell line, compared with Sorafenib. The IC_{50} values for compounds **IIIa** and **IIIb** were in nanomolar scale (0.60 μM and 0.38 μM, respectively), while the IC_{50} value for compound **IIIe** was in micromolar scale (1.9 μM) but still more potent than Sorafenib (IC_{50} = 5.6 μM).

The compounds listed in Table 3 were more potent than those in Tables 1 and 2. This suggests that the cyclic sulfamide moiety is more appropriate for activity, compared with urea and amide moieties. The constrained conformation of the 5-membered sulfamide ring may contribute to appropriate drug-receptor interaction, compared with flexible urea and amide moieties. In addition, the increased bulkness and lipophilicity produced by the ethylene moiety of the 5-membered ring may play a role in appropriate drug-receptor interaction.

Upon comparing the activities of compounds **Ia** and **Ib**, we find that introduction of an electron-donating group, methoxy group, at *m*-position of the terminal phenyl ring enhanced the activity. This may be attributed to the steric and/or electronic effects of methoxy group. In addition, compound **Ib** with *m*-methoxyphenyl moiety was more potent than compound **Ic** possessing *m*-(trifluoromethyl)phenyl moiety. So *m*-methoxyphenyl moiety was optimal for antiproliferative activity of the newly synthesized urea derivatives.

By comparing the activities of derivatives substituted with urea and amide moieties at the side chain as a linker, it was found that derivatives with urea moieties (**Ia**, **Ib**, and **Id**) were more potent than those with amide moieties (**IIa**, **IId**, and **IIh**). These results were seemed to indicate the effect of the linker on the activity.

Upon investigating the activities of cyclic sulfamide derivatives, we find that the potencies of compounds **IIIe**, **IIIa**, and **IIIb** possessing unsubstituted NH, *N*-methyl, and *N*-ethyl moieties, respectively, were in an increasing order. So introduction of alkyl groups on the terminal NH group of **IIIe** enhanced the activity. The longer the alkyl group (ethyl group, **IIIb**), the higher the potency than methyl group (**IIIa**). On the other hand, introduction of bulkier groups, benzyl or Boc (compounds **IIIc** and **IIId**, respectively) diminished the activity, compared with unsubstituted derivative **IIIe**. This increased bulkness may hinder the appropriate drug-receptor interaction.

Table 2. Antiproliferative activity of amide derivatives **IIa-j** against A375P cell line

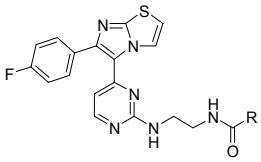
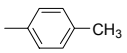
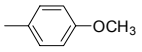
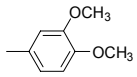
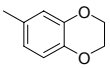
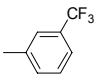
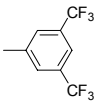
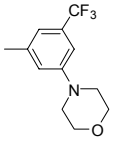
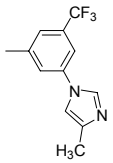
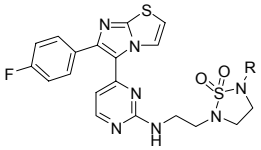
Structure	Comp. No.	R	IC_{50} (μM)
	**IIa**		> 10
	IIb		> 10
	IIc		> 10
	IId		9.7
	IIe		10
	IIf		10
	IIg		> 10
	IIh		> 10
	IIi		> 10
	IIj		> 10
Sorafenib			5.6

Table 3. Antiproliferative activity of sulfamide derivatives **IIIa-e** against A375P cell line

Structure	Comp. No.	R	IC_{50} (μM)
	**IIIa**	CH_3	0.6
	IIIb	C_2H_5	0.38
	IIIc	Bn	> 10
	IIId	Boc	7.1
	IIIe	H	1.9
Sorafenib			5.6

Conclusion

A series of pyrimidinyl-imidazo[2,1-*b*]thiazole derivatives was synthesized based on our previous literature studies. Their antiproliferative activity against A375 human melanoma cell line was tested. Most of the newly synthesized compounds exhibited moderate antiproliferative activity against A375. Among all of these derivatives, the cyclic sulfamide derivatives **IIIa**, **IIIb**, and **IIIe** showed the most potent antiproliferative activity against A375 human melanoma cell line. The IC_{50} values of compounds **IIIa**,**b** were in nanomolar scale. In addition, compound **IIIe** showed more potent antiproliferative activity than Sorafenib but in micromolar scale. Further modification of these compounds in order to improve their potency is currently in progress. Our ultimate goal is to identify several compounds that are highly potent against melanoma cells.

Experimental Section

All melting points were obtained on a Walden Precision Apparatus Electrothermal 9300 apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy was performed using either a Bruker ARX-300, 300 MHz spectrometer or a Bruker ARX-400, 400 MHz spectrometer (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. Unless otherwise noted, all solvents and reagents were commercially available and used without further purification.

6-(4-Fluorophenyl)imidazo[2,1-*b*]thiazole (2). A solution of 2-aminothiazole (2.37 g, 23 mmol) and α-bromo-4-fluoroacetophenone (5.0 g, 23 mmol) in ethanol (60 mL) was heated under reflux for 16 h. The mixture was concentrated to 30 mL under reduced pressure. Ice water (40 mL) was added to the remaning solution, then 30% ammonium hydroxide solution was added. The formed orange coloured solid was filtered, washed with water, and dried overnight under vacuum at 50 °C. 4.3 g of the title compound was obtained (yield 86%). mp 132 - 133 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.00-7.60 (m, 3H), 7.38 (bs, 1H), 7.08 (bs, 1H), 6.79 (bs, 1H).

6-(4-Fluorophenyl)-5-(2-(methylthio)pyrimidin-4-yl)imidazo[2,1-*b*]thiazole (3). A mixture of compound **2** (6.0 g, 27.6 mmol), 4-iodo-2-(methylthio)pyrimidine (10.4 g, 41.3 mmol), cesium carbonate (13.4 g, 41.3 mmol), palladium acetate (1.22 g, 5.5 mmol), and triphenylphosphine (2.896 g, 11.04 mmol) in anhydrous DMF (60 mL) was stirred at 80 °C for 12 h. The mixture was cooled to room temperature and separated between ethyl acetate (150 mL) and water (200 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layer extracts were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The organic solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography. The purified title product was obtained as white solid (3.5 g, 37%). mp 151 - 152 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.61 (d, 1H, J = 4.4 Hz), 8.24 (d, 1H, J = 5.4 Hz), 7.66-7.58 (m, 2H), 7.20-7.12 (m, 2H), 7.00 (d, 1H, J = 4.6 Hz), 6.86 (d, 2H, J = 5.4 Hz), 2.64 (s, 3H).

6-(4-Fluorophenyl)-5-(2-(methylsulfonyl)pyrimidin-4-yl) imidazo[2,1-b]thiazole (4). To a solution of compound **3** (2.05 g, 6 mmol) in methanol (250 mL), a solution of oxone (12.3 g, 18 mmol) in water (50 mL) was added. The mixture was stirred at room temperature for 16 h. The organic solvent was evaporated under reduced pressure and the remaining aqueous solution was extracted with CH_2Cl_2 (50 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The organic solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography. 2.1 g of the title compound was obtained, yield 98%. mp 197 - 198 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.90-8.84 (m, 1H), 8.53 (bd, 1H, J = 18.0 Hz), 7.68-7.58 (m, 2H), 7.38-7.30 (m, 1H), 7.26-7.16 (m, 2H), 7.12-7.08 (m, 1H), 3.38 (s, 3H).

Benzyl 2-hydroxyethylcarbamate (6). To a stirred solution of 2-Aminoethanol (**5**, 4.94 mL, 81.86 mmol) in CH_2Cl_2 (50 mL) at 0 °C, TEA (22.2 mL, 159.6 mmol) was added dropwise. Benzyloxycarbonyl chloride (15.2 mL, 106.42 mmol) was added dropwise over 30 min. After completion of the addition, the mixture was stirred at 0 °C for 1 h. The mixture was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography. The desired product was obtained as white solid (9.5 g, 59%). mp 73 - 75 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.33 (s, 5H), 5.19 (bs, 1H), 5.10 (s, 2H), 3.71 (s, 2H), 3.35 (q, 2H, J = 5.0 Hz).

2-(Benzyloxycarbonylamino)ethyl methanesulfonate (7). To a stirred solution of compound **6** (29.7 g, 152 mmol) in CH_2Cl_2 (300 mL) at 0 °C, TEA (31.58 mL, 227 mmol) was added dropwise. Methanesulfonyl chloride (14.1 mL, 182 mmol) was then added dropwise to the reaction mixture over 30 min. After completion of the addition, the mixture was stirred at 0 °C for 1 h. The mixture was quenched with water (300 mL) and extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography. The desired product was obtained (22 g, 53%). mp 70 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.35 (s, 5H), 5.24 (bs, 1H), 5.11 (s, 2H), 4.28 (t, 2H, J = 4.98 Hz), 3.53 (q, 2H, J = 5.3 Hz), 2.98 (s, 3H).

Benzyl 2-azidoethylcarbamate (8). A mixture of sodium azide (4.75 g, 73.2 mmol) and compound **7** (5.0 g, 18.3 mmol) in DMSO (50 mL) was stirred at 70 °C for 2 h. The mixture was allowed to cool to room temperature, quenched with water (200 mL), and then extracted with ethyl acetate (3 × 200 mL). The combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The title product was obtained as a colorless oil (3.8 g, 94%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.34 (s, 5H), 5.11 (s, 2H), 3.41 (d, 2H, J = 6.0 Hz), 3.35 (t, 2H, J = 4.5 Hz).

Benzyl 2-aminoethylcarbamate (9). Triphenylphosphine (6.7 g, 25.56 mmol) and water (15 mL) were added to a solution of compound **8** (3.8 g, 17.4 mmol) in MeOH (40 mL). The mixture was heated under reflux for 2 h. The mixture was concentrated under reduced pressure and purified by column chromatography. The target product was obtained as light brown

oil (3 g, 90%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, 5H), 5.42 (bs, 1H), 5.09 (s, 2H), 3.21 (q, 2H, *J* = 6.0 Hz), 2.78 (t, 2H, *J* = 6.0 Hz).

Benzyl 2-(3-phenylureido)ethylcarbamate (10a). A solution of compound **9** (0.15 g, 0.772 mmol) and phenyl isocyanate (0.17 g, 0.926 mmol) in THF (5 mL) was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography. The desired product was obtained as white solid (0.2 g, 51%). mp 124 - 125 °C; ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.70 (t, 1H, *J* = 3.0 Hz), 7.34-7.20 (m, 7H), 5.06 (d, 2H, *J* = 6.0 Hz), 3.37-3.26 (m, 4H).

Synthesis of compounds **10b-d** was carried out by the same procedure as described for preparation of **10a**.

10b: Yield: 60%; mp 138 - 139 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, 5H), 7.18-7.14 (m, 1H), 6.99 (s, 1H), 6.78 (d, 1H, *J* = 9.0 Hz), 6.62 (dd, 1H, *J* = 2.4 and 2.4 Hz), 6.56 (bs, 1H), 5.27 (d, 1H, *J* = 14.1 Hz), 5.08 (s, 2H), 3.78 (s, 3H), 3.40-3.32 (m, 4H).

10c: Yield: 87%; mp 108 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.62 (s, 2H), 7.45 (d, 1H, *J* = 9.0 Hz), 7.26 (s, 5H), 5.72 (s, 1H), 5.49 (s, 1H), 5.12 (s, 1H), 5.06 (s, 2H), 3.38-3.29 (m, 4H).

10d: Yield: 75%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.84 (s, 2H), 7.45 (s, 1H), 7.26 (s, 5H), 5.74 (bs, 1H), 5.45 (bs, 1H), 5.08 (s, 2H), 3.34-3.27 (m, 4H).

1-(2-Aminoethyl)-3-phenylurea (11a). Pd/C (0.05 g) was added to a solution of compound **10a** (0.2 g, 0.52 mmol) in MeOH (10 mL). The mixture was stirred under hydrogen atmosphere at room temperature for 1 h. Pd/C was removed by celite filter, and the filtrate was evaporated under reduced pressure. 0.08 g of the title product was obtained and used in the next step without further purification (yield 85.8%).

Synthesis of compounds **11b-d** was carried out by the same procedure as described for preparation of **11a**.

Benzyl 2-benzamidoethylcarbamate (12a). A mixture of compound **9** (0.15 g, 0.772 mmol), HOBt (0.23 g, 1.70 mmol), EDCI (0.37 g, 1.93 mmol), benzoic acid (0.19 g, 1.54 mmol), and TEA (0.32 mL, 2.32 mmol) in dry DMF (20 mL) was stirred at 80 °C for 8 h. The mixture was quenched with water (40 mL), then extracted with ethyl acetate (3 × 40 mL). The combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography. The desired product was obtained as white solid (0.13 g, 56.4%). mp 126 - 128 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, 2H, *J* = 7.6 Hz), 7.51 (t, 1H, *J* = 4.0 Hz), 7.31 (s, 5H), 6.96 (bs, 1H), 5.30 (bs, 1H), 5.10 (s, 2H), 3.59 (q, 2H, *J* = 5.3 Hz), 3.47 (q, 2H, *J* = 5.6 Hz).

Synthesis of compounds **12b-j** was carried out by the same procedure as described for preparation of **12a**.

12b: Yield: 87%; mp 139 - 140 °C; ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.71 (dd, 2H, *J* = 1.6 and 1.7 Hz), 7.35-7.25 (m, 7H), 5.08 (s, 2H), 3.49 (t, 2H, *J* = 5.9 Hz), 3.36 (t, 2H, *J* = 6.1 Hz).

12c: Yield: 54%; mp 105 - 106 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 12.41 (s, 1H), 7.62 (bs, 1H), 7.43-7.28 (m, 7H), 6.95 (d, 1H, *J* = 8.3 Hz), 6.81 (t, 1H, *J* = 7.6 Hz), 5.47 (s, 1H), 5.08 (s, 2H), 3.50 (t, 2H, *J* = 5.2 Hz), 3.42 (t, 2H, *J* = 5.2 Hz).

12d: Yield: 88%; mp 142-143 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, 2H, *J* = 8.7 Hz), 7.32 (s, 5H), 6.90 (d, 2H, *J* = 8.8 Hz), 6.86 (bs, 1H), 5.28 (bs, 1H), 5.10 (s, 2H), 3.84 (s, 3H), 3.58 (q, 2H, *J* = 5.2 Hz), 3.46 (q, 2H, *J* = 5.5 Hz).

12e: Yield: 85%; mp 155 - 157 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.52 (s, 1H), 7.32 (s, 6H), 6.94 (bs, 1H), 6.86 (d, 1H, *J* = 6.2 Hz), 5.25 (bs, 1H), 5.10 (s, 2H), 3.93 (s, 6H), 3.53 (t, 2H, *J* = 3.9 Hz), 3.48 (t, 2H, *J* = 3.8 Hz).

12f: Yield: 62%; mp 140 - 141 °C; ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.35-7.30 (m, 7H), 6.88 (d, 1H, *J* = 8.4 Hz), 5.08 (s, 2H), 4.31-4.26 (m, 4H), 3.46 (t, 2H, *J* = 5.7 Hz), 3.36-3.33 (m, 2H).

12g: Yield: 68%; mp 153 - 155 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.77 (bs, 1H), 8.18 (s, 1H), 8.13 (d, 1H, *J* = 7.8 Hz), 7.90 (d, 1H, *J* = 7.7 Hz), 7.72 (t, 1H, *J* = 7.5 Hz), 7.40-7.32 (m, 7H), 5.01 (s, 2H), 3.49-3.16 (m, 4H).

12h: Yield: 60%; mp 150 - 151 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 2H), 7.99 (s, 1H), 7.67 (bs, 1H), 7.30 (s, 5H), 5.26 (bs, 1H), 5.11 (s, 2H), 3.62 (q, 2H, *J* = 4.7 Hz), 3.50 (q, 2H, *J* = 4.9 Hz).

12i: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.54 (s, 1H), 7.47 (s, 1H), 7.30 (s, 5H), 7.18 (s, 1H), 5.29 (bs, 1H), 5.09 (s, 2H), 3.85 (t, 4H, *J* = 4.8 Hz), 3.58 (q, 2H, *J* = 5.1 Hz), 3.47 (q, 2H, *J* = 5.3 Hz), 3.25 (t, 4H, *J* = 4.8 Hz).

12j: Yield: 73%; mp 135 - 137 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.05 (s, 2H), 8.00 (bs, 1H), 7.84 (s, 1H), 7.68 (s, 1H), 7.25 (s, 5H), 7.08 (s, 1H), 5.57 (bs, 1H), 5.08 (s, 2H), 3.61 (q, 2H, *J* = 4.9 Hz), 3.48 (q, 2H, *J* = 5.3 Hz), 2.26 (s, 3H).

In addition, synthesis of compounds **13a-j** was carried out by the same procedure as described for preparation of **11a**.

2-Methyl-1,2,5-thiadiazolidine-1,1-dioxide (15a). A solution of *N*-Methylethylenediamine (1.8 mL, 20.8 mmol) and sulfuric diamide (**14**, 2.0 g, 20.8 mmol) in pyridine (20 mL) was heated under reflux for 3 h. Toluene (5 mL) was added to the mixture and concentrated under vacuum. Water (20 mL) was added to the residue then extracted with ethyl acetate (3 × 20 mL). The combined organic layer extracts were washed with brine then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography. The title product was obtained (1.5 g, 52.3%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.27 (s, 1H), 3.53-3.19 (m, 2H), 3.42-3.37 (m, 2H,), 2.75 (s, 3H).

Synthesis of compounds **15b-d** was carried out by the same procedure as described for preparation of **15a**.

15b: Yield: 34%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.26 (s, 1H), 3.55-3.51 (m, 2H), 3.42-3.37 (m, 2H), 3.10 (q, 2H, *J* = 7.26 Hz), 1.26 (t, 3H, *J* = 14.5 Hz).

15c: Yield: 40%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.37-7.29 (m, 5H), 4.41 (bs, 1H), 4.17 (s, 2H), 3.47 (q, 2H, *J* = 6.6 Hz), 3.27 (t, 2H, *J* = 13.2 Hz).

15d: Yield: 45%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.91 (s, 1H), 3.81 (t, 2H, *J* = 12.7 Hz), 3.42 (t, 2H, *J* = 12.8 Hz), 1.53 (s, 9H).

1,2,5-Thiadiazolidine, 2-methyl-, 5-benzoxycarbonyl-aminoethyl-1,1-dioxide (16a). 60% Sodium hydride suspension (0.282 g, 11.8 mmol) was added to a solution of compound **15a** (0.856 g, 6.26 mmol) in dry DMF (5 mL) at 0 °C. The mixture was allowed to reach room temperature and stirred for 1 h. The mixture was then cooled to 0 °C then compound **7** (1.5 g, 5.83 mmol) was added. The mixture was stirred at room temperature for 5 h then quenched with water (25 mL). The mixture

was extracted with ethyl acetate (3 × 25 mL), the combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography. The desired product was obtained (0.82 g, 42.9%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.36-7.30 (m, 5H), 5.19 (bs, 1H), 5.10 (s, 2H), 3.46 (q, 2H, *J* = 5.9 Hz), 3.36-3.26 (m, 4H), 3.20 (t, 2H, *J* = 6.0 Hz).

Synthesis of compounds **16b-d** was carried out by the same procedure as described for preparation of **16a**.

16b: Yield: 76%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.38-7.28 (m, 5H), 5.10 (s, 2H), 3.47 (q, 2H, *J* = 5.9 Hz), 3.34-3.30 (m, 4H), 3.19 (t, 2H, *J* = 5.8 Hz), 3.10 (q, 2H, *J* = 7.3 Hz), 1.25 (t, 3H, *J* = 13.3 Hz).

16c: Yield: 74%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.36-7.28 (m, 10H), 5.23 (bs, 1H), 5.11 (s, 2H), 4.18 (s, 2H), 3.48 (q, 2H, *J* = 7.8 Hz), 3.31 (t, 2H, *J* = 5.6 Hz), 3.22 (t, 2H, *J* = 5.8 Hz), 3.16 (t, 2H, *J* = 6.2 Hz).

16d: Yield: 45%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.36-7.30 (m, 5H), 5.18 (bs, 1H), 5.10 (s, 2H), 3.50 (q, 2H, *J* = 5.9 Hz), 3.38-3.30 (m, 4H), 3.25 (t, 2H, *J* = 6.0 Hz), 1.50 (s, 9H).

1,2,5-Thiadiazolidine, 2-methyl-, 5-aminoethyl-1,1-dioxide (17a). Pd/C (0.4 g) was added to a solution of compound **16a** (0.82 g, 2.5 mmol) in MeOH (10 mL). The mixture was stirred under hydrogen atmosphere at room temperature for 1 h. Pd/C was removed by celite filter, and the filtrate was evaporated under reduced pressure. 0.44 g of the product **17a** was obtained and used in the next step without further purification (yield 91%).

Synthesis of compounds **17b-d** was carried out by the same procedure as described for preparation of **17a**.

1-(2-(4-(6-(4-Fluorophenyl)imidazo[2,1-*b*]thiazol-5-yl) pyrimidin-2-ylamino)ethyl)-3-phenylurea (Ia). A mixture of compound **4** (0.34 g, 0.92 mmol), compound **11a** (0.444 g, 2.48 mmol), and DIPEA (0.57 mL, 3.3 mmol) in DMSO (10 mL) was stirred at 80 °C for 8 h. The mixture was cooled to room temperature, quenched with water (20 mL), then extracted with ethyl acetate (3 × 20 mL). The combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography. The title product was obtained as white solid (0.24 g, 56%). mp 140 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, 1H, *J* = 4.4 Hz), 7.93 (d, 1H, *J* = 5.4 Hz), 7.56 (q, 2H, *J* = 4.6 Hz), 7.33 (d, 1H, *J* = 7.3 Hz), 7.21 (s, 4H), 7.12 (t, 2H, *J* = 8.4 Hz), 7.08-6.96 (m, 2H), 6.87 (d, 1H, *J* = 4.2 Hz), 6.41 (d, 1H, *J* = 5.4 Hz), 5.80 (bs, 1H), 3.58 (t, 2H, *J* = 5.2 Hz), 3.45 (d, 2H, *J* = 4.7 Hz). ESI-MS: 474.4 $[M+H]^+$.

Synthesis of the target compounds **Ib-d**, **IIa-j**, and **IIIa-d** was carried out by the same procedure as described for preparation of **Ia**.

Ib: Yield: 68%; mp 194 - 196 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.56 (s, 1H), 8.10 (d, 1H, *J* = 5.7 Hz), 7.63 (q, 1H, *J* = 4.6 Hz), 7.44 (bs, 1H), 7.30 (t, 1H, *J* = 8.8 Hz), 7.15-7.07 (m, 2H), 6.86 (d, 1H, *J* = 8.1 Hz), 6.46 (dd, 1H, *J* = 2.0 and 2.1 Hz), 6.31 (d, 1H, *J* = 5.3 Hz), 3.69 (s, 3H), 3.51-3.24 (m, 4H). ESI-MS: 504.0 $[M+H]^+$.

Ic: Yield: 57%; mp 146 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.49-8.46 (m, 1H), 8.01 (dd, 1H, *J* = 5.5 and 5.4 Hz), 7.66 (s, 1H), 7.62-7.54 (m, 4H), 7.37-7.08 (m, 4H), 6.90 (t, 1H, *J* = 5.1 Hz), 6.50 (dd, 1H, *J* = 5.5 and 5.4 Hz), 5.80 (bs, 1H), 5.66 (bs, 1H), 3.69-3.44 (m, 4H). ESI-MS: 542.9 $[M+H]^+$.

Id: Yield: 60%; mp 157 - 158 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, 1H, *J* = 4.4 Hz), 8.03 (d, 1H, *J* = 5.4 Hz), 7.84 (s, 2H), 7.57 (t, 2H, *J* = 3.7 Hz), 7.48 (s, 1H), 7.12 (t, 2H, *J* = 8.6 Hz), 6.91 (d, 1H, *J* = 4.5 Hz), 5.56 (bs, 1H), 5.50 (bs, 1H), 3.68 (q, 2H, *J* = 5.8 Hz), 3.55 (t, 2H, *J* = 5.5 Hz). ESI-MS: 610.8 $[M+H]^+$.

IIa: Yield: 60%; mp 136 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, 1H, *J* = 4.5 Hz), 8.07 (d, 1H, *J* = 5.4 Hz), 7.68 (brd, 2H, *J* = 5.0 Hz), 7.60-7.56 (m, 2H), 7.41 (t, 1H, *J* = 7.0 Hz), 7.30 (s, 2H), 7.12 (t, 2H, *J* = 8.7 Hz), 6.90 (d, 1H, *J* = 4.5 Hz), 5.84 (bs, 1H), 3.76-7.74 (m, 4H). ESI-MS: 459.2 $[M+H]^+$.

IIb: Yield: 66%; mp 235 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.85 (bs, 1H), 8.54 (s, 1H), 8.11 (d, 1H, *J* = 5.1 Hz), 7.75 (d, 2H, *J* = 7.5 Hz), 7.62 (t, 3H, *J* = 6.6 Hz), 7.46 (d, 1H, *J* = 3.7 Hz), 7.33-7.23 (m, 3H), 6.30 (d, 1H, *J* = 5.3 Hz), 3.49-3.40 (m, 4H), 2.33 (s, 3H). ESI-MS: 473.3 $[M+H]^+$.

IIc: Yield: 63%; mp 165 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 12.40 (s, 1H), 8.47 (d, 1H, *J* = 5.3 Hz), 8.11 (d, 1H, *J* = 5.3 Hz), 7.60-7.57 (m, 2H), 7.29 (s, 1H), 7.13 (t, 3H, *J* = 11.3 Hz), 6.94-6.90 (m, 2H), 6.62 (bs, 1H), 6.54 (d, 1H, *J* = 5.3 Hz), 5.65 (bs, 1H), 7.78-3.71 (m, 4H). ESI-MS: 475.8 $[M+H]^+$.

IId: Yield: 71%; mp 163 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.50 (d, 1H, *J* = 4.3 Hz), 8.07 (d, 1H, *J* = 5.3 Hz), 7.64-7.56 (m, 4H), 7.12 (t, 2H, *J* = 8.56 Hz), 6.91 (d, 1H, *J* = 4.3 Hz), 6.78 (d, 2H, *J* = 6.3 Hz), 6.48 (d, 1H, *J* = 5.3 Hz), 5.49 (bs, 1H), 3.76-3.74 (m, 7H). ESI-MS: 489.8 $[M+H]^+$.

IIe: Yield: 65%; mp 208 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, 1H, *J* = 4.4 Hz), 8.08 (d, 1H, *J* = 5.3 Hz), 7.59 (q, 2H, *J* = 4.5 Hz), 7.40 (s, 1H), 7.37-7.29 (m, 1H), 7.12 (t, 2H, *J* = 8.4 Hz), 6.91 (d, 1H, *J* = 4.5 Hz), 6.60 (bs, 1H), 6.49 (d, 1H, *J* = 5.3 Hz), 5.78 (bs, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.77-3.64 (m, 4H). ESI-MS: 519.5 $[M+H]^+$.

IIf: Yield: 53%; mp 140 - 142 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.45 (t, 1H, *J* = 5.1 Hz), 8.11 (d, 1H, *J* = 5.0 Hz), 7.62 (q, 2H, *J* = 4.6 Hz), 7.46 (s, 1H), 7.38-7.28 (m, 4H), 6.89 (d, 1H, *J* = 5.9 Hz), 6.30 (d, 1H, *J* = 5.3 Hz), 4.37-4.26 (m, 4H), 3.52-3.41 (m, 4H). ESI-MS: 517.3 $[M+H]^+$.

IIg: Yield: 59%; mp 156 - 157 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.49 (d, 1H, *J* = 4.5 Hz), 8.07 (d, 1H, *J* = 5.4 Hz), 7.99 (s, 1H), 7.90 (bs, 1H), 7.68 (d, 1H, *J* = 5.6 Hz), 7.60-7.55 (m, 2H), 7.44 (bs, 1H), 7.12 (t, 2H, *J* = 8.7 Hz), 6.90 (d, 1H, *J* = 4.5 Hz), 6.51 (d, 1H, *J* = 5.4 Hz), 5.78 (s, 1H), 3.77-3.74 (m, 4H). ESI-MS: 527.4 $[M+H]^+$.

IIh: Yield: 55%; mp 204 - 205 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.51 (d, 1H, *J* = 4.4 Hz), 8.24 (s, 2H), 8.06 (d, 1H, *J* = 5.5 Hz), 7.97 (s, 1H), 7.59 (q, 2H, *J* = 4.6 Hz), 7.13 (t, 2H, *J* = 8.5 Hz), 6.91 (d, 1H, *J* = 4.4 Hz), 6.55 (d, 1H, *J* = 5.4 Hz), 5.71 (t, 1H, *J* = 5.7 Hz), 3.78-3.73 (m, 4H). ESI-MS: 595.4 $[M+H]^+$.

IIi: Yield: 48%; mp 164 - 166 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, 1H, *J* = 3.2 Hz), 8.06 (d, 1H, *J* = 5.5 Hz), 7.62-7.54 (m, 3H), 7.29 (s, 1H), 7.15-7.09 (m, 3H), 6.91 (d, 1H, *J* = 4.5 Hz), 6.52 (d, 1H, *J* = 5.5 Hz), 5.69 (t, 1H, *J* = 4.5 Hz), 3.83 (t, 4H, *J* = 4.8 Hz), 3.77-3.72 (m, 4H), 3.21 (t, 4H, *J* = 4.8 Hz). ESI-MS: 611.9 $[M+H]^+$.

IIj: Yield: 42%; mp 155 - 157 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz)

δ 8.50 (d, 1H, J = 4.5 Hz), 8.07 (s, 1H), 8.02 (d, 1H, J = 5.5 Hz), 7.90 (s, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 7.55 (q, 2H, J = 4.6 Hz), 7.11 (t, 2H, J = 8.6 Hz), 7.02 (s, 1H), 6.91 (d, 1H, J = 4.5 Hz), 5.86 (bs, 1H), 3.78-3.76 (m, 4H), 2.24 (s, 3H). ESI-MS: 607.1 $[M+H]^+$.

IIIa: Yield: 72%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, 1H, J = 4.5 Hz), 8.08 (s, 1H), 7.61 (q, 2H, J = 4.6 Hz), 7.13 (t, 2H, J = 8.5 Hz), 6.91 (d, 1H, J = 4.5 Hz), 6.55 (d, 1H, J = 5.5 Hz), 5.81 (bs, 1H), 3.78 (q, 2H, J = 6.1 Hz), 3.43-3.30 (m, 6H), 2.79 (s, 3H). ESI-MS: 474.0 $[M+H]^+$.

IIIb: Yield: 67%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, 1H, J = 4.5 Hz), 8.06 (s, 1H), 7.63 (q, 2H, J = 4.5 Hz), 7.15 (t, 2H, J = 8.4 Hz), 7.03 (d, 1H, J = 4.4 Hz), 6.58 (d, 1H, J = 5.5 Hz), 5.79 (bs, 1H), 3.79 (q, 2H, J = 6.0 Hz), 3.48-3.31 (m, 6H), 3.12 (q, 2H, J = 7.3 Hz), 1.26 (t, 3H, J = 7.3 Hz). ESI-MS: 488.0 $[M+H]^+$.

IIIc: Yield: 75%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.58 (d, 1H, J = 4.4 Hz), 8.46 (s, 1H), 7.40-7.31 (m, 7H), 6.98-6.90 (m, 2H), 6.59 (d, 1H, J = 5.3 Hz), 4.20 (s, 2H), 3.79 (q, 2H, J = 6.0 Hz), 3.39 (q, 4H, J = 6.7 Hz), 3.20 (t, 2H, J = 6.3 Hz). ESI-MS: 550.1 $[M+H]^+$.

IIId: Yield: 54%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, 1H, J = 4.4 Hz), 8.16 (s, 1H), 7.68 (q, 2H, J = 4.4 Hz), 7.14 (t, 2H, J = 8.1 Hz), 7.10 (d, 1H, J = 4.4 Hz), 6.58 (d, 1H, J = 5.4 Hz), 5.82 (bs, 1H), 3.80 (q, 2H, J = 6.0 Hz), 3.47-3.39 (m, 6H), 1.53 (s, 9H). ESI-MS: 560.0 $[M+H]^+$.

2-(2-(4-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-5-yl) pyrimidin-2-ylamino)ethyl)-1,2,5-thiadiazolidine-1,1-dioxide (IIIe). To a stirred solution of **IIId** (0.2 g, 0.357 mmol) in CH_2Cl_2 (5 mL) at 0 °C, trifluoroacetic acid (0.4 mL, 5.36 mmol) was added. The reaction mixture was stirred at the same temperature for 2 h, then allowed to warm to room temperature. The pH of the mixture was adjusted to 7 by dropwise addition of saturated $NaHCO_3$ solution, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer extracts were washed with brine, dried over anhydrous Na_2SO_4, and filtered. Compound **IIIe** was obtained as a white solid (0.12 g, 73.2%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.59 (d, 1H, J = 4.3 Hz), 8.21 (s, 1H), 7.94 (q, 2H, J = 4.3 Hz), 7.18 (t, 2H, J = 8.2 Hz), 7.10 (d, 1H, J = 4.4 Hz), 6.63 (d, 1H, J = 5.7 Hz), 5.88 (bs, 1H), 3.83 (q, 2H, J = 6.0 Hz), 3.58-3.41 (m, 6H). ESI-MS: 459.9 $[M+H]^+$.

Evaluation of the biological activity. A375P cells were purchased from American Type Culture Collection (ATCC, Rockville, MD, USA) and maintained in Dulbecco's modified eagle medium (DMEM, Welgene, Daegu, Korea) supplemented with 10% foetal bovine serum (FBS, Welgene, Daegu, Korea) and 1% penicillin/streptomycin (Welgene, Daegu, Korea) in a humidified atmosphere with 5% CO_2 at 37 °C. A375P cells were taken from culture substrate with 0.05% trypsin-0.02% EDTA and plated at a density of 5×10^3 cells/well in 96 well plates and then incubated at 37 °C for 24 h in a humidified atmosphere with 5% CO_2 prior to treatment with various concentrations (3-fold serial dilution, 12 points) of test compounds. The cells were incubated for 48 h after treatment with the test compounds. The A357P cell viability was assessed by the conventional 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction assay. MTT assays were carried out with CellTiter 96® (Promega) according to the manufacturer's instructions. The absorbance at 590 nm was recorded using EnVision 2103 (Perkin Elmer; Boston, MA, USA). The IC_{50} values were calculated using GraphPad Prism 4.0 software.

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