Synthesis and Antiproliferative Activities of Pyrrolo[2,3-*d*]pyrimidine Derivatives for Melanoma Cell

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The synthesis of a new series of diaryl ureas having a pyrrolo[2,3-*d*]pyrimidine scaffold is reported here. The *in vitro* antiproliferative activities of these diaryl derivatives against human melanoma cell line A375 were tested and the effect of substituents on the phenyl ring was investigated. The para substituted compounds **Ia-g** showed superior or similiar activity to Sorafenib against the A375 cell line. Among these compounds, **Ic-e** showed excellent activity against A375 compared with Sorafenib, a multi-kinase inhibitor.

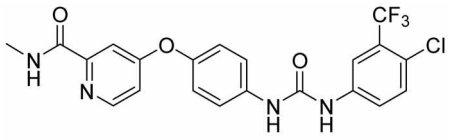
Key Words : Pyrrolo[2,3-*d*]pyrimidine, A375, Antiproliferative activity

Introduction

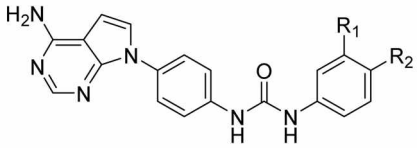
Melanoma, the most aggressive form of skin cancer, is the fastest growing cancer in the United States.[1,2] Early stage melanoma can be cured surgically. However, melanoma metastasizing to major organs (stage IV) is virtually incurable.[2] Patients with disseminated melanoma have a median survival time of less than a year, and the estimated 5-year survival rate is less than 15%.[2,3] 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.[4-6]

Recently, Sorafenib, as well as other diaryl ureas, have been evaluated as potent and selective antiproliferative agents for the treatment of melanoma.[7-12] The promising results have encouraged many research groups to investigate diaryl urea scaffolds to develop new derivatives for the treatment of cancer.[13-17] Accordingly, we have synthesized a new series of diaryl ureas, and report their antiproliferative activity against human melanoma cell line A375.

In this work, we investigate the effect that replacing the 2-(methylaminocarbonyl)-pyridine-4-yl-oxy group in Sorafenib with a pyrrolo[2,3-*d*] pyrimidine moiety has on the antiproliferative activity. The effect of substitution at the other phenyl urea ring is also investigated by using the different substituents R_1 and R_2.



Sorafenib



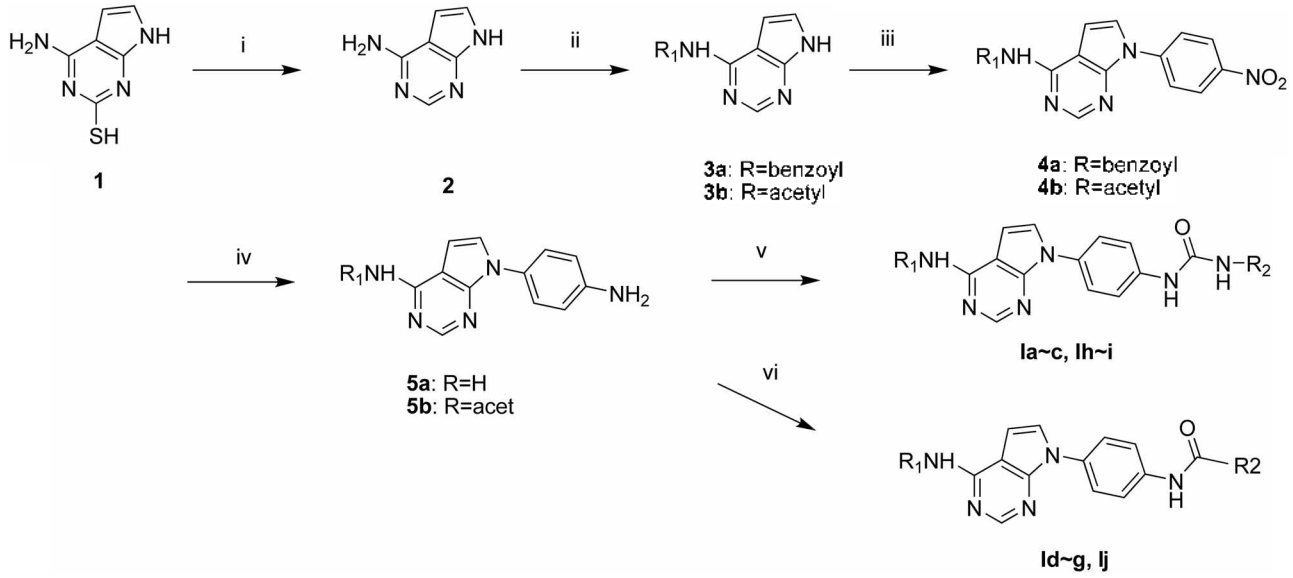
Pyrrolo[2,3-*d*]pyrimidine derivatives

Results and Discussion

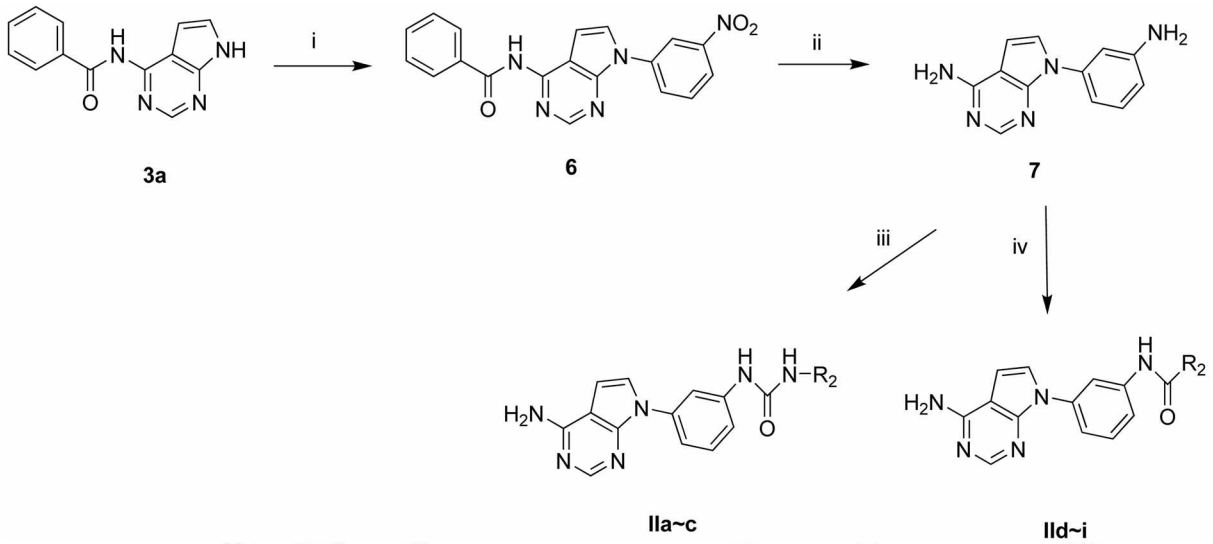
Chemistry. The general synthesis of pyrrolo[2,3-*d*]pyrimidine ureas and amides is shown in Scheme **1** and **2**. The intermediate **2** was obtained by reduction of the thiol compound **1**[18] using Raney nickel. Reaction of **2** with benzoyl chloride in pyridine produced the benzoyl protected compound **3a**. The acetyl compound **3b** was obtained by the coupling of **2** with acetic acid using EDC/HOBt. Preparation of the *p*-nitrophenyl compounds **4a** and **4b** was achieved by treating **3a** and **3b** with 1-iodo-4-nitrobenzene in the presence of potassium carbonate and copper iodide. Reduction of compound **4b** with Pd-C/H_2 produced the amino compound **5b**, whereas the reduction of compound **4a** was carried out using tin(II)chloride to provide the desired compound **5a**. The urea type compounds (**Ia-c** and **Ih-i**) were prepared by the reaction of compounds **5a** and **5b** with the corresponding isocyanates. The amides (**Id-g** and **Ij**) were obtained by condensation with the corresponding carboxylic acid using EDC/HOBt. The synthesis of the *m*-substituted urea and amide compounds (**IIa-c** and **IId-i**) was achieved in a way similar to that used for the preparation of *p*-compounds using the corresponding starting materials (Scheme 2).

***In vitro* activity.** We examined the antiproliferative activities of these newly synthesized compounds human melanoma cell line A375. The ability of pyrrolo[2,3-*d*]pyrimidine derivatives to inhibit the growth of the A375 cell line is summarized in Tables 1 and 2. We selected Sorafenib as the reference standard, because it has been used extensively in clinical trials for melanoma.[19,20]

The para substituted compounds **Ia-g** were superior or similiar to Sorafenib in activity against A375. Among these compounds, **Ic-e** showed excellent activity against A375 compared with Sorafenib. As to the substituent on the phenyl chain, the para substituted compounds **Ia-g** were generally more potent than the meta substituted compounds **IIa-i**. Comparing the linker, the compounds (**Id** and **IId**) having amide moieties were generally more potent than the urea compounds (**Ia** and **IIa**). The activity of the acetyl



Scheme 1. Reagents and conditions: i) Raney nickel, H_2O ii) (a) benzoyl chloride, pyridine (b) acetic acid, HOBt, EDCI.TEA, DMF iii) 1-iodo-4-nitrobenzene, K_2CO_3, CuI, L-proline, DMSO iv) $SnCl_2{\cdot}H_2O$, EtOH or Pd/C, H_2, THF v) R_2NCO, THF vi) R_2COOH, HOBt, EDCI, TEA, DMF.



Scheme 2. Reagents and conditions: i) 1-iodo-3-nitrobenzene, K_2CO_3, CuI, L-proline, DMSO. ii) $SnCl_2{\cdot}H_2O$, EtOH. iii) R_2NCO, THF iv) R_2COOH, HOBt, EDCI, TEA, DMF.

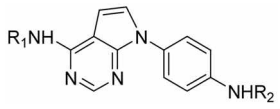
substituted compounds (**Ih-j**) against A375 was found to be inferior to that of amino compounds (**Ia** and **Id**).

Experimental Section

Melting points (mp) were determined on a Walden Precision Apparatus Electrothermal 9300 apparatus and were uncorrected. ^{1}H NMR spectral data were recorded using a Gemini 300 spectrometer. Mass spectra were recorded on a Waters 3100 Mass Detecter.

A375P cell culture and anti-proliferative activity of tested compound on A375P. A375P cells were purchased from American Type Culture Collection (ATCC, Rockville, MD, US) and maintained in a DMEM (Welgene, Daegu, Korea) supplemented with 10% FBS (Welgene) and 1% penicillin/streptomycin (Welene) 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 hours in a humidified atmosphere with 5% CO_2 prior to treatment of various concentration (three fold serial dilution, 12 points) of test compounds. The A375P 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 EnVision2103 (PerkinElmer; Boston, MA,

Table 1. Antiproliferative activity of the *para* substituted compounds



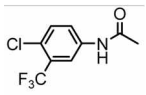
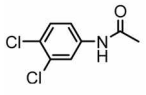
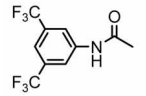
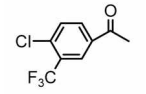
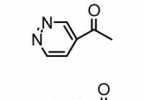
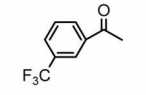
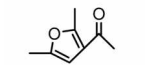
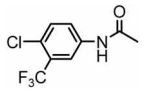
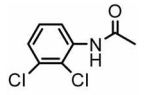
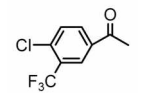
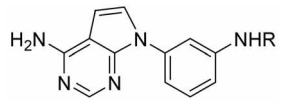
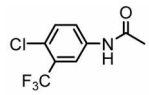
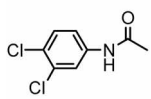
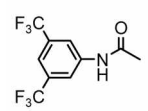
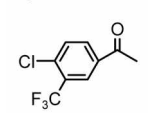
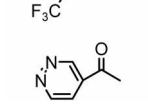
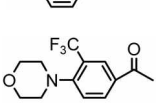
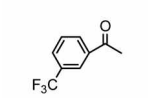
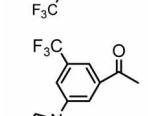
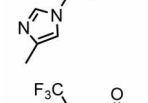
Compd.	R_1	R_2	A375P (IC_{50}, μM)
Ia	H		8.0
Ib	H		5.3
Ic	H		2.9
Id	H		2.8
Ie	H		3.0
If	H		9.6
Ig	H		10.0
Ih	CH_3CO		14.5
Ii	CH_3CO		>20
Ij	CH_3CO		17.1
Sorafenib			5.0

Table 2. Antiproliferative activity of the *meta*-substituted compounds



Compd.	R	A375P (IC_{50}, μM)
IIa		12.9
IIb		10.2
IIc		10.8
IId		9.8
IIe		>20
IIf		18.0
IIg		11.8
IIh		>20
IIi		>20
Sorafenib		5.0

US). The IC_{50} was calculated using GraphPad Prism 4.0 softwere.

4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidine (2). To a suspension of 4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-thiol (**1**, 1.0 g, 6.0 mmol) in water (50 mL) was added Raney nickel (3.0 g). The reaction mixture was heated at reflux for 4 h, and then the hot solution was filtered through celite. The Nikel residue was washed with further water (100 mL). The aqueous filtrate was evaporated to dryness to yield the product (0.7 g, 87.5%). mp: 206-208 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300MHz): δ 12.37 (brs, 1H), 8.22 (brs, 2H), 8.15 (s, 1H), 7.29 (d, 1H, J = 1.5 Hz), 6.80 (d, 1H, J = 1.1 Hz).

***N*-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)benzamide (3a).** To a suspension of 4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidine (**2**, 1.0 g, 7.5 mmol) in pyridine (25 mL) was added benzoyl chloride (1.3 g, 8.9 mmol). The mixture was heated at 50 °C overnight. The mixture was cool and evaporated under reduced pressure. The residue was diluted with ethyl acetate (30 mL) and water (50 mL), and then the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and purification was achieved by flash chromatography (EtOAc:Hexane = 1:2) to afford **3a** (0.6 g, 33%) as a pale yellow solid. mp: 220-222 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 12.03 (s, 1H), 11.00 (s, 1H), 8.53 (s, 1H), 8.06 (d, 2H, J = 7.3 Hz), 7.65-7.60 (m, 1H), 7.56-7.51 (m, 2H), 7.42-7.41 (m, 1H), 6.59-6.57 (m, 1H).

***N*-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)acetamide (3b).** 1-[3-(Dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride (EDCI, 1.8 g, 9.3 mmol) was added in one portion to a suspendsion of 4-amino-7*H*-Pyrrolo[2,3-*d*]pyrimidine (**2**. 0.5 g, 3.7 mmol), acetic acid (0.4 g, 6.6 mmol), and HOBt (1.1 g, 8.1 mmol) in DMF (15 mL) at 0 . The result of

suspension was warmed to room temperature and Et_3N (1.6 mL, 11.4 mmol) were added. The mixture was stirred for 24 h at 80 °C. The suspension was poured into water and the aqueous layer was extracted with ethyl acetate (50 mL). The organic layer was washed with water (230 mL), then a solution of 5% NaOH (20 mL) and brine. The organic layer was separated, dried over Na_2SO_4. Evaporation of the solvent *in vacuo* gave a crude residue, which was purified by silica gel column chromatography (EtOAc) to give **3b** (0.3 g, 45%) as a pale yellow oil. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 12.00 (brs, 1H), 10.65 (brs, 1H), 8.44 (s, 1H), 7.35 (m, 1H), 6.73-6.68 (d, 1H, J = 15.2 Hz), 2.21 (s, 3H).

***N*-(7-(4-Nitrophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-benzamide (4a).** A mixture of 1-iodo-4-nitrobenzene (0.6 g 2.4 mmol), *N*-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)benzamide (**3a**, 0.3 g, 1.3 mmol), K_2CO_3 (0.5 g, 2.4 mmol), CuI (20.0 mg, 0.1 mmol), L-proline (30 mg, 0.3 mmol) in DMSO (5 mL) was heated at 90 under nitrogen atmosphere for 40 h. The cooled solution was partitioned between H_2O and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was removed *in vacuo*, and purification was achieved by flash chromatography (EtOAc: Hexane = 1:2) to afford **4a** (0.3 g, 67%) as a pale yellow solid. mp: 223-224 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.35 (brs, 1H), 8.52-8.43 (m, 3H), 8.38-8.33 (m, 3H), 8.20-8.08 (m, 3H), 7.62-7.60 (m, 2H), 6.89-6.87 (m, 1H).

***N*-[7-(4-Nitrophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-acetamide (4b).** Synthesis of compound **4b** was prepared in a manner similar to the preparation of **4a** from **3b**. Yield 45%. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.93 (s, 1H), 8.65 (brs, 1H), 8.44-8.30 (m, 2H), 8.28-8.17 (m, 2H), 8.04-8.00 (m, 1H), 7.05-7.00 (m, 1H), 2.07 (s, 3H).

4-Amino-7-(4-aminophenyl)-7*H*-pyrrolo[2,3-d]pyrimidine (5a). The mixture of *N*-(7-(4-nitrophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)benzamide (**4a**, 1.0 g, 2.8 mmol), $SnCl_2 \cdot H_2O$ (3.1 g, 13.7 mmol), and ethanol (20 mL) was heated at 70-80 °C overnight and then cooled to room temperature. Most of the ethanol was removed *in vacuo*. The residue was diluted with ethyl acetate (30 mL), $NaHCO_3$ (100 mL) and water (50 mL), and then the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and purification was achieved by flash chromatography (EtOAc) to afford **5a** (0.5 g, 80%) as a pale yellow solid. mp: 231-232 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 8.13-8.06 (m, 1H), 7.32-7.29 (m, 3H), 7.04 (brs, 2H), 6.66-6.63 (m, 3H), 5.21 (brs, 2H).

***N*-[7-(4-Aminophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]acetamide (5b).** To a suspension of *N*-[7-(4-nitrophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]acetamide (**4b**, 0.2 g, 0.7 mmol) in THF (10 mL) was added Pd/C (0.1 g) and was hydrogenated at 50 psi for 2 h, and then filtered through celite. The Pd/C residue was washed with further THF (10 mL) and concentration. The crude residue was purified by silica gel column chromatography (EtOAc) to give **5b** (45 mg, 25%) as a pale yellow oil. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.75 (s, 1H), 8.48 (s, 1H), 7.61-7.59 (d, 1H, J = 3.6 Hz), 7.34-7.31 (m, 2H), 6.88-6.87 (d, 1H, J = 3.6 Hz), 6.72-6.66 (m, 2H), 5.31 (brs, 2H), 2.24 (s, 3H).

***N*-[7-(3-Nitrophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-benzamide (6).** Synthesis of compound **6** was prepared in a manner similar to the preparation of **4a** by using 1-iodo-3-nitrobenzene. Yield 40%. mp: 212-214 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.33 (brs, 1H), 8.98-8.88 (m, 1H), 8.73 (s, 1H), 8.40-8.37 (m, 1H), 8.27-8.24 (m, 1H), 8.20-8.08 (m, 3H), 7.88 (t, 1H, J = 8.2 and 8.3 Hz), 7.68-7.64 (m, 1H), 7.59-7.54 (m, 2H), 6.90 (d, 1H, J = 3.4 Hz).

4-Amino-7-(3-aminophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (7). Synthesis of compound **7** was prepared in a manner similar to the preparation of **5a** from **6**. Yield 50%. mp: 221-224 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 8.09 (s, 1H), 7.40 (d, 1H, J = 3.58 Hz), 7.14-7.09 (m, 3H), 7.02-7.01 (m, 1H), 6.82-6.80 (m, 1H), 6.73 (d, 1H, J = 3.5 Hz), 6.53-6.51 (m, 1H), 5.33-5.31 (m, 2H).

1-[4-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl]-3-[4-chloro-3-(trifluoromethyl) phenyl]urea (Ia). A suspension of 4-Amino-7-(4-aminophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**5a**, 30.0 mg, 0.1 mmol) in THF (5 mL) was treated with dropwise addition of a solution of 4-chloro-3-(trifluromethyl)phenyl isocyante (24.0 mg, 0.1 mmol) in THF at room temperature under N_2 and was stirred for 24 h. The solvent was removed *in vacuo*, and purification was carried out by flash chromatography (EtOAc:acetone = 3:1) to afford **Ia** (24.0 mg, 40%) as a pale yellow solid. mp: 236-239 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 9.26 (brs, 1H), 9.08 (brs, 1H), 8.26 (brs, 1H), 8.16-8.10 (m, 2H), 7.63-7.61 (m, 3H), 7.60-7.59 (m, 1H), 7.55-7.52 (m, 1H), 7.50-7.47 (m, 1H), 7.43 (brs, 2H), 7.33-7.28 (m, 1H). ESI-MS: 447.0 $[M+H]^+$.

The synthesis of compounds **Ib**, **Ic**, **Ih**, **Ii** were carried out by the same procedure as described for the preparation of **Ia**

Ib: Yield 40%. mp: 232-233 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 9.08 (s, 1H), 9.02 (s, 1H), 8.09 (s, 1H), 7.90 (d, 1H, J = 2.4 Hz), 7.72-7.69 (m, 2H), 7.60-7.57 (m, 2H), 7.54 (s, 1H), 7.51-7.49 (m, 2H), 7.13 (brs, 2H), 6.74 (d, 1H, J = 3.8 Hz). ESI-MS: 413.0 $[M+H]^-$.

Ic: Yield 35%. mp: 313-316 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 9.46 (s, 1H), 9.20 (s, 1H), 8.15 (s, 2H), 8.10 (s, 1H), 7.73 (d, 2H, J = 8.9 Hz), 7.65 (brs, 1H), 7.62 (d, 2H, J = 8.9 Hz), 7.51 (d, 1H, J = 3.6 Hz), 7.13 (brs, 2H), 6.75 (d, 1H, J = 3.6 Hz). ESI-MS: 481.0 $[M+H]^-$.

Ih: Yield 31%. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.81 (s, 1H), 9.24 (s, 1H), 9.08 (s, 1H), 8.54 (s, 1H), 8.12 (brs, 1H), 7.71 (d, 1H, J = 3.6 Hz), 7.73-7.70 (m, 3H), 7.65-7.62 (m, 3H), 6.95 (d, 1H, J = 3.5 Hz), 2.24 (s, 3H). ESI-MS: 489.0 $[M+H]^+$.

Ii: Yield 70%. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.82 (s, 1H), 9.76 (s, 1H), 8.55-8.54 (m, 2H), 8.21-8.18 (m, 1H), 7.79-7.77 (m, 3H), 7.66-7.63 (m, 2H), 7.35-7.29 (m, 2H), 6.96 (d, 1H, J = 3.8 Hz), 2.25 (s, 3H). ESI-MS: 455.0 $[M+H]^-$.

***N*-[4-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl]-4-chloro-3-(trifluoromethyl) benzamide (Id).** 1-[3-(Dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride (64 mg, 0.3 mmol) was added in one portion to a suspend-

sion of 4-amino-7-(4-aminophenyl)-7*H*-pyrrolo[2,3-d]pyrimidine (**5a**, 30 mg, 0.1 mmol), 4-chloro-3-trifloromethylbenzoic acid (60 mg, 0.3 mmol), and HOBt (40 mg, 0.3 mmol) in DMF (6 mL) at 0 . The resulting suspension was warmed to room temperature and Et_3N (0.1 mL, 0.4 mmol) were added. The mixture was stirred at 80 °C for 24 h. The suspension was poured into water and the aqueous layer was extracted with ethyl acetate (15 mL). The organic layer was washed with water (215 mL), then a solution of 5% NaOH (10 mL) and brine. The organic layer was separated, dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and purification was carried out by flash chromatography (EaOAc:acetone = 3:1) to afford **Id** (50 mg, 87%) as a pale yellow solid. mp: 223-225 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.69 (s, 1H), 8.43-8.42 (m, 1H), 8.32-8.29 (m, 1H), 8.11 (s, 1H), 7.97-7.92 (m, 2H), 7.91-7.83 (m, 3H), 7.57 (d, 1H, J = 3.6 Hz), 7.18 (brs, 2H), 6.78 (d, 1H, J = 3.6 Hz). ESI-MS: 432.0 $[M+H]^+$.

The synthesis of compounds **Ie-Ig**, **Ij** were carried out by the same procedure as described for the preparation of **Id**.

Ie: Yield 34%. mp: 206-209 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.87 (s, 1H), 9.67 (s, 1H), 9.51 (d, 1H, J = 5.3 Hz), 8.29-8.14 (m, 1H), 8.13-8.12 (m, 1H), 7.92-7.91 (m, 1H), 7.89-7.84 (m, 3H), 7.57 (d, 1H, J = 3.6 Hz), 7.16 (brs, 2H), 6.77 (d, 1H, J = 3.5 Hz). ESI-MS: 332.0 $[M+H]^-$.

If: Yield 48%. mp: 216-218 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.63 (s, 1H), 8.32 (brs, 1H), 8.28 (brs, 1H), 8.12 (s, 1H), 8.00-7.97 (m, 1H), 7.94-7.93 (m, 1H), 7.91-7.90 (m, 1H), 7.85-7.83 (m, 1H), 7.83-7.78 (m, 2H), 7.56 (d, 1H, J = 3.6 Hz), 7.15 (brs, 2H), 6.77 (d, 1H, J = 3.6 Hz). ESI-MS: 397.0 $[M+H]^+$.

Ig: Yield 65%. mp: 223-225 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 9.75 (s, 1H), 8.11 (s, 1H), 7.86 (d, 2H, J = 9.0 Hz), 7.76 (d, 2H, J = 8.9 Hz), 7.53 (d, 1H, J = 3.6 Hz), 7.16 (brs, 2H) 6.76 (d, 1H, J = 3.6 Hz), 6.69 (s, 1H), 2.52 (s, 3H), 2.27 (s, 3H). ESI-MS: 348.0 $[M+H]^-$.

Ij: Yield 47%. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.84 (brs, 1H), 10.73 (brs, 1H), 8.57 (brs, 1H), 8.43-8.38 (m, 1H), 8.32-8.29 (m, 1H), 7.97-7.93 (m, 3H), 7.86-7.82 (m, 3H), 6.98-6.97 (d, 1H, J = 3.5 Hz), 2.26 (s, 3H). ESI-MS: 474.0 $[M+H]^+$.

1-[3-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl]-3-[4-chloro-3-(trifluoromethyl) phenyl]urea (IIa). Synthesis of compound **IIa** was prepared in a manner similar to the preparation of **Ia** from **7**. Yield 60%. mp: 235-237 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 9.23 (s, 1H), 9.13 (s, 1H), 8.12-8.08 (m, 2H), 7.98 (brs, 1H), 7.64-7.63 (m, 2H), 7.52-7.51 (m, 2H), 7.47-7.46 (m, 1H), 7.40-7.39 (m, 1H), 7.16 (brs, 2H), 6.79-6.77 (s, 1H, J = 3.6 Hz). ESI-MS: 447.0 $[M+H]^+$.

The syntheses of compounds **IIb-IIc** were carried out by the same procedure as described for the preparation of **IIa**.

IIb: Yield 35%. mp: 225-226 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 9.09 (s, 1H), 9.08 (s, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.90 (d, 1H, J = 2.4 Hz), 7.52-7.51 (m, 2H), 7.45-7.44 (m, 1H), 7.42-7.41 (m, 1H), 7.39-7.38 (m, 1H), 7.36-7.35 (m, 1H), 7.17 (brs, 2H), 6.78 (d, 1H, J = 3.6 Hz). ESI-MS: 413.0 $[M+H]^+$.

IIc: Yield 46%. mp: 318-320 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 9.63 (s, 1H), 9.46 (s, 1H), 8.70 (brs, 1H), 8.43 (brs, 2H), 8.15 (brs, 1H), 8.01 (brs, 1H), 7.85 (d, 1H, J = 3.6 Hz), 7.78 (brs, 1H), 7.66 (brs, 1H), 7.56-7.48 (m, 2H), 7.42-7.40 (m, 1H) 7.33-7.20 (m, 1H). ESI-MS: 481.0 $[M+H]^+$.

***N*-[3-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl]-4-chloro-3-(trifluoromethyl) benzamide (IId).** Synthesis of compound **IId** was prepared in a manner similar to the preparation of **Id** from **7**. Yield 26%. mp: 221-223 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.74 (s, 1H), 8.42-8.40 (m, 1H), 8.31-8.25 (m, 2H), 8.13 (s, 1H), 7.96-7.93 (m, 1H), 7.79-7.77 (m, 1H), 7.56-7.49 (m, 3H), 7.18 (brs, 2H), 6.80 (d, 1H, J = 3.6 Hz). ESI-MS: 432.0 $[M+H]^-$.

The synthesis of compounds **IIe-IIi** were carried out by the same procedure as described for the preparation of **IId**.

IIe: Yield 10%. mp: 204-207 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.94 (s, 1H), 9.70-9.67 (m, 1H), 9.52-9.50 (m, 1H), 8.32 (brs, 1H), 8.16-8.13 (m, 1H), 7.79-7.77 (m, 1H), 7.56-7.54 (m, 1H), 7.53-7.52 (m, 1H), 7.35-7.32 (m, 1H), 7.28-7.26 (m, 1H), 7.18 (brs, 2H), 6.81 (d, 1H, J = 3.5 Hz). ESI-MS: 332.0 $[M+H]^-$.

IIf: Yield 38%. mp: 207-209 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.59 (s, 1H), 8.36-8.24 (m, 3H), 8.12 (s, 1H), 7.79-7.78 (m, 1H), 7.69-7.66 (m, 1H), 7.48-7.53 (m, 3H), 7.19 (brs, 2H), 6.80 (d, 1H, J = 3.6 Hz), 3.75-3.72 (m, 4H), 2.98-2.97 (m, 4H). ESI-MS: 483.0 $[M+H]^+$.

IIg: Yield 69%. mp: 214-216 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.69 (s, 1H), 8.46-8.45 (m, 1H), 8.39-8.25 (m, 3H), 8.13 (s, 1H), 7.83-7.69 (m, 3H), 7.54-7.49 (m, 2H), 7.18 (brs, 2H), 6.80 (d, 1H, J = 3.5 Hz). ESI-MS: 398.0 $[M+H]^+$.

IIh: Yield 28%. mp: 218-220 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.73 (s, 1H), 8.49-8.47 (m, 1H), 8.43-8.41 (m, 1H), 8.27 (brs, 2H), 8.19 (brs, 1H), 8.13 (s, 1H), 7.78-7.77 (m, 1H), 7.73 (brs, 1H), 7.56-7.53 (m, 2H), 7.35-7.30 (m, 1H), 7.18 (brs, 2H), 6.81 (d, 1H, J = 3.6 Hz), 2.19 (s, 3H). ESI-MS: 478.0 $[M+H]^-$.

IIi: Yield 14%. mp: 215-217 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.58 (s, 1H), 8.23 (brs, 1H), 8.13-8.10 (m, 1H), 7.77-7.74 (m, 2H), 7.68 (brs, 1H), 7.53-7.48 (m, 3H), 7.26-7.24 (m, 1H), 7.18 (brs, 2H), 6.80 (d, 1H, J = 3.5 Hz), 3.79-3.76 (m, 4H), 3.41-3.39 (m, 4H). ESI-MS: 483.0 $[M+H]^+$.

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