Diarylureas and Diarylamides with Pyrrolo[2,3-*d*]pyrimidine Scaffold as Broad-Spectrum Anticancer Agents

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A series of diarylureas and diarylamides possessing pyrrolo[2,3-*d*]pyrimidine scaffold was designed and synthesized. The *in vitro* antiproliferative activities of a selected group of the target compounds against NCI-60 cell line panel were tested and compared with Sorafenib and Imatinib as reference compounds. Most of the compounds showed strong and broad-spectrum antiproliferative activities. Compounds IVa, IVb, and IVd with benzamido moiety at position 4 of the pyrrolo[2,3-*d*]pyrimidine nucleus, *para*-disubstituted phenyl ring at *N*1-position of pyrrolo[2,3-*d*]pyrimidine scaffold, and urea linker showed strong and broad-spectrum anticancer results with high potencies and efficacies. In addition, the amide derivatives Vb and Vc demonstrated one-digit nanomolar IC_{50} values over two and one cell line(s), respectively. Amid all the target compounds, compound IVa demonstrated the best results in both one-dose and five-dose testing modes. It showed 109.18% mean % inhibition over the NCI-60 cancer cell line panel at 10 μM concentration, submicromolar 50% inhibitory concentration (IC_{50}) values over eight cell lines of eight different cancer types, and high efficacy with total growth inhibition (TGI) and 50% lethal concentration (LC_{50}) values less than 4.22 μM over three colon, ovarian, and prostate cancer cell lines. It showed superior potency and efficacy to Sorafenib and Imatinib over most of the tested cell lines.

Key words diarylurea; diarylamide; pyrrolo[2,3-*d*]pyrimidine; anticancer; cytotoxicity

Cancer is a generic term for a large group of diseases that can affect any part of the body. Lung, stomach, liver, colon, and breast cancer cause the most cancer deaths each year. About 30% of cancer deaths are due to the five leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol intake. More than 70% of all cancer deaths occurred in low- and middle-income countries. Deaths from cancer worldwide are projected to exceed 13 million in 2030.[1] In spite of the extensive efforts and investment in research, the management of human malignancies still constitutes a major challenge for contemporary medicinal chemistry. There has been an urgent need for development of more efficient anticancer agents with minimal side effects.

Diarylureas and diarylamides have been highlighted as potential antiproliferative agents against a variety of cancer cell lines.[2–17] Sorafenib (Nexavar®, Fig. 1) is an example of anticancer diarylureas that has been approved by the U.S. Food and Drug Administration (FDA) for treatment of advanced renal cancer.[18] It has also been approved in Europe for treatment of hepatocellular carcinoma (HCC).[19] Sorafenib is currently subjected to clinical trials for other types of cancer. Imatinib (Gleevec®, Fig. 1) is an example of diarylamides which is used for treatment of chronic myeloid leukemia (CML) with diminished side effects.[20]

The target pyrrolo[2,3-*d*]pyrimidine compounds were designed as conformationally restricted analogs of Sorafenib by isosteric replacement of the 4-phenoxypyridine moiety of the lead compound with a pyrrolo[2,3-*d*]pyrimidine nucleus (Fig. 1). The 50% inhibitory concentration (IC_{50}) values for most of the target compounds over A375P human melanoma cell line only were previously reported.[2,3] Upon further testing over NCI-60 cancer cell line panel of nine different cancer types, the target compounds showed broad-spectrum anticancer activities with high efficacies and potencies. Herein the biological results are reported in details.

Results and Discussion

Chemistry The target pyrrolo[2,3-*d*]pyrimidine diarylureas and diarylamides were synthesized by the pathway of reactions illustrated in Charts **2**–**4**.[2,3] But at the beginning, it was essential to synthesize the intermediate compound 7*H*-

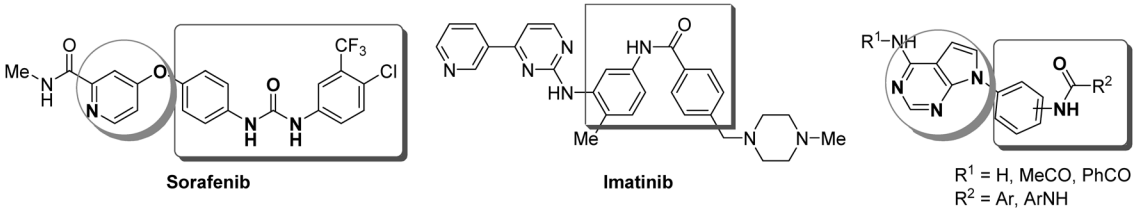

Fig. 1. Structures of Sorafenib, Imatinib, and the Target Compounds

The authors declare no conflict of interest.

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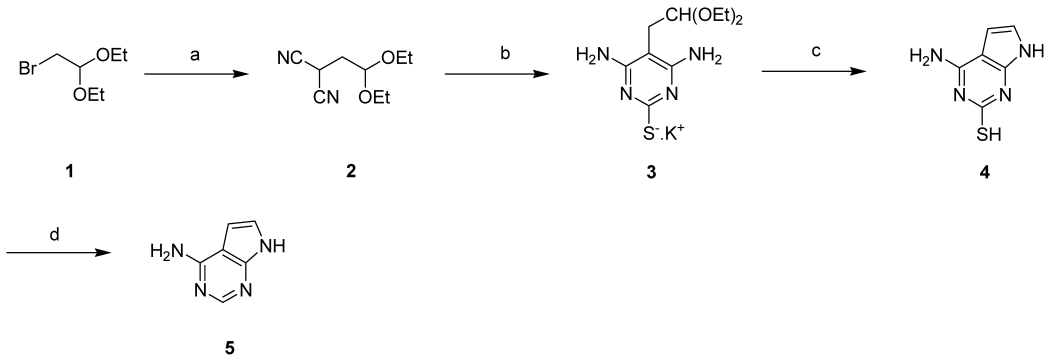
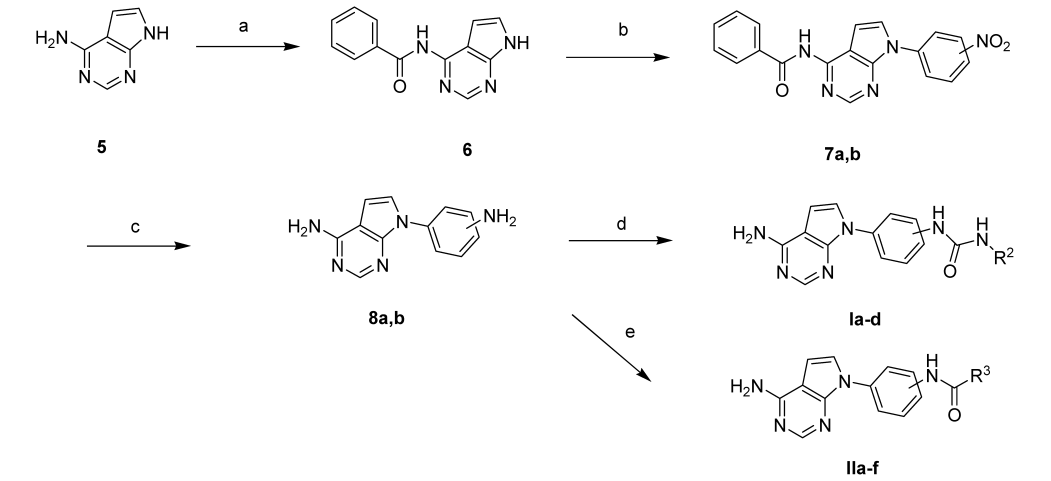


Reagents and conditions: (a) malononitrile, K_2CO_3, DMF, 50°C, 17–18 h, 54%; (b) thiourea, potassium *tert*-butoxide, EtOH, reflux, 16–17 h; rt, 1–2 h, 61%; (c) 5 N HCl, H_2O, 10 N NaOH, 50°C, 50 min, 88%; (d) Raney-Ni, H_2O, reflux, 4 h, 87%.

Chart 1



Reagents and conditions: (a) benzoyl chloride, pyridine, 50°C, overnight, 33%; (b) 1-iodo-4-nitrobenzene or 1-iodo-3-nitrobenzene, K_2CO_3, CuI, L-proline, DMSO, 90°C, 40 h, 67% (**7a**), 40% (**7b**); (c) $SnCl_2 \cdot H_2O$, EtOH, reflux, overnight, 80% (**8a**), 50% (**8b**); (d) aryl isocyanate, THF, rt, 24 h, 27–60%; (e) carboxylic acid derivative, HOBt, EDCI, TEA, DMF, 80°C, 24 h, 10–86%.

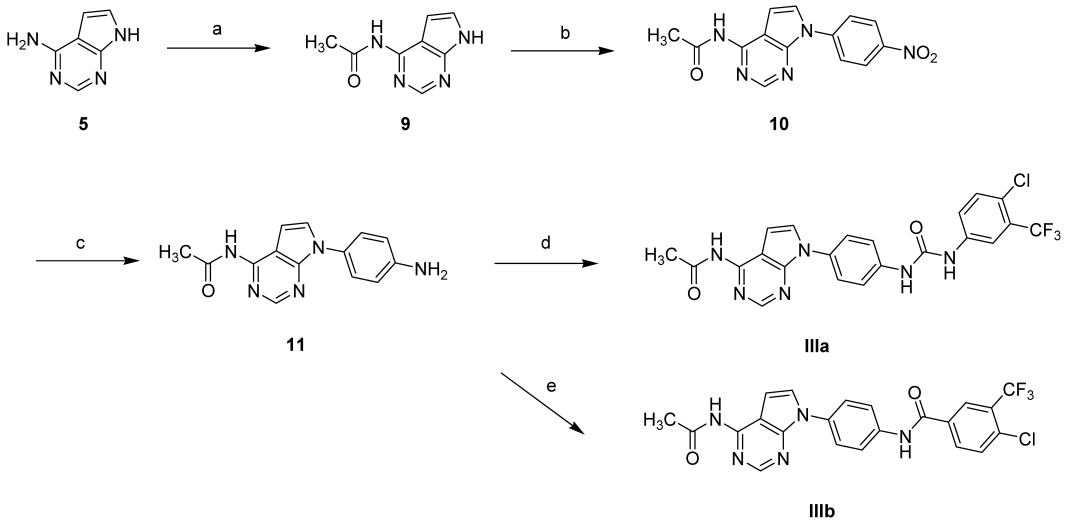
Chart 2

pyrrolo[2,3-*d*]pyrimidin-4-amine (**5**). It could be successfully achieved by the pathway shown in Chart 1. The geminal dicyano intermediate **2** was prepared from compound **1**[21] with malononitrile by heating in *N*,*N*-dimethylformamide (DMF) in the presence of anhydrous K_2CO_3. Synthesis of compound **3** was carried out by refluxing **2** with thiourea in the presence of potassium *tert*-butoxide. Cyclization to **4** could be achieved by neutralization of the thiol potassium salt **3** using 5 N aqueous HCl followed by heating with 10 N aqueous NaOH. Reduction of the thiol compound **4** using Raney nickel afforded 7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**5**) (Chart 1).

The *N*-benzoyl protected compound **6** was prepared by heating **5** with benzoyl chloride in pyridine. *N*-Arylation of **6** using 1-iodo-3(4)-nitrobenzene in the presence of potassium carbonate, copper iodide, and L-proline afforded the *N*-(nitrophenyl) compounds **7a**, **b**. The 4-benzoylamino substituted nitrophenyl compounds **7a**, **b** were reduced and deprotected using tin(II) chloride to provide the diamino compounds **8a**, **b**, which were subsequently treated with the appropriate isocyanates to provide the corresponding urea derivatives **Ia**–**d**. The amide derivatives **IIa**–**f** were obtained by condensation of **8a**, **b** with the corresponding carboxylic acid derivatives using 1-hydroxybenzotriazole (HOBt)/1-ethyl-(3-(3-dimethylamino)-propyl)-carbodiimide hydrochloride (EDCI)/triethylamine acetate (TEA) (Chart 2). In both pathways for synthesis of compounds **Ia**–**d** and **IIa**–**f**, the aniline amino groups reacted while the amino group at position 4 of the pyrrolo[2,3-*d*]-pyrimidine nucleus remained unaffected.

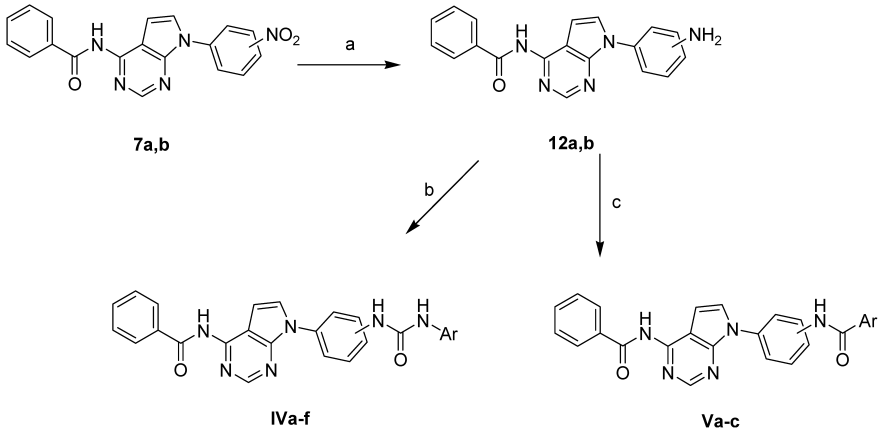
N-Acetylation of compound **5** was carried out by condensation with acetic acid in the presence of HOBt/EDCI/TEA to produce 4-acetamidopyrrolo[2,3-*d*]pyrimidine (**9**). Preparation of the 4-acetylamino substituted *p*-nitrophenyl compound **10** was accomplished by the same procedure described for the preparation of **7a**, **b**. Reduction of the nitro compound **10** using Pd/C in hydrogen atmosphere afforded the corresponding amino compound **11**, which was subsequently treated with 4-chloro-3-(trifluoromethyl)phenyl isocyanate to provide the corresponding urea derivative **IIIa**. The amide derivative **IIIb** was obtained by condensation of **11** with 4-chloro-3-(trifluoromethyl)benzoic acid using HOBt/EDCI/TEA (Chart 3).

The 4-benzamido substituted nitrophenyl compounds **7a**, **b** were reduced with Pd/C in hydrogen atmosphere to the corresponding amino compound **12a**, **b**. Compounds **IVa**–**f** and **Va**–**c** were also prepared as described for the preparation of compounds **Ia**–**d** and **IIa**–**f**, respectively (Chart 4). Table 1 illustrates structures of the final compounds, their yield percentages, and their melting points.



Reagents and conditions: (a) acetic acid, HOBt, EDCI, TEA, DMF, 80°C, 24 h, 45%; (b) 1-iodo-4-nitrobenzene, K_2CO_3, CuI, L-proline, DMSO, 90°C, 40 h, 45%; (c) Pd/C, H_2, THF, 50 psi, rt, 2 h, 25%; (d) 4-chloro-3-(trifluoromethyl)phenyl isocyanate, THF, rt, 24 h, 31%; (e) 4-chloro-3-(trifluoromethyl)benzoic acid, HOBt, EDCI, TEA, DMF, 80°C, 24 h, 47%.

Chart 3



Reagents and conditions: (a) Pd/C, H_2, 50 psi, THF, rt, 2 h, 85% (**12a**), 70% (**12b**); (b) aryl isocyanate, THF, rt, 24 h, 22–82%; (c) benzoic acid derivative, HOBt, EDCI, TEA, DMF, 80°C, 24 h, 23–36%.

Chart 4

Antiproliferative Activities against 60 Cell Line Panel at the National Cancer Institute (NCI). Single-Dose Testing Structures of the target compounds were submitted to the (NCI), Bethesda, Maryland, U.S.A.,[22] and the eleven compounds shown in Fig. 2 were selected on the basis of degree of structural variation and computer modeling techniques for evaluation of their antineoplastic activity. The selected compounds were subjected to *in vitro* anticancer assay against tumor cells in a full panel of 60 cell lines taken from nine different tissues (blood, lung, colon, central nervous system (CNS), skin, ovary, kidney, prostate, and breast). The compounds were tested at a single dose concentration of 10 μM, and the percentages of growth inhibition over the 60 tested cell lines were determined. The mean inhibition percentages for each of the tested compounds over the full panel of cell lines are illustrated in Fig. 2.

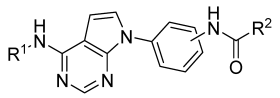
Regarding the substituents on the 4-position of pyrrolo[2,3-*d*]pyrimidine nucleus, compound **Vc** with benzamido moiety was more active than the corresponding acetamido derivative **IIIb**. This can be attributed to the steric and/or electronic differences between benzoyl and acetyl groups. This suggests that the aromatic amide substituent at this position is more favorable.

By comparing the activities of derivatives with amide and urea moieties at pyrrolo[2,3-*d*]pyrimidine side chain as a linker, it was found that compounds **IVb** and **IVd** possessing urea moiety were more active than the corresponding amide analogues **Va** and **Vc**. This may be attributed to that the longer spacer, urea moiety, may geometrically permit appropriate fitting of the molecule at the receptor site. Or the terminal NH group of the urea moiety may form additional hydrogen bond(s) at the receptor site. Any or both of these effects would enable optimal drug–receptor interaction, and hence higher antiproliferative activity.

Compound **IVd** with *para*-disubstituted phenyl ring at *N*1 position of the pyrrolo[2,3-*d*]pyrimidine nucleus showed higher mean %inhibition than its *meta*-disubstituted phenyl positional isomer **IVf**. This can be rationalized that the direction of terminal moiety can affect the appropriate fitting at the receptor site and hence affinity and activity.

The effect of substituents of the terminal aryl ring on mean %inhibition was also investigated. The introduction of *meta*-

Table 1. Structures of the Target Compounds, and Their Yield Percentages and Melting Points



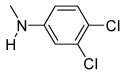
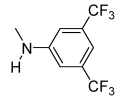
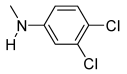
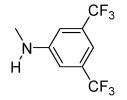
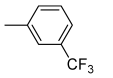
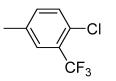
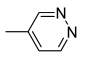
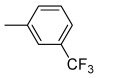
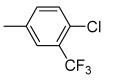
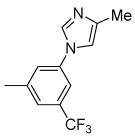
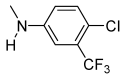
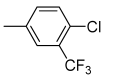
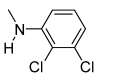
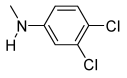
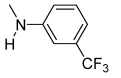
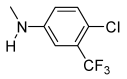
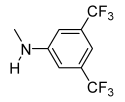
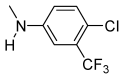
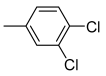
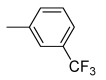
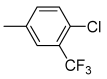
Compound No.	R^1	Site of attachment of phenyl ring	R^2	Yield%	Melting point (°C)
Ia	H	*para*		27	232–235 (dec.)
Ib	H	*para*		35	>300
Ic	H	*meta*		60	225–226 (dec.)
Id	H	*meta*		46	>300
IIa	H	*para*		47	216–218 (dec.)
IIb	H	*para*		86	215–217 (dec.)
IIc	H	*meta*		10	204–207 (dec.)
IId	H	*meta*		69	214–216 (dec)
IIe	H	*meta*		26	221–223
IIf	H	*meta*		28	218–220 (dec.)
IIIa	CH_3CO	*para*		31	274–276 (dec.)
IIIb	CH_3CO	*para*		47	241–242 (dec.)
IVa	PhCO	*para*		22	225–227 (dec.)
IVb	PhCO	*para*		25	249–250 (dec.)
IVc	PhCO	*para*		82	234–236 (dec.)
IVd	PhCO	*para*		54	190–192 (dec.)

Table 1. Continued.

Compound No.	R^1	Site of attachment of phenyl ring	R^2	Yield%	Melting point (°C)
IVe	PhCO	*para*		56	220–221 (dec.)
IVf	PhCO	*meta*		56	140–141
Va	PhCO	*para*		23	193–195
Vb	PhCO	*para*		36	181–183 (dec.)
Vc	PhCO	*para*		33	193–195 (dec.)

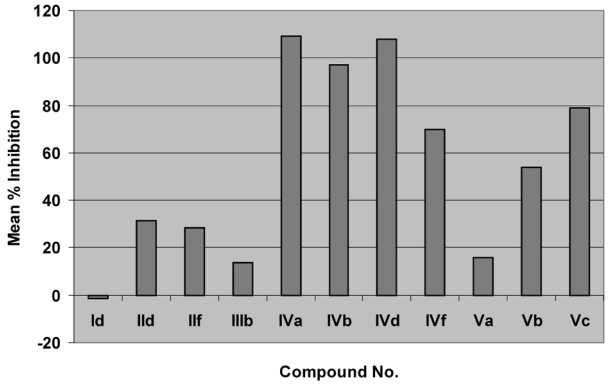


Fig. 2. Mean Inhibition Percentages Observed with the Final Compounds in Single-Dose (10 μM) 60-Cancer Cell Line Screening

Mean %inhibition represents the mean inhibition percentages over the 60 cell lines. The inhibition percentages were calculated by subtracting the growth percentages from 100.

(4′-methylimidazol-1-yl) moiety on the 3′-(trifluoromethyl)-phenyl ring (compound **IIf**) slightly reduced the activity compared with compound **IId**. On the other hand, *para*-chloro group improved the activity of compound **Vc** compared with **Vb** with 4′-unsubstituted 3′-(trifluoromethyl)phenyl terminal ring. Compound **IVa** with 2′,3′-dichlorophenyl terminal ring exhibited higher mean %inhibition than the corresponding positional isomer compound **IVb** with 3′,4′-dichlorophenyl terminal moiety.

Among all the target compounds, it was found that compounds **IVa**, **IVb**, and **IVd** possessing benzamido moiety at position 4 of the pyrrolo[2,3-*d*]pyrimidine nucleus, *para*-disubstituted phenyl ring at *N*1-position of pyrrolo[2,3-*d*]-pyrimidine scaffold, and urea linker demonstrated the highest mean %inhibition values; 109.18%, 96.91%, and 107.86%, respectively. So it can be concluded that the presence of those three moieties together is essential for antiproliferative activity this series of pyrrolo[2,3-*d*]pyrimidine compounds.

Compounds **IVa** and **IVd** exerted lethal effect on the NCI-60 cancer cell line panel with mean IC_{50} values more than 100%. The % inhibitions of these two compounds over each cell line of the NCI-60 panel are illustrated in Fig. 3. At 10 μM concentration, both compounds showed lethal effects (>100% inhibition) over 32 and 25 cell lines, respectively. Both compounds demonstrated broad-spectrum cytotoxicities over all the nine tested cancer types.

Five-Dose Testing Compounds **IVa**, **IVb**, **IVd**, **IVf**, **Vb**, and **Vc** with promising results in single-dose testing were further tested in a five-dose testing mode, in order to determine their IC_{50}, total growth inhibition (TGI), and 50% lethal concentration (LC_{50}) values over the 60 cancer cell lines. The results of these six compounds over the most sensitive cell line of the nine tested cancer subpanels are shown in Table 2. The results of Sorafenib and Imatinib were obtained from NCI datawarehouse index[23] and are inserted in Table 2. It is noteworthy that all the selected six compounds possess benzamido moiety at position 4 of the pyrrolo[2,3-*d*]pyrimidine nucleus and *para*-disubstituted phenyl ring at *N*1-position of pyrrolo[2,3-*d*]pyrimidine scaffold.

As shown in Table 2, most of the compounds exhibited broad-spectrum activities with high potency (in sub-micromolar and micromolar scale) over all the nine cell lines. Most of the IC_{50} values were less than 10 μM. Compound **IVa**, with the highest mean %inhibition value in one-dose testing mode (Fig. 2), showed the highest potency among the six compounds tested in five-dose testing mode. Its IC_{50} values were in sub-micromolar scale over eight cell lines. It demonstrated higher potency than Sorafenib against eight cell lines. Its TGI results showed higher efficacy than Sorafenib over seven cell lines. And its potency and efficacy against all the nine cell lines were higher than Imatinib. In addition, the diarylamide derivative **Vb** exhibited one-digit nanomolar IC_{50} values, 7 and 8 nM, over NCI-H460 non-small cell lung and HCT-15 colon cancer cell lines, respectively. The diarylamide derivative **Vc** exerted high potency over HCT-15 colon cancer cell line also with IC_{50} value of 7 nM. Compounds **Vb** and **Vc** demonstrated sub-micromolar IC_{50} values over five and six cell lines, respectively. Both compounds **Vb** and **Vc** showed higher potencies and efficacies than Sorafenib and Imatinib against most of the tested cell lines.

Compounds **IVa**, **IVb**, **IVd**, **IVf**, **Vb**, and **Vc** showed high efficacies also over the nine cell lines. The TGI and LC_{50}

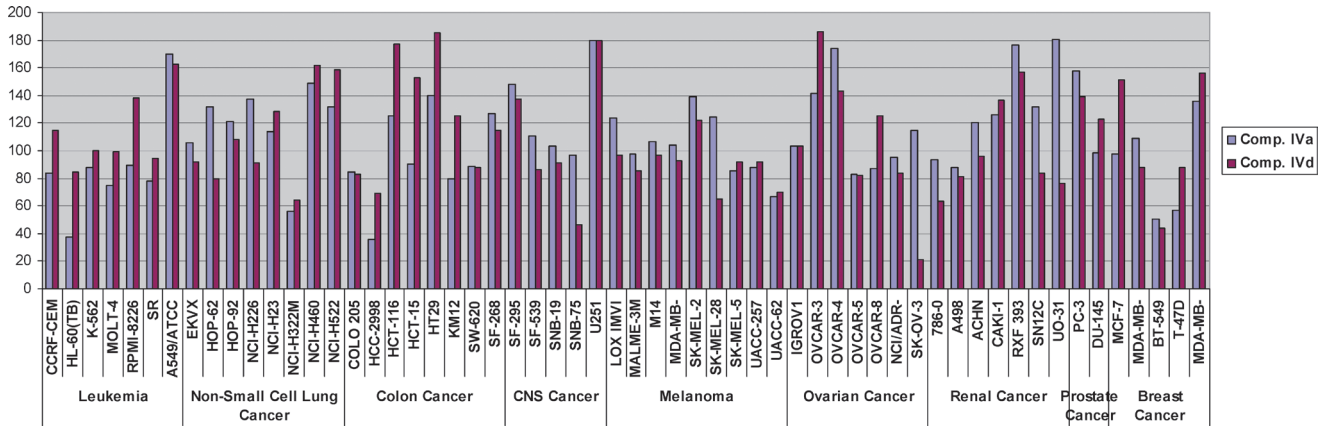


Fig. 3. %Inhibition Expressed by Compounds **IVa** and **IVd** at a Single-Dose Concentration of 10 μM over the NCI-60 Cancer Cell Lines

Table 2. IC_{50}, TGI, and LC_{50} Values (μM) of the Tested Compounds over the Most Sensitive Cell Line of Each Subpanel

Compd. No.	Results (μM)	Cancer cell line								
		CCRF-CEM[a]	NCI-H460[b]	HCT-15[c]	U251[d]	LOX IMVI[e]	OVCAR-4[f]	CAKI-1[g]	PC-3[h]	HS 578T[i]
IVa	IC_{50}[j]	0.53	0.36	0.16	0.57	0.76	0.88	3.84	0.58	0.86
	TGI[k]	3.21	1.21	5.42	1.40	2.04	1.91	24.90	1.57	2.60
	LC_{50}[l]	>50	NA[m]	42.70	3.46	>50	4.14	>50	4.21	>50
IVb	IC_{50}[j]	0.99	1.71	1.74	0.94	2.38	0.89	8.79	1.06	1.19
	TGI[k]	2.83	5.85	6.97	2.29	16.30	1.80	21.20	2.86	5.77
	LC_{50}[l]	38.70	40.10	22.00	7.37	>50	3.67	>50	11.70	>50
IVd	IC_{50}[j]	0.81	1.35	0.77	1.20	2.00	1.57	1.69	1.25	1.27
	TGI[k]	3.73	3.06	2.19	2.55	6.77	3.48	3.81	3.01	4.61
	LC_{50}[l]	>50	6.89	5.30	5.43	>50	7.70	8.60	7.25	>50
IVf	IC_{50}[j]	0.66	2.13	2.51	2.09	2.82	2.36	2.04	1.25	2.55
	TGI[k]	9.05	9.88	10.20	8.39	15.00	8.18	10.90	5.93	22.60
	LC_{50}[l]	>50	>50	32.80	28.60	>50	21.90	>50	29.00	>50
Vb	IC_{50}[j]	NA[m]	0.008	0.007	0.13	0.23	5.46	0.82	10.10	6.01
	TGI[k]	NA[m]	12.90	45.70	18.60	2.45	49.20	19.90	41.00	49.70
	LC_{50}[l]	NA[m]	46.40	>50	>50	19.50	>50	>50	>50	>50
Vc	IC_{50}[j]	0.85	0.14	0.007	0.36	0.30	1.44	0.40	1.26	1.48
	TGI[k]	18.20	1.74	2.27	2.23	2.75	4.06	5.91	7.41	4.88
	LC_{50}[l]	>50	6.08	14.50	5.70	>50	13.80	49.80	>50	>50
Sorafenib	IC_{50}[j]	2.00	2.51	2.51	2.00	1.58	3.16	3.16	2.00	2.51
	TGI[k]	5.01	5.01	3.16	3.16	2.51	25.12	12.59	5.01	3.98
	LC_{50}[l]	100	25.12	7.94	6.31	6.31	100	100	100	100
Imatinib	IC_{50}[j]	15.85	15.85	19.95	19.95	19.95	19.95	31.62	19.95	15.85
	TGI[k]	63.10	31.62	79.43	50.12	39.81	63.10	79.43	63.10	39.81
	LC_{50}[l]	100	79.43	100	100	79.43	100	100	100	100

a) Leukemia cell line; *b*) non-small cell lung cancer cell line; *c*) colon cancer cell line; *d*) CNS cancer cell line; *e*) melanoma cell line; *f*) ovarian cancer cell line; *g*) renal cancer cell line; *h*) prostate cancer cell line; *i*) breast cancer cell line; *j*) IC_{50} is the concentration producing 50% inhibition; *k*) TGI is the concentration producing 100% inhibition; *l*) LC_{50} is the concentration causing 50% lethality (50% tumor regression); *m*) NA means that the datum is not available.

values were less than 50 μM over most of the cell lines. Of special interest, compound **IVa** with the best results was able to induce TGI and LC_{50} at U251 CNS cancer cell line, OVCAR-4 ovarian cancer cell line, and PC-3 prostate cancer cell line at concentrations below 4.22 μM. Similarly, compound **IVb** showed TGI and LC_{50} values of 1.80 μM and 3.67 μM, respectively, over OVCAR-4 ovarian cancer cell line. The six tested compounds showed higher potencies and efficacies than Sorafenib and Imatinib against most of the tested cell lines.

Kinase Screening In an attempt to study the possible mechanism(s) of antiproliferative activity of the most active target compounds, compounds **IVa**, **IVb**, and **IVd** were tested for inhibitory effect over wild type B-RAF, vascular endothelial growth factor receptor 1 (VEGFR1), and platelet-derived growth factor receptor (PDGFR) kinases. The three compounds showed weak potency against these kinases, compared with Sorafenib (Table 3). So it can be concluded that these target compounds inhibit cancer cell growth through other

Table 3. IC_{50} Values of Compounds **IVa**, **IVb**, **IVd**, and Sorafenib over Potential Kinases

	B-RAF (wild type)	VEGFR1	PDGFR
IVa	>3 μM	>3 μM	>3 μM
IVb	>3 μM	>3 μM	>3 μM
IVd	>3 μM	>3 μM	>3 μM
Sorafenib	25 nM	26 nM	90 nM

mechanism(s) other than B-RAF, VEGFR1, and PDGFR kinase inhibition.

Conclusion

A series of diarylureas and diarylamides possessing pyrrolo[2,3-*d*]pyrimidine scaffold was designed with structural similarity to Sorafenib and synthesized. Eleven final compounds were tested at a single-dose concentration of 10 μM at the NCI over 60 cancer cell line panel of nine different cancer types, and six of them were subsequently tested in five-dose testing mode. Compounds **IVa**, **IVb**, **IVd**, **IVf**, **Vb**, and **Vc** showed broad-spectrum anticancer activities with strong potencies and high efficacies. Among them, compounds **IVa**, **IVb**, and **IVd** possessing benzamido moiety at position 4 of the pyrrolo[2,3-*d*]pyrimidine nucleus, *para*-disubstituted phenyl ring at *N*1-position of pyrrolo[2,3-*d*]pyrimidine scaffold, and urea linker exerted the highest mean % inhibition in one-dose testing mode, and high potency and efficacy in five-dose testing experiments. So we can conclude that these moieties together with the pyrrolo[2,3-*d*]pyrimidine nucleus constitute the pharmacophore of this series of compounds as potential anticancer agents.

Compound **IVa** demonstrated the best results in both one-dose and five-dose testing modes. It showed 109.18% mean % inhibition over the NCI-60 cancer cell line panel at 10 μM concentration, submicromolar IC_{50} values over eight cell lines of eight different cancer types, and high efficacy with TGI and LC_{50} values less than 4.22 μM over three colon, ovarian, and prostate cancer cell lines. Its potency and efficacy results were promising compared with Sorafenib and Imatinib. So this compound can be considered as promising lead for future development of potential anticancer agents with high potency and efficacy.

Experimental

General All melting points were obtained on a Walden Precision Apparatus Electrothermal 9300 apparatus and are uncorrected. Mass spectra (MS) were taken in electrospray ionization (ESI) mode on a Waters 3100 Mass Detector (Waters, Milford, MA, U.S.A.). Nuclear magnetic resonance (NMR) spectroscopy was performed using a Bruker ARX-300, 300 MHz (Bruker Bioscience, Billerica, MA, U.S.A.) with TMS as an internal standard. Purities of the target compounds (>95%) were determined by LC-MS analysis using the following system: Waters 2998 photodiode array detector, Waters 3100 mass detector, Waters SFO system fluidics organizer, Waters 2545 binary gradient module, Waters reagent manager, Waters 2767 sample manager, Sunfire™ C18 column (4.6×50 mm, 5 μm particle size); Solvent gradient=95% A at 0 min, 1% A at 5 min; solvent A: 0.035% trifluoroacetic acid (TFA) in water; solvent B: 0.035% TFA in CH_3OH; flow rate=3.0 mL/min; the area under curve (*AUC*) was calculated using Waters MassLynx 4.1 software. Unless otherwise noted, all solvents and reagents were commercially available and used without further purification.

2-(2,2-Diethoxyethyl)malononitrile (2) To a suspension of anhydrous potassium carbonate (1.4 g, 10.1 mmol) in dry DMF (3 mL), malononitrile (0.6 g, 9.1 mmol) was slowly added. The resulting mixture was heated at 41°C for 8 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature, then 2-bromo-1,1-diethoxyethane (**1**, 1.0 g, 5.1 mmol) was added portionwise thereto. The reaction mixture was heated to 50°C for 17–18 h. After completion of the reaction, the reaction mixture was cooled to room temperature, and extracted between toluene (50 mL×3) and water (40 mL). The combined organic layer extracts were dried over anhydrous $MgSO_4$, the organic solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate–hexane 1 : 6, v/v) to obtain the title product (0.5 g, 54%). IR (KBr): 3350, 2978, 2250, 1748, 1633, 1441, 1375, 1124 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.69 (t, 1H, J=5.3 Hz), 4.03 (t, 1H, J=7.3 Hz), 3.75–3.67 (m, 2H), 3.58–3.53 (m, 2H), 2.32–2.27 (m, 2H), 1.27–1.21 (m, 6H).

4,6-Diamino-5-(2,2-diethoxyethyl)pyrimidine-2-thiol Potassium Salt (3) A solution of compound **2** (5.0 g, 27.4 mmol) in ethanol (60 mL) was cooled to 0°C, and thiourea (2.4 g, 31.5 mmol) was added portionwise thereto. Then a suspension of potassium *tert*-butoxide (3.5 g, 31.2 mmol) in ethanol (5.5 mL) was added dropwise. The reaction mixture was heated under reflux for 16–17 h, then cooled to room temperature. Ethanol (30 mL) was added, and the mixture was stirred at room temperature for 1–2 h. The produced solid was filtered out, washed with ethanol (20 mL), and dried to get the pure title compound (5.0 g, 61%). mp: 223–225°C (dec.); IR (KBr): 3434, 1630, 1435, 1314, 1050 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 4.92 (br s, 4H), 4.40 (t, 1H, J=5.3 Hz), 3.65–3.55 (m, 2H), 3.42–3.36 (m, 2H), 2.43–2.41 (m, 2H), 1.11–1.03 (m, 6H).

4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-thiol (4) To a solution of compound **3** (7.5 g, 25.3 mmol) in distilled water (40 mL), 5 N HCl aqueous solution (11.8 mL) was added dropwise. After 20 min, distilled water (7 mL) was added thereto. The reaction mixture was heated at 50°C for 50 min, then cooled to room temperature. The reaction mixture was neutralized to pH 7 by dropwise addition of 10 N NaOH aqueous solution. The precipitated solid was filtered out, washed with acetonitrile (50 mL), and vacuum dried to obtain the pure title product (3.7 g, 88%). mp: 218–220°C (dec.); IR (KBr): 3413, 3171, 2884, 1655, 1584, 1133 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 11.59 (br s, 1H), 11.30 (br s, 2H), 6.88 (d, 1H, J=6.0 Hz), 6.47 (d, 1H, J=5.9 Hz).

7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-amine (5) To a suspension of compound **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 nickel residue was washed with water (100 mL). The combined 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, 300 MHz) δ: 12.37 (br s, 1H), 8.22 (br s, 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 (6)** To a suspension of compound **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 evaporated under reduced pressure, and purification was achieved by flash column chromatography (silica gel, ethyl acetate–hexane 1 : 2, v/v) to afford the title compound (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).

Synthesis of Compounds 7a, b A mixture of compound **6** (0.3 g, 1.3 mmol), 1-iodo-4-nitrobenzene or 1-iodo-3-nitrobenzene (0.6 g, 2.4 mmol), anhydrous potassium carbonate (0.5 g, 2.4 mmol), CuI (20.0 mg, 0.1 mmol), and L-proline (30 mg, 0.3 mmol) in dry DMSO (5 mL) was heated at 90°C under nitrogen atmosphere for 40 h. The cooled solution was partitioned between H_2O (20 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layer extracts were washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and purification was achieved by flash chromatography (silica gel, ethyl acetate–hexane 1 : 2, v/v) to afford the target compound **7a** or **7b**.

N-(7-(4-Nitrophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-benzamide (**7a**): Yield: 67%; 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-(3-Nitrophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-benzamide (**7b**): 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 Hz), 7.68–7.64 (m, 1H), 7.59–7.54 (m, 2H), 6.90 (d, 1H, J=3.4 Hz).

Synthesis of Compounds 8a, b A mixture of compound **7a** or **7b** (1.0 g, 2.8 mmol) and $SnCl_2 \cdot H_2O$ (3.1 g, 13.7 mmol) in ethanol (20 mL) was heated under reflux overnight, and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate (30 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic layer was separated, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and purification was achieved by flash column chromatography (silica gel, ethyl acetate) to afford the target compounds.

4-Amino-7-(4-aminophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**8a**): Yield: 80%; 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).

4-Amino-7-(3-aminophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**8b**): 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).

General Procedure for Synthesis of Compounds Ia–d To a solution of compound **8a**, **b** (30.0 mg, 0.1 mmol) in anhydrous tetrahydrofuran (THF) (3 mL), a solution of the appropriate aryl isocyanate (0.1 mmol) in anhydrous THF (3 mL) was added dropwise at room temperature under N_2 atmosphere. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure, and purification was carried out by flash column chromatography using the appropriate proportion of ethyl acetate and hexane as mobile phase.

1-(4-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)-3-(3,4-dichlorophenyl)urea (**Ia**): ^{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 $[M+1]^+$.

1-(4-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea (**Ib**): ^{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 $[M+1]^+$.

1-(3-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)-3-(3,4-dichlorophenyl)urea (**Ic**): ^{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 $[M+1]^+$.

1-(3-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea (**Id**): ^{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 $[M+1]^+$.

General Procedure for Synthesis of Compounds IIa–f A mixture of compound **8a**, **b** (30 mg, 0.1 mmol), the appropriate carboxylic acid derivative (0.2 mmol), HOBt (36 mg, 0.3 mmol), and EDCI (38 mg, 0.2 mmol) in dry DMF (1.0 mL) was cooled to 0°C under nitrogen atmosphere. Triethylamine (0.03 mL, 0.2 mmol) was added thereto at the same temperature. The mixture was then stirred at 80°C for 24 h. The reaction mixture was cooled and then partitioned between saturated aqueous sodium carbonate and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic layer extracts were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the organic solvent, the residue was purified by column chromatography using the appropriate proportion of ethyl acetate and hexane as mobile phase.

N-(4-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)-3-(trifluoromethyl)benzamide (**IIa**): ^{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 $[M+1]^+$.

N-(4-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)-4-chloro-3-(trifluoromethyl)benzamide (**IIb**): ^{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 $[M+1]^+$.

N-(3-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)-pyridazine-4-carboxamide (**IIc**): ^{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 $[M+1]^+$.

N-(3-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)-3-(trifluoromethyl)benzamide (**IId**): ^{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 $[M+1]^+$.

N-(3-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)-4-chloro-3-(trifluoromethyl)benzamide (**IIe**): ^{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 $[M+1]^+$.

N-(3-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)-3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)benzamide (**IIf**): ^{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 $[M+1]^+$.

***N*-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)acetamide (9)** A mixture of compound **5** (0.5 g, 3.7 mmol), acetic acid (0.4 g, 6.6 mmol), HOBt (1.1 g, 8.1 mmol), and EDCI (1.8 g, 9.3 mmol) in dry DMF (15 mL) was cooled to 0°C under nitrogen atmosphere. Triethylamine (1.6 mL, 11.4 mmol) was added thereto at the same temperature. The mixture was then stirred at 80°C for 24 h. The reaction mixture was cooled and then partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layer extracts were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the organic solvent, the residue was purified by column chromatography (silica gel, ethyl acetate) to get the pure title compound (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)-acetamide (10)** It was prepared by the same method utilized for synthesis of compounds **7a**, **b**. 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).

***N*-(7-(4-Aminophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-acetamide (11)** To a solution of compound **10** (0.2 g, 0.7 mmol) in dry 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 column chromatography (silica gel, ethyl acetate) to give the title product (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).

Synthesis of Compounds IIIa and b They were prepared by the same method utilized for synthesis of **Ia**–**d** and **IIa**–**f**, respectively.

N-(7-(4-(3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido)-phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)acetamide (**IIIa**): ^{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 $[M+1]^+$.

N-(4-(4-Acetamido-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-phenyl)-4-chloro-3-(trifluoromethyl)benzamide (**IIIb**): ^{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 $[M+H]^+$.

Synthesis of Compounds 12a, b They were synthesized in the same way as synthesis of compound **11**.

N-(7-(4-Aminophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-benzamide (**12a**): Yield 85%; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 11.19 (brs, 1H), 8.62 (s, 1H), 8.09–8.07 (m, 2H), 7.68–7.56 (m, 4H), 7.37–7.34 (m, 2H), 6.71–6.69 (m, 3H), 5.33 (brs, 2H).

N-(7-(3-Aminophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-benzamide (**12b**): Yield 70%; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 11.22 (brs, 1H), 8.65 (s, 1H), 8.12–8.09 (m, 2H), 7.70–7.57 (m, 4H), 7.40–7.36 (m, 2H), 6.73–6.70 (m, 3H), 5.35 (brs, 2H).

Synthesis of Compounds IVa–f This was carried out by the same procedure utilized for synthesis of compounds **Ia**–**d**.

N-{{7-{4-[3-(2,3-Dichlorophenyl)ureido]phenyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}}benzamide (**IVa**): IR (KBr): 3310, 1512, 1250, 708 cm^{-1}; ^{1}H-NMR(DMSO-d_6, 300 MHz) δ: 11.23 (brs, 1H), 9.72 (brs, 1H), 8.65 (s, 1H), 8.56 (s, 1H), 8.22–8.18 (m, 1H), 8.09 (d, 2H, J=7.7 Hz), 7.85 (d, 1H, J=3.7 Hz), 7.78 (d, 2H, J=8.9 Hz), 7.68–7.63 (m, 4H), 7.59–7.54 (m, 2H), 7.33–7.32 (m, 1H), 6.81 (d, 1H, J=6.6 Hz); ESI-MS: 516.1 $[M+1]^+$.

N-{{7-{4-[3-(3,4-Dichlorophenyl)ureido]phenyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}}benzamide (**IVb**): IR (KBr): 3290, 1521, 1230, 689 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 11.23 (brs, 1H), 9.21–9.18 (m, 2H), 8.65 (s, 1H), 8.10–8.08 (m, 2H), 7.92–7.91 (m, 1H), 7.85 (d, 1H, J=3.6 Hz), 7.70–7.76 (m, 2H), 7.67–7.64 (m, 3H), 7.59–7.54 (m, 3H), 7.39–7.35 (m, 1H), 6.81 (d, 1H, J=3.3 Hz); ESI-MS: 417.1 $[M+1]^+$.

N-{{7-{4-[3-(3-(Trifluoromethyl)phenyl)ureido]phenyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}}benzamide (**IVc**): IR (KBr): 3320, 1523, 1339, 1123, 698 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 11.21 (brs, 1H), 9.48 (brs, 1H), 9.38 (brs, 1H), 8.65 (s, 1H), 8.10–8.05 (m, 3H), 7.84 (d, 1H, J=3.6 Hz), 7.76–7.73 (m, 6H), 7.62–7.50 (m, 3H), 7.33–7.30 (m, 1H), 6.82 (d, 1H, J=3.6 Hz); ESI-MS: 517.1 $[M+1]^+$.

N-{{7-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-phenyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}}benzamide (**IVd**): IR (KBr): 3331, 1522, 1310, 1175, 1032, 711 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 11.23 (brs, 1H), 9.38 (brs, 1H), 9.22 (brs, 1H), 8.65 (s, 1H), 8.14–8.08 (m, 3H), 7.85–7.83 (m, 1H), 7.77–7.74 (m, 2H), 7.70–7.61 (m, 5H), 7.58–7.47 (m, 2H), 6.81 (d, 1H, J=3.6 Hz); ESI-MS: 551.1 $[M+1]^+$.

N-{{7-{4-[3-(3,5-Bis-trifluoromethyl-phenyl)ureido]-phenyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}}benzamide (**IVe**): IR (KBr): 3311, 1527, 1276, 1124, 879, 681 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 11.21 (brs, 1H), 9.63 (brs, 1H), 9.37 (brs, 1H), 8.65 (s, 1H), 8.17 (s, 2H), 8.09 (d, 2H, J=7.3 Hz), 7.84 (d, 1H, J=3.7 Hz), 7.78–7.75 (m, 2H), 7.70–7.63 (m, 4H), 7.58–7.56 (m, 2H), 6.82 (d, 1H, J=3.6 Hz); ESI-MS: 585.1 $[M+1]^+$.

N-(7-(3-(3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido)-phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)benzamide (**IVf**): ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 11.25 (brs, 1H), 9.41 (brs, 1H), 9.24 (brs, 1H), 8.67 (s, 1H), 8.17–8.11 (m, 3H), 7.88–7.85 (m, 1H), 7.79–7.76 (m, 2H), 7.73–7.63 (m, 5H), 7.61–7.50 (m, 2H), 6.83 (d, 1H, J=3.6 Hz); ESI-MS: 551.1 $[M+1]^+$.

Synthesis of Compounds Va–c This was carried out by the same procedure utilized for synthesis of compounds **IIa**–**f**.

N-[4-(4-Benzoylamino-pyrrolo[2,3-*d*]pyrimidin-7-yl)-phenyl]-3,4-dichlorobenzamide (**Va**): IR (KBr): 3427, 1620, 1401, 1027, 753 cm^{-1}; ^{1}H-NMR(DMSO-d_6, 300 MHz) δ: 11.23 (brs, 1H), 10.59 (brs, 1H), 8.67 (s, 1H), 8.27 (d, 1H, J=1.7 Hz),

8.11–8.08 (m, 2H), 8.00–7.95 (m, 3H), 7.89–7.85 (m, 4H), 7.59–7.54 (m, 3H), 6.84 (d, 1H, J=3.8 Hz); ESI-MS: 502.0 $[M+1]^+$.

N-[4-(4-Benzoylamino-pyrrolo[2,3-*d*]pyrimidin-7-yl)-phenyl]-(3-trifluoromethyl)benzamide (**Vb**): IR (KBr): 3223, 1523, 1312, 1123, 708 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 11.24 (brs, 1H), 10.68 (brs, 1H), 8.67 (s, 1H), 8.34–8.30 (m, 2H), 8.11–8.08 (m, 2H), 8.02–7.97 (m, 2H), 7.89–7.76 (m, 4H), 7.69–7.64 (m, 1H), 7.59–7.54 (m, 3H), 6.84 (d, 1H, J=3.7 Hz); ESI-MS: 502.1 $[M+1]^+$.

N-[4-(4-Benzoylamino-pyrrolo[2,3-*d*]pyrimidin-7-yl)-phenyl]-4-chloro-3-(trifluoromethyl)benzamide (**Vc**): IR (KBr): 3300, 1523, 1312, 1138, 750 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 11.27 (brs, 1H), 10.75 (brs, 1H), 8.68 (s, 1H), 8.43–8.41 (m, 1H), 8.11–8.08 (m, 3H), 7.98–7.85 (m, 4H), 7.68–7.64 (m, 2H), 7.59–7.54 (m, 3H), 6.84 (d, 1H, J=3.6 Hz); ESI-MS: 536.1 $[M+1]^+$.

Sixty Cancer Cell Line Screening at the NCI Screening against a panel of 60 cancer cell lines was carried out at the National Cancer Institute (NCI), Bethesda, Maryland, U.S.A.,[22] applying the standard protocol of the NCI.[23,24]

Kinase Profiling Reaction Biology Corp. Kinase HotSpot^{SM} service[25] was used for screening of the test compound, and IC_{50} Profiler Express for IC_{50} measurement. Assay protocol: In a final reaction volume of 25 μL, kinase (5–10 mU) is incubated with 25 mM Tris pH 7.5, 0.02 mM EGTA, 0.66 mg/mL myelin basic protein, 10 mM magnesium acetate and [γ^{33}P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the Mg-ATP mix. After incubation for 40 min at room temperature, the reaction is stopped by the addition of 5 μL of a 3% phosphoric acid solution. Ten microliter of the reaction is then spotted onto a P30 filtermat and washed three times for 5 min in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

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