Article

Synthesis and *In Vitro* Antiproliferative Activity of New -Phenyl-3-(4-(Pyridin-3-Yl)Phenyl)Urea-Scaffold Based Compounds

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Abstract: Synthesis of new series of 1-phenyl-3-(4-(pyridin-3-yl) phenyl) urea derivatives and its *in vitro* antiproliferative activities against NCI-60 human cancer cell lines of nine different cancer types are described. Fourteen compounds **5a-n** have been synthesized with three different hydrogen bondable moieties (4-hydroxylmethylpiperidinyl and trimethoxyphenyloxy and 4-hydroxyethylpiperazine) attached to the core structure 1-phenyl-3-(4-(pyridin-3-yl) phenyl) urea. Different substituents with different π and σ values were added on the terminal phenyl group. Compounds with 4-hydroxymethylpiperidine moiety showed higher mean percentage inhibition values over the 60-cell line panel at 10-μM concentration. They showed broad-spectrum antiproliferative activity over many cell lines of different cancer types. For instance, compound **5a** elicited some lethal rather than inhibition effects on SK-MEL-5 melanoma cell line, 786-0, A498, RXF 393 renal cancer cell lines, and MDA-MB-468 breast cancer cell line by 146.1, 108.7, 136.2, 134.8, 116.6 % at 10 μM, respectively. Compounds **5a-e** exhibited superior antiproliferative activity than Paclitaxel and Gefitinib against the most sensitive cell lines. Two compounds, **5a** and **5d** showed promising mean growth inhibitions and thus were further tested at five-dose testing mode to determine their IC_{50} values. The data revealed that **5a** and **5d** urea compounds are the most active derivatives with significant efficacies and superior potencies than Paclitaxel in 21 different cancer cell lines, belonging particularly to renal cancer and melanoma cell lines. Moreover, **5a** and **5d** had superior potencies than Gefitinib in 38 and 34 cancer cell lines, respectively; belonging particularly to colon cancer, breast cancer and melanoma cell lines.

Keywords: cancer; cell line; synthesis; urea derivatives; antiproliferative; activity

1. Introduction

Cancer in its essence is a genetic disease; accumulation of inherited and/or acquired defects in cell proliferation and survival regulatory genes is responsible for cancer precipitation. [1] Oncogenes, tumor-suppressor genes and stability genes are the three types of genes in which the variations are the possible causes of cancer. These defects are required for a clinically significant

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cancer to occur and drive transformation of normal cell into cancerous one. [2] In spite of the availability of developed drugs including targeted tumor therapies, the World Health Organization (WHO) has announced the great possibility of increasing the universal cancer burden by 15 million new cancer cases per year by 2020, unless further preventive measures are considered. The developments of new anticancer drugs signify a major attention and challenge to the modern medicinal chemistry.

The urea chemotype is one of the most interesting scaffold-based compounds in the treatment of cancer diseases.[3] Apart from anticancer activity, other biological activities have been reported for urea derivatives such as antidiabetic [4-6], antitubercular [7-9], antimicrobial [10-12], and anti-inflammatory activities [10,11,13]. Much attention has been paid to the chemistry and biological activities of diaryl urea nucleus. Several compounds possessing diaryl urea scaffold have been recently reported as potential antiproliferative agents. [12,14-20]

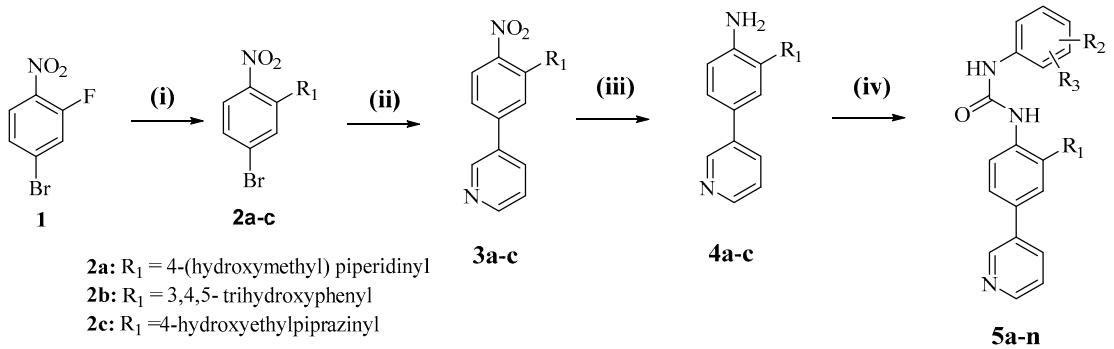
In the present study, a new series of diaryl urea derivatives possessing 1-phenyl-3-(4-(pyridin-3-yl) phenyl) urea were designed, synthesized and tested for their in vitro antiproliferative activities against NCI-60 cancer cell lines. Various substituted terminal phenyl moieties were introduced to investigate the influence of electronic and hydrophobic effects on the antiproliferative activity of the titled compounds. Furthermore, three hydrogen bondable moieties were introduced to the internal phenyl moiety to explore whether such adding of these moieties would bring a significant rise in anticancer activity.

2. Results

2.1. Chemistry

Synthesis of the target compounds **5a-n** was achieved through the pathway illustrated in Figure 1. Regioselective nucleophilic aromatic substitution of 2-fluoro-4-bromonitrobenzene (1) with 3 hydrogen bondable moieties (4-hydroxylmethylpiperidinyl and trimethoxyphenyloxy and 4-hydroxyethylpiperazine) was the first step. The nitro group in 2-Fluoro-4-bromonitrobenzene increases the reactivity of the aryl halide by decreasing the energy of the transition state according to Hammond postulate and stabilizes the intermediate carbanion, furthermore fluorine atom is more electronegative and then its reactivity is much more than the bromine atom. Therefore, the substitution reaction will be directed to ortho position of nitro group rather than the para position forming monosubstituted nitro benzene (**2a-c**) (Figure 1).

The negatively polarized carbon-metal bond is well suited for the purpose of carbon-carbon forming reaction. Monosubstituted nitrobenzene **2a-c** were subjected to coupling reaction with 3-pyridineboronic acid in the presence of bis(triphenylphosphine)palladium(II) dichloride to afford disubstituted nitrobenzenes (**3a-c**).



2a: R_1 = 4-(hydroxymethyl) piperidinyl
2b: R_1 = 3,4,5- trihydroxyphenyl
2c: R_1 =4-hydroxyethylpiprazinyl

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Reagents and reaction condition (i) R_1H, K_2CO_3, DMF, 90 °C, 5 h; (ii) $Pd(PPh_3)_2Cl_2$, K_2CO_3, 95 °C, 3 h; (iii) 10% Pd/C, H_2, ethanol, 9 h; (iv) arylisocyanate, THF, RT.

Comp. No.	R_1	R_2	R_3
5a	4-hydroxymethylpiperidine	4-CH_3	H
5b		4-CF_3	H
5c		4-OCH_3	H
5d		3-Cl	4-CF_3
5e		2-Cl	4-Cl
5f	3,4,5-trimethoxyphenol	2-F	2-F
5g		4-OCH_3	H
5h		2-F	H
5i		2-Cl	4-Cl
5j		3-CF_3	4-Cl
5k	4-hydroxyethylpiperazine	2-F	H
5l		4-CH_3	H
5m		2-Cl	4-Cl
5n		3-CF_3	4-Cl

Figure 1. Synthetic scheme of diaryl urea derivatives **5a-n.**

2.2. In vitro antiproliferative activities against NCI-60 cell line panel

2.2.1. Single dose testing

The newly synthesized target compounds (**5a-n**) were submitted to National Cancer Institute (NCI), Bethesda, Maryland, USA (NCI website: www.dtp.nci.nih.gov. (Retrieved on Dec. 4th), and the seven compounds (**5a-g**) shown in Table 1 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, 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 58 tested cell lines were determined.

2.2.2. Five dose testing

Compounds **5a** and **5d** with promising results in single-dose test and satisfying the criteria set by the NCI for activity in that preliminary assay were further tested in a five dose testing mode at 10-fold dilution (100 - 0.01 μM) on the full panel. For each of these compounds, three response parameters; the IC_{50} (the concentration producing 50% GI, a measure of compound potency), TGI (the concentration producing 100% GI, a measure of compound efficacy) and LC_{50} (the concentration causing 50% lethality, a measure of compound efficacy and cytotoxicity) were determined. The two tested compounds **5a** and **5d** showed high potency with one-digit micro molar IC_{50} values over most of the cell lines.

3. Discussion

3.1. Chemistry

The structure of the newly synthesized compounds **3a-c** was confirmed on the basis of 1H-NMR, 13C-NMR spectroscopic data. The 1H NMR spectra of compound **3c** exhibited triplet signals at δ 2.67 ppm and 3.69 ppm (2H) corresponding to NCH_2CH_2OH. Triplet signals at δ 2.748 ppm and 3.21 ppm (4H) corresponding to $(NCH_2CH_2N)_2$ of piperazine moiety. In addition, characteristic signals corresponding to aromatic protons. The newly formed disubstituted nitrobenzenes **3a-c** were

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subjected to palladium-catalyzed reduction to the corresponding amines (**4a-c**). The 1H NMR spectra of compounds **4a-c** exhibited a multiplet signal at δ 7.29- 7.30 ppm (2H) corresponding to NH_2. Finally, nucleophilic attach of anilinic amino group on the electrophilic carbon of phenyl isocyanate group was followed to successfully get the final target diaryl urea compounds (**5a-n**) in yield between 64% and 91%.

3.2. In vitro antiproliferative activities against NCI-60 cell line panel

3.2.1. Five dose testing

Upon comparing the effect of hydrogen bondable moieties directly attached to internal phenyl ring on activity, it was found that compounds 5a-e possessing 4-hydroxymethylpiperidine were more active than compounds **5f-g** with 3,4,5-trimethoxyphenol where compounds which reflects the influences of such moieties on the antiproliferative activity. The mean % growth of the NCI-60 cancer cell line panel after treatment with each of the tested compounds is illustrated in Table 1.

Table 1. % growth inhibition results exerted by compounds **5a-e** over the most sensitive cell lines.

Cell lines		Percentage inhibition (at 10 μM)				
		5a	**5b**	**5c**	**5d**	**5e**
Leukemia	**CCRF-CEM**				90.3	82.2
	HL-60(TB)	86.1			**106.9**	93.7
	K-562	90.6			84.9	82.3
	MOLT-4	82.4			95.2	**100.6**
	RPMI-8226	80.6			87.9	90.8
	SR	82.9			97.7	93.4
NSCLC	**A549/ATCC**	93.0				
	NCI-H23	96.0				
	NCI-H460				81.5	
	NCI-H522	90.7				
Colon cancer	**COLO 205**				**126.6**	83.9
	HCC-2998	85.9			86.1	
	HCT-116	91.6		87.5	88.2	81.9
	HCT-15				85.2	
	HT29	94.3		90.2	90.8	
	KM12					
	SW-620					82.4
CNS cancer	**SF-295**				82.2	
	SF-539	98.7		84.9	81.1	
	SNB-19	84.7				
	U251	88.7				
Melanoma	**MDA-MB-435**	95.7			84.5	
	SK-MEL-2				**110.3**	
	SK-MEL-28	90.6		81.3		
	SK-MEL-5	**146.1**	80.0	**138.3**	88.7	
	UACC-62	95.3				
Ovarian cancer	**OVCAR-3**	95.3				
	SK-OV-3					95.7
Renal Cancer	**786-0**	**108.7**			84.4	
	A498	**136.2**		90.9	85.7	93.6
	ACHN				82.7	
	RXF 393	**134.8**				
	TK-10	83.5				
	UO-31					83.0
Prostate Cancer	**PC-3**				87.6	83.4
Breast Cancer	**MCF7**	90.2			83.8	80.0
	MDA-MB-231/ATCC	90.7			**117.5**	86.4
	HS 578T	89.4				
	T-47D				94.4	82.5
	MDA-MB-468	**116.6**			87.4	

The bold figure indicates lethal effect.

Compounds **5a**, **5d** and **5e** showed higher antiproliferative activity than the corresponding *p*-methoxyphenyl and p-trifluoromethylphenyl analogues **5d** and **5c**. It has been clear that compounds with trimethoxyphenyl derivatives are not suitable as potential anticancer agents, while those having pipredin-4-yl methanol moiety are promising anticancer agent. The average growth percentage of compounds **5a**, **5d** and **5e** which has piperidin-4-yl methanol are 22.16%, 24.67% and 32.41%, respectively (Table 2).

Compounds **5d** and **5e** with di-substituted terminal phenyl ring have superior activity than the corresponding mono-substitution derivatives against most of leukemia cell lines. Compound **5a** with electron-donating group (methyl) showed lethal effect on SK-MEL-5 melanoma cell line, MDA-MB-468 breast cancer cell line and three renal cancer cell lines 786-0, A498 and RXF 393. Therefore, it can be concluded that the antiproliferative activity of tested compounds against diverse

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cancer cell lines differs with different steric and/or electronic properties of substituents on the terminal phenyl moiety.

Table 2: Mean % growth of the 60 cell lines after treatment with tested target compounds (10 μM)

Comp. No.	Mean % growth
5a	**22**
5b	59
5c	53
5d	**24**
5e	**32**
5f	99
5g	97

The bold figure indicates the most active compound.

The percentage inhibition values of the most active compounds over the most sensitive cell lines are summarized in Table 2. SK-MEL-5 melanoma cell line was the most sensitive cell line to this series of compounds. The most active compounds against SK-MEL-5 were **5a** and **5c** with percentage inhibitions of 146.1 % and 138.3 %, respectively. K-562 leukemia and A498 renal cancer cell lines were also sensitive to the potential compounds.

Compounds **5a-e** were active against three cell lines, while compounds **5a** and **5c** showed the higher inhibitory effect over SK-MEL-2 (Figure 2). Among all the target compounds, compound **5a** and 5d showed the most promising results. It exerted broad-spectrum antiproliferative activity against different cell lines of different cancer types; leukemia, colon, renal cancer and breast cancer. So they can be considered as potential lead compounds for future development of broad-spectrum anticancer agents.

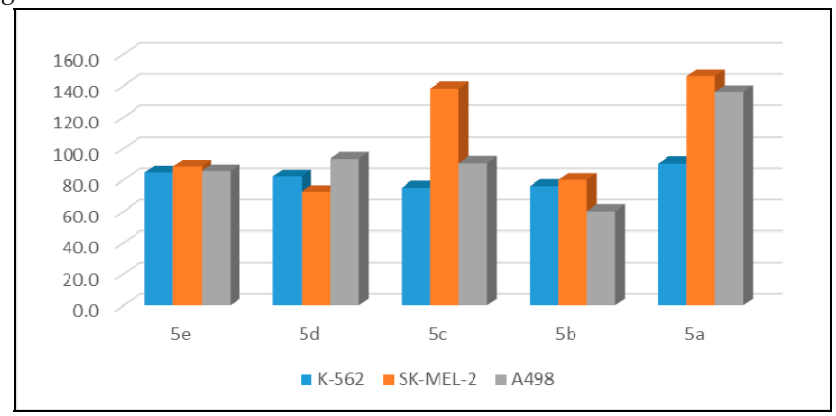

Figure 2. The % inhibition values of compounds **5a-d** against SK-MEL-5, A498 and K-562 cell lines.

Among all the tested derivatives, compounds **5a**, **5d**, and **5e** showed the highest mean inhibitions. The percentages of inhibition of these three compounds over each tested cell line of the NCI-60 panel at 10-μM concentration are depicted in Figure 3.

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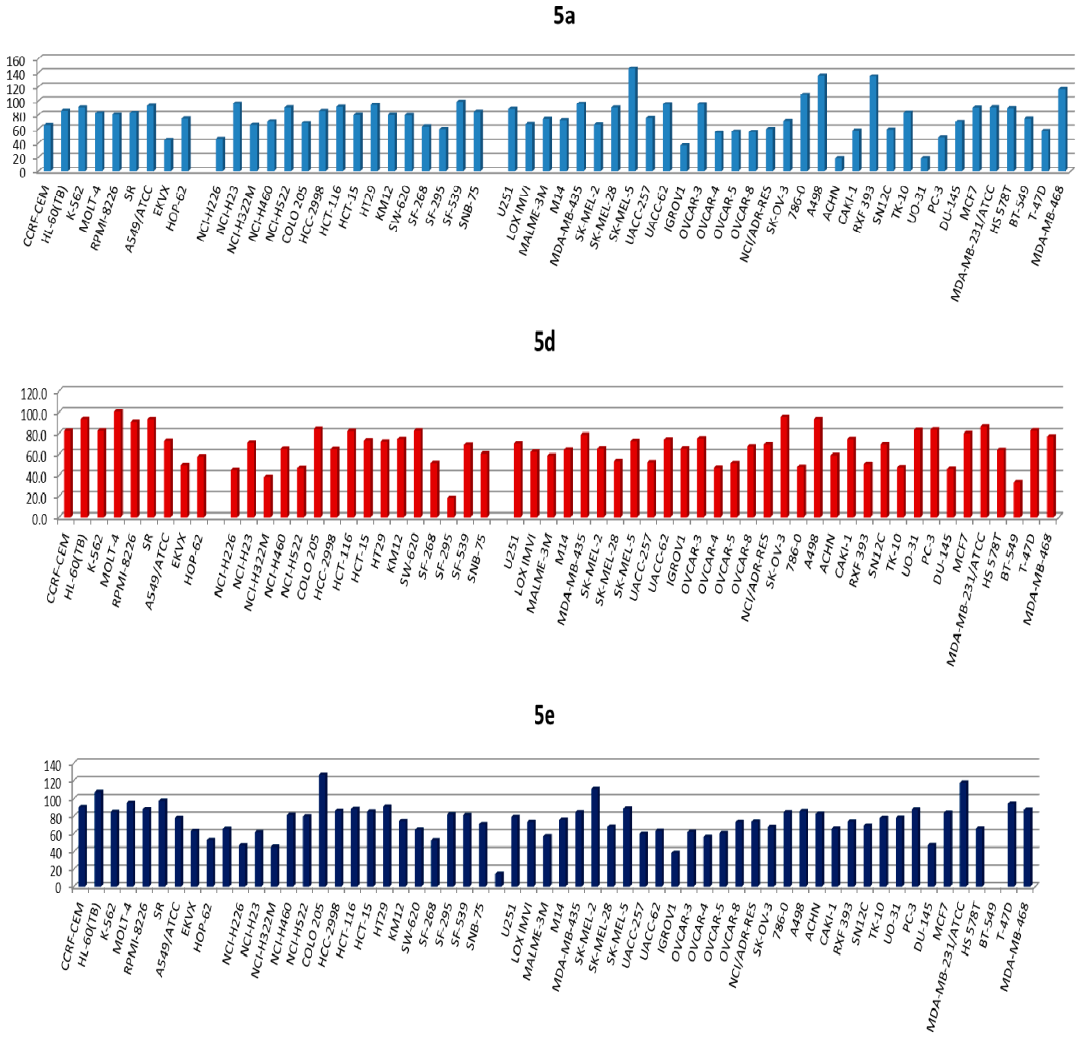

Figure 3. % Growth of 60 cell line panel upon treatment with compounds **5a**, **5d** and **5e** at 10 μM.

The three compounds **5a, 5d** and **5e** exerted broad-spectrum antiproliferative activities against different cell lines of different cancer types. Among them, compound **5a** was the most active. It showed the highest percentage inhibition values with more than 70% inhibition against SR leukemia cell line, SK-MEL-5 and UACC-257 melanoma cell lines, and T-47D and MDA-MB-468 breast cancer cell lines. The results of compound **5a** against those five cell lines were compared with Paclitaxel and Gefitinib as reference standard drugs, as illustrated in Figure 4. The results of Paclitaxel were obtained from NCI data warehouse index, and are inserted in Figure 4. Compound **5a** and 5d were more active than the reference compound against SK-MEL-5 and T-47D cell lines. It showed higher activity also than Paclitaxel against SK MEL, MDA, 786-0 and RXF cell lines.

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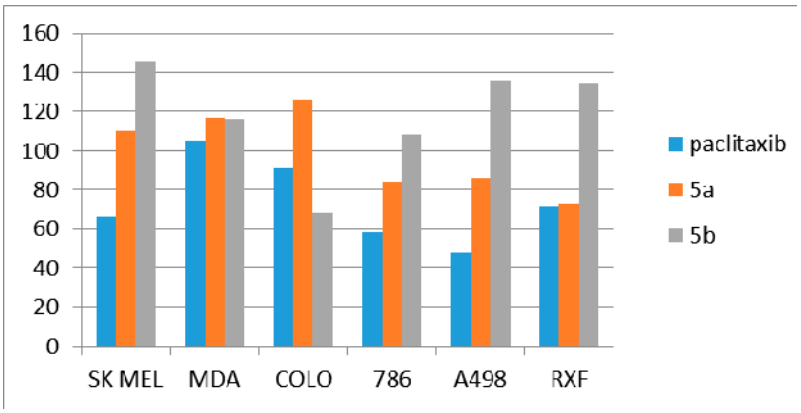

Figure 4. Comparison of % inhibition values expressed by **5a**, **5d** and Paclitaxel against the most sensitive cell lines towards **5a** and **5d**.

3.2.2. Five dose testing

Compounds **5a** and **5d** (NCS: 781358 and 782653) satisfied pre-determined threshold growth inhibition criteria and were further selected for NCI full panel five dose assay at 10-fold dilutions of five different concentrations (0.01, 0.1, 1, 10 and 100 μM).

The result of tested compound **5a** is given by three response parameters (GI_{50}, TGI and LC_{50}) for each cell line from log concentration vs. percentage growth inhibition curves on nine cancer diseases (Figure 5).

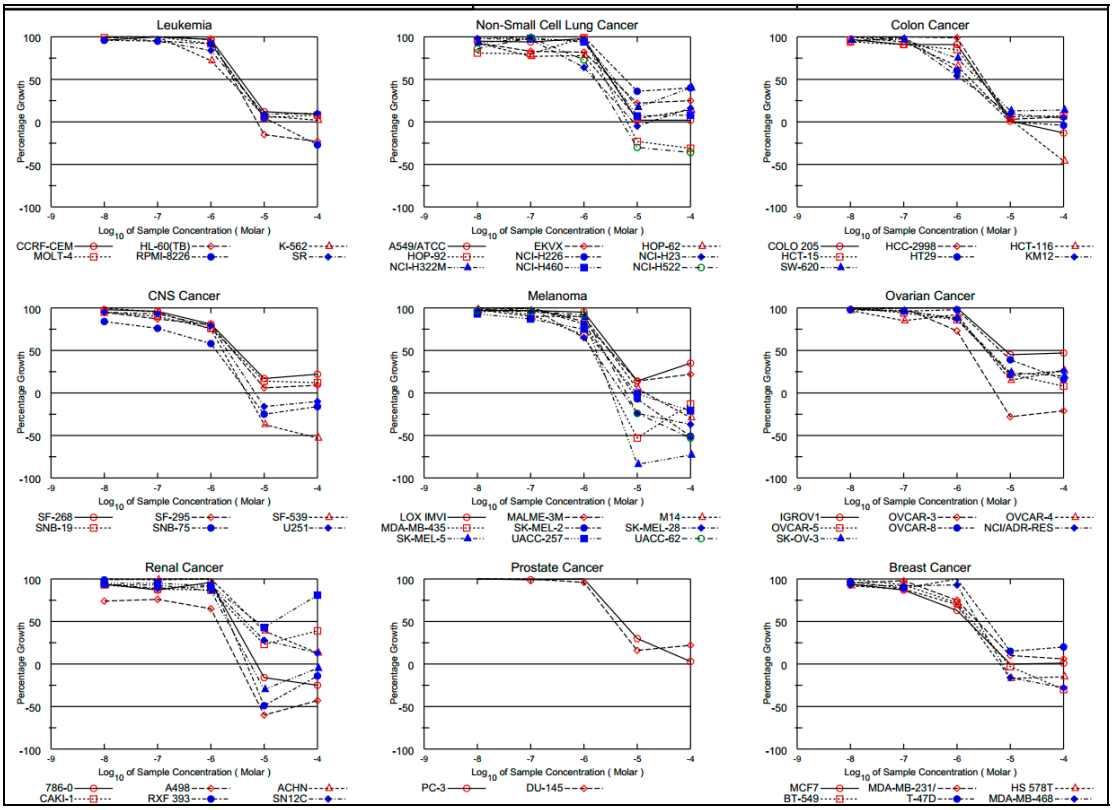

Figure 5. Dose-Antiproliferative response of compound **5a** against nine different cancer cell lines

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Compounds **5a** and **5d** showed remarkable broad-spectrum potency over other multiple cell lines in the range of IC_{50} values of 1.25-8.44 and 1.26-3.75 μM, respectively. By referring to the efficacy parameter (TGI values) of the target compounds **5a** and **5d**, it was demonstrated that the most potent compound **5a** was efficacious towards A498 renal, RXF 393 renal cancer cells, SF-539 CNS cancer cell, an d NCI-H522 non- small cell lung cancer cell line with TGI values of 3.32, 4.69, 4.67, and 5.12 μM, respectively. While compound **5d** exerted remarkable efficacies against NCI-H522, COLO 205, LOX IMVI, SK-MEL-5 and RXF 393 cell lines, being able to induce total growth inhibition (TGI) at concentrations below 3.66 μM and 50% lethality (LC_{50}) concentrations below 6.96 μM.

4. Materials and Methods

The NMR spectra were recorded with a Bruker spectrometer, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. The multiplicities were abbreviated as s: singlet, d: doublet, t: triplet, m: multiplet, q: quartet. The coupling constants *J* are recorded in Hertz (Hz) and it's liable to a little difference because they used the intact values measured by spectrometer. The relative shift values of peak are recorded by ppm unit using tetramethylsilane (TMS) as standard material. Melting points were determined on a SRS OPTIMELT. The FT-IR spectra were obtained on Perkin Elmer 16E PC FT-IR spectrometer. Thin layer chromatography (TLC) was performed using precoated plates (0.25 mm, Merck) of silica gel 60 F_{254} (230 ~ 400 mesh) for monitoring all reactions and under ultraviolet irradiation (254 nm). Column chromatography separations are performed using silica gel (230 ~ 400 mesh, Merck). All the commercially available reagent chemicals were obtained from Aldrich, TCI, Wako Pure Chemical, Acros and Dae-Jung Chemicals, and generally used without further purification.

*4.1. General method for synthesis of compounds (**2a-c**)*

4-bromo-2-fluoro-1-nitrobenzene (0.50 g, 2.28 mmol), piperidin-4-ylmethanol, 2-(piperazin-1-yl)ethanol and 3,4,5-trimethoxyphenol (2.28 mmol), K_2CO_3 (0.32 g, 2.28 mol) were mixed in DMF (10 mL) and heated at 90 °C under N_2 for 5 h. After cooling, the reaction mixture was filtered to remove solid and the solvent was evaporated. The residue was dissolved in dichloromethane and washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue solid was applied on column of silica gel and then eluted with the mixed solvent of ethylacetate and hexanes (3:1, v/v) to give the pure product as a white solid.

- ***1-(5-Bromo-2-nitrophenyl)piperidin-4-yl)methanol* (2a)**

Yield: 0.61 g (85%), ^{1}H-NMR ($CDCl_3$) δ 1.50 (m, 2H), 1.72 (s, 1H), 1.87 (d, *J* = 12.8 Hz, 2H), 2.89 (t, *J* = 12.4 Hz, 2H), 3.34 (d, *J* = 12.4 Hz, 2H), 3.60 (d, *J* = 6.4 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 1H), 7.27 (s, 1H), 7.69 (d, *J* = 8.8 Hz, 1H).

- ***2-(4-(5-Bromo-2-nitrophenyl)piperazin-1-yl)ethan-1-ol* (2b)**

Yield: 0.7 g (93%). ^{1}H-NMR ($CDCl_3$) δ 2.661 (t, *J* = 5.2 Hz, 2H), 2.714 (t, *J* = 4.8 Hz, 4H), 3.136 (t, *J* = 4.8 Hz, 4H), 3.688 (t, *J* = 5.2 Hz, 2H), 7.164 (d, *J* = 8.8 Hz, 1H), 7.274 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 1H).

- ***5-(5-Bromo-2-nitrophenoxy)-1,2,3-trimethoxybenzene* (2c)**

Yield: 0.8 g (92%). ^{1}H-NMR ($CDCl_3$) δ 3.72 (s, 6H), 3.78 (s, 3H), 6.33 (s, 2H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.31 (s, 1H), 7.68 (d, *J* = 8.8 Hz, 1H).

*4.2. General method for synthesis of compounds (**3a-c**)*

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Compounds **2a-***c*, 3-pyridine boronic acid (120 mole %) $Pd_2(PPh_3)_2Cl_2$ (5 mole %) and K_2CO_3 (200 mole %) were mixed and dissolved in degassed mixed solvent of acetonitrile and water (4:1, v/v). The mixture was bubbled with nitrogen for 15 mins and then heated at 95 °C for 3 h. After being cooled to room temperature, the mixture was diluted with water and extracted with ethyl acetate (3 × 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was then subjected to flash chromatography using the appropriate ratios of hexanes and ethyl acetate as mobile phases.

- ***1-(2-Nitro-5-(pyridin-3-yl)phenyl)piperidin-4-yl)methanol* (3a)**

Yield: 0.42 g (87%). ^{1}H-NMR ($CDCl_3$) δ 1.50 (m, 2H), 1.72 (s, 1H), 1.87 (d, J = 12.8 Hz, 2H), 2.95 (t, J = 12 Hz, 2H), 3.41 (d, J = 12.4 Hz, 2H), 3.61 (d, J = 6.4 Hz, 2H), 7.18 (dd, J = 1.6 and 8.4 Hz, 1H), 7.29 (s, 1H), 7.49 (dd, J = 4.8 and 8 Hz, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 8.70 (d, J = 4.8 Hz, 1H), 8.87 (s, 1H).

- ***3-(4-Nitro-3-(3,4,5-trimethoxyphenoxy)phenyl)pyridine* (3b)**

Yield: 0.66 g (83%). ^{1}H-NMR ($CDCl_3$) δ 3.75 (s, 6H), 3.75 (s, 3H), 6.34 (s, 2H), 7.14 (d, J = 2.0 Hz, 1H), 7.32 (m, 2H), 7.75 (td, J = 8.0 and 2.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.55 (dd, J = 5.2 and 2.0 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H).

- ***2-(4-(2-Nitro-5-(pyridin-3-yl)phenyl)piperazin-1-yl)ethan-1-ol* (3c)**

Yield: 0.60 g (86%). ^{1}H-NMR ($CDCl_3$) δ 2.67 (t, J = 5.2 Hz, 2H), 2.748 (t, J = 4.8 Hz, 4H), 3.21 (t, J = 4.8 Hz, 4H), 3.69 (t, J = 5.2 Hz, 2H), 7.24 (dd, J = 8.4 and 1.6 Hz, 1H), 7.29 (s, 1H), 7.45 (dd, J = 4.8 and 8 Hz, 1H), 7.90 (dt, J = 1.6 and 8 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 8.70 (dd, J = 1.6 and 4.8 Hz, 1H), 8.86 (d, J = 1.6 Hz, 1H).

*4.3. General way of palladium catalyzed reduction of nitrobenzene to the corresponding anilines (**4a-c**)*

To a solution of compound **3a-c** (0.5 g, 22.6 mmol) in ethanol (150 mL), (0.05 g) of 10% Pd/C was added. The reaction mixture was stirred at room temperature under an atmosphere of hydrogen for 9 h. After completion of the reaction, the resulting mixture was filtered through celite, and the filtered catalyst was washed with ethanol. The filtrate was concentrated under vacuum to afford compound **4a-c** which was used in the next step without further purification.

- ***(1-(2-Amino-5-(pyridin-3-yl)phenyl)piperidin-4-yl)methanol* (4a)**

Yield: 0.39 g (88%). ^{1}H-NMR ($CDCl_3$) δ 1.50 (m, 2H), 1.69 (s, 1H), 1.92 (d, J = 12.4 Hz, 2H), 2.72 (t, J = 9.6 Hz, 2H), 3.26 (d, J = 11.2 Hz, 2H), 3.63 (t, J = 2.8 Hz, 2H), 6.85(d, J = 8 Hz, 1H), 7.29 (m, 3H), 7.85 (d, J = 8 Hz, 1H), 8.51 (d, J = 4.8 Hz, 1H), 8.82 (d, J = 2.8 Hz, 1H).

- ***4-(Pyridin-3-yl)-2-(3,4,5-trimethoxyphenoxy)aniline* (4b)**

Yield: 0.42 g (91%). ^{1}H-NMR ($CDCl_3$) δ 3.74 (s, 6H), 3.77 (s, 3H), 6.34 (s, 2H), 6.88(d, J = 8.0 Hz, 1H), 7.30 (m, 3H), 7.86 (d, J = 8 Hz, 1H), 8.49 (d, J = 4.8 Hz, 1H), 8.79 (d, J = 2.8 Hz, 1H).

- ***2-(4-(2-Amino-5-(pyridin-3-yl)phenyl)piperazin-1-yl)ethanol* (4c)**

Yield: 0.40 g (88%). ^{1}H-NMR ($CDCl_3$) δ 2.67 (t, J = 5.2 Hz, 2H), 2.748 (t, J = 4.8 Hz, 4H), 3.21 (t, J = 4.8 Hz, 4H), 3.69 (t, J = 5.2 Hz, 2H), 6.79 (d, J = 8 Hz, 1H), 7.15 (dd, J = 8.0 and 1.6 Hz, 1H), 7.20 (s, 1H), 7.29 (dd, J = 4.8 and 1.6 Hz, 1H), 7.77 (dt, J = 1.6 and 8.0 Hz, 1H), 8.46 (dd, J = 1.6 and 4.8 Hz, 1H), 8.76 (d, J = 1.6 Hz, 1H).

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*4.4. General procedure for synthesizing urea derivatives (**5a-n**)*

To a solution of arylisocyanate (0.2 mmol) in THF (1 mL), the appropriate aniline compounds **4a-c** (0.2 mmol) were added. The mixture was stirred at room temperature until arylisocyanate was completely reacted. The solvent was removed in vacuo, and the residue was then subjected to flash chromatography using the appropriate ratios of hexanes and ethyl acetate as mobile phases to obtain urea compounds (**5a-n)**.

- ***1-(2-(4-(Hydroxymethyl)piperidin-1-yl)-4-(pyridin-3-yl)phenyl)-3-(4-methylphenyl)urea* (5a)**

Yield: 0.045 g (64%). mp: 215-217 °C. IR (KBr) 3663, 3315, 3185, 1678, 1519, 838 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.53 (s, 3H), 1.80 (s, 2H), 2.27 (s, 3H), 2.74 (t, J = 10.0 Hz, 2H), 3.03 (s, 2H), 3.4 (s, 2H), 4.56 (t, J = 5.2 Hz, 1H), 7.11 (s, 1H), 7.13 (s, 1H), 7.39 (s, 1H), 7.41 (s, 1H), 7.45 (m, 2H), 7.49 (d, J = 2 Hz, 1H), 8.05 (td, J = 2.0 and 8.4 Hz, 1H), 8.11 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.52 (dd, J = 1.2 and 4.4 Hz, 1H), 8.89 (d, J = 2.0 Hz, 1H), 9.54 (s, 1H).^{13}C-NMR (DMSO-d_6) δ 20.83, 29.46, 38.66, 52.62, 66.48, 119.07, 119.17, 119.88, 122.92, 124.20, 129.7, 130.98, 131.31, 134.03, 134.65, 136.00, 137.64, 143.39, 147.79, 148.26, 152.97.

- ***1-(2-(4-(Hydroxymethyl)piperidin-1-yl)-4-(pyridin-3-yl)phenyl)-3-(4-(trifluoromethyl) phenyl)thiourea* (5b)**

Yield: 0.07 g (86%). mp: 98-100 °C. IR (KBr) 3580, 3210, 3041, 2926, 1590, 1520, 838 cm^{-1}. ^{1}H-NMR (CD_3OD) δ 1.23 (m, 2H), 1.59 (s, 1H), 1.81 (d, J = 10.8, 2H), 2.76 (t, J = 10 Hz, 2H), 3.13 (d, J = 12.0 Hz, 2H), 3.37 (d, J = 6.4 Hz, 2H), 7.39 (dd, J = 2.0 and 8.4 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H),, 7.52 (dd, J = 5.2 and 8.0 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 8.09 (dt, J = 1.6 and 8.0 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.51 (dd, J = 1.2 and 4.8 Hz, 1H), 8.80 (d, J = 2 Hz, 1H). ^{13}C-NMR (CD_3OD) δ 29.18, 38.04, 51.94, 66.44, 118.47, 121.85, 123.75, 124.10, 124.24, 125.82, 126.74, 133.22, 134.31, 135.04, 136.80, 142.29, 146.04, 146.67, 147.09, 178.85.

- ***1-(2-(4-(Hydroxymethyl)piperidin-1-yl)-4-(pyridin-3-yl)phenyl)-3-(4-methoxyphenyl)urea* (5c)**

Yield: 0.061 g (84%). mp: 205-207 °C. IR (KBr) 3585, 3314, 3196, 2927, 1673, 1506, 835 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.51 (m, 3H), 1.80 (d, J = 9.6 Hz, 2H), 2.74 (t, J = 10.0 Hz, 2H), 3.02 (d, J = 11.2 Hz, 2H), 3.37 (s, 2H), 3.74 (s, 3H), 4.55 (t, J = 5.2 Hz, 1H), 6.90 (s, 1H), 6.92 (s, 1H), 7.41 (m, 1H), 7.43 (m, 1H), 7.46 (m, 2H), 7.49 (d, J = 2.0 Hz, 1H), 8.04 (t, J = 2.4 Hz, 1H), 8.06 (s, 1H), 8.19 (d, J = 8.8 Hz, 1H), 8.52 (dd, J = 1.2 and 4.8 Hz, 1H), 8.89 (d, J = 2.0 Hz, 1H), 9.41 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ 29.50, 38.64, 52.67, 55.64, 66.48, 114.56, 119.10, 119.68, 121.10, 122.98, 124.20, 130.85, 133.11, 134.01, 134.78, 136.00, 143.25, 147.78, 148.24, 153.12, 155.18.

- ***1-(2-(4-(Hydroxymethyl)piperidin-1-yl)-4-(pyridin-3-yl)phenyl)-3-(3-chloro-4-trifluoromethyl-phenyl)urea* (5d)**

Yield: 0.072 g (85%). mp: 170-173 °C. IR (KBr) 3657, 3298, 3120, 2935, 1679, 1548, 804 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.55 (s, 3H), 1.81 (s, 2H), 2.74 (s, 2H), 3.03 (s, 2H), 3.4 (s, 2H), 4.56 (t, J = 5.2 Hz, 1H), 7.44 (d, J = 2.0, 1H), 7.46 (s, 1H), 7.53 (d, J = 1.6 Hz, 1H), 7.64 (s, 1H), 7.72 (s, 1H), 8.06 (s, 1H), 8.12 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.21 (s, 1H), 8.54 (dd, J = 1.2 and 4.4 Hz, 1H), 8.89 (d, J = 2.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ 29.51, 38.64, 52.67, 66.45, 117.13, 119.23, 120.06, 123.01, 123.33, 124.20, 131.65, 132.56, 133.98, 134.11, 135.89, 139.90, 143.64, 147.84, 148.38, 152.67.

- ***1-(2-(4-(Hydroxymethyl)piperidin-1-yl)-4-(pyridin-3-yl)phenyl)-3-(2,4-dichlorophenyl)urea***

(5e)

Yield: 0.062 g (78%). mp: 189-191 °C. IR (KBr) 3582, 3305, 3097, 2924, 1677, 1587, 874 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.55 (s, 3H), 1.81 (s, 2H), 2.74 (s, 2H), 3.04 (s, 2H), 3.4 (s, 2H), 4.56 (t, J = 5.2 Hz, 1H), 7.37 (dd, J = 2.0 and 8.8 Hz, 1H), 7.44 (m, 2H), 7.54 (m, 2H), 7.95 (d, J = 2.4 Hz, 1H), 8.05 (d, 1H), 8.18 (m, 2H), 8.53 (d, J = 4 Hz, 1H), 8.89 (s, 1H), 9.96 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ 29.49, 38.64, 52.65, 66.46, 118.74, 119.17, 119.79, 120.10, 122.97, 123.62, 124.19, 131.08, 131.58, 134.03, 134.09, 135.91, 140.51, 143.64, 147.83, 148.35, 152.61.

- ***1-(2,4-Difluorophenyl)-3-(4-(pyridin-3-yl)-2-(3,4,5-trimethoxyphenoxy)phenyl)urea*(5f)**

Yield: 0.201 g (70%). mp: 165-167 °C. IR (KBr) 3291, 3039, 2937, 1710, 1597, 844 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 3.67 (s, 3H), 3.752 (s, 6H), 6.50 (s, 2H), 7.076 (t, J = 8.4 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.32 (dt, J = 2.8 and 11.6 Hz, 1H), 7.43 (dd, J = 8.0 and 4.8 Hz, 1H), 7.43 (dd, J = 2.4 and 8.8 Hz, 1H), 7.96 (td, J = 8.8 and 1.6 Hz, 1H), 8.19 (m, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.51 (dd, J = 4.8 and 1.6 Hz, 1H), 8.79 (d, J = 2.4 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ 56.55, 60.62, 97.48, 103.98, 104.24, 104.49, 111.39, 111.58, 115.93, 120.70, 122.51, 124.28, 129.25, 131.02, 131.63, 131.98, 134.12, 134.57, 135.23, 146.61, 147.72, 148.61, 152.67, 154.16.

- ***1-(4-Methoxyphenyl)-3-(4-(pyridin-3-yl)-2-(3,4,5-trimethoxyphenoxy)phenyl)urea* (5g)**

Yield: 0.11 g (77.5%). mp: 180-183 °C. IR (KBr) 3330, 3059, 2938, 1705, 1597, 830 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 3.67 (s, 3H), 3.73 (s, 3H), 3.75 (s, 6H), 6.49 (s, 2H), 6.89 (s, 1H), 6.91 (s, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.38 (s, 1H), 7.40 (s, 1H), 7.43 (m, 1H), 7.49 (dd, J = 8.8 and 2 Hz, 1H), 7.95 (dd, J = 8.0 and 2.0 Hz, 1H), 8.42 (d, J = 8.0 Hz, 1H), 8.51 (s, 2H), 8.80 (d, J = 2.4 Hz, 1H), 9.21 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ 55.62, 56.52, 60.63, 97.26, 114.56, 115.98, 120.25, 120.37, 122.61, 124.28, 131.05, 131.63, 133.04, 134.07, 134.44, 135.29, 146.17, 147.69, 148.53, 152.75, 152.89, 154.15, 155.02.

- ***1-(2-Fluorophenyl)-3-(4-(pyridin-3-yl)-2-(3,4,5-trimethoxyphenoxy)phenyl)urea* (5h)**

Yield: 0.103 g (74%). mp: 103-106 °C. IR (KBr) 3424, 3030, 2938, 1707, 1533, 822 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 3.67 (s, 3H), 3.76 (s, 6H), 6.50 (s, 2H), 7.04 (m, 1H), 7.25 (m, 3H), 7.43 (dd, J = 4.8 and 8.0 Hz, 1H), 7.51 (dd, J = 8.4 and 2.0 Hz, 1H), 7.96 (td, J = 8.0 and 2.0 Hz, 1H), 8.22 (dt, J = 1.6 and 8.4 Hz, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.52 (dd, J = 4.8 and 1.6 Hz, 1H), 8.80 (d, J = 2.4 Hz, 1H), 9.12 (s, 1H), 9.31 (d, J = 1.6 Hz, 1H).

- ***1-(2,4-Dichlorophenyl)-3-(4-(pyridin-3-yl)-2-(3,4,5-trimethoxyphenoxy)phenyl)urea* (5i)**

Yield: 0.12 g (78%). mp: 186-188 °C. IR (KBr) 3333, 3096, 2938, 1712, 1591, 806 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 3.67 (s, 3H), 3.75 (s, 6H), 6.50 (s, 2H), 7.20 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 2.8 and 8.8 Hz, 1H), 7.42 (dd, J = 4.8 and 8 Hz, 1H), 7.50 (dd, J = 8.8 and 2.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 2.8 Hz, 1H), 7.95 (d, J = 4.4 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.52 (dd, J = 4.4 and 1.6 Hz, 1H), 8.68 (s, 1H), 8.80 (d, J = 2.4 Hz, 1H).

- ***1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-(pyridin-3-yl)-2-(3,4,5-trimethoxyphenoxy) phenyl)urea* (5j)**

Yield: 0.144 g (88%). mp: 110-112 °C. IR (KBr) 3333, 3070, 2940, 1711, 1595, 822 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 3.67 (s, 3H), 3.76 (s, 6H), 6.51 (s, 2H), 7.21 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 4.4 and 8.0 Hz, 1H), 7.51 (dd, J = 2.4 and 8.4 Hz, 1H), 7.62 (s, 1H), 7.95 (dt, J = 2.4 and 6 Hz, 1H), 8.11 (s, 1H), 8.38 (d,

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J = 8.8, 1H), 8.51 (d, *J* = 4.4 Hz, 1H), 8.69 (s, 1H), 8.79 (d, *J* = 2.4 Hz, 1H), 9.82 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ 56.54, 60.60, 97.42, 115.96, 116.93, 116.99, 120.78, 122.58, 122.93, 123.17, 124.25, 130.79, 131.92, 132.55, 134.12, 134.61, 135.19, 139.60, 146.62, 147.73, 148.63, 152.60, 154.18.

- ***1-(2-Fluorophenyl)-3-(2-(4-(2-hydroxyethyl)piperazin-1-yl)-4-(pyridin-3- yl)phenyl)urea (5k)***

Yield: 0.105 g (72%). mp: 95-97 °C. IR (KBr) 3303, 3042, 2923, 1728, 1525, 804 cm^{-1}. ^{1}H-NMR (DMSO-*d6*) δ 2.73-2.95 (m, 6H), 2.95 (s, 4H), 4.26 (t, J = 5.6 Hz, 2H), 7.15 (m, 4H), 7.43 (m, 2H), 8.10 (m, 2H), 8.52 (s, 1H), 8.54 (d, J = 4.8 Hz, 1H), 8.90 (s, 1H), 8.91 (s, 1H), 9.36 (s, 1H).

- ***1-(4-Methylphenyl)-3-(2-(4-(2-hydroxyethyl)piperazin-1-yl)-4-(pyridin-3- yl)phenyl)urea (5l)***

Yield: 0.102 g (70%). mp: 166-168 °C. IR (KBr) 3306, 3473, 3031, 2923, 1707, 1517, 813 cm^{-1}. ^{1}H-NMR (CD_3OD) δ 2.33 (s, 3H), 2.79-2.82 (m, 6H), 2.97 (t, J = 4.4 Hz, 4H), 4.34 (t, J = 5.6 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.32-7.36 (m, 3H), 7.41 (d, J = 2.0 Hz, 1H), 7.49 (s, 1H), 8.06 (dt, J = 2.0 and 8.4 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.48 (d, J = 4.4 Hz, 1H), 8.79 (s, 1H).

- ***1-(2,4-Dichlorophenyl)-3-(2-(4-(2-hydroxyethyl)piperazin-1-yl)-4-(pyridin-3-yl) phenyl)urea (5m)***

Yield: 0.14 g (88%). mp: 203-205 °C. IR (KBr) 3310, 3582, 2921, 1729, 1522, 806 cm^{-1}. ^{1}H-NMR (CD_3OD) δ 2.86 (m, 6H), 3.01 (t, J = 4.4 Hz, 4H), 4.38 (t, J = 5.6 Hz, 2H), 7.32 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.42 (m, 3H), 7.51 (m, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.84 (d, J = 2.4 Hz, 1H), 8.06 (td, J = 1.6 and 8.0 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H), 8.49 (t, J = 3.2 Hz, 1H), 8.78 (s, 1H).

- ***1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(2-(4-(2-hydroxyethyl)piperazin-1- yl)-4-(pyridin-3-yl)phenyl)urea (5n)***

Yield: 0.155 g (91%). mp: 120-122 °C. IR (KBr) 3305, 3441, 3052, 2931, 1728, 1524, 830 cm^{-1}. ^{1}H-NMR (DMSO-*d6*) δ 2.75 (t, *J* = 5.6 Hz, 2H), 2.81 (s, 4H), 2.93 (s, 4H), 4.38 (t, *J* = 5.6 Hz, 2H), 7.46 (m, 1H), 7.48 (m, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.62 (s, 1H), 7.64 (s, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.76 (d, *J* = 2.4 Hz, 1H), 8.06 (s, 1H), 8.15 (d, *J* = 2.4 Hz, 1H), 8.29 (s, 1H), 8.53 (dd, *J* = 1.6 and 4.8 Hz, 1H), 8.90 (dd, *J* = 2.4 and 0.4 Hz, 1H).

5. Conclusions

A new series of 1-phenyl-3-(4-(pyridin-3-yl)phenyl)urea derivatives have been synthesized and biologically evaluated as antiproliferative agents against nine different cancer cell lines. The present investigation highlights the significance of adding hydrogen bodable moiety on the titled scaffold. Compounds **5a-e** with hydroxymethyl piperidine moiety exhibited superior antiproliferative activity than Paclitaxel and Gefitinib against the most sensitive cell lines. Among the five compounds, compounds, **5a** and **5d** showed promising mean growth inhibitions with significant efficacies and superior potencies than Paclitaxel and Gefitinib in different cancer cell lines, belonging particularly to melanoma cell lines. Moreover, compound **5a** elicited some lethal rather than inhibitory effects on SK-MEL-5 melanoma cell line, 786-0, A498, RXF 393 renal cancer cell lines, and MDA-MB-468 breast cancer cell line. The findings of present study points towards the potential of 1-phenyl-3-(4-(pyridin-3-yl)phenyl)urea derivatives as promising leads for future development of broad spectrum anticancer agents.

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Author Contributions:

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References

1. Vogelstein, B.; Kinzler, K.W. The multistep nature of cancer. *Trends in genetics* **1993**, *9*, 138-141.
2. Vogelstein, B.; Kinzler, K.W. Cancer genes and the pathways they control. *Nature medicine* **2004**, *10*, 789-799.
3. Dumas, J. Protein kinase inhibitors from the urea class. *Current opinion in drug discovery & development* **2002**, *5*, 718-727.
4. Canal, N.; Garattini, S.; Tessari, L. Peripheral effect of new urea derivatives with hypoglycemic action. *Bollettino della Societa italiana di biologia sperimentale* **1956**, *32*, 491.
5. Faidallah, H.M.; Khan, K.A.; Asiri, A.M. Synthesis and biological evaluation of new 3-trifluoromethylpyrazolesulfonyl-urea and thiourea derivatives as antidiabetic and antimicrobial agents. *Journal of Fluorine Chemistry* **2011**, *132*, 131-137.
6. Li, Y.; Tian, K.; Qin, A.; Zhang, L.; Huo, L.; Lei, L.; Shen, Z.; Song, H.; Feng, Z. Discovery of novel urea derivatives as dual-target hypoglycemic agents that activate glucokinase and pparγ. *European journal of medicinal chemistry* **2014**, *76*, 182-192.
7. Brown, J.R.; North, E.J.; Hurdle, J.G.; Morisseau, C.; Scarborough, J.S.; Sun, D.; Korduláková, J.; Scherman, M.S.; Jones, V.; Grzegorzewicz, A. The structure–activity relationship of urea derivatives as anti-tuberculosis agents. *Bioorganic & medicinal chemistry* **2011**, *19*, 5585-5595.
8. Doub, L.; Richardson, L.; Herbst, D.; Black, M.; Stevenson, O.; Bambas, L.; Youmans, G.; Youmans, A. Some phenylthiourea derivatives and their antituberculous activity. *Journal of the American Chemical Society* **1958**, *80*, 2205-2217.
9. Kale, R.R.; Kale, M.G.; Waterson, D.; Raichurkar, A.; Hameed, S.P.; Manjunatha, M.; Reddy, B.K.; Malolanarasimhan, K.; Shinde, V.; Koushik, K. Thiazolopyridone ureas as DNA gyrase b inhibitors: Optimization of antitubercular activity and efficacy. *Bioorganic & medicinal chemistry letters* **2014**, *24*, 870-879.
10. Keche, A.P.; Hatnapure, G.D.; Tale, R.H.; Rodge, A.H.; Birajdar, S.S.; Kamble, V.M. A novel pyrimidine derivatives with aryl urea, thiourea and sulfonamide moieties: Synthesis, anti-inflammatory and antimicrobial evaluation. *Bioorganic & medicinal chemistry letters* **2012**, *22*, 3445-3448.
11. Tale, R.H.; Rodge, A.H.; Hatnapure, G.D.; Keche, A.P. The novel 3, 4-dihydropyrimidin-2 (1h)-one urea derivatives of n-aryl urea: Synthesis, anti-inflammatory, antibacterial and antifungal activity evaluation. *Bioorganic & medicinal chemistry letters* **2011**, *21*, 4648-4651.
12. Zheng, Q.-Z.; Cheng, K.; Zhang, X.-M.; Liu, K.; Jiao, Q.-C.; Zhu, H.-L. Synthesis of some n-alkyl substituted urea derivatives as antibacterial and antifungal agents. *European journal of medicinal chemistry* **2010**, *45*, 3207-3212.
13. Sashidhara, K.V.; Rosaiah, J.N.; Tyagi, E.; Shukla, R.; Raghubir, R.; Rajendran, S.M. Rare dipeptide and urea derivatives from roots of moringa oleifera as potential anti-inflammatory and antinociceptive agents. *European journal of medicinal chemistry* **2009**, *44*, 432-436.

14. Chen, J.-N.; Wang, X.-F.; Li, T.; Wu, D.-W.; Fu, X.-B.; Zhang, G.-J.; Shen, X.-C.; Wang, H.-S. Design, synthesis, and biological evaluation of novel quinazolinyl-diaryl urea derivatives as potential anticancer agents. *European journal of medicinal chemistry* **2016**, *107*, 12-25.
15. Gable, K.L.; Maddux, B.A.; Penaranda, C.; Zavodovskaya, M.; Campbell, M.J.; Lobo, M.; Robinson, L.; Schow, S.; Kerner, J.A.; Goldfine, I.D. Diarylureas are small-molecule inhibitors of insulin-like growth factor i receptor signaling and breast cancer cell growth. *Molecular cancer therapeutics* **2006**, *5*, 1079-1086.
16. Kansal, N.; Silakari, O.; Ravikumar, M. 3d-qsar studies of various diaryl urea derivatives of multi-targeted receptor tyrosine kinase inhibitors: Molecular field analysis approach. *Letters in Drug Design & Discovery* **2008**, *5*, 437-448.
17. Gandin, V.; Ferrarese, A.; Dalla Via, M.; Marzano, C.; Chilin, A.; Marzaro, G. Targeting kinases with anilinopyrimidines: Discovery of n-phenyl-n′-[4-(pyrimidin-4-ylamino) phenyl] urea derivatives as selective inhibitors of class iii receptor tyrosine kinase subfamily. *Scientific reports* **2015**, *5*, 16750.
18. Luo, C.; Tang, K.; Li, Y.; Yin, D.; Chen, X.; Huang, H. Design, synthesis and in vitro antitumor evaluation of novel diaryl urea derivatives bearing sulfonamide moiety. *Science China Chemistry* **2013**, *56*, 1564-1572.
19. Xuan, W.; Ding, W.; Hui, H.-x.; Zhang, S.-q. Synthesis and cytotoxic activity of diaryl urea derivatives with a 4-methylpiperazinylcarbonyl moiety. *Medicinal Chemistry Research* **2013**, *22*, 3857-3862.
20. Zhao, Y.-F.; Liu, Z.-J.; Zhai, X.; Ge, D.-D.; Huang, Q.; Gong, P. Synthesis and in vitro antitumor activity of novel diaryl urea derivatives. *Chinese Chemical Letters* **2013**, *24*, 386-388.