Synthesis and Antiproliferative Activities of 1-Substituted-3-(3-chloro-5-methoxyphenyl)-4-pyridinylpyrazole Derivatives Against Melanoma Cell Line

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The synthesis of a new series of diarylureas and amides having a 1-substituted-3-(3-chloro-5-methoxyphenyl)-4-pyridinylpyrazole 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. Most of the newly synthesized compounds generally showed superior or similiar activity against A375 to Sorafenib. Among these compounds, **IId**, **IIg** and **IIh** showed excellent activity against A375 compared to Sorafenib.

Key Words: 4-Pyridinylpyrazole, A375, Antiproliferative activity, Melanoma

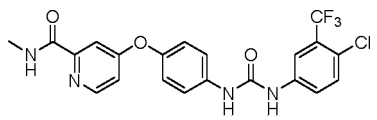
Introduction

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-years survival rate is less than 15%.[2,3] With the rapid incidence of melanoma in the United States and other developed countries, there is an urgent need to develop more effective drugs.[4-6]

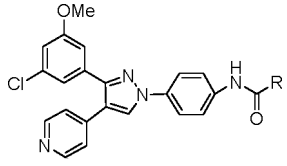
Recently, Sorafenib, as well as other diarylureas, have been evaluated as potent and selective antiproliferative agents for the treatment of melanoma.[7-12] The promising results have encouraged many research groups to investigate diarylurea scaffolds to develop new derivatives for the treatment of cancer.[13-17]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

In this work, we investigated the effect of replacing the 2-(methylaminocarbonyl)pyridine-4-yloxy group in Sorafenib with a 3-(3-chloro-5-methoxyphenyl)-4-pyridinyl-pyrazole moiety on the antiproliferative activity. The effect of substitution at the other phenylurea ring is also investigated by using the different substituents R.

Sorafenib



1-Substituted-3-(3-chloro-5-methoxyphenyl)-4-pyridinyl-pyrazole

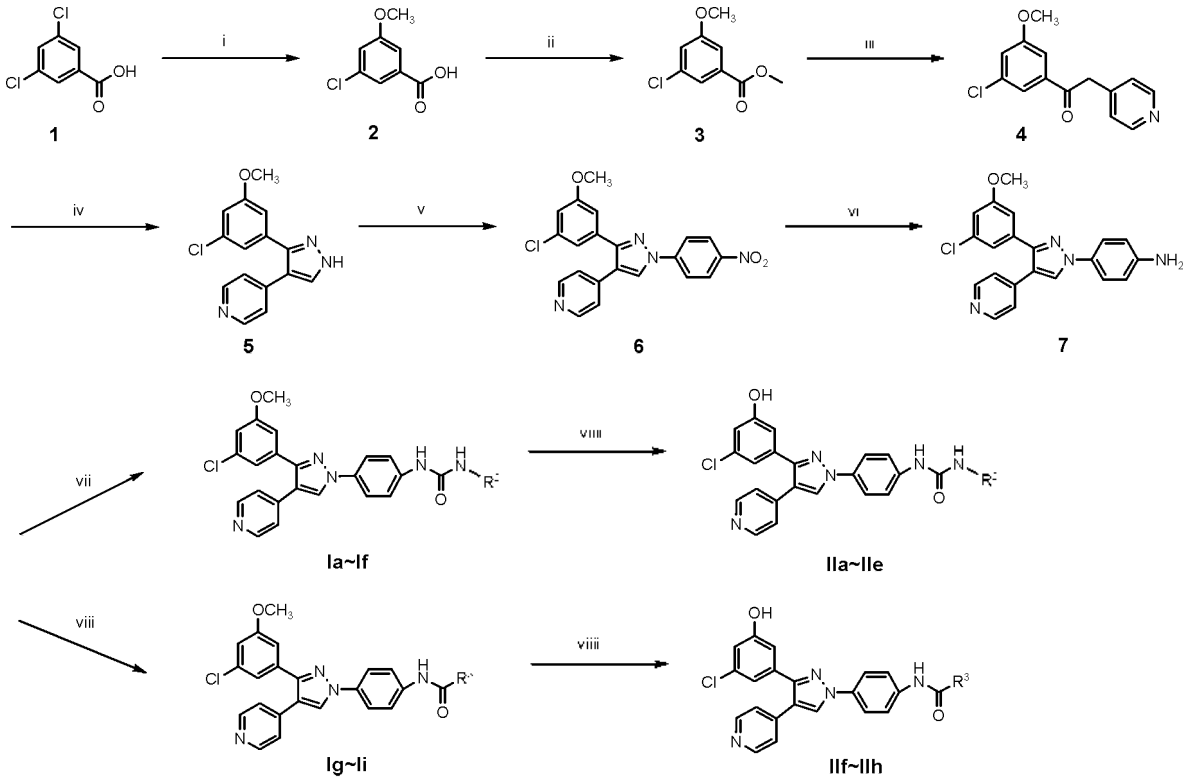


Results and Discussion

Chemistry. 1,3,4-Triarylpyrazole derivatives (**Ia-f** and **IIa-e**) with urea moiety at the terminal part were prepared according to the sequence of reactions shown in Scheme 1. Heating 3,5-dichlorobenzoic acid (**1**) with two molecular equivalents of sodium methoxide in hexamethylphosphoramide (HMPA) gave 3-chloro-5-methoxybenzoic acid (**2**), which upon esterification with methanol in the presence of acetyl chloride afforded the corresponding methyl ester **3**. The pyridyl derivative **4** was obtained by treatment of **3** with 4-picoline in THF in the presence of lithium bis(trimethylsilyl)amide (LHMDS). 3,4-Diarylpyrazole derivative **5** was obtained by treatment of **4** with dimethylformamide dimethyl acetal (DMF-DMA), and subsequent treatment with hydrazine monohydrate. 1,3,4-Triarylpyrazole derivative **7** with amino group was prepared through *N*-arylation of **5** using 1-iodo-4-nitrobenzene in DMSO in the presence of anhydrous K_2CO_3, and subsequent reduction of the nitro group of **6** using stannous chloride. Interaction of the amino group with phenylisocyanate derivatives in THF afforded the corresponding urea derivatives (**Ia-f**). Demethylation of the methoxy group of compounds **Ia-f** using BBr_3 afforded the corresponding hydroxy derivatives (**IIa-e**).

The synthesis of **Ig-i** and **IIf-h** with amide moiety at the terminal part was carried out by the same procedure described for synthesis of urea derivatives (**Ia-f** and **IIa-e**). Benzoic acid derivatives were used instead of phenylisocyanate derivatives for acylation of amino group of **7** in DMF in the presence of HOBt and EDCI to afford **Ig-i**. Demethylation of the methoxy group in order to obtain the corresponding hydroxy derivatives (**IIf-h**) was achieved by the same method described for preparation of **IIa-e**.

***In vitro* activity.** The antiproliferative activity of the newly synthesized compounds against A375 human melanoma cell line was examined. The ability of these compounds to inhibit the growth of A375 cell line is summarized in Tables 1 and 2. Sorafenib was selected as a reference standard, because it has been extensively used in clinical trials for melanoma.[4-18] Regarding the terminal substituents on the phenyl ring of the



Scheme 1. Reagents and conditions: i) sodium methoxide, HMPA; ii) acetyl chloride, MeOH; iii) 4-picoline, LHMDS, THF; iv) (a) DMF-DMA (b) hydrazine monohydrate, EtOH; v) 1-iodo-4-nitrobenzene, K_2CO_3, CuI, L-proline, DMSO; vi) Raney nickel, 1,4-dioxane; vii) R^2NCO, THF; viii) R^3COOH, HOBt, EDCI, TEA, DMF; viiii) BBr_3, CH_2Cl_2.

tail. it was found that compounds **Ih**, **IIf**, **IIg**, and **IIh** having amide moiety were more potent than compounds **Ib**, **IIa**, **IIb**, and **IIc** having urea moiety. As to the substituents on the chlorophenyl ring, compounds **IIb**, **IId**, **IIe**, **IIf**, **IIg**, and **IIh** with hydroxyl group showed higher antiproliferative activity in comparison with the corresponding methoxy derivatives **Ib**, **Id**, **Ie**, **Ig**, **Ih**, and **Ii**. This indicates that the more polar substituent at this position is preferable. Most of the newly synthesized compounds generally showed superior or similiar activity against A375 to Sorafenib. Among these compounds, **IId**, **IIg** and **IIh** showed excellent activity against A375 compared to Sorafenib.

Experimental Section

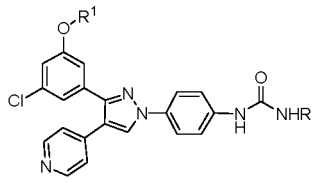
Melting points (mp) were determined on a Walden Precision Apparatus Electrothermal 9300 apparatus and were uncorrected. ^{1}H-NMR spectral data were recorded using a Gemini 300 spectrometer. Mass spectra were recorded on a Waters 3100 Mass Detecter.

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 with various concentrations (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, US). The IC_{50} was calculated using GraphPad Prism 4.0 softwere.

3-Chloro-5-methoxybenzoic acid (2). A mixture of 3,5-dichlorobenzoic acid (**1**, 1.0 g, 5.2 mmol) and NaOMe (3.5 mL, 25 wt% solution in methanol, 16.2 mmol) in HMPA (2.0 mL) was heated at 120 °C for 15 h. The mixture was poured into ice-water and acidified with conc. HCl to give 3-chloro-5-methoxybenzoic acid (**2**, 1.2 g, 80%) as a precipitate which was collected by filtration and used in the next step without purification. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.47 (t, 1H, J = 1.6 Hz), 7.38 (q, 1H, J = 1.3 Hz), 7.30 (t, 1H, J = 2.0 Hz), 3.82 (s, 3H).

Methyl 3-chloro-5-methoxybenzoate (3). Acetyl chloride (1.9 mL, 28.1 mmol) was added dropwise to a solution of (**2**, 1.0 g, 5.4 mmol in MeOH (40.0 mL) at 0 °C and the reaction mixture was then stirred at room temperature for 15 h. After evaporation of the organic solvent, the residue was purified by flash column chromatography (silica gel, hexanes-ethyl acetate 5:1 v/v) to give (**3**, 1.7 g, 65%) as an oil. ^{1}H-NMR ($CDCl_3$,

Table 1. Antiproliferative activity of the urea substituted compounds



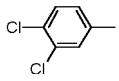
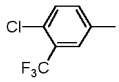
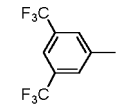
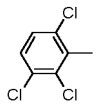
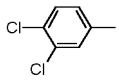
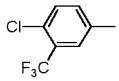
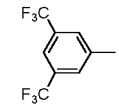
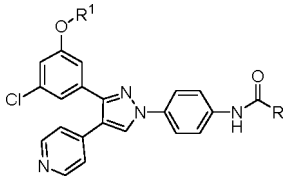
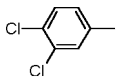
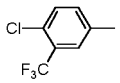
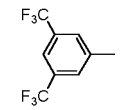
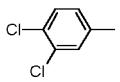
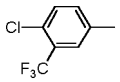
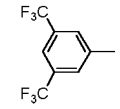
Comd.	R^1	R	A375P (IC_{50},μM)
Ia	CH_3		2.3
Ib	CH_3		4.2
Ic	CH_3		3.0
Id	CH_3		> 20
Ie	CH_3		19.5
If	CH_3		2.3
IIa	H		5.3
IIb	H		3.4
IIc	H		5.2
IId	H		1.5
IIe	H		3.3
Sorafenib			5.0

Table 2. Antiproliferative activity of the amide substituted compounds



Comd.	R^1	R	A375P (IC_{50},μM)
Ig	CH_3		> 20
Ih	CH_3		2.5
Ii	CH_3		> 20
IIf	H		2.2
IIg	H		1.7
IIh	H		0.9
Sorafenib			5.0

300 MHz) δ 7.61 (t, 1H, J = 1.6 Hz), 7.45 (q, 1H, J = 1.3 Hz), 7.09 (t, 1H, J = 2.2 Hz), 3.92 (s, 3H), 3.85 (s, 3H).

1-(3-Chloro-5-methoxyphenyl)-2-(pyridin-4-yl)ethanone (4). To a mixture of compound (**3**, 1.0 g, 5.0 mmol) and 4-picoline (0.5 mL, 5.6 mmol) in THF (5.0 mL) in a water bath at −20 °C, LHMDS (3.7 mL, 1.0 M solution in THF, 19.9 mmol) was slowly added to maintain the temperature at −20 °C. The reaction mixture was stirred overnight at room temperature. The mixture was quenched with saturated aqueous NH_4Cl. Ethyl acetate was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer extracts were washed with brine and dried over Na_2SO_4. The organic solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, hexanes-ethyl acetate 1:1 v/v then switching to hexanes-ethyl acetate 1:5 v/v) to yield compound (**4**, 3.3 g, 40%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.58 (d, 2H, J = 5.7 Hz), 7.54 (t, 1H, J = 1.5 Hz), 7.39 (q, 1H, J = 1.4 Hz), 7.19 (d, 2H, J = 5.7 Hz), 7.12 (t, 1H, J = 2.0 Hz), 4.25 (s, 2H), 3.85 (s, 3H).

4-[3-(3-Chloro-5-methoxyphenyl)-1*H*-pyrazol-4-yl]pyridine (5). Compound (**4**, 1.0 g, 3.8 mmol) was added to DMF-DMA (5.14 mL, 38.2 mmol) and the mixture was stirred at room temperature for 18 h. The resulting solution was concentrated to dryness to furnish an oil which was used in the next step without any purification. To a portion of the oil from the previous step (0.137 g, 0.457 mmol) in EtOH (3.0 mL) was added hydrazine monohydrate (0.04 mL, 0.76 mmol) and the reaction was stirred overnight at room temperature. Water (5.0 mL) was added to the reaction mixture and the organics were extracted with ethyl acetate. The combined organic layer extracts were washed

with brine and dried over $MgSO_4$. After evaporation of the organic solvent, the residue was purified by column chromatography (silica gel, hexanes-ethyl acetate 1:1 v/v then switching to hexanes-ethyl acetate 1:5 v/v) to yield compound (**5**, 0.11 g, 81%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.55 (d, 2H, J = 5.3 Hz), 7.83 (s, 1H), 7.23 (d, 2H, J = 5.4 Hz), 7.06 (brs, 1H), 6.94 (brs, 1H), 6.85 (brs, 1H), 3.77 (s, 3H).

4-[3-(3-Chloro-5-methoxy-phenyl)-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]pyridine (6). A mixture of compound (**5**, 0.5 g, 1.7 mmol), 1-iodo-4-nitrobenzene (0.9 g, 3.5 mmol), K_2CO_3 (0.7 g, 5.2 mmol), CuI (0.033 g, 0.2 mmol), and L-proline (0.04 g, 0.2 mmol) in DMSO (7.0 mL) was heated at 90 °C under nitrogen atmosphere for 8 h. The cooled solution was partitioned between water and ethyl acetate. The organic phase was washed with brine (3 times) and dried over Na_2SO_4. After evaporation of the organic solvent, the residue was purified by column chromatography (silica gel, hexanes-ethyl acetate 1:5 v/v) to yield compound (**6**, 0.8 g, 84%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 9.25 (s, 1H), 8.44 (d, 2H, J = 9.5 Hz), 8.25 (d, 2H, J = 8.5 Hz), 8.06 (d, 2H, J = 8.7 Hz), 7.97 (d, 2H, J = 8.0 Hz), 7.41 (brs, 2H), 6.98 (brs, 1H), 3.74 (s, 3H).

4-[3-(3-Chloro-5-methoxyphenyl)-1-(4-aminophenyl)-1*H*-pyrazol-4-yl]pyridine (7). A mixture of compound (**6**, 0.5 g, 1.2 mmol) and Raney nickel (1.0 g) in 1,4-dioxane (5.0 mL) was stirred at room temperature under hydrogen atmosphere for 6 h. The mixture was filtered through celite and the filtrate was evaporated under reduced pressure to give compound (**7**, 0.5 g, 87%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.55 (d, 2H, J = 4.6 Hz), 7.98 (s, 1H), 7.53 (d, 2H, J = 8.7 Hz), 7.25 (d, 2H, J = 5.2 Hz), 7.19 (brs, 1H), 6.93 (brs, 1H), 6.92 (brs, 1H), 6.77 (d, 2H, J = 8.7 Hz), 3.73 (s, 1H).

1-{4-[3-(3-Chloro-5-methoxyphenyl)-4-pyridin-4-yl-pyrazol-1-yl]-phenyl}-3-(3,4-dichlorophenyl)urea (Ia). A solution of compound (**7**, 50 mg, 0.1 mmol) in THF (1.0 mL) was treated with dropwise addition of a solution of 3,4-dichlorophenyl isocyanate (25.0 mg, 0.1 mmol) in THF (1.0 mL) at room temperature under N_2 and the mixture was stirred at room temperature for 12 h. The mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes-ethyl acetate 1:5 v/v) to yield compound **Ia** (18.0 mg, 24%). mp: 173 - 175 °C. (dec.). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.56 (d, 2H, J = 6.0 Hz), 7.93 (brs, 1H), 7.86 (d, 2H, J = 8.5 Hz), 7.65 (d, 2H, J = 8.4 Hz), 7.51 (s, 1H), 7.36 (brs, 4H), 7.13 (s, 1H), 7.10 (s, 1H), 6.96 (s, 1H), 7.75 (s, 3H). ESI-MS: 564.0 $[M+H]^-$.

The synthesis of compounds Ib-If were carried out by the same procedure as described for the preparation of Ia.

Ib: Yield 23%. mp: 195 - 197 °C. (dec.). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.58 (brs, 2H), 8.10 (s, 1H), 7.80 (s, 1H), 7.77 (s, 1H), 7.73 (s, 1H), 7.61 (s, 1H), 7.54 (d, 2H, J = 8.9 Hz), 7.46 (brs, 2H), 6.92 (brs, 2H), 6.68 (s, 1H), 6.62 (s, 1H), 3.74 (s, 3H). ESI-MS: 598.0 $[M+H]^+$.

Ic: Yield 29%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.58 (brs, 2H), 8.08 (s, 1H), 7.94 (brs, 1H), 7.73 (d, 2H, J = 8.9 Hz), 7.56 (s, 1H), 7.53 (brs, 2H), 7.36 (s, 3H), 7.19 (brs, 1H), 6.92 (brs, 2H), 3.74 (s, 3H). ESI-MS: 632.0 $[M+H]^-$.

Id: Yield 35%. mp: 222 - 224 °C. (dec.). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.78 (brs, 1H), 8.94 (s, 1H), 8.61 (brs, 1H), 8.56 (d, 2H, J = 6.1 Hz), 7.89 (d, 2H, J = 8.9 Hz), 7.64 (d, 2H, J = 9.0 Hz), 7.36 (d, 2H, J = 6.2 Hz), 7.32 (s, 1H), 7.13 (brs, 1H), 7.09 (brs, 1H), 6.96 (brs, 1H), 3.74 (s, 3H). ESI-MS: 564.0 $[M+H]^-$.

Ie: Yield 43%. mp: 237 - 239 °C. (dec.). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.54 (brs, 2H), 7.96 (s, 1H), 7.61 (d, 2H, J = 8.5 Hz), 7.54 (s, 1H), 7.40 (s, 1H), 7.36 (s, 1H), 7.26 (s, 1H), 7.21 (d, 2H, J = 4.4 Hz), 7.15 (d, 2H, J = 5.2 Hz), 6.99 (brs, 1H), 6.88 (brs, 2H), 3.70 (s, 3H). ESI-MS: 530.1 $[M+H]^-$.

If: Yield 40%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.93 (s, 1H), 8.56 (d, 2H, J = 5.7 Hz), 8.50 (s, 1H), 7.91 (s, 1H), 7.88 (s, 2H), 7.64 (d, 2H, J = 8.1 Hz), 7.36 (d, 2H, J = 5.9 Hz), 7.12 (s, 1H), 7.09 (s, 1H), 6.96 (s, 1H), 3.74 (s, 3H). ESI-MS: 598.0 $[M+H]^-$.

3,4-Dichloro-*N*-{4-[3-(3-chloro-5-methoxyphenyl)-4-pyridin-4-yl-pyrazol-1-yl]phenyl}benzamide (Ig). A mixture of compound (**7**, 50.0 mg, 0.1 mmol), 3,4-dichlorophenyl benzoic acid (38.0 mg, 0.2 mmol), HOBt (36.0 mg, 0.3 mmol), and EDCI (38.0 mg, 0.2 mmol) in DMF (1.0 mL) was cooled to 0 °C under nitrogen atmosphere. The mixture was warmed to room temperature and Et_3N (0.03 mL, 0.2 mmol) was added. The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled and then partitioned between H_2O and ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the organic solvent, the residue was purified by column chromatography (silica gel, hexanes-ethyl acetate 1:5 v/v) to yield compound **Ig** (22.0 mg, 31%). mp: 224 - 226 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.92 (s, 1H), 8.55 (t, 3H, J = 4.8 Hz), 7.88 (d, 2H, J = 9.0 Hz), 7.63 (d, 2H, J = 9.0 Hz), 7.36 (d, 3H, J = 5.8 Hz), 7.32 (s, 1H), 6.97 (brs, 1H), 8.84 (brs, 2H). ESI-MS: 550.8 $[M+H]^+$.

The synthesis of compounds Ih and Ii was carried out by the same procedure as described for the preparation of Ig.

Ih: Yield 25%. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.93 (s, 1H), 8.56 (d, 2H, J = 5.3 Hz), 8.17 (brs, 2H), 7.87 (d, 2H, J = 9.0 Hz), 7.67 (brs, 3H), 7.36 (d, 2H, J = 6.0 Hz), 6.97 (brs, 1H), 6.84 (brs, 2H). ESI-MS: 583.0 $[M+H]^-$.

Ii: Yield 39%. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.90 (s, 1H), 8.55 (d, 2H, J = 4.4 Hz), 7.83 (d, 2H, J = 8.9 Hz), 7.75 (s, 1H), 7.65 (d, 2H, J = 8.3 Hz), 7.36 (brs, 3H), 7.01 (s, 1H), 6.99 (s, 1H), 6.97 (s, 1H), 6.83 (brs, 2H). ESI-MS: 617.1 $[M+H]^-$.

1-{4-[3-(3-Chloro-5-methoxy-phenyl)-4-pyridin-4-yl-pyrazol-1-yl]-phenyl}-3-(3,4-dichlorophenyl)urea (IIa). To a mixture of compound **Ia** (50.0 mg, 0.1 mmol) in methylene chloride (1.0 mL), BBr_3 (0.02 mL of a 1 M solution in MC, 0.3 mmol) was added dropwise at −78 °C under N_2 and the reaction mixture was stirred for 30 min. The mixture was warmed to room temperature and stirred for 1 h. The mixture was quenched with saturated aqueous $NaHCO_3$. Ethyl acetate was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer extracts were washed with brine, dried with Na_2SO_4. After evaporation of the organic solvent, the residue was purified by short column chromatography (silica gel, hexanes-ethyl acetate 1:5 v/v) to yield compound **IIa** (45.0 mg, 92%). mp: 245 - 247 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.61 (s, 1H), 9.00 (s, 1H), 8.57 (d, 2H, J = 4.9 Hz), 8.26 (s, 1H), 7.96 (s, 4H), 7.86 (d, 1H, J = 8.6 Hz), 7.37 (d, 2H, J = 4.8 Hz), 7.14 (s, 1H), 7.11 (s, 1H), 6.97 (s, 1H), 3.75 (s, 3H). ESI-MS: 550.0 $[M+H]^+$.

The synthesis of compounds IIb-IIh was carried out by the same procedure as described for the preparation of IIa.

IIb: Yield 40%. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.71 (s, 1H), 9.02 (brs, 1H), 8.57 (brs, 2H), 8.42 (brs, 1H), 8.27 (brs, 1H), 7.96 (s, 4H), 7.37 (brs, 2H), 7.10 (s, 1H), 7.08 (s, 1H), 6.97 (s, 1H), 3.74 (s, 3H). ESI-MS: 584.0 $[M+H]^+$.

IIc: Yield 56%. mp: 245 - 247 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.59 (d, 2H, J = 4.9 Hz), 8.38 (brs, 1H), 8.18 (brs, 1H), 8.14 (brs, 1H), 8.10 (brs, 1H), 7.85 (s, 3H), 7.27 (s, 3H), 7.22 (brs, 1H), 6.94 (brs, 2H), 3.75 (s, 3H). ESI-MS: 618.1 $[M+H]^+$.

IId: Yield 87%. mp: 225 - 227 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.92 (s, 1H), 8.55 (d, 2H, J = 4.8 Hz), 8.17 (brs, 1H), 7.85 (d, 2H, J = 8.4 Hz), 7.67 (s, 3H), 7.64 (brs, 1H), 7.35 (d, 2H, J = 4.4 Hz), 6.97 (brs, 1H), 6.84 (brs, 2H). ESI-MS: 550.0 $[M+H]^-$.

IIe: Yield 54%. mp: 220 - 222 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 9.09 (d, 2H, J =11.9 Hz), 8.92 (s, 1H), 8.56 (d, 2H, J = 6.0 Hz), 7.91 (s, 1H), 7.86 (d, 1H, J = 8.8 Hz), 7.62 (d, 2H, J = 8.9 Hz), 7.35 (s, 3H), 6.97 (brs, 1H), 6.84 (brs, 2H). ESI-MS: 516.0 $[M+H]^-$.

IIf: Yield 62%. mp: 185 - 187 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 9.26 (s, 1H), 8.77 (d, 2H, J = 5.2 Hz), 8.26 (s, 1H), 7.97 (s, 5H), 7.86 (d, 1H, J = 8.3 Hz), 7.76 (d, 2H, J = 5.4 Hz), 7.03 (brs, 1H), 6.92 (brs, 1H), 6.86 (brs, 1H). ESI-MS: 535.0 $[M+H]^+$.

IIg: Yield 61%. mp: 160 - 162 °C. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.99 (s, 1H), 8.59 (brs, 2H), 8.43 (brs, 2H), 7.96 (s, 4H), 7.52 (s, 1H), 7.39 (s, 2H), 6.99 (brs, 1H), 6.88 (brs, 1H), 6.86 (brs, 1H). ESI-MS: 569.3 $[M+H]^+$.

IIh: Yield 72%. mp: 240 - 242 °C. (dec.). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.99 (s, 1H), 8.64 (brs, 2H), 8.57 (d, 2H, J = 6.1 Hz), 8.41 (s, 1H), 7.97 (s, 4H), 7.37 (d, 2H, J = 6.0 Hz), 7.00 (brs, 1H), 6.85 (brs, 1H). ESI-MS: 603.0 $[M+H]^+$.

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