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Design, Synthesis, and *In Vitro* Cytotoxic Activity of Certain 2-[3-Phenyl-4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]acetamide Derivatives

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Abstract—With a view to finding new anticancer agents, different aryloxy groups were attached to C^2 of the pyrimidine ring in 2-[3-phenyl-4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]acetamide in five steps using methyl 3-methoxy-5-methylbenzoate as the key intermediate product. The anticancer activity of the synthesized compounds was tested on 60 cancer cell lines at 10 μM. One compound showed an appreciable cancer cell growth inhibition (about 20%) against eight cancer cell lines (HOP-92, NCI-H226, 79SNB-75, A498, SN12C, UO-31, T-47D, and MDA-MB-468).

Keywords: 3-phenyl-4-pyrimidinyl-1*H*-pyrazole, acetamide analogs, anticancer activity

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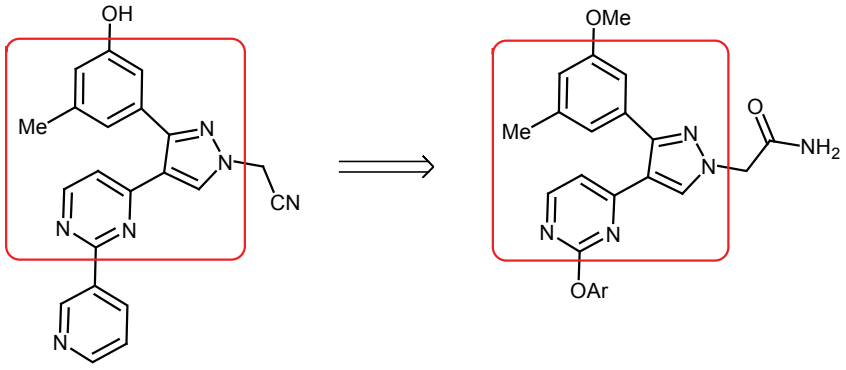
Cancer is a genetic disease acquired by the accumulation of mutated genes responsible for cell proliferation and survival. The incidence of new types of human neoplasms has alarmingly increased, resulting in a big public health crisis and the leading cause of death. Because of a series of genetic defects, cancer leads to the transformation of normal cells into cancerous ones associated with abnormalities in the regulation of cell proliferation, growth, and survival processes [1]. Thus, there is a critical need to develop new and innovative potent anticancer agents. Different kinds of classical cancer therapies, such as chemotherapy, irradiation, and immunotherapy have achieved significant improvements in the prevention and control of different human malignancies; however, the emergence of severe toxicity has restricted their application. Due to the reported toxicity of classical anticancer drugs, many selective less toxic anticancer drugs have been extensively studied [2–5].

Phenylpyridinyl and phenylpyrimidinyl pyrazole scaffold-based compounds are promising anti-proliferative agents targeting different types of human cancers [5–12]. The purpose of this study was to discover newer and efficient anti-proliferative agents for further developments [12–15]. Herein, we report the synthesis of a series of 2-[3-phenyl-4-(pyrimidin-4-yl-1*H*-pyrazol-1-yl]acetamide derivatives with different aryloxy substituents at the 2-position of the pyrimidine ring, which were designed in coherence with the lead compound **A** [14] (Scheme 1). The synthesized compounds were subjected to primary screening over a panel of 60 cancer cell lines at a single dose concentration of 10 μM.

The target diarylpyrazole-based compounds were synthesized through methyl 3-methoxy-5-methylbenzoate (**4**) as the key intermediate product, which was prepared according to the reported procedures [12, 15–19] (Scheme 2). The first step was condensa-

Scheme 1.



Lead compound **A** Designed compounds

tion of diethyl oxalate with acetone in the presence of NaOEt in anhydrous ethanol, which produced ethyl 2-hydroxy-4-oxopent-2-enoate sodium salt (**1**) [20].

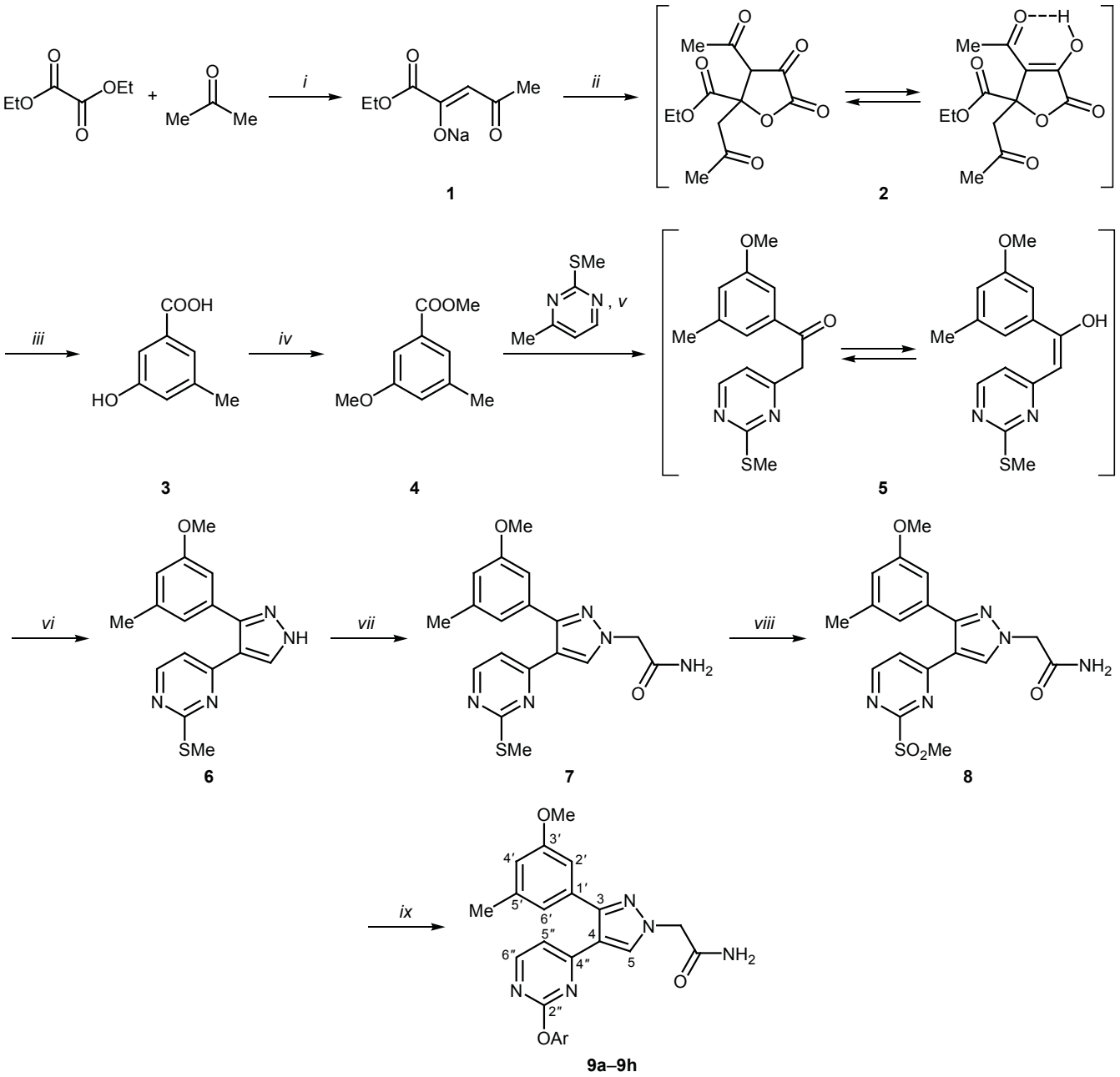
Salt **1** was then heated in acetic acid, and subsequent acidification with sulfuric acid gave tetrahydrofuran-2,3-dione derivative **2**. Compound **2** underwent rearrangement and aromatization into 3-hydroxy-5-methylbenzoic acid (**3**) on heating with magnesium oxide in boiling water for 45 min, followed by acidification with hydrochloric acid [21]. Acid **3** was treated with methyl iodide in boiling acetone in the presence of excess potassium carbonate and a catalytic amount of DMAP to obtain methyl 3-methoxy-5-methylbenzoate (**4**) in 94% yield (cf. [22]). Ester **4** was reacted with lithium salt derived from 4-methyl-2-(methylsulfanyl)-pyrimidine by the action of lithium bis(trimethylsilyl)-amide (LiHMDS) in anhydrous THF at room temperature. The resulting tautomeric α,β-unsaturated ketone **5** was converted to pyrazole derivative **6** by heating with excess *N*,*N*-dimethylformamide dimethyl acetal for 12 h, followed by cyclization with hydrazine hydrate in anhydrous ethanol. The reaction of **6** with iodoacetamide in the presence of excess potassium carbonate produced pyrazolylacetamide **7** as a single isomer. 2-{4-[2-(Methanesulfonyl)pyrimidin-4-yl]-3-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl}acetamide (**8**) was prepared in a good yield (70%) by oxidation of **7** with *m*-chloroperoxybenzoic acid and magnesium sulfate in anhydrous methylene chloride for 2 h. Finally, compound **8** was subjected to nucleophilic substitution reaction with different substituted aromatic hydroxy compounds on heating at 80°C in anhydrous dimethylformamide for 3 h.

The structures of **9a**–**9h** were selected by the National Cancer Institute (NCI, Bethesda, Maryland, USA) on the basis of the degree of structural variation and computer modeling techniques for evaluation of their antineoplastic activities. The compounds were subjected to *in vitro* anticancer assay against a panel of 60 different human tumor cell lines representing nine different tissues (leukemia, melanoma, and lung, colon, brain, ovarian, breast, prostate, and renal cancers). The compounds were tested at a single dose concentration of 10 μM, and the cultures were incubated for 48 h. The results for each compound were represented as mean graphs of the percent growth of the treated cells relative to the untreated cells (control). The percent cell growth of 19 most sensitive cell lines treated with compounds **9a**–**9h** at a concentration of 10 мМ is illustrated by Table 1.

All the compounds tested displayed a growth inhibitory profile of <27% in 19 most sensitive tumor cell lines. Compound **9h** showed 25.4 and 20.8% growth inhibition toward SNB-75 and A498 cell lines, respectively. Compound **9a** with a trimethoxyphenyl moiety exhibited 26% growth inhibition against breast cancer cell line MDA-MB-468. Compound **9b** exhibited 21% inhibition on NCI-H226 and MDA-MB-468 cell lines and 22.2% growth inhibition on SNB-75. Compound **9c** restricted the growth of renal A498 cells by 26.7%. This was the maximum inhibitory effect observed among the synthesized molecules against the tested cell lines. It also showed 17.3% growth inhibition in breast cancer cell line MDA-MB-468, and compound **9f** prevented the growth of NSCLC-HOP-92 and UO-31 cells by 25.9 and 20.3%, respectively. On the other hand, compounds **9d** and **9e** did not exert any appreciable effect. Similarly, compound **9g** specifically retarded the growth of renal cancer cell lines A498 and UO-31 by 23.7 and 20.2%, respectively.

Based on the threshold inhibition criteria, compounds **9a**–**9h** displayed no any significant cytotoxic activity. However, 3,4-dimethoxyphenyl derivative **9b** was found to be effective as it showed up to 22.2%

Scheme 2.



9, Ar = 3,4,5-$(MeO)_3C_6H_2$ (**a**), 3,4-$(MeO)_2C_6H_3$ (**b**), pyridin-3-yl (**c**), pyridin-4-yl (**d**), 1-oxidopyridin-1-ium-4-yl (**e**), 4-$MeOC_6H_4$ (**f**), 2-$EtOC_6H_4$ (**g**), pyridin-2-yl (**h**). Reagents and conditions: *i*: NaOEt, EtOH, r.t.,4 h, yield 87%; *ii*: AcOH–H_2O (1:1), r.t., 2 h, 50%; *iii*: MgO, H_2O, reflux, 45 min, 42%; *iv*: K_2CO_3, MeI, DMAP, acetone, 65°C, 12 h, 94%; *v*: LiHMDS, THF, N_2, r.t., 24 h; *vi*: (1) DMFDMA, 90°C, 20 h; (2) $N_2H_4 \cdot H_2O$, EtOH, r.t., 12 h, 79%; *vii*: K_2CO_3, ICH_2CONH_2, DMF, reflux, 2 h, 43%; *viii*: *m*-CPBA, $MgSO_4$, CH_2Cl_2, r.t., 2 h ; *ix*: ArOH, DMF, 80°C, 3 h.

growth inhibition in 19 sensitive cell lines. The reduced cytotoxic activity may be due to hindrances in the structural orientation to adopt a conformation/pose favoring the required activity profile. Taking compound **9b** as a template, further modifications are in progress to achieve a better antiproliferative activity.

In summary, we have designed, synthesized, and characterized a series of 2-[3-phenyl-4-(pyrimidin-4-yl)-1*H*-pyrazole]acetamide derivatives, and their *in vitro* antiproliferative activity has been assessed against 60 NCI cell lines at a single dose concentration of 10 μM. One of the synthesized compounds, namely

Table 1. Percent growth of cells treated with compounds **9a**–**9h** (10 μM) for 19 most sensitive tumor cell lines[a]

Cancer cell line		**9a**	**9b**	**9c**	**9d**	**9e**	**9f**	**9g**	**9h**
Leukemia	K-562	NI	NI	NI	NI	NI	88	NI	NI
	SR	NI	88	NI	NI	99	NI	93	NI
NSCLC	HOP-92	89	78	82	95	96	74	78	89
	NCI-H226	87	79	97	99	NI	NI	93	NI
CNS cancer	SF-295	95	87	99	92	NI	92	88	NI
	SF-539	97	88	96	98	NI	94	90	93
	SNB-75	88	78	93	98	96	94	83	74
Melanoma	LOX IMVI	98	99	96	99	NI	89	NI	93
	UACC-62	NI	92	93	96	95	88	87	98
Ovarian cancer	OVCAR-4	97	95	99	95	NI	NI	89	90
	OVCAR-5	99	87	NI	NI	NI	NI	93	NI
Renal cancer	A498	93	83	73	96	92	98	76	79
	CAKI-1	NI	89	99	97	NI	95	87	94
	SN12C	95	82	96	NI	92	93	94	NI
Prostate cancer	UO-31	92	88	93	90	95	80	80	92
	PC-3	96	93	89	NI	98	91	94	96
Breast cancer	HS 578T	NI	NI	NI	NI	89	NI	NI	97
	T-47D	NI	80	NI	94	NI	92	83	98
	MDA-MB-468	74	80	83	NI	NI	92	97	93

[a] NI stands for no inhibition or increase of cell growth.

2-{4-[2-(3,4-dimethoxyphenoxy)pyrimidin-4-yl]-3-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl}acetamide showed an appreciable cytotoxicity (up to 22.2% cell growth inhibition) against eight cancer cell lines covering four human malignancies (NSCLC, CNS, renal, and breast cancers). It could be considered as a promising hit compound and is currently subjected to further minor structural modifications to improve its antiproliferative potency.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 and 100 MHz, respectively. The melting points were measured with a Thomas Hoover capillary melting apparatus and are uncorrected. Column chromatography was performed on Merck silica gel 60 (230–400 mesh). Thin-layer chromatography was carried out using glass sheets pre-coated with silica gel 60 F254 (Merck). All commercial reagents were obtained from Aldrich and Tokyo Kasei Chemicals and generally used without further purification. Compounds **1**–**6** were prepared according to the reported methods [16–18].

2-{3-(3-Methoxy-5-methylphenyl)-4-[2-(methylsulfanyl)pyrimidin-4-yl]-1*H*-pyrazol-1-yl}acetamide (7). Iodoacetamide (2.96 g, 40 mmol) and freshly ground potassium carbonate (5.52 g, 40 mmol) were added to a solution of 4-[3-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-4-yl]-2-(methylsulfanyl)pyrimidine (**6**, 5 g, 16 mmol) in DMF (65 mL). The mixture was heated at 50°C on an oil bath for 16 h, cooled, and treated with brine and ethyl acetate. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography using hexane–ethyl acetate (4:1). Yield 43%, mp 265–267°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.31 s (3H, CH_3), 2.37 s (3H, SCH_3), 3.73 s (3H, OCH_3), 4.88 s (2H, CH_2CO), 6.81–6.83 m (2H, 2′-H, 4′-H), 6.90 s (1H, 6′-H), 6.98 d (J = 5.6 Hz, 1H, 5″-H), 7.36 s (1H, 5-H), 8.44 s (2H, NH_2), 8.45 d (1H, 6″-H, J = 5.6 Hz). ^{13}C NMR spectrum (DEPT135, DMSO-d_6), δ_C, ppm: 13.58 (SCH_3), 21.52 (CH_3), 54.46 (OCH_3), 55.51 (CH_2), 111.71 (C^4), 113.42 ($C^{2'}$), 115.11 ($C^{4'}$), 121.15 ($C^{6'}$), 122.4 ($C^{5''}$), 131.76 (C^5), 135.36 ($C^{1'}$), 139.51 ($C^{5'}$), 155.98 (C^3), 157.79 ($C^{6''}$), 162.43 ($C^{3'}$), 164.54 ($C^{4''}$), 168.24 ($C^{2''}$), 173.52 (C=O). Found, %: C 58.70; H 5.10; N 18.90. $C_{18}H_{19}N_5O_2S$. Calculated, %: C 58.52; H 5.18; N 18.96.

2-{4-[2-(Methanesulfonyl)pyrimidin-4-yl]-3-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl}acetamide (8). A mixture of *m*-chloroperoxybenzoic acid

(4.71 g, 27.3 mmol) and $MgSO_4$ (6.57 g, 54.6 mmol) in methylene chloride (100 mL) was stirred for 1 h at room temperature. 2-{3-(3-Methoxy-5-methylphenyl)-4-[2-(methylsulfanyl)pyrimidin-4-yl]-1*H*-pyrazol-1-yl}acetamide (**7**, 1.6 g, 4.55 mmol) was then added, and the mixture was stirred at room temperature for 2 h. The mixture was filtered, the precipitate was washed with methylene chloride, the filtrate was combined with the washings, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography using hexane–ethyl acetate (1:1) as eluent. Yield 70%, white solid, mp 280–282°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.39 s (3H, CH_3), 3.31 s (3H, SCH_3), 3.83 s (3H, OCH_3), 4.92 s (2H, CH_2CO), 6.86 s (1H, 2′-H), 6.93 s (1H, 4′-H), 6.99 s (1H, 2′-H), 7.31 d (1H, 5″-H, J = 5.6 Hz), 8.39 s (1H, 5-H), 8.56 s (2H, NH_2), 8.63 d (1H, 6″-H, J = 5.6 Hz). ^{13}C NMR spectrum (DEPT135, $CDCl_3$), δ_C, ppm: 21.53 (CH_3), 38.95 (SO_2CH_3), 55.39 (OCH_3), 55.50 (CH_2), 111.42 (C^4), 115.85 ($C^{2'}$), 119.56 ($C^{4'}$), 122.02 ($C^{6'}$), 132.32 ($C^{5''}$), 131.52 (C^5), 134.88 ($C^{1'}$), 140.53 ($C^{5'}$), 154.32 (C^3), 157.96 ($C^{6''}$), 162.27 ($C^{3'}$), 164.44 ($C^{4''}$), 168.05 ($C^{2''}$), 173.11 (C=O). Found, %: C 53.80; H 4.90; N 17.50. $C_{18}H_{19}N_5O_2S$. Calculated, %: C 53.85; H 4.77; N 17.45.

General procedure for the synthesis of 2-[4-(2-R-oxypyrimidin-4-yl)-3-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl]acetamides 9a–9h. A mixture of compound **8** (7.8 mmol) and aromatic hydroxy compound (7.8 mmol) in anhydrous DMF (5 mL) was heated under reflux at 80°C in an oil bath for 3 h. The mixture was cooled, diluted with ethyl acetate, and washed with saturated aqueous ammonium chloride and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was purified by column chromatography.

2-{3-(3-Methoxy-5-methylphenyl)-4-[2-(3,4,5-trimethoxyphenoxy)pyrimidin-4-yl]-1*H*-pyrazol-1-yl}-acetamide (9a). Yield 2.36 g (60%), mp >300°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.38 s (3H, CH_3), 3.79 s (3H, OCH_3), 3.82 s (6H, OCH_3), 3.83 s (3H, OCH_3), 4.87 s (2H, CH_2CO), 6.13 s (2H, C_6H_2), 6.49–6.51 m (2H, 2′-H, 4′-H), 6.87 d (1H, 5″-H, J = 5.6 Hz), 6.88 s (2H, NH_2), 6.96 s (1H, 6′-H), 8.19 s (1H, 5-H), 8.31 d (1H, 6″-H, J = 5.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.39 (CH_3), 55.03 (OCH_3), 55.30 (CH_2), 56.06 (2C, OCH_3), 56.22 (OCH_3), 93.51 ($C^{2'''}$, $C^{6'''}$), 99.64 (C^4), 111.79 ($C^{2'}$), 112.86 ($C^{4'}$), 115.62 ($C^{5''}$), 119.36 ($C^{6'}$), 122.18 ($C^{4'''}$), 133.43 (C^5), 134.06 ($C^{1'}$), 139.99 ($C^{5'}$), 147.22 ($C^{1'''}$), 149.09 ($C^{3'''}$, $C^{5'''}$), 152.65 (C^3), 153.67 ($C^{6''}$), 159.21 ($C^{3'}$), 159.85 ($C^{4''}$), 161. 83 ($C^{2''}$), 168.26 (C=O). Found, %: C 61.70; H 5.5; N 14.00. $C_{26}H_{27}N_5O_6$. Calculated, %: C 61.77; H 5.38; N 13.85.

2-{4-[2-(3,4-Dimethoxyphenoxy)pyrimidin-4-yl]-3-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl}-acetamide (9b). Yield 2.68 g (70%), mp >300°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.38 s (3H, CH_3), 3.80 s (3H, OCH_3), 3.81 s (3H, OCH_3), 3.92 s (3H, OCH_3), 4.85 s (2H, CH_2CO), 6.82–6.86 m (5H, 2′-H, 2‴-H, 4′-H, 5‴-H, 6‴-H), 6.90 d (1H, 5″-H, (J = 5.2 Hz), 6.99 s (2H, NH_2), 7.09 s (1H, 6′-H), 8.16 s (1H, 5-H), 8.29 d (J = 5.2 Hz, 1H, 6″-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.48 (CH_3), 55.02 (OCH_3), 55.32 (CH_2), 56.07 (OCH_3), 56.21 (OCH_3), 122.34 (C^4), 109.73 ($C^{2'''}$), 111.47 ($C^{2'}$), 112.75 ($C^{4'}$), 115.21 ($C^{5''}$), 115.71 ($C^{6'''}$), 119.36 ($C^{6'}$), 122.15 ($C^{4'''}$), 123.61 ($C^{5'''}$), 133.38 (C^5), 134.27 ($C^{1'}$), 140.04 ($C^{5'}$), 146.52 ($C^{3'''}$), 147.43 ($C^{1'''}$), 152.68 (C^3), 153.87 ($C^{6''}$), 159.12 ($C^{3'}$), 159.77 ($C^{4''}$), 161.60 ($C^{2''}$), 168.59 (C=O). Found, %: C 63.10; H 5.4; N 14.70. $C_{25}H_{25}N_5O_6$. Calculated, %: C 63.15; H 5.30; N 14.73.

2-{3-(3-Methoxy-5-methylphenyl)-4-[2-(pyridin-3-yloxy)pyrimidin-4-yl]-1*H*-pyrazol-1-yl}acetamide (9c). Yield 2.11 g (65%), mp >300°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.39 s (3H, CH_3), 3.82 s (3H, OCH_3), 4.88 s (2H, CH_2CO), 6.85 s (2H, NH_2), 6.92 s (1H, 2′-H),6.93 s (1H, 4′-H), 7.38–7.42 m (1H, 5‴-H), 7.59–7.62 m (2H, 4‴-H, 6‴-H), 8.13 s (1H, 6′-H), 8.34 d (1H, 5″-H, J = 5.6 Hz), 8.16 s (1H, 5-H), 8.54 d (1H, 6″-H, J = 5.6 Hz), 8.62 s (1H, 2‴-H). ^{13}C NMR spectrum (DEPT135, $CDCl_3$), δ_C, ppm: 21.53 (CH_3), 55.06 (OCH_3), 55.35 (CH_2), 99.69 (C^4), 111.54 ($C^{2'}$), 113.34 ($C^{4'}$), 115.68 ($C^{5''}$), 119.34 ($C^{6'}$), 122.10 ($C^{5'''}$), 129.26 (C^5), 133.26 ($C^{3'''}$), 133.85 ($C^{4'''}$), 134.11 ($C^{1'}$), 139.62 ($C^{5'}$), 143.90 ($C^{6'''}$), 146.21 ($C^{2'''}$), 152.23 (C^3), 153.12 ($C^{6''}$), 159.58 ($C^{3'}$), 159.41 ($C^{4''}$), 161.15 ($C^{2''}$), 168.29 (C=O). Found, %: C 63.50; H 4.80; N 20.20. $C_{22}H_{20}N_6O_3$. Calculated, %: C 63.45; H 4.84; N 20.18.

2-{3-(3-Methoxy-5-methylphenyl)-4-[2-(pyridin-4-yloxy)pyrimidin-4-yl]-1*H*-pyrazol-1-yl}acetamide (9d). Yield 1.78 g (55%), mp >300°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.39 s (3H, CH_3), 3.82 s (3H, OCH_3), 4.94 s (2H, CH_2CO), 6.44 d (2H, 3‴-H, 5‴-H, J = 8 Hz), 6.88 s (2H, NH_2), 6.95 s (1H, 2′-H), 7.09 s (1H, 4′-H), 7.13 d (1H, 5″-H, J = 5.2 Hz), 8.19 s (1H, 6′-H), 8.28 s (1H, 5-H), 8.51 d (1H, 6″-H, J = 5.6 Hz), 8.66 d (2H, 2‴-H, 6‴-6, J = 8 Hz). ^{13}C NMR spectrum (DEPT135, $CDCl_3$), δ_C, ppm: 21.53 (CH_3), 55.16 (OCH_3), 55.34 (CH_2), 112.27 ($C^{2'}$), 114.64 ($C^{4'}$), 115.22 ($C^{5''}$), 111.35 (C^4), 119.67 ($C^{6'}$), 122.25 ($C^{3'''}$, $C^{5'''}$), 129.77 (C^5), 133.57 ($C^{2'''}$, $C^{6'''}$), 134.72 ($C^{1'}$),

139.53 ($C^{5'}$), 143.90 ($C^{4'''}$), 152.75 (C^{3}), 153.46 ($C^{6''}$), 159.43 ($C^{3'}$), 159.41 ($C^{4''}$), 161.15 ($C^{2''}$), 168.29 (C=O). Found, %: C 63.40; H 4.90; N 20.10. $C_{22}H_{20}N_6O_3$. Calculated, %: C 63.45; H 4.84; N 20.18.

3-({[4-(1-(2-Amino-2-oxoethyl)-3-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-4-yl]pyrimidin-2-yl}-oxy)pyridine 1-oxide (9e). Yield 2.01 g (60%), mp >300°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.30 s (3H, CH_3), 3.74 s (3H, OCH_3), 4.88 s (2H, CH_2CO), 6.79 s (2H, NH_2), 6.85 s (1H, 2′-H), 7.07 d (1H, 5″-H, *J* = 5.2 Hz), 7.25 d (1H, 4‴-H, *J* = 8.8 Hz), 7. 37 s (1H, 2‴-H), 7.39 d (1H, 6‴-H, *J* = 6.8 Hz), 7.67 s (1H, 4′-H), 8.33 s (1H, 6′-H), 8.34 t (1H, 5‴-H, *J* = 2 Hz), 8.37 s (1H, 5-H), 8.59 d (1H, 6″-H, *J* = 5.2 Hz). ^{13}C NMR spectrum (APT, DMSO-d_6), δ_C, ppm: 21.51 (CH_3), 54.45 (OCH_3), 55.52 (CH_2), 99.84 (C^4), 111.76 ($C^{2'}$), 114.03 ($C^{4'}$), 115.16 ($C^{5''}$), 117.41 ($C^{4'''}$), 119.93 ($C^{6'}$), 122.27 ($C^{5'''}$), 126.47 (C^5), 134.13 ($C^{2'''}$), 134.42 ($C^{1'}$), 135.48 ($C^{5'}$), 136.43 ($C^{6'''}$), 139.41 ($C^{3'''}$), 150.59 (C^3), 151.75 ($C^{6''}$), 159.46 ($C^{3'}$), 160.15 ($C^{4''}$), 162.54 ($C^{2''}$), 168.47 (C=O). Found, %: C 61.10; H 4.60; N 19.40. $C_{22}H_{20}N_6O_4$. Calculated, %: C 61.10; H 4.66; N 19.43.

2-{3-(3-Methoxy-5-methylphenyl)-4-[2-(4-methoxyphenoxy)pyrimidin-4-yl]-1*H*-pyrazol-1-yl}-acetamide (9f). Yield 2.25 g (65%), mp >300°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.39 s (3H, CH_3), 3.83 s (3H, OCH_3), 3.87 s (3H, OCH_3), 4.89 s (2H, CH_2CO), 6.11 d (2H, 2‴-H, 6‴-H, *J* = 7.2 Hz), 6.39 d (2H, 3‴-H, 5‴-H, *J* = 7.2 Hz), 6.86 s (2H, NH_2), 6.91 s (1H, 2′-H), 6.95-6.98 m (2H, 4′-H, 6′-H), 7.98–8.17 m (2H, 5″-H, 5-H), 8.17 d (1H, 6″-H, *J* = 5.6 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.23 (CH_3), 55.17 (OCH_3), 56.03 (OCH_3), 60.64 (CH_2), 103.45 (C^4), 111.67 ($C^{2'}$), 112.65 ($C^{4'}$), 115.73 ($C^{5''}$), 115.88 ($C^{3'''}$, $C^{5'''}$), 119.19 ($C^{6'}$), 123.61 ($C^{2'''}$, $C^{6'''}$), 133.73 (C^5), 134.15 ($C^{1'}$), 140.09 ($C^{5'}$), 146.32 ($C^{1'''}$), 152.68 (C^3), 153.65 ($C^{6''}$), 154.87 ($C^{4'''}$), 159.12 ($C^{3'}$), 159.74 ($C^{4''}$), 161.45 ($C^{2''}$), 168.77 (C=O). Found, %: C 64.60; H 5.10; N 15.50. $C_{24}H_{23}N_5O_4$. Calculated, %: C 64.70; H 5.20; N 15.72.

2-{4-[2-(2-Ethoxyphenoxy)pyrimidin-4-yl]-3-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl}acetamide (9g). Yield 1.96 g (55%), mp >300°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20 t (3H, C**H**$_3$CH$_2$, *J* = 8 Hz), 2.39 s (3H, CH_3), 3.82 s (3H, OCH_3), 4.03 q (2H, OCH_2, *J* = 8 Hz), 4.88 s (2H, CH_2CO), 6.84–6.88 m (3H, 3‴-H, 5‴-H, 6‴-H), 6.88 s (2H, NH_2), 6.96 s (1H, 2′-H), 7.02–7.04 m (2H, 4′-H. 6′-H), 7.23–7.29 m (1H, 4‴-H), 8.07 d (1H, 5″-H, *J* = 5.2 Hz), 8.18 s (1H, 5-H), 8.30 d (1H, 6″-H, *J* = 5.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.32 (CH_3), 21.23 (CH_3), 55.17 (OCH_3), 60.64 (CH_2), 65.11 (CH_2), 104.23 (C^4), 111.23 ($C^{2'}$), 112.78 ($C^{4'}$), 115.23 ($C^{5''}$), 115.88 ($C^{3'''}$), 120.45 ($C^{6'}$), 122.65 ($C^{6'''}$), 123.45 ($C^{2'''}$), 125.55 ($C^{4'''}$), 131.34 ($C^{3'''}$), 133.55 (C^5), 134.19 ($C^{1'}$), 140.24 ($C^{5'}$), 146.32 ($C^{1'''}$), 152.46 (C^3), 153.34 ($C^{6''}$), 159.69 ($C^{3'}$), 159.21 ($C^{4''}$), 161.08 ($C^{2''}$), 168.99 (C=O). Found, %: C 65.60; H 5.20; N 15.30. $C_{25}H_{25}N_5O_4$. Calculated, %: C 65.35; H 5.48; N 15.24.

2-{3-(3-Methoxy-5-methylphenyl)-4-[2-(pyridin-2-yloxy)pyrimidin-4-yl]-1*H*-pyrazol-1-yl}acetamide (9h). Yield 1.62 g (50%), mp >300°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.39 s (3H, CH_3), 3.82 s (3H, OCH_3), 4.88 s (2H, CH_2CO), 5.91 s (1H, 5‴-H), 6.54 s (1H, 2′-H), 6.68 d (1H, 6‴-H, *J* = 8.8 Hz), 6.85 s (1H, 4′-H), 6.88 s (2H, NH_2), 6.96 s (1H, 6′-H), 7.18 d (1H, 5″-H, *J* = 5.2 Hz), 7.41–7.43 m (1H, 4‴-H), 7.61 d (1H, 3‴-H, *J* = 6.4 Hz), 8.31 s (1H, 5-H), 8.63 d (1H, 6″-H, *J* = 5.6 Hz). ^{13}C NMR spectrum (APT, DMSO-d_6), δ_C, ppm: 21.52 (CH_3), 55.00 (OCH_3), 55.38 (CH_2), 105.79 (C^4), 111.52 ($C^{2'}$), 115.73 ($C^{4'}$), 116.53 ($C^{5''}$), 118.77 ($C^{6'}$), 122.14 ($C^{4'''}$), 122.63 ($C^{5'''}$), 133.24 ($C^{1'}$), 134.55 ($C^{5'}$), 135.92 (C^5), 140.25 ($C^{2'''}$), 140.37 (C^3), 152.65 ($C^{6''}$), 158.77 ($C^{3'''}$), 159.33 ($C^{3'}$), 159.87 ($C^{4''}$), 161.32 ($C^{1'''}$), 162.00 ($C^{2''}$), 168.37 (C=O). Found, %: C 63.60; H 4.70; N 20.30. $C_{22}H_{20}N_6O_3$. Calculated, %: C 63.45; H 4.84; N 20.18.

Cytotoxicity assay. The cell line screening was performed at the National Cancer Institute (NCI, Bethesda, Maryland, USA; *www.dtp.nci.nih.gov*) by MTT assay according to the reported procedure [23].

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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