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ORIGINAL PAPER

Design, synthesis, characterization, and antiproliferative activity of novel pyrazole-3-carboxylic acid derivatives

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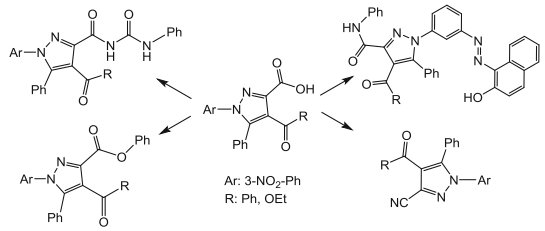
Abstract In this study several novel 4-substituted-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid derivatives were synthesized. The structures of these pyrazole-3-carboxylic acid derivatives were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis methods. Synthesized molecules were screened to evaluate their antiproliferative activities against Vero (African green monkey kidney), C6 (rat brain tumor), and HeLa (human uterus carcinoma) cells as in vitro. The tests were carried out as dose-dependent assay starting from 100 to 500 μg/cm^3. Ethyl 1-(3-nitrophenyl)-5-phenyl-3-(phenylcarbamoyl)-1*H*-pyrazole-4-carboxylate exhibited the highest performance against HeLa, Vero, and C6 cells among the synthesized derivatives. Also, it showed better antiproliferative activity compared with 5-fluorouracil (5-FU) against Vero cell. Two compounds showed moderate antiproliferative activities against C6 cell line when compared with 5-FU. Also moderate antiproliferative activities against Vero and HeLa cell lines were found.

Graphical abstract



Keywords Pyrazole · Heterocycles · Carboxylic acids · NMR spectroscopy · Vero cells · Antiproliferative activity

Introduction

Cancer remains the leading cause of death and in 2030 an estimated 12 million deaths from cancer are projected in the world [1–3]. This is a group of diseases characterized by loss of cellular growth control and spreads the cells to other tissues of body via lymph or blood [4–9]. Some of the antitumor drugs have side effects such as acute nephrotoxicity and chronic neurotoxicity [10]. Undoubtedly, there is a need for novel antitumor agents that demonstrate efficiency in currently refractory tumors without adding to the toxicity of therapy [11].

Pyrazole and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activities such as antibacterial [12, 13], antifungal [14, 15], antipyretic [16, 17], inhibitors of carbonic anhydrases [18, 19], antiobesity [20, 21], herbicidal [22, 23], and insecticidal [24, 25]. Also pyrazoles are widely used as core motifs for development of novel therapeutics for

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inflammation and cancer [26–30]. For instance Celecoxib is a new NSAID that specifically inhibits COX-2. Therewithal recent studies show Celecoxib possesses strong chemopreventive activity against mammary carcinogenesis [31]. Appreciation of these findings motivated us to synthesize a novel series of pyrazole-3-carboxylic acid derivatives as a potential candidate for antiproliferative studies.

Hence, we report here the synthesis of a series of novel pyrazole-3-carboxylic acid derivatives, and the preliminary results of their in vitro ability to inhibit proliferation of the Vero, C6 and HeLa cells.

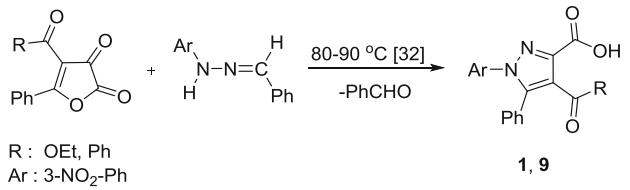
Results and discussion

Chemistry

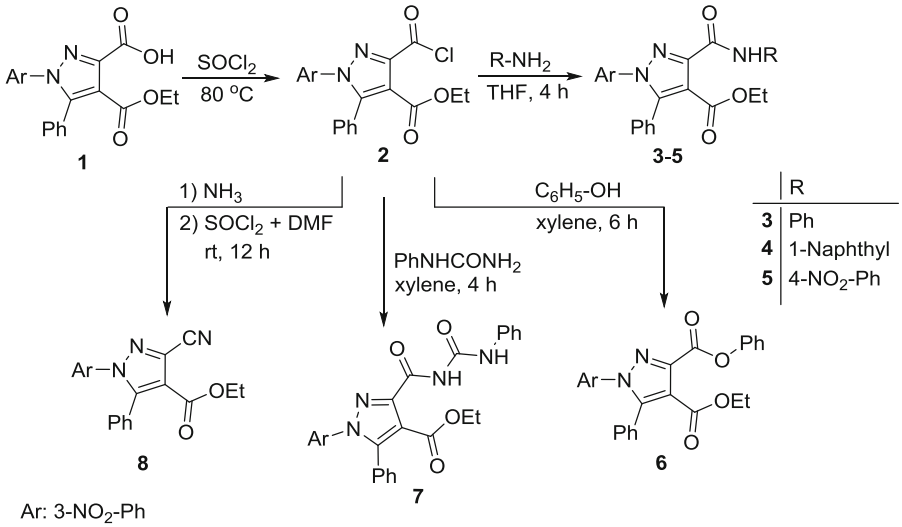
In this study our starting compounds pyrazole carboxylic acids **1** and **9** obtained from the reaction of furan-2,3-diones with 3-nitrophenylhydrazine hydrazones [32] (See Scheme 1). And their acid chlorides were synthesized via published procedures [32, 33]. Then novel 1*H*-pyrazole-3-carboxamides **3–5** were synthesized from the reaction of acid chloride **2** with the corresponding amine derivatives. Also an ester derivative **6** was synthesized from the reaction of **2** with phenol in the presence of pyridine. The structures of all amide **3–5** and ester **6** derivatives were confirmed by analytical, FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data, based on the structural analogy of similar compounds [32]. Absorption bands of amide or ester groups at about 1667–1692 and 1766/cm, respectively, are structural characteristics. An ureide derivative **7** was prepared from the acid chloride **2** and *N*-phenylurea in the usual way. The ^{13}C NMR and ^{1}H NMR spectra of **7** are also in full agreement with the proposed structure (see "Experimental"). As shown in Scheme 2, a new nitrile derivative **8** was prepared from **2** through a two-step reaction route. In the first step a primary amide was synthesized according to the literature [32]. Then a cold solution of the amide in a mixture of *N*,*N*-dimethylformamide (DMF) and thionyl chloride ($SOCl_2$) was stirred at 0–5 °C for 2 h to give a nitrile derivative **8**. The ^{13}C NMR and FT-IR absorptions of the nitrile group in **8** were found at 112.17 ppm and 2162/cm, respectively (see "Experimental").

Other starting compound **9** in this study was converted to its amide derivative **10** as described in our previous studies [32]. Then reduction of the nitro group of **10** by sodium polysulfide hydrogenation ($Na_2S/S/H_2O$) afforded **11** [32]. Finally, **11** were diazotized [34] and a novel coupling product **12** was obtained from the reaction with *β*-naphthol. ^{1}H NMR, ^{13}C NMR, FT-IR, and elemental analysis results all of the synthesized compounds were in full agreement with the proposed structures (Schemes 2, 3).

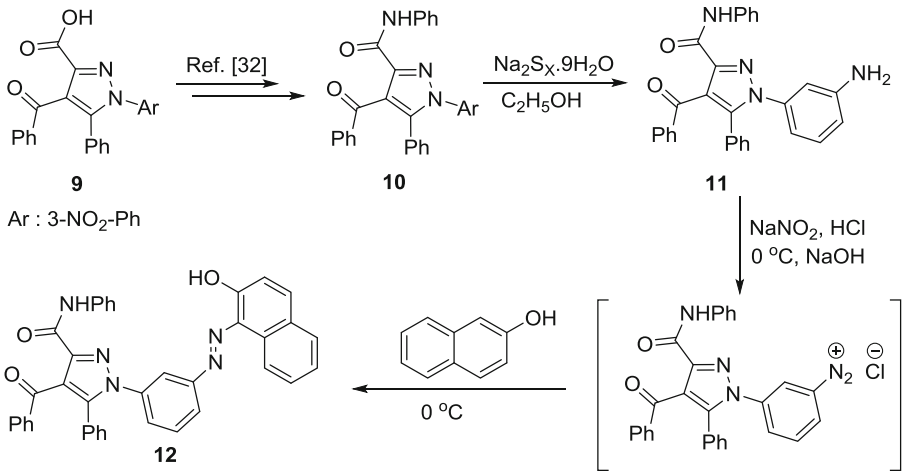
Scheme 1



Scheme 2



Scheme 3



Antiproliferative activity

The antiproliferative activities of all compounds were determined against HeLa, Vero, and C6 cells. 5-Fluorouracil (5-FU) was used as standard. Cells were treated with compounds **3**–**8**, **12**, and 5-FU at final concentrations of 500, 250, and 100 μg/cm^3. IC_{50} and IC_{75} values of the compounds were given at Table 1.

The antiproliferative activites of the compounds against HeLa cells

In terms of antiproliferative activity against HeLa cell line, compound **3** exhibited the highest performance among the other compounds (Fig. 1). The synthesized compounds were shown to increase of the activities depending to dose increasing against HeLa cells. But the compounds in all concentrations have the lower activity compared with positive controls, 5-FU (Fig. 1). The potency of inhibition (at 500 μg/cm^3) for HeLa cells is in the order of: 5-FU > **3** > **12** > **6** > **5** > **4** > **7** > **8**.

The antiproliferative activites of the compounds against Vero cells

In the investigation the antiproliferative activity of compound **3**–**8**, **12**, and 5-FU against Vero cells, compound **3** was determined to have the higher antiproliferative activity than all the other compounds as well as 5-FU. The compounds exhibited antiproliferative activities against Vero cell in a concentration-dependent manner. But according to the standard compound, in all compounds have been observed weak activity (Fig. 2). The potency of inhibition (at 500 μg/cm^3) for Vero cells is in the order of: **3** > 5-FU > **7** > **6** > **4** > **5** ~ **12** > **8**.

Table 1 IC_{50} and IC_{75} values/μg/cm^3 of compounds **3**–**8** and **12**

Comp.	HeLa cell		Vero cell		C6 cell	
	IC_{50}	IC_{75}	IC_{50}	IC_{75}	IC_{50}	IC_{75}
3	348	443	343	425	335	426
4	370	441	368	446	252	364
5	364	447	375	445	386	455
6	382	468	356	436	327	420
7	326	424	308	414	320	426
8	378	455	441	480	365	453
12	346	436	341	438	346	427

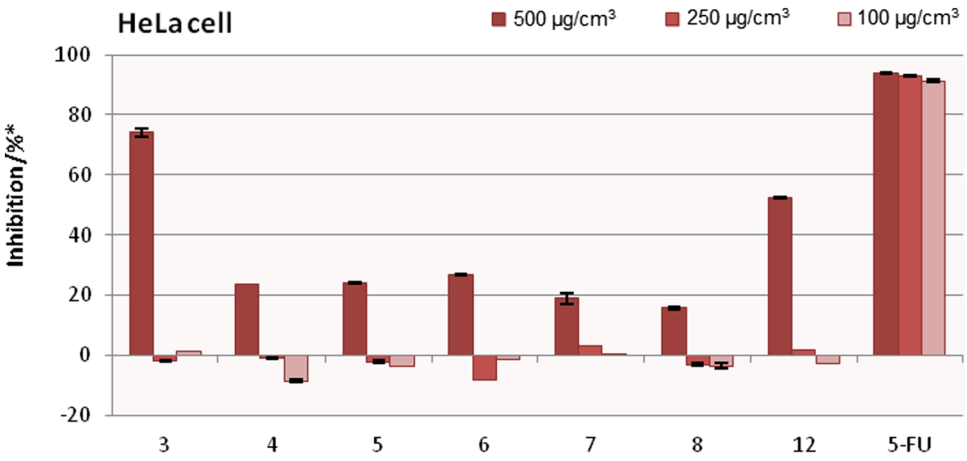


Fig. 1 Antiproliferative activities of the compounds **3–8** and **12** against HeLa cell. *Asterisk* indicates that each substance was tested twice in triplicates against cell lines. Data show average of two individual experiments ($p < 0.01$)

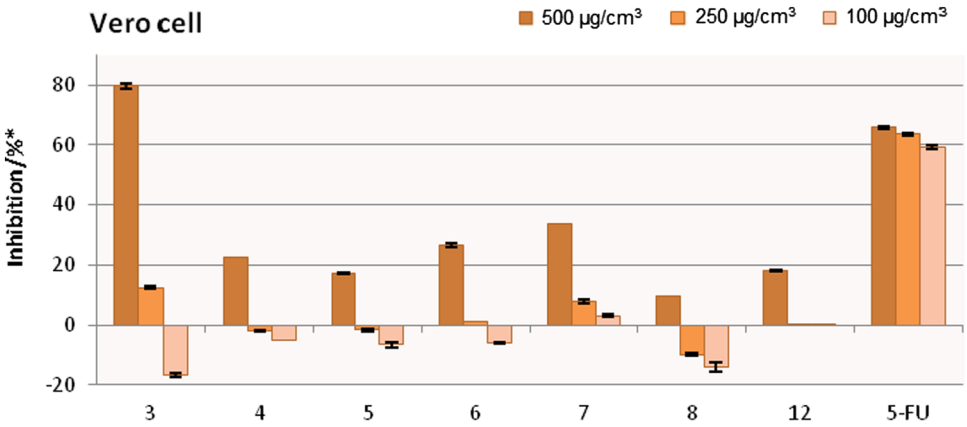


Fig. 2 Antiproliferative activities of the compounds **3–8** and **12** against Vero cell. *Asterisk* indicates that each substance was tested twice in triplicates against cell lines. Data show average of two individual experiments ($p < 0.01$)

The antiproliferative activites of the compounds against C6 cells

In the investigation the antiproliferative activity of compound **3–8**, **12**, and 5-FU against C6 cells, compound **3** was determined to have the strongest antiproliferative activity than all compounds. The compounds exhibited antiproliferative activities against C6 cell in a concentration-dependent manner. But, all compounds have weak activities than 5-FU (Fig. 3). The potency of inhibition (at 500 µg/cm^3) for C6 cells is in the order of: 5-FU > **3** > **6** > **8** > **7** > **5** ~ **12** > **4**.

Conclusions

In this study we reported the preparation of novel pyrazole-3-carboxylic acid derivatives and their antiproliferative activities against some cancer cell lines. All of the compounds showed antiproliferative activities against HeLa, Vero, and C6 cells in a dose-dependent manner. Compounds **4–8** and **12** have weak activities than 5-FU. Only **3** showed the higher activity than 5-FU against Vero cell line and it has moderate antiproliferative activity against HeLa and C6 cell lines.

Experimental

Chemical compounds used in this research were at analytical purity, and the solvents were purified by using appropriate purifying agents and distillation. Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use. All reactions were monitored by analytical thin-layer chromatography (TLC) on 0.25 mm precoated Kieselgel 60F 254 plates (E. Merck Co., Darmstadt, Germany); compounds were visualized by Camag TLC devices (Camag, Upland, CA, USA) UV (254 and 366 nm). Melting points were determined using Bibby Stuart Scientific SMP3 apparatus (Stuart Scientific, Stone, UK). The structures of each compound were supported by Bruker Vertex 70 FT-IR (Bruker Optik GmbH, Ettlingen, Germany) with using of KBr pellets and by ^{1}H NMR and ^{13}C NMR at 400 MHz on a BRUKER DPX-400 (Bruker BioSpin GmbH, Rheinstetten,

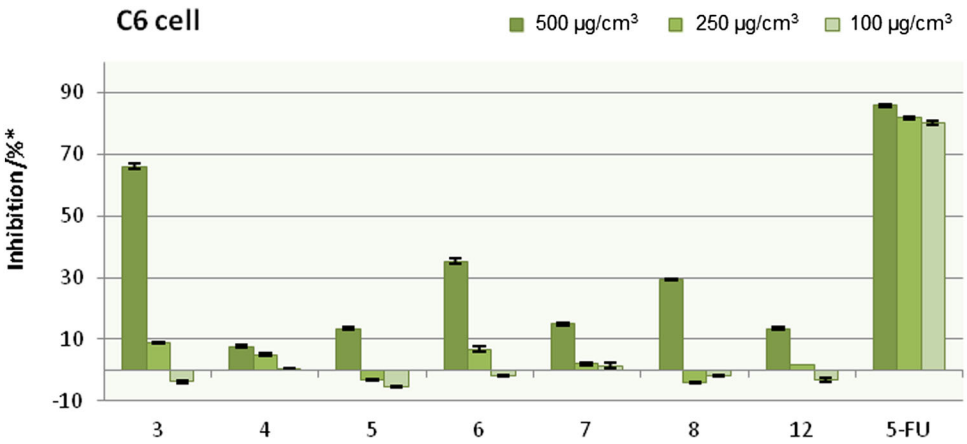


Fig. 3 Antiproliferative activities of the compounds **3–8** and **12** against C6 cell. *Asterisk* indicates that each substance was tested twice in triplicates against cell lines. Data show average of two individual experiments ($p < 0.01$)

Germany) and High Performance Digital FT-NMR (100 MHz) spectrometers. Elemental analyses (C, H, N) were performed on a Leco CHNS-932 elemental analyser (LECO Corporation, Saint Joseph, MI, USA). In this study the starting compounds (**1** and **9**) were prepared as described in our previous studies and their carboxyl groups were activated with $SOCl_2$ [32, 33].

General procedure for amide derivatives 3–5

Ethyl 3-(chlorocarbonyl)-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-4-carboxylate (**2**, 0.4 g, 1 mmol) was dissolved in 20 cm^3 dry and freshly distilled THF. To this solution 2 mmol of the corresponding amine was added. Mixture was refluxed for 4 h and solvent was evaporated. The crude product was washed with water and purified from an appropriate solvent.

Ethyl 1-(3-nitrophenyl)-5-phenyl-3-(phenylcarbamoyl)-1H-pyrazole-4-carboxylate (**3**, $C_{25}H_{20}N_4O_5$)
Synthesized from 0.4 g **2** (1 mmol) and 0.184 cm^3 aniline (2 mmol) according to the general procedure. Crude product was crystallized from ethanol to afford 411 mg (90 %) of **3**. M.p.: 165–166 °C; FT-IR (KBr): $\overline{\nu} = 3314$ (NH), 3032 (Ar CH), 2938 (aliphatic CH), 1739 (C=O, ester), 1689 (C=O, amide), 1614–1444 (Ar C=C and C=N)/cm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (t, $J = 7.1$ Hz, 3H, CH_3), 4.17 (q, $J = 7.1$ Hz, 2H, OCH_2), 7.12–8.17 (m, 14H, ArH), 10.79 (s, 1H, CONH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.4$ (CH_3), 61.6 (OCH_2), 115.1 (pyrazole C-4), 120.5, 123.6, 126.7, 127.3, 128.7, 129.0, 129.5, 129.7, 129.9, 130.2, 133.1, 133.8, 138.2, 144.9 (pyrazole C-5), 147.7 (pyrazole C-3), 148.2 (C–NO_2), 159.2 (amide C=O), 163.7 (ester C=O) ppm.

Ethyl 3-(naphthalen-1-ylcarbamoyl)-1-(3-nitrophenyl)-5-phenyl-1H-pyrazole-4-carboxylate (**4**, $C_{29}H_{22}N_4O_5$)
Synthesized from 0.4 g **2** (1 mmol) and 0.292 g 1-naphthylamine (2 mmol) according to the general procedure. Crude product was crystallized from ethanol to afford 369 mg (73 %) of **4**. M.p.: 186–187 °C; FT-IR (KBr): $\overline{\nu} = 3733$ (NH), 3047 (Ar CH), 2982 (aliphatic CH), 1738 (C=O, ester), 1692 (C=O, amide), 1528–1432 (Ar C=C and C=N)/cm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$ (t, $J = 7.1$ Hz, 3H, CH_3), 4.21 (q, $J = 7.1$ Hz, 2H, OCH_2), 7.25–8.29 (m, 16H, ArH), 10.94 (s, 1H, CONH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5$ (CH_3), 61.8 (OCH_2), 114.0 (pyrazole C-4), 120.4, 120.6, 121.5, 123.1, 125.6, 125.8, 126.0, 126.3, 127.1, 128.3, 128.6, 128.7, 129.9, 130.0, 130.1, 131.1, 132.7, 134.1, 139.4, 147.2 (pyrazole C-5), 147.4 (pyrazole C-3), 148.0 (C–NO_2), 158.7 (amide C=O), 164.5 (ester C=O) ppm.

Ethyl 1-(3-nitrophenyl)-3-(4-nitrophenylcarbamoyl)-5-phenyl-1H-pyrazole-4-carboxylate (**5**, $C_{25}H_{19}N_5O_7$)
Synthesized from 0.4 g **2** (1 mmol) and 0.282 g 4-nitroaniline (2 mmol) according to the general procedure. Crude product was crystallized from toluene to afford 371 mg (74 %) of **5**. M.p.: 223–224 °C; FT-IR (KBr): $\overline{\nu} = 3330$ (NH), 3050 (Ar CH), 2978 (aliphatic CH), 1703 (C=O ester), 1667 (C=O amide), 1570–1444 (Ar C=C and C=N)/cm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.97$ (t, $J = 7.1$ Hz, 3H, CH_3), 4.10 (q, $J = 7.1$ Hz, 2H, OCH_2), 7.25–8.19 (m, 13H, ArH), 11.22 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.4$ (CH_3), 66.1 (OCH_2), 119.1 (pyrazole C-4), 120.2, 124.6, 124.8, 125.1, 128.0, 128.4, 129.7, 132.5, 133.5, 134.8, 135.0, 135.8, 144.1 (pyrazole C-5), 147.9 (pyrazole C-3), 149.5, 152.9 (C–NO_2), 164.5 (amide C=O), 167.9 (ester C=O) ppm.

4-Ethyl 3-phenyl 1-(3-nitrophenyl)-5-phenyl-1H-pyrazole-3,4-dicarboxylate (**6**, $C_{25}H_{19}N_3O_6$)
A mixture of 0.4 g acid chloride **2** (1 mmol) and 0.094 g phenol (1 mmol) was refluxed in xylene together with a catalytic amount of pyridine for 6 h. After cooling, the solution was acidified by adding diluted hydrochloric acid (12 %) to give a crude solid that was recrystallized from ethanol to afford 351 mg (77 %) of **6**. M.p.: 112–113 °C;

FT-IR (KBr): $\bar{\nu} = 3062$ (Ar CH), 2986 (aliphatic CH), 1766, 1722 (C=O, ester), 1591–1430 (Ar C=C and C=N)/cm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.16$ (t, $J = 7.1$ Hz, 3H, CH_3), 4.24 (q, $J = 7.1$ Hz, 2H, OCH_2), 7.26–8.21 (m, 14H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5$ (CH_3), 61.8 (OCH_2), 114.2 (pyrazole C-4), 120.5, 123.4, 125.9, 126.5, 127.3, 128.6, 129.6, 129.8, 129.9, 130.2, 132.6, 133.8, 139.3, 144.5 (pyrazole C-5), 147.4 (pyrazole C-3), 148.1 (C-NO_2), 163.6, 164.1 (ester C=O) ppm.

Ethyl 1-(3-nitrophenyl)-5-phenyl-3-(phenylcarbamoylcarbamoyl)-1H-pyrazole-4-carboxylate (**7**, $C_{26}H_{21}N_5O_6$)
A mixture of 0.4 g acid chloride **2** (1 mmol) and 0.136 g *N*-phenylurea (1 mmol) was refluxed in xylene for 4 h. The solvent was evaporated and the formed crude product was recrystallized from ethanol to afford 404 mg (81 %) of **7**. M.p.: 155–156 °C; FT-IR (KBr): $\bar{\nu} = 3234$ (NH), 3066 (Ar CH), 2974 (aliphatic CH), 1707 (C=O), 1595–1443 (Ar C=C and C=N)/cm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.06$ (t, $J = 7.1$ Hz, 3H, CH_3), 4.23 (q, $J = 7.1$ Hz, 2H, OCH_2), 7.10–8.21 (m, 14H, ArH), 10.39 (s, 1H, NH), 10.57 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.6$ (CH_3), 61.9 (OCH_2), 115.4 (pyrazole C-4), 120.2, 120.3, 123.4, 124.2, 127.6, 128.8, 129.0, 130.0, 130.1, 130.3, 130.7, 137.3, 139.1, 144.7 (pyrazole C-5), 147.2 (pyrazole C-3), 148.2 (C–NO_2), 150.5 (urea C=O), 161.1 (amide C=O), 163.3 (ester C=O) ppm.

Ethyl 3-cyano-1-(3-nitrophenyl)-5-phenyl-1H-pyrazole-4-carboxylate (**8**, $C_{19}H_{14}N_4O_4$)
Firstly, amide derivative was prepared and purified of acid chloride **2** with excess amount of ammonia according to the literature [32]. Then 0.38 g (1 mmol) of this amide derivative was dissolved in 5 cm^3 DMF, and 0.292 cm^3 $SOCl_2$ (4 mmol) was added. After stirring for 2 h in ice bath and 12 h in room temperature, some ice water was added to the mixture. Precipitated solid product was filtered and purified from ethanol by crystallization to afford 300 mg (83 %) of **8**. M.p.: 117–118 °C; FT-IR (KBr): $\bar{\nu} = 3087$ (Ar CH), 2975 (aliphatic CH), 2162 (CN), 1721 (C=O ester), 1611–1447 (Ar C=C and C=N)/cm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.30$ (t, $J = 7.1$ Hz, 3H, CH_3), 4.32 (q, $J = 7.1$ Hz, 2H, OCH_2), 7.28–8.24 (m, 9H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3), 61.5 (OCH_2), 112.2 (CN), 117.4 (pyrazole C-4), 120.3, 123.6, 126.4, 128.3, 128.8, 130.2, 130.3, 130.6, 130.7, 138.9 (pyrazole C-5), 147.0 (pyrazole C-3), 148.3 (C–NO_2), 160.0 (ester C=O) ppm.

4-Benzoyl-1-[3-[(2-hydroxynaphthalen-1-yl)diazenyl]phenyl]-N,5-diphenyl-1H-pyrazole-3-carboxamide (**12**, $C_{39}H_{27}N_5O_3$)
Firstly the diazonium solution of **11** was prepared according to the literature [34]. β-Naphthol (0.144 g, 1 mmol) was dissolved in a sufficient amount of ethanol, then cooled and added dropwise into the prepared diazonium solution. The pH of the mixture was maintained at 7–8 through the coupling process by adding 1 M NaOH solution. Then the resulting red precipitate was filtered under vacuum and the residue recrystallized from ethanol to give bright red crystals of **12**. Yield: 398 mg (65 %); m.p.: 246–247 °C; FT-IR (KBr): $\bar{\nu} = 3550$ (OH), 3042 (Ar CH), 2966 (aliphatic CH), 1698 (C=O), 1602–1456 (Ar C=C and C=N)/cm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.95$–8.30 (m, 25H, ArH), 10.52 (s, 1H, CONH), 15.99 (s, 1H, Ar–OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 115.4$ (pyrazole C-4), 119.9, 120.9, 122.1, 122.5, 124.1, 124.8, 124.9, 126.9, 127.7, 128.1, 128.9, 129.0, 129.4, 129.5, 129.8, 129.9, 130.1, 130.2, 131.2, 133.1, 133.6, 133.9, 138.2, 138.8, 140.5, 142.6, 144.1, 146.0 (pyrazole C-5), 147.2 (pyrazole C-3), 159.8 (C–OH), 171.4 (amide C=O), 191.4 (benzoyl C=O) ppm.

Preparation of samples

Stock solution of the samples were prepared in DMSO and diluted with Dulbecco's modified eagle medium (DMEM). The final concentration of DMSO is below 1 % in all tests.

Cell culture and antiproliferative activity

Vero, C6 and HeLa cells were grown in Dulbecco's modified eagle's medium (DMEM, Sigma), supplemented with 10 % (v/v) fetal bovine serum (Sigma, Germany) and PenStrep solution (Sigma, Germany) at 37 °C in a 5 % CO_2 humidified atmosphere. For proliferation assay, cells were plated in 96-well culture plates (COSTAR, Corning, USA) at a density of 3×10^4 cells per well. Vehicle (DMSO), 5-fluorouracil, and the samples in various concentrations (100–500 μg/cm^3) were added to each well. Cells were than incubated for overnight before applying the BrdU Cell Proliferation ELISA assay reagent (Roche, Germany) according to manufacturer's procedure [35–37]. Briefly, cells were pulsed with BrdU labeling reagent for 4 h followed by fixation in FixDenat solution for 30 min at room temperature. Thereafter, cells were incubated with 1:100 dilution of anti-BrdU-POD for 1.30 h at room temperature. The amount of cell proliferation was assessed by determining the absorbance at 450 nm of the culture media after addition of the substrate solution by using a microplate reader (Ryto, China). Results were reported as percentage of the inhibition of cell proliferation, where the optical density measured from vehicle-treated cells was considered to be 100 % of proliferation. All assays were repeated at least twice using against HeLa, Vero, and C6 cells. Percentage of inhibition of cell proliferation was calculated as follows:

$[1 - (A_{\text{treatment}}/A_{\text{vehicle control}})] \times 100.$

Statistical analysis

The results of investigation in vitro are the mean ± SD of nine measurements for each cell type. Differences between treated groups were tested with ANOVA. p values of <0.01 were considered as significant.

Determination of IC_{50} and IC_{75} values

In this paper, IC_{50} and IC_{75} values were determined using ED50 plus v1.0.

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