Synthesis, Crystal Structure and Antitumor Activity of 3-(2,4-dichlorophenyl)-2-phenyl-5-(*p*-tolyl)-7-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine

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Summry: The title compound, 3-(2,4-dichlorophenyl)-2-phenyl-5-(*p*-tolyl)-7-(trifluoromethyl)pyrazolo[1,5-a] pyrimidine ($C_{26}H_{16}Cl_2F_3N_3$, Mr = 498.32) has been synthesized by condensation of 4,4,4-trifluoro-1-(p-tolyl)butane- 1,3-dione with 4-(2,4-dichlorophenyl)-3-phenyl-1*H*-pyrazol-5-amine. The latter was prepared from 2,4-dichlorophenylaceton itrile and ethyl benzoate through Claisen condensation and then cyclization with hydrazine hydrate. The crystal structure of the title compound was determined. In addition, the title compound possesses marked inhibition against the proliferation of human lung adenocarcinoma cell line A549 and human gastric cancer cell line MKN45, displaying promising anticancer activities.

Keywords: pyrazolo[1,5-a]pyrimidine, condensation, X-ray diffraction, antitumor activity

Introduction

Heterocyclic building blocks are considered useful scaffolds for applications in medicinal chemistry. Among the various heterocyclic compounds, pyrazolo[1,5-*a*]pyrimidine is an important heterocycle, due to biological activity of many of its derivatives [1]. They are well known to exhibit a wide range of biological activities, including hepatitis C virus inhibitors [2], antagonists of serotonin 5-HT6 receptors [3], kinase inhibitors [4], PET tumour imaging agents [5], and inhibitors of amyloid β-peptide 1–42 aggregation [6]. Insomnia agent indiplon [7], anticancer agent dinaciclib [8], Type 2 diabetes mellitus agent anagliptin [9] are all approved drugs containing a pyrazolo[1,5-*a*]pyrimidine core. Based upon the prospect of pyrazolo[1,5-*a*]pyrimidine derivatives in the field of medicinal chemistry and in continuation of our research program on the development of novel potent antitumor agents [10-13]. Now we reported the synthesis a new pyrazolo[1,5-a]pyrimidine derivative, 3-(2,4-dichlorophenyl)-2-phenyl-5-(*p*-tolyl)-7-(trifluoro methyl) pyrazolo[1,5-a] pyrimidine, by a four-step synthetic route.

Experimental

Chemistry

General

Unless specified otherwise, , all starting materials and reagents were obtained commercially without further purification. All melting points were taken on a Beijing Taike X-4 microscopy melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker Biospin 600 MHz or Bruker Biospin 300 MHz instrument using TMS as the internal standard. All chemical shifts were reported in ppm. IR spectra were recorded as KBr pellets on a Perkin-Elmer Spectrum one FT-IR spectrometer. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC-MS (Agilent, Palo Alto, CA, U.S.A.). Elemental analysis of the newly synthesized compounds was carried out on Carlo Erba 1108 analyzer and are found within the range of theoretical value.

Synthesis of 4,4,4-trifluoro-1-(p-tolyl)butane-1,3-dione (**2**)

4-methyl acetophenone (10.52 g, 78.4 mmol) was dissolved in 50 mL of methanol under argon and 24 mL (105.0 mmol) sodium methoxide in methanol (25%) was added. The mixture was stirred for 5 minutes and (13.4 g, 94.3 mmol) ethyl trifluoroacetate was added. After refluxing for 10 hours, the mixture was cooled to room temperature and concentrated to dryness. The sodium salt obtained was dissolved in 50 mL of water and acidified with 1 N HCl and extracted three times with 80 mL of ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give 17.1 g of a brown oil, which was taken forward without further purification. Yield 95 %. ^{1}H NMR (300 MHz, $CDCl_3$) 2.34 (s, 3H), 6.25 (brs, 2H), 7.19-7.30 (m, 2H), 7.70-7.82 (m, 2H); MS (ESI) m/z(%): 231.1 $[M+H]^+$; Anal. calcd. for $C_{11}H_9F_3O_2$ (%): C, 57.40; H, 3.94. Found (%): C, 57.50; H, 3.99.

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Synthesis of 2-(2,4-dichlorophenyl)-3-oxo-3-phenylpropanenitrile (**4**)*:*

To a suspension of 60% sodium hydride (4.0 g, 100.0 mmol) in THF (70 mL) was added the 2,4-dichlorophenylacetonitrile (9.3 g, 50.0 mmol) and ethyl benzoate (8.27 g, 55.0 mmol). The mixture was stirred at 60 °C for 24 h. Water (20 mL) was added, and the mixture was concentrated by rotary evaporation. An additional 120 mL of water was added and extracted with CH_2Cl_2 (3 × 80 mL). The organic phases were combined and discarded, and the aqueous portion was acidified with 4 M HCl until pH 3. The aqueous solution was then extracted with CH_2Cl_2 (3 × 90 mL), and the organic phases were combined. The combined organic phase was washed with saturated NaCl solution (2 × 100 mL) and the organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated under reduced pressure. The crude product obtained was purified by silica gel chromatography to give 8.43 g (58 %) of **4** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15-8.05 (m, 2H, Ar-H), 7.90 -7.75 (m, 2H, Ar-H), 7.60-7.50 (m, 2H, Ar-H), 7.40-7.25 (m, 2H, Ar-H), 5.75 (s, 1H, CH); MS (ESI) m/z(%): 290.1 $[M+H]^+$; Anal. calcd. for $C_{15}H_9Cl_2NO$ (%): C, 62.10; H, 3.13; N, 4.83. Found (%): C, 62.18; H, 3.16; N, 4.87.

Synthesis of 4-(2,4-dichlorophenyl)-3-phenyl-1H-pyrazol-5-amine (**5**):

A mixture of compound **4** (6.00 g, 20.68 mmol) and 80% hydrazine monohydrate (10 mL) in EtOH (50 mL) was refluxed overnight with vigorous agitation. The reaction mixture was concentrated under reduced pressure and then partitioned between water (100 mL) and CH_2Cl_2 (80 mL). The organic layer was separated and the aqueous layer was then extracted with CH_2Cl_2 (80 mL × 2). The combined organic extracts were sequentially washed with saturated water (100 mL × 3), brine (80 mL × 2) and dried over anhydrous Na_2SO_4. After evaporation of the organic solvent, the residue was purified by column chromatography to afford 4.80 g of compound **5** as white solids in 76 % yield. IR(KBr. cm^{-1}): 3435(-NH_2), 3221(-NH_2), 1619, 1582(-Ar), 1516(-Ar), 1464(-Ar), 1375, 1282, 1111, 1061, 1013; MS (ESI) m/z(%): 304.2 $[M+H]^+$; Anal. calcd. for $C_{15}H_{11}Cl_2N_3$ (%): C, 59.23; H, 3.65; N, 13.81. Found (%): C, 59.31; H, 3.70; N, 13.86.

Synthesis of 3-(2,4-dichlorophenyl)-2-phenyl-5-(p-tolyl)-7-(trifluoro methyl)pyrazolo[1,5-a]pyrimidine (**6**)*:*

A mixture of 4-(2,4-dichlorophenyl)-3-phenyl-1*H*-pyrazol-5-amine (1.52 g, 5.0 mmol) and 4,4,4-trifluoro-1-(p-tolyl) butane-1,3-dione (1.38 g, 6.0 mmol) in a 25 mL flask was heated at 165-170 °C for 2.0 h, allowing elimination of the water evolved. After cooling to room temperature, the solid in the flask was recrystallised from methanol to afford 1.76 g the title compound as a yellow solid in 71 % yields. mp 188～190 °C; IR (KBr) ν: 1624, 1607(-Ar), 1568(-Ar), 1409, 1337(-CF_3), 1262, 1198, 1175, 1147, 1061; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.18 (s, 1H, Ar-H), 8.11 (d, 2H, J = 7.8 Hz, Ar-H), 7.81 (s, 1H, Ar-H), 7.60-7.45 (m, 4H, Ar-H), 7.38-7.42 (m, 3H, Ar-H), 7.34 (d, 2H, J = 7.8 Hz, Ar-H), 2.36 (s, 3H, CH_3); (ESI) m/z(%): 498.2 $[M+H]^+$; Anal. calcd for $C_{26}H_{16}Cl_2F_3N_3$: C 62.67, H 3.24, N 8.43; found C 62.72, H 3.25, N 8.48.

Crystal data structure determination

The powder of the title compound was dissolved in ethanol/acetone mixed solvents = 1: 2 (V/V). After slowly evaporating the solvents for several days, some single crystals suitable for X-ray analysis were obtained. A yellow crystal ($C_{26}H_{16}Cl_2F_3N_3$) with dimensions of 0.28 × 0.26 × 0.20 mm was selected for data collection which was performed on a CrysAlisPro, Oxford Diffraction Ltd, Version 1.171.34.36 CCD automatic diffractometer with graphite-monochromatized Mo *Ka* radiation (λ = 0.71073 Å) using multi-scan mode at 293(2) K. A total of 9338 reflections were collected in the range of 3.4<θ< 25.0° (index ranges: -11<h<12, -14<k<14, -15<l<13) and 4615 were independent (R_{int} = 0.022), of which 3202 observed reflections with $I > 2\sigma(I)$ were used in the structure determination and refinements. The structure was solved by direct methods with SHELXS-97 program[14] and expanded by Fourier technique. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms bound to carbon were determined with theoretical calculations and those attached to nitrogen and oxygen were determined with successive difference Fourier syntheses. The structure was refined by full-matrix Least-squares techniques on F^2 with SHELXL-97[15]. The final refinement gave the final R = 0.058 and wR = 0.234 (w=1/ [σ^2 (Fo^2) + (0.160P)^2 + 0.0286P]) where P = (Fo^2+2Fc^2)/3). S = 1.01, (Δ/σ) max = 0.001, ($\Delta\rho$) max = 0.34 and ($\Delta\rho$) min = –0.38e/Å^{-3}. Crystallographic data and experimental details of structural analyses for compound was

summarized in Table-1. Supplementary material for compound **6** has been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 1899389 (**6**) deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Table-1: Crystal data for the title compound.

Crystal size	**0.28 × 0.26 × 0.20**
Formula	**$C_{26}H_{16}Cl_2F_3N_3$**
Fw	**498.32**
T/K	**293(2)**
Crystal system	**triclinic**
Space group	**P-1**
a/Å	**10.1877(8)**
b/Å	**11.9532(10)**
c/Å	**12.9903(13)**
α/°	**109.332(8)**
β/°	**113.071(9)**
γ/°	**97.313(7)**
V/Å^3	**1311.8(2)**
Z	**2**
Dc/g · cm^{-3}	**1.262**
F(000)	**508**
GOF on F^2	**1.015**
Reflection/unique	**9338/4615**
R_1,wR_2 [I >2 (I)]	**0.0577, 0.2119**
***R_1,wR_2* (all data)**	**0.0789, 0.2338**

$R_1=\sum(||F_o|-|F_c||)/\sum|F_o|$ $wR_2=[\sum w(F_o^2-F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$

Biological part

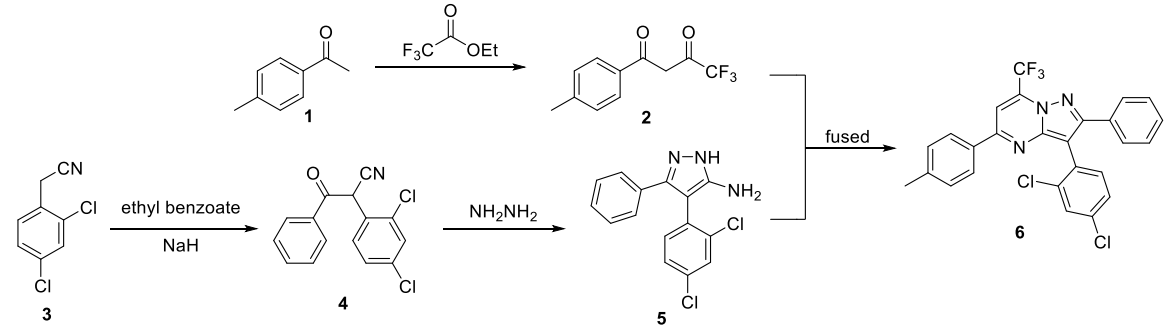
Cell proliferative assay

Cells were seeded in 96-well plate. After seeding 24 h, the medium was removed. The title compound was dissolved in dimethyl sulfoxide and diluted with culture medium to different concentrations (the final concentration of dimethyl sulfoxide was 0.1%). 20 μL of the test compound solution was added in duplicates, and incubation continued for 72 h in a humidified atmosphere of 5% CO_2 at 37 ℃. Remove the medium, Fresh MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-*H*-tetrazolium bromide] solution (20 μL) was added to each well at the terminal concentration of 5 mg/mL in PBS and incubated for additional 3 - 4 h at 37 ℃. The medium was replaced by 150 mL dimethyl sulfoxide to solubilize the purple formazan crystals produced and the absorbance was measured on a microplate reader at 490 nm.

Results and Discussion

Chemistry

The title compound was synthesized according to the routes outlined in Scheme-1. The condensation of 4-methyl acetophenone (**1**) with ethyl trifluoroacetate in MeOH afforded 4,4,4-trifluoro-1-(p-tolyl)butane-1,3-dione (**2**) as brown oil. On the other hand, the condensation of commercially available 2,4-dichlorophenylacetonitrile (**3**) with ethyl benzoate in THF given 2-(2,4-dichlorophenyl)-3-oxo-3-phenylpropanenitrile (**4**), which were then reacted with hydrazine monohydrate in EtOH provided 4-(2,4-dichlorophenyl)-3-phenyl-1H-pyrazol-5-amine (**5**). Finally, the cyclization of compound **2** with compound **5** at 165-170 °C for 2.0 h afforded the title compound 3-(2,4-dichlorophenyl)-2-phenyl-5-(*p*-tolyl)-7-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine (**6**). Compound **6** was characterized by IR, ^{1}H NMR and MS and elemental analyses. IR shows the peak at 1337 cm^{-1} results from the CF_3 group stretching vibration of **6**. The ^{1}H NMR spectrum for compound **6** exhibits thirteen protons from 7.20 ppm to 8.30 ppm, corresponding to the aromatic proton of the title compound. In the mass spectrum of **6**, the peak appeared at m/z 498.2 ([M+H]$^+$, 100%), which is in accordance with its molecular formula. IR, ^{1}H NMR, MS and elemental analyses of the target compounds confirmed their structural integrity. The biological tests suggested the compound displayed distinct effective inhibition on the proliferation of cancer cell lines.



Scheme-1: Synthetic route of the title compound.

Table-2: Geometric Parameters of the Title Compound.

Bond Lengths	X-ray/ Å	Bond angles	X-ray/°
Cl(2)-C(3)	1.730(3)	C(9)-C(7)-C(8)	104.8(3)
Cl(1)-C(1)	1.728(4)	N(3)-C(9)-C(7)	132.3(3)
F(3)-C(13)	1.324(4)	N(3)-C(9)-N(1)	121.8(2)
C(7)-C(9)	1.386(4)	C(5)-C(4)-C(7)	120.0(3)
C(7)-C(8)	1.400(4)	C(1)-C(2)-C(3)	118.7(3)
C(7)-C(4)	1.457(4)	N(2)-C(8)-C(14)	118.4(3)
C(9)-N(3)	1.340(3)	C(2)-C(1)-Cl(1)	119.1(3)
C(9)-N(1)	1.405(3)	C(12)-N(1)-C(9)	120.2(2)
C(2)-C(1)	1.371(5)	C(10)-N(3)-C(9)	118.4(2)
C(8)-N(2)	1.355(4)	N(1)-N(2)-C(8)	103.9(2)
C(8)-C(14)	1.484(4)	N(3)-C(10)-C(20)	117.1(3)
N(1)-N(2)	1.345(3)	C(12)-C(11)-C(10)	120.8(3)
N(1)-C(12)	1.366(4)	C(11)-C(12)-N(1)	117.3(3)
N(3)-C(10)	1.320(4)	N(1)-C(12)-C(13)	118.2(3)
C(10)-C(11)	1.418(4)	C(19)-C(14)-C(8)	121.3(3)
C(10)-C(20)	1.472(4)	C(24)-C(23)-C(26)	120.6(4)
C(20)-C(21)	1.376(4)	Torsion angles	X-ray/°
C(11)-C(12)	1.356(4)	C(8)-C(7)-C(9)-N(3)	177.0(3)
C(12)-C(13)	1.475(5)	C(8)-C(7)-C(4)-C(5)	115.5(3)
C(14)-C(15)	1.375(5)	N(3)-C(9)-N(1)-N(2)	177.5(2)
C(23)-C(26)	1.529(5)	C(7)-C(8)-C(14)-C(19)	29.1(5)

Table-3: Hydrogen Bond Lengths (Å) and Bond Angles (°).

D–H···A	d(D–H)	d(H···A)	d(D···A)	∠DHA
C(26)-H(26)B···F(2)	0.96	2.65	3.323	127.46

Crystal Structure

The structure of the title compound with atomic numbering scheme is shown in Fig. 1, and Fig. 2 depicts the molecular packing and hydrogen bonds in a unit cell. The geometric parameters (selected bond lengths, bond angles and torsion angles) and hydrogen bond data of title compound are listed in Table-2 and Table-3, respectively. In the crystal, the average bond lengths and bond angles of pyrazolo[1,5-*a*]pyrimidine and phenyl rings are in normal ranges. The C(9)-N(3) (1.340(3) Å) and C(9)-N(1) (1.405(3) Å) bonds are significantly shorter than a normal single C–N bond (1.47 Å) and longer than a C=N bond (1.28 Å), indicating significant electron delocalization in the pyrazolo[1,5-*a*]pyrimidine ring system. The torsion angle of C(8)-C(7)-C(9)-N(3) and C(8)-C(7)-C(4)-C(5) are 177.0(3)° and 115.5(3)°. The dihedral angles between pyrazolo[1,5-*a*]pyrimidine and three phenyl rings are 29.06°, 63.98° and 23.78°. And these three phenyl planes are not coplanar with a dihedral angle (θ) of 58.14°, 34° and 3.08°, respectively. Furthermore, the intermolecular C(26)-H(26)B···F(2) hydrogen bond found in the title compound play a major role in stabilizing the molecule. It is worth noting that the crystal packing is further stabilized by weak π-π interactions. These interactions together with intermolecular hydrogen bond result in the formation of a three-dimensional framework.

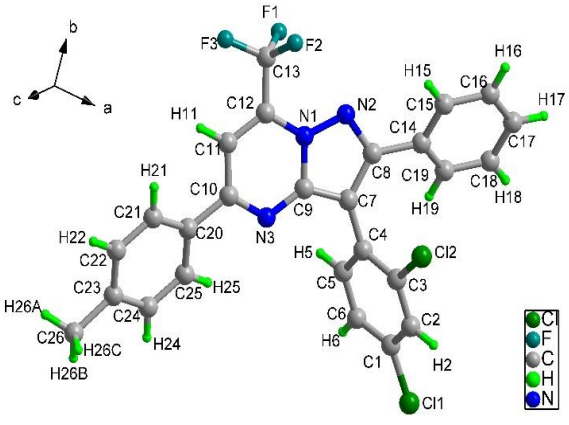


Fig. 1: The structure of $C_{26}H_{16}Cl_2F_3N_3$ with all non-H atom-labelling scheme and ellipsoids drawn at the 30% probability level.

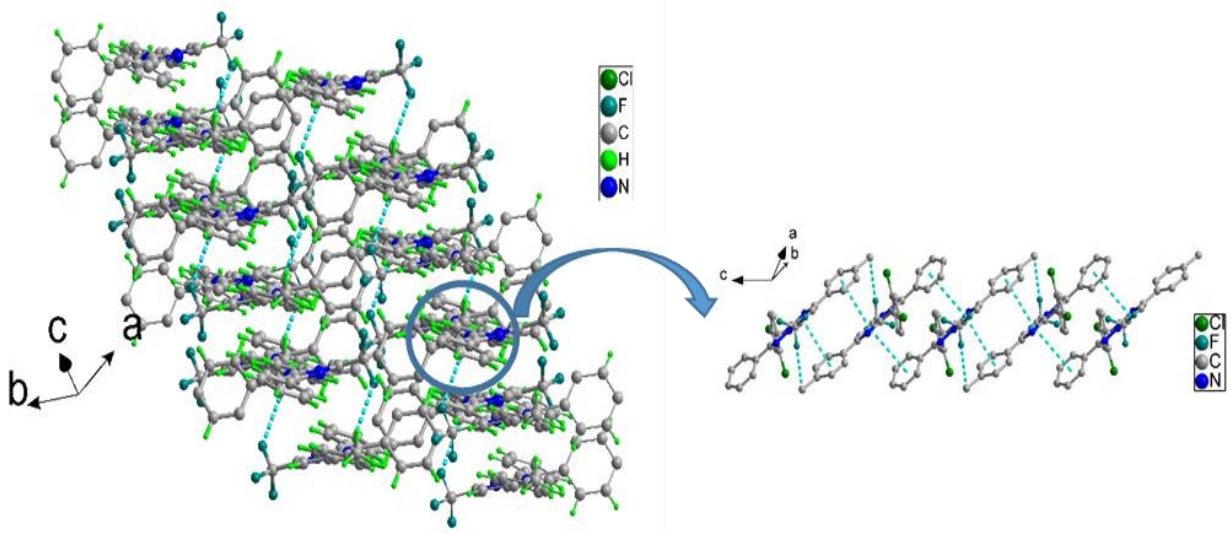


Fig. 2: A packing diagram of $C_{26}H_{16}Cl_2F_3N_3$.

In vitro antiancer activity test of the title compound on MKN45 and A549 cell lines

The named compound **6** was screened for their in vitro cytotoxic activity by the MTT-based assay using doxorubicin as a positive control. They were tested against two human cancer cell lines, namely human gastric cancer cell line MKN45 and human lung adenocarcinoma cell line A549. Biological activity determination results indicated that the title compound exhibited significant inhibitory activity in A549 cell line and slightly more potent than doxorubicin, but obviously less potent than doxorubicin in MKN45 cell line. The percentage inhibition determined is reported in Table-4. Further structure optimization may result in more active anticancer compounds, and the activity data are still waiting for further analysis. Further studies on structural optimization and biological activities about these derivatives are still underway in our laboratory and will be reported in the future.

Table-4: *In vitro* anticancer activity test[a] of the title compound on MKN45 andA549 cell lines.

Compound	% inhibition at 50 µg/mL in	
	MKN45	A549
The title compound	53.9	66.2
doxorubicin	81.1	65.8

[a]Test MTT colourimetric assay in MKN45 and A549 human cancer cell lines.

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