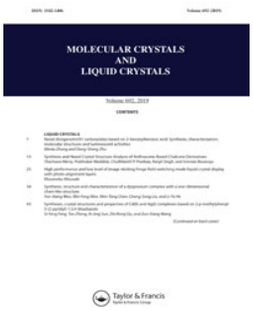

Molecular Crystals and Liquid Crystals

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Synthesis, crystal and antiproliferative activity of 2-[2-(2-fluorobenzylidene) hydrazinyl]-4-(1-methyl-1*H*-indol-3-yl)thieno[3,2-d]pyrimidine

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ABSTRACT

The title compound 2-[2-(2-fluorobenzylidene)hydrazinyl]-4-(1-methyl-1*H*-indol-3-yl) thieno[3,2-d]pyrimidine ($C_{22}H_{16}FN_5S$) was prepared and its structure was confirmed by IR, ^{1}H NMR, MS, elemental analyses and X-ray diffraction. The crystal of the title compound belongs to the monoclinic system, space group $P2_1/c$ with $a = 14.4546(17)$ Å, $b = 17.0895(19)$ Å, $c = 17.9621(15)$ Å, $\alpha = 90°$, $\beta = 122.717(6)$, $\gamma = 90°$, $V = 3733.1(7)$ Å^3, $Z = 4$, and $R = 0.0412$ for 4816 observed reflections with $I > 2\sigma(I)$. In addition, the compound possesses distinct effective inhibition on the proliferation of HT-29, A549 and MKN45 cell lines.

KEYWORDS

antiproliferative activity; synthesis; thieno[3,2-d] pyrimidine; X-ray diffraction

Introduction

In recent years, fused bicyclic pyrimidines are attractive scaffolds for drug design due to their biological importance [1–3], especially the thienopyrimidine ring. The thienopyrimidine derivatives often exhibit diverse biological activities, including anticancer [4,5], anti-microbial [6], anti-inflammatory activities [7]. Among these active compounds, thieno[3,2-d]pyrimidines have been reported to show remarkable antitumor activities with different biotargets and mechanisms [5], and some of them are already being marketed or are under clinical/preclinical studies, such as Olmutinib [8], Pictilisib (GDC-0941) [9], SNS-314 [10], PF-03758309 [11] and Fimepinostat (CUDC-907) [12]. On the other hand, indoles are *N*-heterocycles with a wide range of pharmacological and biological properties, such as anticancer [13], anti-inflammatory [14], antioxidant [15], antihistamine [16] and antiviral [17] agents. One of the noteworthy drugs based on indole moiety is Osimertinib (AZD9291) which is a FDA-approved targeted therapy medicine for the treatment of metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) [18].

In view of the facts mentioned above and also as a part of our work [19,20] on the synthesis of bioactive lead compounds for the anticancer drug discovery, the title compounds were designed by introducing indole scaffold into the thieno[3,2-d]pyrimidine

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pharmacophore. A new thieno[3,2-d]pyrimidine derivative, 2-[2-(2-fluorobenzylidene) hydrazinyl]-4-(1-methyl-1*H*-indol -3-yl)thieno[3,2-d]pyrimidine, was synthesized and characterized by IR, ^{1}H NMR, MS and elemental analyses. The single crystal structure of the title compound was determined by X-ray diffraction. The antiproliferative activity of the title compound against human cancer cell lines HT-29 and MKN45 was tested.

Experimental

Materials and methods

Unless specified otherwise, all starting materials and reagents were obtained from commercial supplies without further purification. All melting points (°C) 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 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. Crystal data were obtained on a Bruker P4 X-diffractometer.

Synthesis of thieno[3,2-d]pyrimidine-2,4-diol (2)

A mixture of 3-amino-2-thiophene carboxylic acid methyl ester (12.48 g, 79.38 mmol) and urea (27.54 g, 397.02 mmol) was heated at 190 °C. After 2 h, 7.5% NaOH solution (60 mL) was poured into the reaction mixture and a white solid precipitated. The solid was filtered off and the filtrate washed with 2 M HCl. A large amount of white solid was precipitated, filtered and the filter cake was dried to give 12.10 g of thieno[3,2-d]pyrimidine-2,4-diol as a white solid. Yield: 90.6%. m.p. 102–104 °C (lit. [21] 102.9 °C); MS (ESI) m/z(%): 169.0 $[M+H]^+$.

Synthesis of 2,4-dichlorothieno[3,2-d]pyrimidine (3)

A mixture of thieno[3,2-d]pyrimidine-2,4-diol (7.4 g, 44.0 mmol), phosphorus oxychloride (40 mL) was heated at reflux for 10 h. After cooling to room temperature, the reaction mixture was slowly added to ice/water with vigorous stirring. The mixture was then filtered, washed with cold water and dried to yield 6.36 g of 2,4-dichlorothieno[3,2-d]pyrimidine as an off-white solid. Yield: 70.5%. m.p. 138–140 °C (lit. [22] 138.8 − 139.3 °C); MS (ESI) m/z(%): 169.0 $[M+H]^+$.

Synthesis of 2-chloro-4-(1-methyl-1H-indol-3-yl)thieno[3,2-d]pyrimidine (5)

A suspension of 2,4-dichlorothieno [3,2-d]pyrimidine (4.10 g, 20.00 mmol) and aluminum chloride (3.20 g, 24.00 mmol) in dried 1,4-dioxane (50 mL) was stirred at ambient temperature for 10 min. To this was added 1-methylindole (2.90 g, 22.10 mmol), and the mixture was heated to 80 °C for 3 h. The cool reaction mixture was added dropwise to vigorously stirring water (250 mL) over 15 min. Upon complete addition the mixture was stirred for 1 h, filtered and the solid washed with water (50 mL). The crude product was purified by flash silica chromatography to give 4.70 g of 2-chloro-4-(1-methyl-1*H*-indol-3-yl)thieno[3,2-d]pyrimidine as a

yellow solid. Yield: 78.4%. m.p. 202–204 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (s, 1 H), 7.94 (br, 2 H), 7.47 (s, 1 H), 7.37 (s, 3 H), 3.92 (s, 3 H); MS (ESI) m/z(%): 205.0 $[M+H]^+$.

Synthesis of 2-hydrazinyl-4-(1-methyl-1H-indol-3-yl)thieno[3,2-d]pyrimidine (6)

A mixture of 2-chloro-4- (1-methyl-1*H*-indol-3-yl)thieno[3,2-d]pyrimidine (5.10 g, 17.00 mmol) and 80% hydrazine monohydrate (15 mL) in EtOH (60 mL) was refluxed overnight with vigorous agitation. Most of the solvent was evaporated under reduced pressure when white solid appeared. After cooling to 10 °C, the resulting precipitate was filtered off, washed with water, and dried under vacuum to afford 3.50 g of 2-hydrazinyl-4-(1-methyl-1*H*-indol-3-yl)thieno[3,2-d]pyrimidine as a yellow solid, yield: 69.65%. m.p. 251–253 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (d, $J = 7.9$ Hz, 1 H), 7.95 (s, 1 H), 7.79 (d, $J = 5.4$ Hz, 1 H), 7.43 – 7.27 (m, 4 H), 6.43 (s, 1 H), 4.57 – 3.93 (m, 2 H), 3.90 (s, 3 H); MS (ESI) m/z(%): 296.1 $[M+H]^+$.

Synthesis of 2-[2-(2-fluorobenzylidene)hydrazinyl]-4-(1-methyl-1H-indol-3-yl)thieno[3,2-d] pyrimidine (8)

To a solution of 2-hydrazinyl-4-(1-methyl-1*H*-indol-3-yl)thieno[3,2-d]pyrimidine (0.40 g, 1.35 mmol) in EtOH (8 mL), 2-fluorobenzaldehyde (0.20 g, 1.61 mmol) and acetic acid (2 drop) were added, and the mixture was refluxed for 8 h until TLC showed the completion of the reaction. After cooling to room temperature, the resultant precipitate was filtered and dried under vacuum to afford 0.41 g of the title compound as a light yellow solid, yield: 75.41%. m.p. 253–255 °C;.IR (KBr) ν: 3436.7, 31998, 1576.0, 1523.3, 1469.8, 1412.5, 1353.2, 1303.1, 1233.1, 1140.2, 1088.8, 853.9, 788.6, 749.2, 704.3; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.45 (s, 1 H), 9.22 (s, 1 H), 8.45 (s, 1 H), 8.37 (s, 1 H), 8.33 (d, $J = 5.4$ Hz, 1 H), 8.15 (t, $J = 7.2$ Hz, 1 H), 7.61 (d, $J = 7.2$ Hz, 1 H), 7.48 – 7.25 (m, 6 H), 4.01 (s, 3 H); MS (ESI) m/z(%): 402.1 $[M+H]^+$; Elemental analysis for $C_{22}H_{16}FN_5S$ (%), calculated: C 65.82, H 4.02, N 17.44. Found (%): C 65.94, H 3.96, N 17.40.

Crystal data structure determination

The light yellow powder of the title compound was dissolved in ethanol/ethyl acetate mixed solvents = 5:5 (V/V). After slowly evaporating the solvents for several days, some single crystals suitable for X-ray analysis were obtained. A light yellow crystal ($C_{22}H_{16}FN_5S$) with dimensions of 0.28 mm × 0.26 mm × 0.22 mm was selected for data collection which was performed on a Bruker APEX-II CCD automatic diffractometer with a graphite-monochromatic Mo *Ka* radiation ($\lambda = 0.71073$ Å) by using the φ and ω-scan mode at 293(2) K. A total of 18811 reflections were collected in the range of $2.6 < \theta < 26.2°$ (index ranges: $-17 < h < 15$, $-12 < k < 20$, $-21 < l < 21$) and 6568 were independent ($R_{int} = 0.027$), of which 4816 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 [23] 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 [24]. The final refinement gave the final $R = 0.041$ and $wR = 0.116$ ($w = 1/[\sigma^2(F_o^2) + (0.070\,P)^2 + 0.010\,P]$, where $P = (F_o2 + 2\,F_c2)/3$). $S = 1.03$, $(\Delta/\sigma)_{max} < 0.001$, $(\Delta\rho)_{max} = 0.20$ and $(\Delta\rho)_{min} = -0.29$ e/Å^{-3}. CCDC 1910419 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44) 1223 336 033; or email: deposit@ccdc.cam.ac.uk.

In vitro antiproliferative activity evaluation

The title compound was evaluated for its *in vitro* antiproliferative activity against three cancer cell lines (human colon cancer cell line HT-29, human lung adenocarcinoma cell line A549 and human gastric cancer cell line MKN45) by the MTT-based assay method under standard conditions [20] using sorafenib tosylate as a positive control. Cells were seeded in 96-well plate. After seeding 24 h, the medium was removed. The test compounds were dissolved in DMSO and diluted with culture medium to different concentrations (the final concentration of DMSO 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 °C. Remove the medium, 20 μL MTT solution (5 mg/mL, pH = 7.4, PBS was the solvent) was added to each well and incubated for additional 3 - 4 h. The medium was replaced by 150 mL DMSO to solubilize the purple formazan crystals produced and the absorbance was measured on a microplate reader at 490 nm. Cellular proliferation inhibition rate was calculated as follows: inhibition rate (%) = [1 − OD_{490} (treated)/OD_{490}(control)] × 100%.

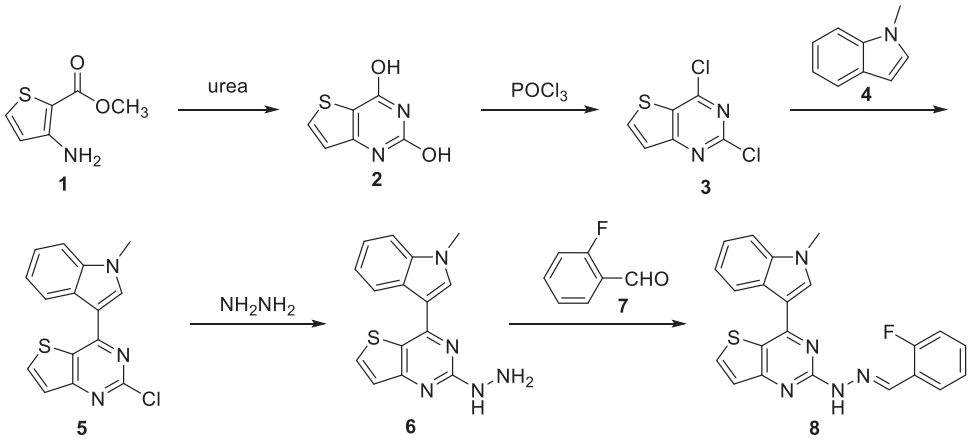
Results and discussion

Synthesis

The synthesis of the title compound by five steps was described in Scheme 1. The commercially available methyl 3-amino-2-thiophenecarboxylate(**1**)was condensed with urea at 190 °C for 2.0 h to give thieno[3,2-d]pyrimidine-2,4-diol (**2**). Chlorination of **two** with phosphorus oxychloride proceeded smoothly to 2,4-dichlorothieno[3,2-d]pyrimidine(**3**) as a pale solid. 4-chloro of 2,4-dichlorothieno[3,2-d]pyrimidine(**3**) was substituted by 1-methylindole to give 2-chloro-4-(1-methyl-1*H*-indol-3-yl)thieno[3,2-d]pyrimidine (**5**), which was then condensed with hydrazine hydrate to the key intermediate **6**. Finally, intermediate **six** condensed with 2-fluorobenzaldehyde in EtOH at refluxing condition for 8 h to yield the title compound and its structure was established by IR, ^{1}H NMR, MS and elemental analyses. All data of the title compound confirmed its structural integrity.

Crystal structure

Crystallographic data and experimental details of structural analyses for the title compound are summarized in Table 1. The hydrogen bond data and selected geometric



Scheme 1. Synthetic route of the title compound.

Table 1. One Crystal data and refinement details for the title compound.

System, sp. gr., Z	Monoclinic, $P2_1/c$, 4
a, *b*, *c* Å	14.4546(17), 17.0895(19), 17.9621(15)
α, β, γ deg	90, 122.717(6), 90
V, Å^3	3733.1(7)
Dx g.cm^{-3}	1.429
Radiation, λ, Å	Mo$K\alpha$, 0.71073
μ, mm^{-1}	0.20
T, K	293(2)
Sample size, mm	0.28 × 0.26 × 0.22
Diffractometer	Bruker APEX-II CCD
Scan mode	Multi-scan
Absorption correction, T_{min}, T_{max}	Semi-empirical from equivalents, 0.946, 0.957
θ_{max}, deg	2.30 ~ 25.00
h, *k*, *l* ranges	−17< =h< =15, −12< =k< =20, −21< =l< =21
Number of reflections: measured /unique (*N*1), R_{int}/with $I > 2\sigma(I)$ (*N*2)	18811/6568 0.0272
Refinement method	Full-matrix least-squares on F^2
Number of refined parameters	525
R_1/wR_2 relative to *N*1	0.0412, 0.1064
R_1/wR_2 relative to *N*2	0.0645, 0.1162
S	1.03
$\Delta\rho_{max}/\Delta\rho_{min}$, e/Å^3	0.20, −0.29
Program package	SADABS

parameters (bond lengths, bond angles and torsion angles) of title compound are listed in Table 2 and Table 3, respectively.

The single crystal of the title compound was cultured using ethanol/ethyl acetate mixed solvents = 5:5 (V/V) at room temperature and determined by X-ray diffraction method to confirm its structure. Its crystal structure shows that the molecule has a thieno[3,2-d]pyrimidine skeleton, in which all bond lengths and bond angles fall in normal ranges. It could be seen from X-ray single-crystal analysis (Figure 1) that the molecule consists of one benzene ring C(17)~C(22), one nine-membered thieno[3,2-d]pyrimidine ring S(1)~C(6) and one another nine-membered 1*H*-indole ring (N(5)~C(8). The 1*H*-indole ring and thieno[3,2-d]pyrimidine ring are connected through the C(5) atom of thieno[3,2-d]pyrimidine ring and the C(7) atom of 1*H*-indole ring, and the dihedral angles of them is 5.802°, which indicate the two nine-membered

Table 2. Hydrogen bond lengths (Å) and bond angles (°).

D–H···A	d(D–H)	d(H···A)	d(D···A)	∠DHA
C(37)-H(37C)···N(9) #1	0.96	2.56	3.403(3)	146.5
C(37)-H(37C)···N(7) #1	0.96	2.65	3.525(3)	151.4
C(30)-H(30)···S(2)	0.93	2.60	3.239(2)	126.4
N(8)-H(8A)···N(1)#2	0.86	2.24	3.072(2)	164.0
C(15)-H(15C)···F(2)#3	0.96	2.46	3.244(3)	138.2
C(8)-H(8)···S(1)	0.93	2.60	3.233(2)	126.1
N(3)-H(3A)···N(6)#4	0.86	2.22	3.082(2	178.3

Symmetry codes: (#1) $-x+1$, $-y+1$, $-z$; (#2) $-x+1$, $-y+1/2$, $-z+1/2$; (#3) x − 1, y, $z+1$; (#4) $-x+1$, y − 1/2, $-z+1/2$.

Table 3. Geometric parameters of the title compound.

Bond lengths	X-ray	Bond angles	X-ray
S(1)-C(1)	1.715(2)	C(1)-S(1)-C(4)	90.90(10)
F(1)-C(22)	1.367(2)	C(6)-N(1)-C(3)	113.52(15)
N(1)-C(6)	1.331(2)	N(4)-N(3)-C(6)	119.64(15)
N(2)-C(6)	1.336(2)	C(8)-N(5)-C(9)	108.59(16)
N(3)-N(4)	1.359(2)	C(2)-C(1)-S(1)	114.00(17)
N(3)-C(6)	1.377(2)	C(1)-C(2)-C(3)	111.84(19)
N(4)-C(16)	1.270(2)	N(1)-C(3)-C(4)	123.14(17)
N(5)-C(8)	1.351(2)	N(2)-C(5)-C(7)	115.50(16)
N(5)-C(15)	1.457(2)	C(4)-C(5)-C(7)	125.92(17)
C(1)-C(2)	1.342(3)	N(2)-C(6)-N(1)	128.24(17)
C(2)-C(3)	1.427(3)	C(8)-C(7)-C(5)	127.98(19)
C(4)-C(5)	1.411(3)	N(5)-C(9)-C(10)	108.30(17)
C(5)-C(7)	1.448(2)	N(4)-C(16)-C(17)	120.14(18)
C(7)-C(8)	1.378(3)	Torsion angles	
C(9)-C(14)	1.391(3)	C(6)-N(3)-N(4)-C(16)	177.80(18)
C(16)-C(17)	1.455(3)	S(1)-C(4)-C(5)-C(7)	1.2(3)
C(17)-C(22)	1.377(3)	N(4)-C(16)-C(17)-C(18)	−4.4(3)

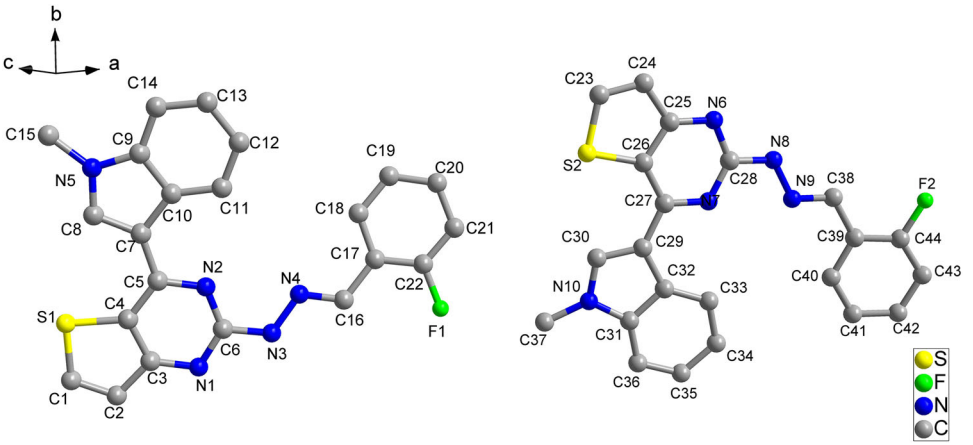


Figure 1. Structure of the title compound ($C_{22}H_{16}FN_5S$) with all non-H atom-labelling scheme and ellipsoids drawn at the 30% probability level.

rings are almost coplanar. Meanwhile, the dihedral angles between the benzene ring and the two nine-membered rings are 15.018, 14.045, respectively. The distances of N(5)–C(9), N(3)–C(6) and N(1)–C(3) are 1.383(3), 1.377(2) and 1.359(2) Å, respectively. They are remarkably shorter than the typical C(sp^2)–N bond (1.426 Å), but closer

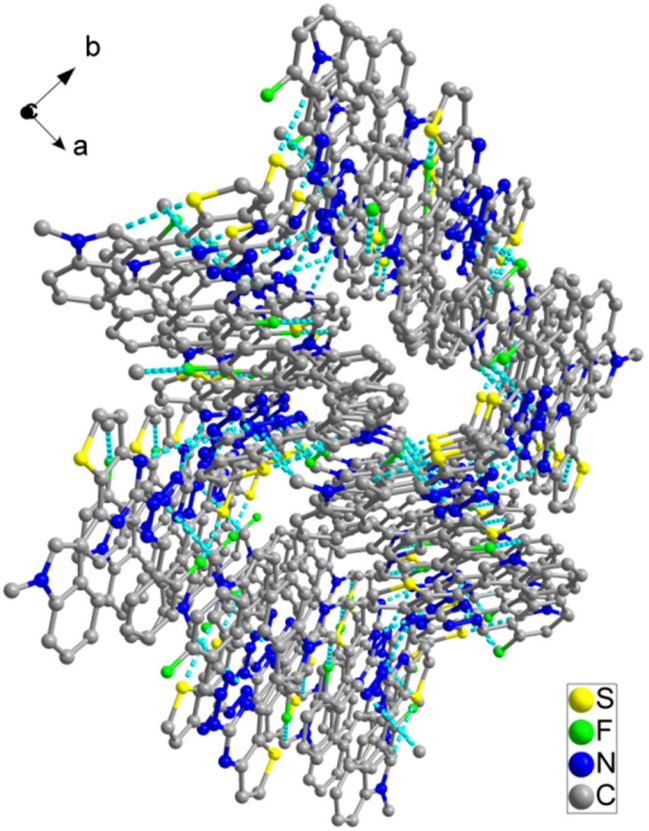


Figure 2. A packing diagram of the title compound ($C_{22}H_{16}FN_5S$).

Table 4. In vitro anticancer activity test[a] of the title compound on HT-29, A549 and MKN45 cell lines.

	IC_{50} (μmol/L)		
Compound	HT-29	A549	MKN45
The title compound	4.02	6.80	8.71
Sorafenib Tosylate	4.11	3.53	3.13

aTest MTT colourimetric assay in HT-29, A549 and MKN45 human cancer cell lines.

to the C = N double bond (1.33 Å). Furthermore, a mass of intermolecular and intramolecular hydrogen bond found in compound eight play a major role in stabilizing the molecule. Then, a 3 *D* supramolecular architectures are formed in the crystals by self-assembly of the molecules via weak $\pi \ldots \pi$ stacking interactions and various hydrogen bonds (Figure 2).

Evaluation of bioactivity

The bioassay results showed the title compound exhibited remarkable inhibitory activities against HT-29, A549 and MKN45 cell lines, which were similar to that of the positive control sorafenib. The title compound showed remarkable antiproliferative against

HT-29 cell line with IC_{50} values of 4.02 μM, and it was slightly more potent than sorafenib tosylate. The IC_{50}s were reported in Table 4. Further structure optimization may result in more active anticancer compounds.

Conclusions

In summary, a new crystal structure 2-[2-(2-fluorobenzylidene)hydrazinyl]-4-(1-methyl-1*H*-indol-3-yl)thieno[3,2-d]pyrimidine has been synthesized by a five-steps synthetic route and characterized by IR, ^{1}H NMR, MS, elemental analyses and X-ray diffraction. The biological evaluation showed that it possessed antiproliferative activitygainst HT-29, A549 and MKN45 cell lines.

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