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ORIGINAL PAPER

Regioselective synthesis and evaluation of novel sulfonamide 1,2,3-triazole derivatives as antitumor agents

Sameh R. Elgogary[2,3] · Rizk E. Khidre[1,2] · Emad M. El-Telbani[1,2]

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Abstract
A novel series of 1,2,3-triazole containing sulfonamide moiety was synthesized. Treatment of 4-acetyl 1,2,3-triazole **3** with different aldehydes gave α,β-unsaturated ketones **4a–c**. Condensation of **3** with dimethylformamide dimethylacetal (DMF-DMA) gave formimidamide **5**. Chalcone **7** was achieved via two ways from the reaction of **5** with benzaldehyde or from treatment of **4a** with DMF-DMA. Reaction of **7** with hydrazine hydrate afforded pyrazoline **8**. 5-Methyl pyrazole **12** was synthesized from Claisen condensation reaction of **3** or **5** with ethyl acetate to give 1,3-diketone adduct **9** or **10**, respectively, followed by treatment with hydrazine hydrate. 5-Aminopyrazole **17** was synthesized from the reaction of ester **13** or formimidamide ester **13a** with acetonitrile to afford cyanoacetyl derivatives **14** or **15**, respectively, followed by treatment with hydrazine hydrate. The new compounds were screened for their in vitro antitumor activity. The results of this investigation revealed that compounds **12**, **7**, and **17** had a significant anticancer activity against MCF-7 cancer cell line with IC_{50} values 12.4, 19.8, and 23.4 μM, respectively, in relation to the standard drug, doxorubicin.

Keywords 1,2,3-Triazole · Sulfonamide · Chalcone · Pyrazole · Anticancer activity · Molecular docking

Introduction

Sulfa drugs are sulfonamide antibiotics largely used as preventive and chemotherapeutic agents against various infectious diseases [1–3]. Due to the mechanism of sulfonamides, antimicrobial action involves competitive inhibition of folic acid synthesis, which prevents the growth and reproduction of microorganisms, and sulfonamides belong to the group of bacteriostatic agents [4]. Although sulfonamides were applied in therapy for more than 70 years, still more than 30 drugs containing this functionality are in clinical use and drugs of choice for the treatment of several conditions and diseases including antibacterial [3], antifungal [5], anti-inflammatory [6], anti-protozoal [7], antihypertensive agent bosentan [8], nonpeptidic vasopressin receptor antagonists [9], and translation initiation inhibitors [10]. Some important modified sulfonamides with various heterocyclic rings are used as carbonic anhydrase inhibitors of commercial importance [11]. They are also effective for the treatment of urinary, intestine, and ophthalmic infections, scalds, ulcerative colitis [12], male erectile dysfunction as the phosphodiesterase-5 inhibitor sildenafil—better known under its commercial name, Viagra [13], rheumatoid arthritis [14], and obesity [15]. Recently, sulfonamides are performed as an anticancer agent [16], as the antiviral HIV protease inhibitor amprenavir [17] and in Alzheimer's disease [12]. There are many drugs containing sulfonamide moiety (Fig. 1).

In addition, 1,2,3-triazole derivatives are known to exhibit various pharmacological applications such as antimicrobial [18–20], anti-inflammatory [21], anti-convulsant [19], antimalarial [22], antiviral [23, 24], anti-proliferative [25, 26], as carbonic anhydrase I, II, IV, and IX inhibitors [27], and anticancer activities [28–30]. For the design and search of

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✉ Rizk E. Khidre
rizkkhidre@yahoo.com

✉ Emad M. El-Telbani
dremad1966@yahoo.co.uk

[1] Chemical Industries Division, National Research Centre, Dokki, Giza 12622, Egypt

[2] Chemistry Department, Faculty of Science, Jazan University, Jazan 2079, Saudi Arabia

[3] Chemistry Department, Faculty of Science, Damietta University, Damietta, Egypt

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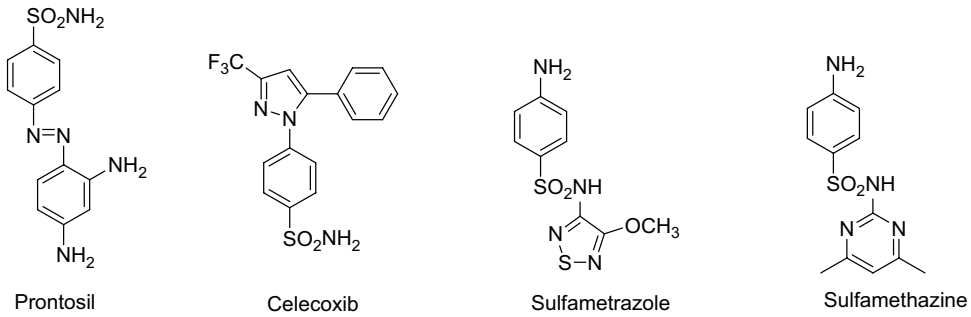


Fig. 1 Structures of some sulfonamide drugs

new drugs, the development of hybrid molecules through the binding of various pharmacophores in one frame could lead to molecules with interesting pharmaceutical properties.

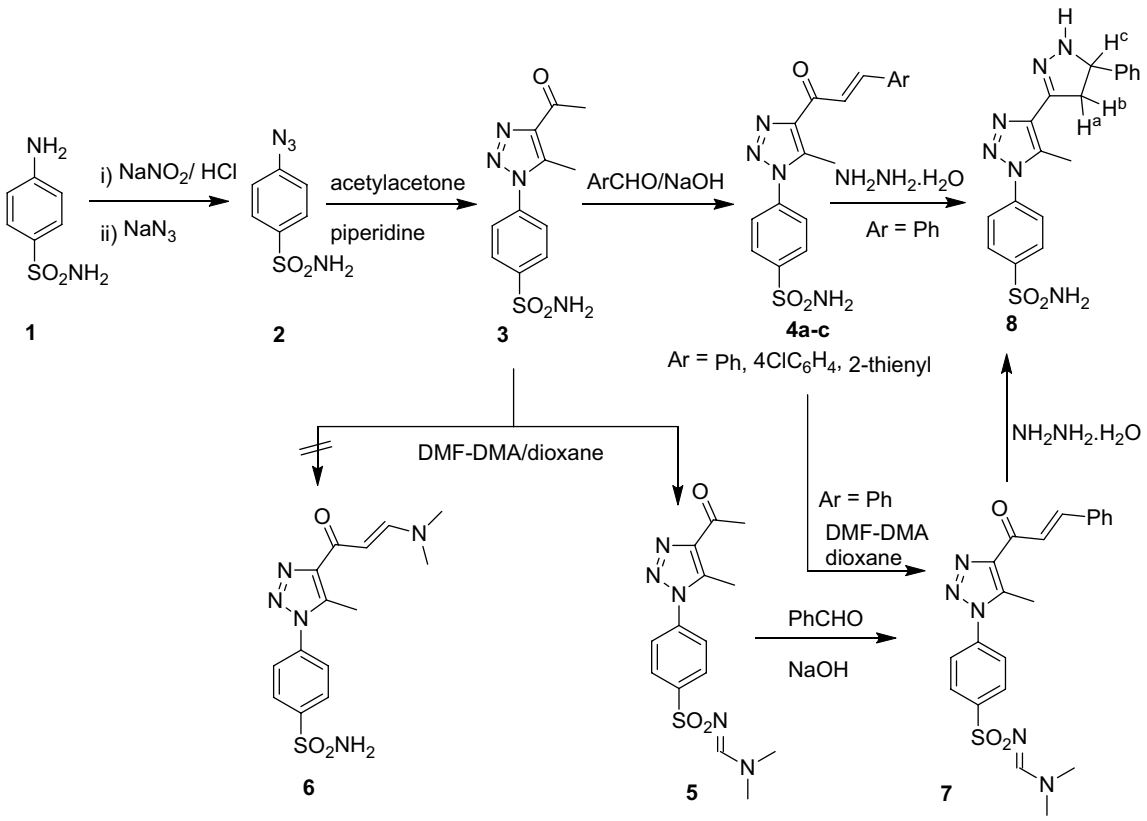
Taking into account all previous commentaries of the biological activities of sulfonamide, 1,2,3-triazole derivatives, and in continuation of our interest in the synthesis of biologically active heterocycles [31–37], efforts have been made to synthesize a series of new 1,2,3-triazole derivatives incorporating sulfonamide moiety to evaluate their antitumor activity.

Results and discussion

Diazotization of the sulfonamide **1** using sodium nitrite followed by coupling with sodium azide gave the corresponding azido derivative **2**. Reaction of **2** with acetyl acetone in the presence of piperidine afforded triazolobenzenesulfonamide derivative **3** in fairly good yield. The structure of **3** was established using both spectral and analytical analyses; the IR spectrum exhibited an absorption peak at 1689 cm^{-1} corresponding to the acetyl group, while the ^{1}H-NMR revealed a singlet signal at 2.64 ppm owing to acetyl group. Treatment of **3** with different aldehydes, namely benzaldehyde, 4-chlorobenzaldehyde, and thiophene-2-carbaldehyde, gave the corresponding chalcone derivative **4a–c**. The ^{1}H-NMR of **4a** (as a represented example) shows two doublet protons at 8.02 and 7.87 ppm with *J* coupling 16 Hz, indicating that the chalcone derivatives exist in *E*-configuration (Scheme 1). Condensation of **3** with dimethylformamide dimethylacetal (DMF-DMA) gave *N,N*-dimethylformimidamide derivative **5** as a sole product without any detection of the compound **6**. The disappearance of the amino group with the presence of the acetyl group at $\delta = 2.55$ ppm indicates that the condensation occurred with a great performance at the amino group rather than the acetyl group and supported the suggested structure by X-ray analysis (Fig. 2). The adduct **7** was achieved by the treatment of the acetyl derivative **5** with benzaldehyde in aqueous basic medium and readily reacted with an equimolar amount of hydrazine hydrate in boiling ethanol to give the pyrazoline derivative **8** with the cleavage of the *N,N*-dimethylformimidamide residue. The presence of two signals at δ 10.21 (s, 1H, NH) and 7.60 ppm (s, 2H, NH_2), with the other protons in their expected locations, supported the suggested structure (see "Experimental" section). To prove the structure of **8**, it was prepared by another two pathways of its preparation either by the reaction of **4a** directly with hydrazine hydrate or by the reaction of **4a** firstly with DMF-DMA followed by treatment with hydrazine hydrate (Scheme 1).

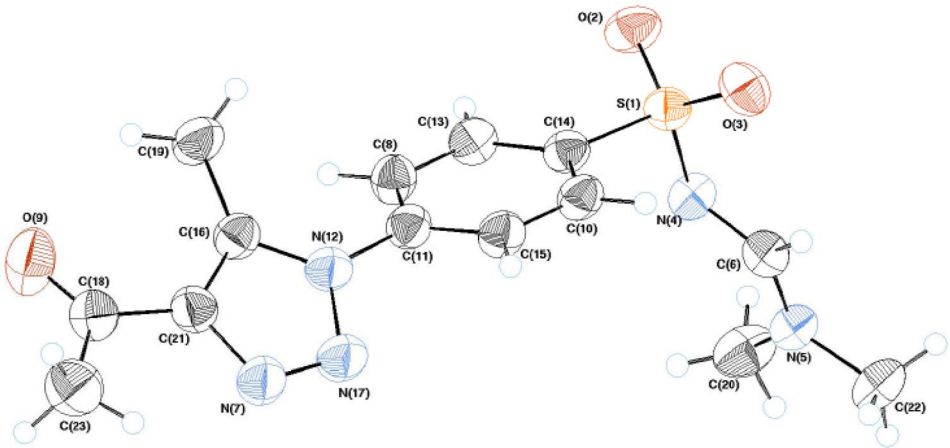
The regioselective reaction of **3** with DMF-DMA was widely studied; to this aim, Claisen–Schmidt condensation of **3** with ethyl acetate in the presence of a sodium sand gave the corresponding 1,3-diketone derivative **9**. The structure of **9** was elucidated on the basis of spectral and analytical analyses. The IR spectrum exhibited two absorption peaks at 1703 and 1618 cm^{-1} (2CO), while ^{1}H-NMR showed a new singlet signal at δ 4.25 ppm (2H, CH_2), with the disappearance of the acetyl group previously detected at δ 2.64 ppm of the parent **3**. Treatment of **9** with DMF-DMA in dioxane gave sulfonyl formimidamide derivative **10** rather than **11**. The disappearance of the amino group with the appearance of a new singlet signals at δ 6.59 (N=CH) supported the suggested structure. Reaction of **10** with hydrazine hydrate gave pyrazole benzenesulfonamide **12**. ^{1}H-NMR spectrum showed two exchangeable signals at 12.90 (s, 1H, NH) and 6.42 (s, 2H, NH_2) which indicated the cleavage of *N,N*-dimethylformimidamide residue. To prove the structure of compound **12**, it was prepared by another method of its preparation by application of Claisen condensation on compound **5** followed by treatment with hydrazine hydrate (see Scheme 2 and "Experimental" section).

To demonstrate regioselective performance of reaction of DMF-DMA with amino group rather than active methylene groups, Claisen condensation was successfully achieved by treatment of ethyl 5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazole-4-carboxylate **13**, which was synthesized from the reaction of azide **2** with ethyl acetoacetate in EtOH containing piperidine at reflux temperature [38], with acetonitrile in the presence of a sodium sand to give cyanoacetyl benzenesulfonamide derivative **14**. Then compound **14** was reacted



Scheme 1 Synthesis of triazolosulfonamide derivatives **3**, **4**, **5**, **7,** and **8**

Fig. 2 X-ray structure of 5



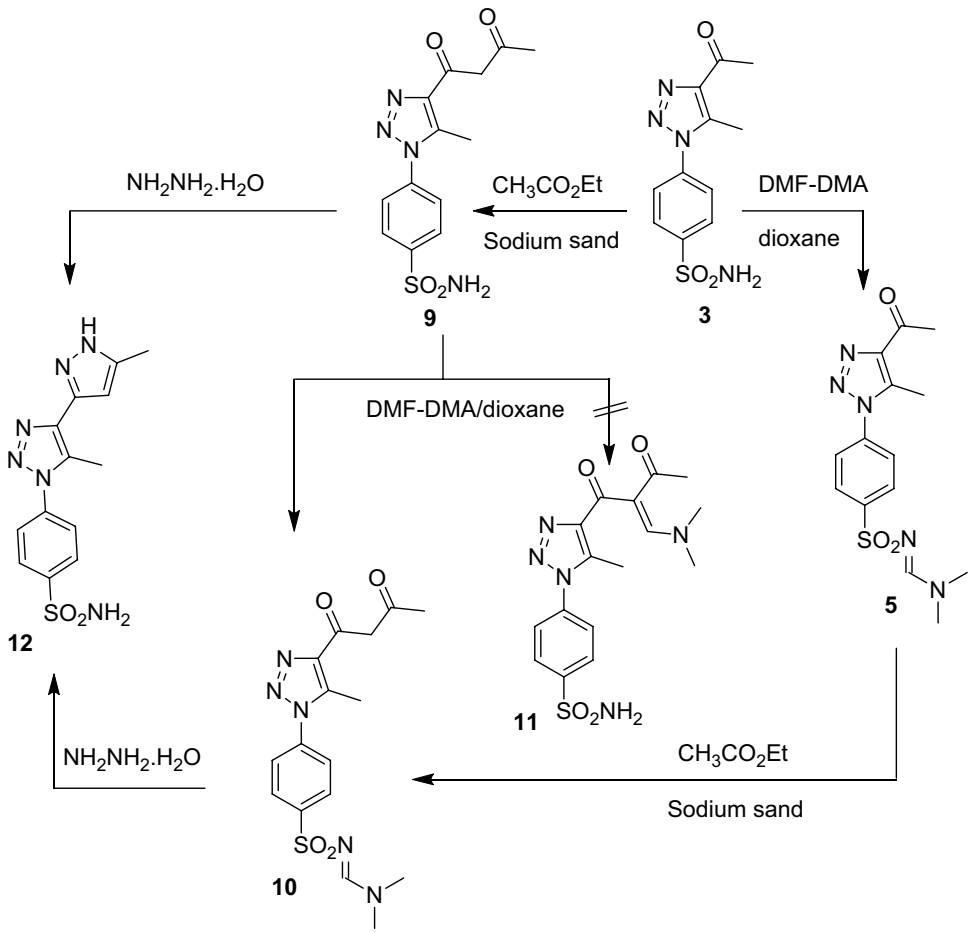
with DMF-DMA followed by treatment with hydrazine hydrate to give 5-amino pyrazole benzenesulfonamide **17** with the cleavage of *N,N*-dimethylformimidamide residue. On the other hand, the structure of pyrazole **17** was proved either by spectral data or by its preparation from Claisen condensation of enamine **13a** with acetonitrile to give **15**, which either was prepared from cyanoacetyl **14**, followed by treatment with hydrazine hydrate (Scheme 3 and "Experimental" section).

Anticancer activity screening

Cytotoxicity assay

Cytotoxicity assays were done to govern the level of sensitivity as well as the selectivity of malignancy and normal cells to the experimental compound. Some of the newly synthesized compounds were tested for their anticancer activity against MCF-7 cancer cell line using

Scheme 2 Synthesis of triazol derivatives **9**, **10**, and **8**



high-throughput screening technique, and the outcomes are presented in Table 1.

The investigation of the IC_{50} results in Table 1 displayed that compound **12** exhibited high anticancer activity against MCF-7 cancer cell line with IC_{50} values 12.41 µM. Since this compound has the uppermost IC_{50} values, it can be considered as primary hits. Compounds **7** and **17** showed high proliferative activity against the cell line taken for the study with IC_{50} values 19.8 and 23.41 µM, respectively. Compounds **4a** and **8** displayed poor anticancer activity against MCF-7 cancer cell line with IC_{50} values 105.47 and 99.54 µM, respectively. From the formerly mentioned study, we could accomplish that compounds **12**, **17**, and **7** showed a good anticancer activity among all the tested compounds expressed by their IC_{50} values related to doxorubicin $IC_{50} = 1.19$ µM. These compounds can be used as lead compounds and by further optimization could have a high biological profile.

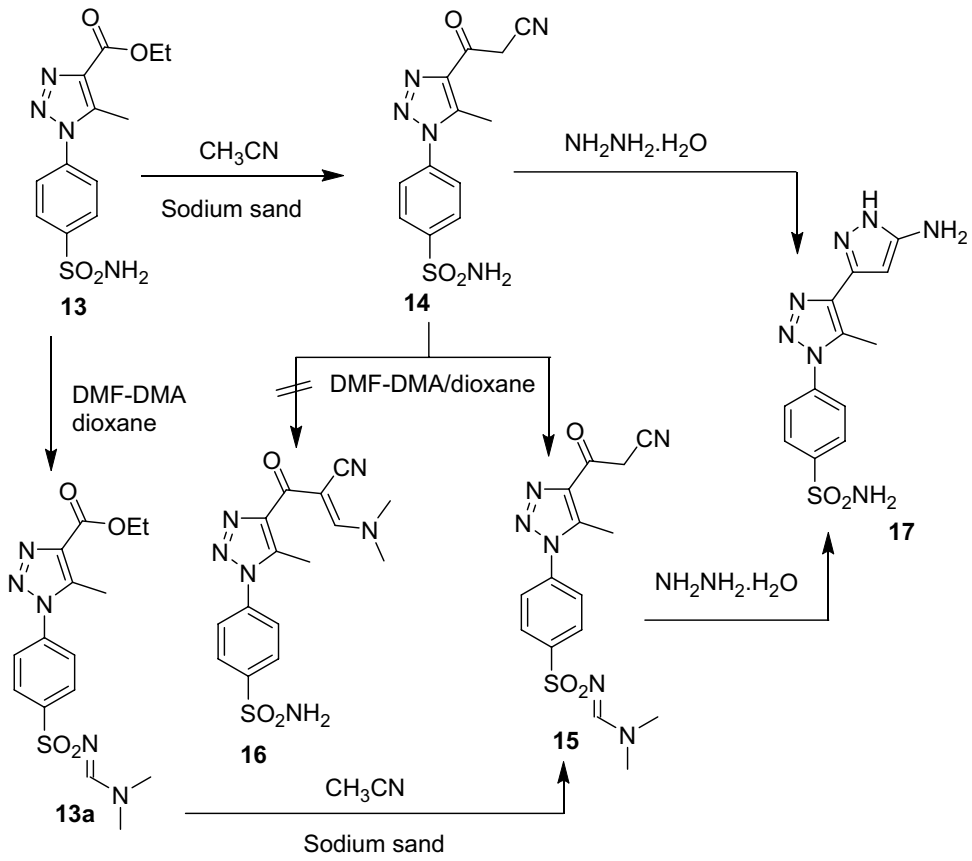
Molecular docking

To understand the variability of the biological results of the newly synthesized compounds as antitumor, we decided to dock them into the active site of the CDK2 enzyme. Starting from a triazole scaffold, eight analogs were designed based on the structure (active site) of the CDK2 enzyme. Molecular docking studies were performed with the default parameter of CDOCKER. For docking simulation of CDK2, five optimized inhibitors were docked with the enzyme (PDB:2FVD). Top-ranked conformations were selected for further analysis and visual interaction studies. Binding energy calculations are used to evaluate the compound's overall potential to qualify a ligand as a potential drug candidate. Compound **12** ranks highest among all studied triazole derivatives from the docking methodologies as shown in Table 1. The most active compound **12** is ranked as second by considering its binding energy obtained from the extensible protocol of Accelrys Discovery studio 2.5.

Receptor–ligand interaction analysis

Results obtained from interaction analysis of all newly designed ligands have proposed that a group of amino acid residues located on the binding cavity such as Ile10, Ala31, Val64, Phe80, Asp86, and Leu134 in the target CDK2 enzyme play an important role in ligand binding.

Scheme 3 Synthesis of triazol derivatives **13**, **13a**, **14**, **15,** and **17**



Best ranked compounds **6** and **3** are docked deeply into the active site region, forming interactions with the residues Asp86, Ile10, Ala31, Val64, Phe80, and Phe146 (Table 1).

From the interactive analysis, it can be concluded that top-ranked inhibitor **12** mainly interacts with main chain residues Asp86 (hydrogen bond), Ile10, Ala31, Val64, Phe80, and Leu134 (electrostatic and hydrophobic interactions) during the docking simulation by CDOCKER programs (Figs. 2, 3; Table 1).

The binding sites of CDK2 enzyme were explored to be located in the active site near to Leu83 and Asp86. Compounds **4a** and **8** which contain a phenyl pyrazole and α,β-unsaturated ketone in their structure have not obtained comparatively good docking scores in all 10 poses (Fig. 4).

Experimental

Chemistry

Melting points were determined on a digital Gallen-KampMFB-595 instrument using open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FTIR-440 spectrometer using KBr pellets. Mass spectra were performed at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. ^{1}H NMR (500 MHz) and ^{13}CNMR (125 MHz) were recorded on a Bruker model UltraShield NMR spectrometer in DMSO-d6 using tetramethylsilane (TMS) as an internal standard; chemical shifts are reported as ppm units. The elemental analyses (% C, H, N) were done at the Microanalytical Center, Cairo University, Cairo, Egypt. The appropriate precautions in handling moisture-sensitive compounds were taken. Solvents were dried by standard techniques. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out and was run using thin-layer chromatography (TLC) aluminum sheets silica gel 60 F254 (Merck).

Synthesis of 4-(4-acetyl-5-methyl-*1H*-1,2,3-triazol-1-yl) benzenesulfonamide (3)

Azide compound (**2**) (0.01 mol) has been cautiously added to a cold solution of acetyl acetone (0.01 mol, 1.3 g) and piperidine (1 ml) in ethanol (100 ml), and the mixture has been heated under reflux on a water bath for 3 h. The resulting solid was separated and recrystallized from acetic acid. M.p. 292–294 °C. Yield: 86%. FT-IR (KBr, ν, cm^{-1}):

Table 1 Docking, binding energy calculations, and antitumor activity assay against MCF-7 of the newly synthesized compounds

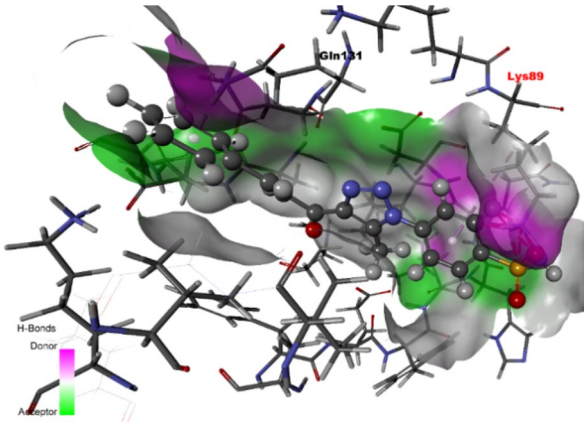
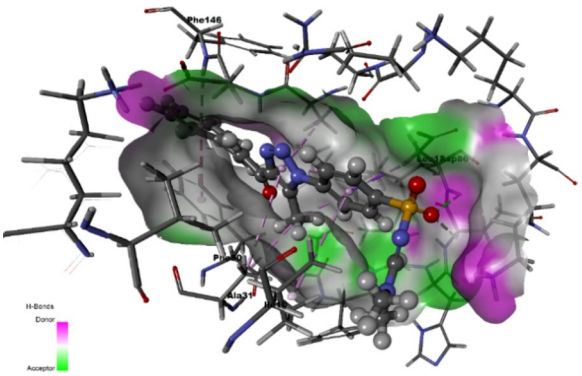
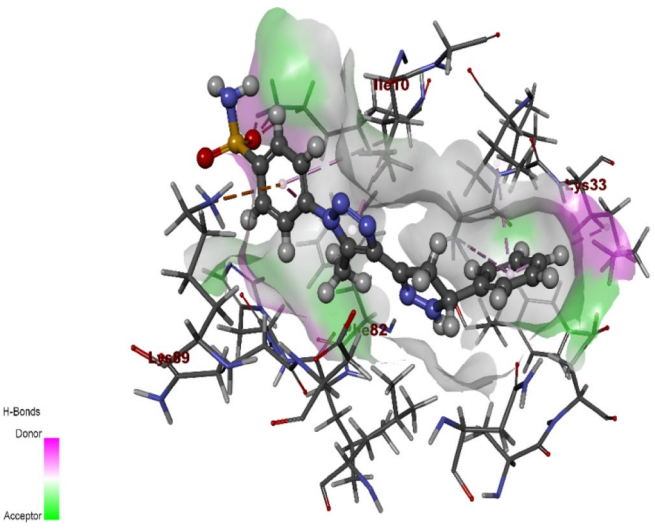
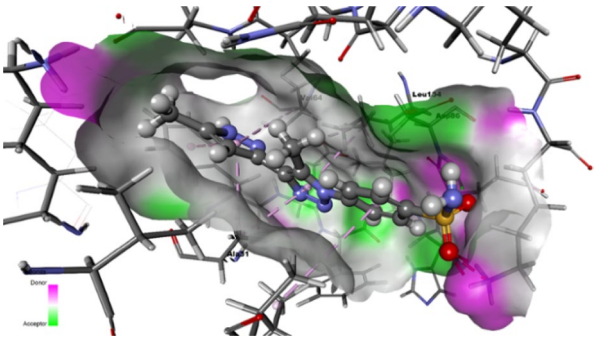
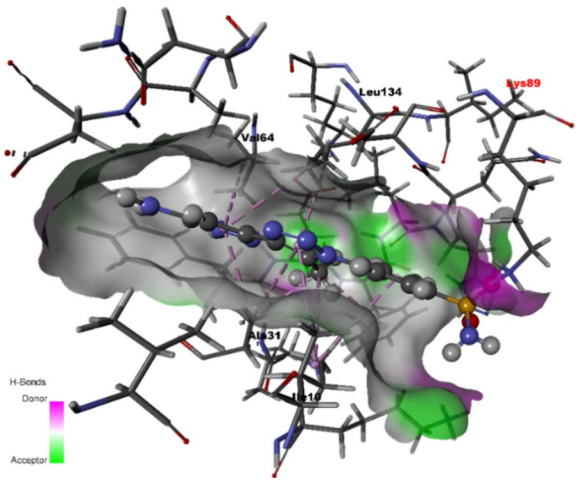
No.	MCF-7 IC_{50} (μM)	Docking score	Binding energy	3D interaction
4a	105.47	− 19.7064	− 10.2719	
7	19.8	− 9.68375	− 28.709-S3	
8	99.54	− 15.87	− 9.414	

Table 1 (continued)

No.	MCF-7 IC_{50} (μM)	Docking score	Binding energy	3D interaction
12	12.41	− 17.3531	− 31.407	
17	23.41	− 16.3296	− 12.6568	
Doxorubicin	1.19	–	–	–

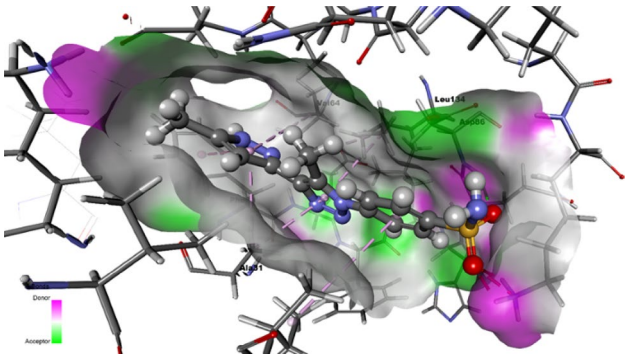


Fig. 3 Hydrogen bonding and electrostatic and hydrophobic interactions of compound **12** with the CDK2 active site

$\nu = 3278$, 3197 (NH_2), 1689 (C=O), 1357, 1168 (SO_2). ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 8.0$ (d, 2H, $J = 8.6$ Hz, Ar–H), 7.84 (d, 2H, $J = 8.6$ Hz, Ar–H), 7.59 (s, 2H, NH_2), 2.60 (s, 3H, CH_3CO), 2.56 (s, 3H, CH_3); MS, *m/z* (%): 280 [M^+] (15), 210 (100). Anal. Calcd for $C_{11}H_{12}N_4O_3S$ (280.30): C, 47.14; H, 4.32; N, 19.99. Found C, 47.10; H, 4.50; N, 19.80.

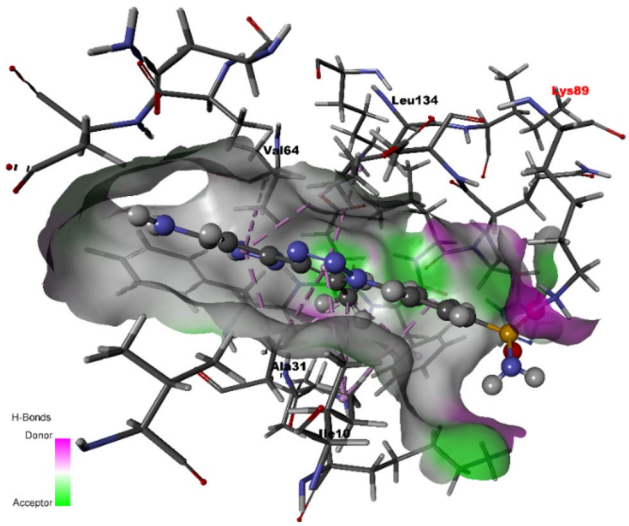


Fig. 4 Hydrogen bonding and electrostatic and hydrophobic interactions of compound **17** with the CDK2 active site

General procedure for the preparation of compounds 4a–c

To a well-stirred solution of **3** (10 mmol) in alcoholic NaOH (5%, 25 ml) at 0–5 °C, a solution of the appropriate aldehydes (10 mmol) was added gradually. Stirring was continued for 24 h at r.t. The resulting precipitate after neutralization with diluted HCl was filtrated, washed with water, and crystallized from ethanol to give **4a**–**c**.

(*E*)-4-(4-Cinnmoyl-5-methyl-*1H*-1,2,3-triazol-1-yl)benzenesulfonamide (4a)

As colorless needles, M.p. 238–240 °C, yield (81%). FT-IR (KBr, ν, cm^{-1}): $\nu = 3284$, 3163 (NH_2), 1658(C=O), 1595 (C=C), 1350, 1168 (SO_2). ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 8.09$ (d, 2H, $J = 8.6$ Hz, Ar–H), 8.02 (d, 1H, $J = 16$ Hz, CH=CH), 7.90 (d, 2H, $J = 8.6$ Hz, Ar–H), 7.87 (d, 1H, $J = 16$ Hz, CH=CH), 7.82 (m, 2H, Ar–H), 7.63 (s, 2H, NH_2), 7.47 (m, 3H, Ar–H), 2.64 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d6) δc 10.01 (CH_3), 122.65 (CH=), 125.72, 126.0, 127.24, 128.75, 129.11, 130.65, 134.11, 134.34, 137.40, 139.26, 143.25, 143.29, 145.35 (=CH), 182.89 (C=O). MS, *m/z* (%): 368 [M^+] (12), 197 (100). Anal. Calcd for $C_{18}H_{16}N_4O_3S$ (368.41): C, 58.68; H, 4.38; N, 15.21. Found C, 58.60; H, 4.50; N, 15.10.

(*E*)-4-(4-(3-(4-chlorophenyl)acryloyl)-5-methyl-*1H*-1,2,3-triazol-1-yl)benzenesulfonamide (4b)

As a pale brown color, M.p. 240–241 °C, yield (79%). FT-IR (KBr, ν, cm^{-1}): $\nu = 3352$, 3251 (NH_2), 1662 (C=O), 1591 (C=C), 1357, 1163 (SO_2). ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 8.07$ (d, 2H, $J = 9$ Hz, Ar–H), 8.02 (d, 1H, $J = 16.5$ Hz, CH=CH), 7.92 (d, 2H, $J = 9$ Hz, Ar–H), 7.88 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.83 (d, 1H, $J = 16.5$ Hz, CH=CH), 7.62 (s, 2H, NH_2), 7.52 (d, 2H, $J = 8.5$ Hz, Ar–H), 2.62 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δc 10.00 (CH_3), 123.32 (CH=), 125.70, 127.22, 129.12, 130.43, 133.28, 135.33, 137.36, 139.31, 141.82, 143.18, 145.35 (=CH), 183.16 (C=O). MS, *m/z* (%): 402 [M^+] (10), 197 (100). Anal. Calcd for $C_{18}H_{15}ClN_4O_3S$ (402.85): C, 53.67; H, 3.75; N, 13.91. Found C, 53.60; H, 3.60; N, 13.80.

(*E*)-4-(5-methyl-4-(3-(thiophen-2-yl)acryloyl)-*1H*-1,2,3-triazol-1-yl)benzenesulfonamide (4c)

As a pale yellow color, M.p. 262–264 °C, yield (77%). FT-IR (KBr, ν, cm^{-1}): $\nu = 3363$, 3217 (NH_2), 1658 (C=O), 1587 (C=C), 1330, 1172 (SO_2). ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 8.09$ (d, 2H, $J = 8.5$ Hz, Ar–H), 8.02 (d, 1H, $J = 15.00$ Hz, CH=CH), 7.90 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.80 (d, 1H, $J = 5.5$ Hz, thiophene–H), 7.71 (d, 1H, $J = 15.5$ Hz, CH=CH), 7.66 (d, 1H, $J = 4$ Hz, thiophene–H), 7.62 (s, 2H, NH_2), 7.20 (d, 1H, $J = 4$ Hz, thiophene–H), 2.63 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d6) δc 9.99 (CH_3), 121.03 (CH=), 126.96, 127.32, 128.93, 130.54, 133.63, 136.02, 137.40, 139.12, 139.66, 143.15, 145.34 (=CH), 182.68 (C=O). MS, *m/z* (%): 374 [M^+] (10%), 197 (100%). Anal. Calcd for $C_{16}H_{14}N_4O_3S_2$ (374.43): C, 51.32; H, 3.77; N, 14.96. Found C, 51.50; H, 3.60; N, 14.80.

Synthesis of *N′*-[(4-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1yl)phenyl)sulfonyl]-*N,N*-dimethylformimidamide (5)

To a well-stirred solution of **3** (10 mmol) in dioxane, dimethylformamide dimethylacetal (10 mmol) was added gradually. Stirring was continued for 6 h at r.t. The resulting precipitate was filtrated and crystallized from ethanol to give **5** as colorless crystals, M.p. 298–299 °C, yield (77%). FT-IR (KBr, ν, cm^{-1}): $\nu = 1658$(C=O), 1587 (C=C), 1330, 1172 (SO_2). ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 8.00$ (s, 1H, N=CH), 7.98 (d, 2H, $J = 8.6$ Hz, Ar–H), 7.80 (d, 2H, $J = 8.6$ Hz, Ar–H), 2.91 (s, 3H, NCH_3), 2.60 (s, 3H, NCH_3), 2.55 (s, 3H, CH_3CO), 2.52 (s, 3H, CH_3). MS: $m/z = 335$ [M^+]. Anal. Calcd for $C_{14}H_{17}N_5O_3S$ (335.38): C, 50.14; H, 5.11; N, 20.88. Found C, 50.20; H, 5.20; N, 20.80.

Synthesis of (E)-*N′*-[(4-(4-cinnamoyl-5-methyl-1*H*-1,2,3-triazol-1yl)phenyl)sulfonyl]-*N,N*-dimethylformimidamide (7)

To a well-stirred solution of **5** (10 mmol) in alcoholic NaOH (5%, 25 ml) at 0–5 °C, benzaldehyde (10 mmol) was added gradually. Stirring was continued for 24 h at r.t. The resulting precipitate after neutralization with diluted HCl was filtrated, washed with water, and crystallized from ethanol to give **7** as a pale yellow color, M.p. > 300 °C, yield (79%). FT-IR (KBr, ν, cm^{-1}): $\nu = 1658$ (C=O), 1622 (N=CH), 1595 (C=C), 1336, 1151 (SO_2); ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 8.79$ (s, 1H, N=CH), 8.03 (d, 1H, $J = 16$ Hz, CH=CH), 7.90 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.87-7.83 (m, 3H, CH=CH, Ph-H), 7.76 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.47 (m, 3H, Ph-H), 2.64 (s, 3H, CH_3), 2.48 (s, 6H, $2NCH_3$). ^{13}C NMR (125 MHz, DMSO-d_6) δc 9.97 (CH_3), 39.00 (NCH_3), 122.70 (CH=), 125.55, 126.93, 128.78, 129.15, 130.89, 134.36, 136.16, 139.23, 143.18, 143.27, 147.86 (=CH), 169.68 (N=CH), 183.35 (C=O). MS: $m/z = 423$ [M^+]. Anal. Calcd for $C_{21}H_{21}N_5O_3S$ (423.49): C, 59.56; H, 5.00; N, 16.54. Found C, 59.50; H, 5.10; N, 16.60.

4-(5-Methyl-4-(5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide (8)

A mixture of compounds **4a** or **7** (10 mmol) and hydrazine hydrate (10 mmol) in ethanol (50 ml) was refluxed for

5 h. The resulting precipitate formed after cooling, filtered off, dried, and crystallized from ethanol to give as colorless crystals, M.p. >300 °C, yield (80% and 77%). FT-IR (KBr, ν, cm^{-1}): $\nu = 3358$, 3251 (NH_2), 3185 (NH), 1595 (C=C), 1348, 1168 (SO_2). ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 10.21$ (s,1H, NH), 8.04 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.87 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.60 (s, 2H, NH_2), 7.59 (s, 1H, Ph-H), 7.33 (d, 2H, $J = 7.5$ Hz, Ph-H), 7.27 (d, 2H, $J = 7.5$ Hz, Ph-H), 4.83 (dd, 1H, $J = 20.5$, 10.5 Hz, Hc), 3.59 (dd, 1H, $J = 16$, 10 Hz, Hb), 3 (dd, 1H, $J = 16$, 10 Hz, Ha), 2.57 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δc 10.02 (CH_3), 41.97 (CH_2), 62.65 (CH), 125.51, 126.61, 127.17, 128.45, 131.86, 132.5, 138.06, 139.34, 142.82, 143.32, 144.85; MS, *m/z:* 382 [M^+] (20). Anal. Calcd for $C_{18}H_{18}N_6O_2S$ (382.4 4): C, 56.53; H, 4.74; N, 21.98. Found C, 56.33; H, 4.80; N, 21.54.

Synthesis of 4-(5-methyl-4-(3-oxobutanoyl)-1*H*-1,2,3-triazol-1-yl) benzenesulfonamide (9)

A mixture of compound **3** (10 mmol) and ethyl acetate (50 ml) was cautiously added to a freshly prepared sodium sand (15 mmol) and heated on a water bath for 2 h. After the reaction is complete, methanol (5 ml) is added, poured into ice-cold water, and neutralized with diluted hydrochloric acid. The resulting precipitate was filtered off, dried, and crystallized from ethanol to give as a colorless crystal M.p. 265-267 °C, yield (82%). FT-IR (KBr, ν, cm^{-1}): $\nu = 3390$, 3222 (NH_2), 1703 and 1618 (CO), 1591(C=C), 1340, 1153 (SO_2). ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 8.11$ (d, 2H, $J = 8.6$ Hz, Ar–H), 7.91 (d, 1H, $J = 8.6$ Hz, Ar–H), 6.80 (s, 2H, NH_2), 4.25 (s, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.17 (s, 3H, CH_3). MS, *m/z* (%): 322 [M^+] (34). Calcd for $C_{13}H_{14}N_4O_4S$ (322.34): C, 48.44; H, 4.38; N, 17.38. Found C, 48.60; H, 4.20; N, 17.20.

Synthesis of *N′N′*-dimethyl-*N′*-[(4-(5-methyl-4-(3-oxobutanoyl)-1*H*-1,2,3-triazol-1-yl)phenyl)sulfonyl] formimidamide (10)

Method A A mixture of compound **5** (10 mmol) and ethyl acetate (50 ml) was cautiously added to a freshly prepared sodium sand (15 mmol) and heated on a water bath for 2 h. After the reaction is complete, methanol (5 ml) is added, poured into ice-cold water, and neutralized with diluted hydrochloric acid. The resulting precipitate was filtered off, dried, and crystallized from ethanol to give **10** as pale yellow crystals, M.p. 189–190 °C, yield (75%).

Method B To a well-stirred solution of **9** (10 mmol) in dioxane, dimethylformamide dimethylacetal (10 mmol) was added gradually. Stirring was continued for 8 h at r.t. The resulting precipitate was filtrated and crystallized from ethanol to give **10**, yield (82%). FT-IR (KBr, ν, cm^{-1}): $\nu = 1695$ and 1633 (2C=O), 1593 (C=C), 1332, 1153 (SO_2). ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 8.13$ (d, 2H, $J = 8.6$ Hz, Ar–H), 7.91 (d, 1H, $J = 8.6$ Hz, Ar–H), 6.59 (s, 1H, N=CH), 4.25 (s, 2H, CH_2), 3.13 (s, 3H, NCH_3), 2.90 (s, 3H, NCH_3), 2.56 (s, 3H, CH_3), 2.25 (s, 3H, CH_3); MS: *m/z* (%): 327 [M^+] (27). Calcd for $C_{16}H_{19}N_5O_4S$ (327.42): C, 50.92; H, 5.07; N, 18.56. Found C, 50.80; H, 5.20; N, 18.60.

Synthesis of 4-(5-methyl-4-(5-methyl-1*H*-pyrazol-3-yl)-1*H*-1,2,3-triazol-1-yl) benzenesulfonamide (12)

A mixture of compound **10** (10 mmol) and hydrazine hydrate (10 mmol) in ethanol (50 ml) was refluxed for 5 h. The resulting precipitate formed after cooling, filtered off, dried, and crystallized from ethanol to give colorless crystals M.p. 286-288 °C, yield (79%). FT-IR (KBr, ν, cm^{-1}): $\nu = 3325$, 3180 (NH_2), 3120 (NH), 1597 (C=C), 1300, 1166 (SO_2). ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 12.90$ (s,1H, NH), 8.01 (d, 2H, $J = 8.6$ Hz, Ar–H), 7.85 (d, 2H, $J = 8.6$ Hz, Ar–H), 7.57 (s, 1H, pyrazole-H4), 6.42 (s, 2H, NH_2), 2.56 (s, 3H, CH_3), 2.26 (s, 3H, CH_3). MS: $m/z = 318$ [M^+]. Calcd for $C_{13}H_{14}N_6O_2S$ (318.36): C, 49.05; H, 4.43; N, 26.40. Found C, 49.10; H, 4.20; N, 26.60.

Ethyl-1-(4-(*N*-((dimethylamino)methylene)sulfamoyl) phenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (13a)

To a well-stirred solution of **13** (10 mile) in dioxane, dimethylformamide dimethylacetal (10 mmol) was added gradually. Stirring was continued for 8 h at r.t. The resulting precipitate was filtrated and crystallized from ethanol to give **13a**, yield (79%). FT-IR (KBr, ν, cm^{-1}): $\nu = 1726$ (C=O), 1589 (C=C), 1342, 1149 (SO_2). ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 8.00$ (s, 1H, N=CH), 7.98 (d, 2H, $J = 8.6$ Hz, Ar–H), 7.80 (d, 2H, $J = 8.6$ Hz, Ar–H), 4.31(q, 2H, $J = 6.7$ Hz, OCH_2), 3.14 (s, 3H, NCH_3), 2.91 (s, 3H, NCH_3), 2.56 (s, 3H, CH_3), 1.29 (t, 3H, $J = 6.7$ Hz, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δc 9.80 (CH_3), 14.18 (CH_3), 35.18 (NCH_3), 41 (NCH_3), 60(CH_2), 125.99, 127.17, 127.47, 136.07, 137.43, 139.59, 144.33 (CH=N), 161 (C=O); MS: $m/z = 365$ [M^+]. Anal. Calcd for $C_{15}H_{19}N_5O_4S$ (365.41): C, 49.31; H, 5.24; N, 19.17. Found C, 49.13; H, 5.32; N, 18.97.

Synthesis of 4-(4-(2-cyanoacetyl)-5-methyl-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide (14)

A mixture of compound **13** (10 mmol) and acetonitrile (50 ml) was cautiously added to a freshly prepared sodium sand (15 mmol) and heated on a water bath for 2 h. After the reaction is complete, methanol (5 ml) is added, poured into ice-cold water, and neutralized with diluted hydrochloric

acid. The resulting precipitate was filtered off, dried, and crystallized from ethanol to give as colorless crystals M.p. 225–227 °C, yield (80%). FT-IR (KBr, ν, cm^{-1}): 3390, 3210 (NH_2), 2210 (CN), 1703 (C=O), 1596(C=C), 1340, 1153 (SO_2). ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 8.04$ (d, 2H, $J = 7.65$ Hz, Ar–H), 7.92 (d, 2H, $J = 7.65$ Hz, Ar–H), 7.60 (s, 2H, NH_2), 4.72 (s, 2H, CH_2), 2.46 (s, 3H, CH_3). MS: $m/z = 305$ [M^+]. Calcd for $C_{12}H_{11}N_5O_3S$ (305.31): C, 47.21; H, 3.63; N, 22.94. Found C, 47.40; H, 3.70; N, 22.80.

Synthesis of *N′*-((4-(4-(2-cyanoacetyl)-5-methyl-1*H*-1,2,3-triazol-1-yl)phenyl)sulfonyl)-*N,N*-dimethylformimidamide (15)

To a well-stirred solution of **14** (10 mmol) in dioxane, dimethylformamide dimethylacetal (10 mmol) was added gradually. Stirring was continued for 6 h at r.t. The resulting precipitate was filtrated, washed with water, and crystallized from ethanol to give **15** as colorless crystals, M.p. 263–265 °C, yield (77%). FT-IR (KBr, ν, cm^{-1}): $\nu = 2208$ (CN), 1716 (C=O), 1635 (N=CH), 1589 (C=C), 1342, 1148 (SO_2); ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 8.28$ (s, 1H, N=CH), 8.02 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.82 (d, 2H, $J = 8.5$ Hz, Ar–H), 4.34 (s, 2H, CH_2), 3.16 (s, 3H, NCH_3), 2.93 (s, 3H, NCH_3), 2.54 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δc 9.82 (CH_3), 14.19 (CH_2), 41.05 [$N(CH_3)_2$], 126, 127.48, 136.06, 137.44, 139.61, 144.33, 159.9, 160.98 (N=C), 183.16 (C=O). MS: $m/z = 360$ [M^+]. Anal. Calcd for $C_{15}H_{16}N_6O_3S$ (360.39): C, 49.99; H, 4.48; N, 23.32. Found C, 49.80; H, 4.30; N, 23.40.

Synthesis of 4-(4-(5-amino-1*H*-pyrazol-3-yl)-5-methyl-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide (17)

A mixture of compound **15** (10 mmol) and hydrazine hydrate (10 mmol) in ethanol (50 ml) was refluxed for 5 h. The resulting precipitate formed after cooling, filtered off, dried, and crystallized from ethanol to give colorless crystals M.p. > 300 °C, yield (79%). FT-IR (KBr, ν, cm^{-1}): ν 3325, 3180 (NH_2), 3120 (NH), 1597(C=C), 1300, 1166 (SO_2); ^{1}H-NMR (500 MHz, δ, ppm, DMSO-d_6): $\delta = 9.79$ (s, 1H, NH), 8.01 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.95 (s, 2H, NH_2), 7.87 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.52 (s, 1H, pyrazole-H4), 7.42 (s, 2H, NH_2), 2.56 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δc 9.39 (CH_3), 125.41, 127.16, 136.48, 137.77, 137.85, 138.51, 145.11, 160.07, 162.67. MS: $m/z = 319$ [M^+]. Calcd for $C_{12}H_{13}N_7O_2S$ (319.34): C, 45.13; H, 4.10; N, 30.70. Found C, 45.10; H, 4.20; N, 30.60.

X-ray crystallography of compound 5 A single crystal of compound **5** was obtained by slow evaporation at room temperature, from dimethylformamide (DMF). The crystal structure was solved and refined using MaXus (Bruker Nonius, Deflt and Mac Science, Japan) [39]. Mo Kα radiation ($\lambda = 0.71073$ Å) and a graphite monochromator were used for data collection. The chemical formula and ring labeling system are shown in Fig. 2. Crystal data for compound 5: $C_{14}H_{17}N_5O_3S$, Mr, 335.386; system, monoclinic; space group, $P2_1/c$; unit cell dimensions, a, 7.7615 (2)Å; b, 26.1958 (7)Å; c, 8.0542 (2)Å; α, 90.00° (2)°; β, 106.455 (2)°; γ, 90.00°; V, 1570.50 (7)Å^3; Z, 4; Dx, 1.419 Mg m^{-3}; θ range for data collection, 2.910–30.034°; μ (Mo–Kα), 0.23 mm^{-1}; $T = 298$ K; independent reflections, 4479; measured reflections, 9424; observed reflections, 2595; R(all), 0.1230; R(gt), 0.0652; wR(ref), 0.2099; wR(gt), 0.1835; S(ref), 1.163; δ/σ_{max}, 0.001; $\delta\rho_{max}$, 0.410eÅ^3; $\delta\rho_{min}$, −0.409eÅ^3. Crystallographic data for the structure **5** have been deposited with the Cambridge Crystallographic Data Center (CCDC) under the number 1574930. Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or at www.ccdc.cam.ac.uk.

Materials and methods

Three-dimensional structure of human cycline-dependant kinase CDK2, PDB:2FVD, was obtained from protein data bank. Energy minimization of newly designed compounds was done by employing discovery studio 2.5 for structure refinement. Geometry of all designed analogues is typed with CHARMm [40] force field; then partial charges are calculated by Momany Rone method [41]. Further, they are optimized through a smart minimizer algorithm, which performs 1000 steps of steepest descent with a root mean square (RMS) gradient tolerance of 0.1. Same as the preparation of ligands for the target, its active site was also passed with the energy minimization process and it was done using CHARMm force field which is defined by equation given below:

$$E = E_b + E_q + E_f + E_w + E_{vdw} + E_{el} + E_{hd} + E_{cr} + E_{cj}$$

where E = total energy, E_b = bond potential energy, E_q and E_f = bond angle potential energy, E_w = torsion energy, E_{vdw} = van der Waals interaction energy, E_{el} = electrostatic potential energy, E_{hb} = hydrogen bond energy, E_{cr} = energy constraints, and E_{cj} = energy function [40].

CDOCKER

CDOCKER (CHARMm-based DOCKER), a docking program provided by discovery studio 2.5, uses a CHARMm-based molecular dynamics (MD) scheme to dock ligands into a receptor binding site and then random conformations

will be produced using high-temperature molecular dynamics. When these conformations are translated to the active site, candidate poses are then generated using random rigid body rotations followed by simulated annealing. CDOCKER offers all the advantages of full ligand flexibility (including bonds, angles, and dihedrals) and reasonable computation times. CDOCKER uses soft core potentials, which are found to be effective in exploring the conformational space of macromolecules used in various docking studies. The nonbonded interactions which involve van der Waals (vdW) and electrostatics are softened at different levels, except during the final minimization step [42]. Initially, ten conformations for each inhibitor are generated in the active site of the target enzyme, which is created as a spherical region with a diameter of 10 Å. Simulated annealing is performed using a flexible ligand and a rigid protein. Receptor–ligand interactions are calculated from grid extension 8.0, random conformations are generated using specific molecular dynamics steps, and the system is heated to 700 K in 2000 steps, cooling steps to 5000, and cooling temperature to 300 K. The final refinement step of minimization is performed using full potential. Minimized docking poses are then clustered, based on a heavy atom RMSD approach. The ranking is based on the total docking energy, which is composed of the ligand's intramolecular energy and the ligand–receptor interaction.

Conclusions

In summary, new 1,2,3-triazole derivative containing sulfonamide moiety was synthesized, in good yields, starting from 4-acetyl 1,2,3-triazole 3 and ethyl-1,2,3-triazole-4-carboxylate **13**. A number of prepared compounds showed moderate-to-good anticancer activities. Pyrazolyl 1,2,3-triazole **12** showed excellent anticancer activity with against MCF-7 cancer cell line with IC_{50} values 12.4

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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