Synthesis, Molecular Docking, and Antitumor Evaluation of Some New Pyrazole, Pyridine, and Thiazole Derivatives Incorporating Sulfonamide Residue

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ABSTRACT
Cancer is the second leading cause of death worldwide. There is always a huge demand for novel anticancer. New series of pyrazole, pyridine, thiazole derivatives containing sulfonamide moiety were prepared and screened for their antitumor activity against breast cancer cell line (MCF-7). The results of this investigation revealed that compounds 3 and 8 had a significant anticancer activity against MCF-7 cancer cell line with IC\textsubscript{50} values 19.2 and 14.2 \textmu M, respectively, in relation to the standard drug, doxorubicin.

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1. Introduction
Cancer is one of the most dreadful diseases in the world and despite immense advances in the field of basic and clinical research, which have resulted in higher cure rates for a number of malignancies\textsuperscript{1,2}. Tumor growth and metastasis depend on various factors, including the physiological process of angiogenesis. For example, elevated expression of vascular endothelial growth factor, epidermal growth factor, fibroblast growth factor, and platelet-derived growth factor are associated with tumor angiogenesis, metastases, survival, and resistance to apoptosis. Therefore, these growth factors have represented potential molecular targets for inhibition of tumor growth and progression\textsuperscript{3–6}. Presently, a large number of anti-cancer drugs in clinical practice have showed pervasive side effect, low specificity, and multidrug resistance, so, there is always an urgent demand to develop novel anticancer drugs and diverse new natural or synthetic compounds are developed continuously by scientists\textsuperscript{7}. Sulfa drugs were the first broadly effective antibacterial to be used systemically, and paved the way for the antibiotic revolution in medicine (see Figure 1). In addition, sulfonyl or sulfonamide hybrids were broadly explored for their anticancer activities via different mechanisms\textsuperscript{8–18} and it was found that they possess minimum side effect along with multi-drug resistance activity.

In addition, heterocyclic compounds containing pyrazole, thiazole, and pyridine moieties have attracted the interest of medicinal chemists due to its wide range of various pharmacological activities\textsuperscript{19–27}. In view of the facts mentioned above and as a part of our ongoing effort to develop a series of novel small molecules as potential antitumor agents that can block biologically relevant molecular targets,\textsuperscript{28–33} we prepared certain pyrazoles, pyridines, thiazoles derivatives containing sulfonamide pharmacophores and studied their activity against breast cancer cell line (MCF-7).
2. Results and discussion

2.1. Chemistry section

Compounds 1a and 1b were prepared according to literature procedure [34] Condensation of 1a and 1b and phenylhydrazine provided the hydrazones derivatives 2a and 2b. The Vilsmeier-Haack reaction using 2.5 equiv. of phosphoryl chloride performed a double addition of reagent to afford, ultimately after hydrolysis, the desired pyrazole 4-carbaldehyde derivative 3 (Scheme 1). The structure of 3 was established using both spectral and analytical analyses, in addition to X-ray analysis (Figure 2). The IR spectrum of 3 showed absorption bands at $\nu = 1672$ (CHO), 1633 (N=CH–), and 1342, 1153 (SO2), whereas $^1$HNMR showed signals at 10.52 (s, 1H, CHO) and 9.28 (s, 1H, pyrazole H-5) besides the rest of protons in its expected locations.

Treatment of the pyrazole carbaldehyde derivative 3 with some selected nitrogenous active reagents, namely (thiosemicarbazide, carbothiohydrazide, and cyanoacetohydrazide), afforded the condensed adduct 4, 5, and 6 as a sole product respectively, without any observation of cyclized products. The versatile $\alpha$, $\beta$- unsaturated nitrile 7 is obtained upon treatment of 3 with ethyl cyanoacetate in the presence of few drops of triethylamine which was directly subjected to react with aceto phenone in boiling ethanol containing catalytic amount of ammonium acetate to afford 1, 2-dihydropyridine derivatives 8. The structure of 8 was established by both spectral and analytical analysis, the infrared spectrum of compound 8 showed absorption peaks $\nu = 3360$ (NH), 2218 (CN), 1655 (CO), in addition the $^1$H NMR exhibited signals at $\delta = 12.54$ (NH), 9.28 (s, 1H, pyrazole H-5), and 7.74 (pyridine H-5), supported the suggested structure. Treatment of 3 with aceto phenone and/or 2- acetylthiophene, gave the corresponding chalcone derivatives 9a and 9b. The $^1$H-NMR of 9a (as a represented example) shows two doublet protons with $J$ coupling 15.30 Hz, indicating that the chalcone derivatives exist in E-configuration (Scheme 2).

The pyrazole derivative 10 was achieved in good yield, via treatment of 9a with hydrazine hydrate in boiling ethanol. The disappearance of the two doublets protons which were appeared
in the parent product 9a and the appearance of a new signal at $\delta = 11.21$ (s, 1H, NH) is supported by the suggested structure 10 (cf. experimental section).

Bromination of compounds 2a and 2b using bromine in acetic acid afforded the bis-dibromide derivatives 12a and 12b as sole products in very high yields. The structures of 12a and 12b were established by both spectral and analytical analyses. The appearance of singlet signal at $\delta = 7.57$ ppm (CH) is supported by the suggested structures.

The isolation of monobromo derivative 11a as a side product with very poor yield indicated that the mechanism of the reaction involving the formation of the monobromo derivative as an intermediate. It is known that the thiazole ring could be obtained when $\alpha$, $\alpha$- dibromoethanone derivatives with thiourea derivatives,35 to this aim, compounds 12a and 12b were treated with thiourea or N-phenylthiourea afforded the thiazoles derivatives 13a-d in good yields (see, Scheme 3 and experimental section).
2.2. Anticancer activity screening

2.2.1. 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 high-throughput screening technique, and the outcomes are presented in Table 1. The investigation of the IC_{50} results in Table 1 displayed that compounds 3 and 8 exhibited high anticancer activity against MCF-7 cancer cell line with IC_{50} values 19.2 and 14.2 μM. Since this compound has the uppermost IC_{50} values, it can be considered as primary hits. Compounds 13a and 13b showed high proliferative activity against the cell line taken for the study with IC_{50} values 28.1 and 35.1 μM, respectively. Compounds 2a and 10 displayed poor anticancer activity against MCF-7 cancer cell line with IC_{50} values 149.2 and 210.8 μM, respectively. From the formerly mentioned

Scheme 2. Synthesis of pyrazole and pyridone drivatives incorporating sulfonamide moiety.
study, we could accomplish that compounds 3 and 8 showed a good anticancer activity among all the tested compounds expressed by their IC50 values related to doxorubicin IC50 = 1.19 μM. These compounds can be used as lead compounds and by further optimization could have a high biological profile.

2.2.2. Molecular modeling
CDK2 has a vital role in cell cycle progression from the late G1-phase to the S-phase alongside initiating DNA repair36 and several studies have demonstrated that inhibition of CDK2 could induce breast cancer cell apoptosis without destruction normal cells37,38 So, molecular docking for synthesized compounds was performed to explore their biological profile due to their binding with CDK2. Subsequently, their bound conformations and binding affinities were estimated. The
structure preparation of the receptor was done by the removal of co-crystallized ligands and water molecules before energy minimization using the CHARMM force field. Hydrogens were added to the protein followed by adding the charges. The CDK2 coordinates were gained from protein data bank (PDB 6GUH) and the structure was adjusted by Accelry’s Discovery Studio 2.5. The missing residues were added as well as the structure was relaxed to correct the protein errors. Finally, the active site of CDK2 was distinct and all the synthesized compounds were docked, and their binding energies were calculated. The synthesized derivatives were docked utilizing the default parameters of C-Docker protocol (see Figures 3 and 4) (Table 1).

3. Materials and methods

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 Ultra Shield NMR spectrometer in DMSO-d$_6$ using tetra methyl silane (TMS) as an internal standard; chemical shifts are reported as ppm units. The elemental analyses (% C, H, N) were done at the Micro analytical 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 were carried out and was run using thin-layer chromatography (TLC) aluminum sheets silica gel 60 F254 (Merck).

3.1. General procedure for synthesizing of hydrazones derivatives 2a and 2b

To 1a and 1b (10 mmol) in acetic acid (100 mL) and water (10 mL), phenylhydrazine (11 mmol) was added. The reaction mixture was stirred at room temperature until completion (TLC, 5 h). The solid which was formed was filtered off, washed with water, dried and crystallized from acetic acid to give:
3.1.1. 4-[5-Methyl-4-(1-(2-phenylhydrazineylidine) ethyl)-1H-1,2,3-triazol-1-yl]benzene-sulfomide (2a)

Colorless crystals; yield (3.33 g, 90%); m.p. 256-258°C. IR (KBr, cm⁻¹) ν = 3323, 3165 (NH₂), 3136 (NH), 1371, 1141 (SO₂); ¹H-NMR (500 MHz, δ, ppm, DMSO-d₆): δ = 9.35 (s, 1H, NH), 8.06 (d, 2H, J = 8.5 Hz, Ar-H), 7.88 (d, 2H, J = 8.5 Hz, Ar-H), 7.60 (s, 2H, NH₂), 6.73-7.17 (m, 5H, Ph-), 2.62 (s, 3H, CH₃-), 2.43 (s, 3H, CH₃-). Anal. Calcd. For. C₁₇H₁₈N₆O₂S (370.43): C, 55.12; H, 4.90; N, 22.69%. Found: C, 55.20; H, 4.80; N, 22.80%.

3.1.2. N,N-Dimethyl-N’-(4-(4-(5-methyl-4-(1-(2-phenylhydrazineylidine)ethyl)-1H-1,2,3-triazol-1-yl)sulfonyl)formimidamide (2b)

Colorless crystals; yield (3.74 g, 88%); m.p. 179-180°C. IR (KBr, cm⁻¹) ν = 3321, (NH), 1629 (N=CH), 1373, 1149 (SO₂); ¹H-NMR (500 MHz, δ, ppm, DMSO-d₆): δ = 9.33 (s, 1H, NH), 8.29 (s, 1H, N=CH), 8.02 (d, 2H, J = 8.5 Hz, Ar-H), 7.82 (d, 2H, J = 8.5 Hz, Ar-H), 6.73-7.17 (m, 5H, Ph-), 3.16 (s, 3H, N-CH₃), 2.94 (s, 3H, N-CH₃) 2.63(s, 3H, CH₃-), 2.46(s, 3H, CH₃-). MS, m/z (%): 425 [M⁺] (100). Anal. Calcd. For. C₂₀H₂₃N₇O₂S (425.51): C, 56.45; H, 5.45; N, 23.04%. Found: C, 56.30; H, 5.60; N, 23.10%.

3.1.3. N’-(4-(4-(4-Formyl-1-phenyl-1H-pyrazol-3-yl)-5-methyl-1H-1,2,3-triazol-1-yl)sulfonyl)-N,N-dimethylformimidamide (3)

Phosphorous oxychloride (25 mmol) was added to DMF (100 mL) at 0°C and stirred for 30 min. 2a or 2b (10 mmol) were added slowly to this mixture and stirred for 5 h. The crude reaction was then quenched into water (1 L) and stirred for an additional 1 h the solid formed was separated, washed with water, dried, and crystallized from methanol to afford 3.

Colorless crystals; yield (4.07 g, 88%); m.p. 250-251°C. IR (KBr, cm⁻¹) ν = 1672, (CO), 1633 (N=CH–), 1342, 1153 (SO₂); ¹H-NMR (500 MHz, δ, ppm, DMSO-d₆): δ = 10.52 (s, 1H, CHO), 9.28 (s, 1H, pyrazole H-S), 8.02 (s, 1H, N=CH), 8.00 (d, 2H, J = 8.6 Hz, Ar-H), 7.82 (d, 2H, J = 8.6 Hz, Ar-H), 7.86-7.54 (m, 5H, Ph–), 3.14 (s, 3H, NCH₃), 2.92 (s, 3H, NCH₃), 2.66 (s, 3H, CH₃–). MS, m/z (%): 463 [M⁺] (100). Anal. Calcd. For. C₂₂H₂₁N₅O₃S (463.52): C, 57.01; H, 4.57; N, 21.15%. Found: C, 57.20; H, 4.60; N, 21.10%.

Figure 4. Hydrogen bond interactions of compound 3 with the active site residues of CDK2. It forms 1 HB with Lys33.
3.1.4. X-ray crystallography of compound 3

A single crystal of compound 3 was obtained by slow evaporation at room temperature, from dimethylformamide (DMF). The crystal structure was solved and refined using MaXus (Bruker Nonius, Delft and Mac Science, Japan). Mo Kα radiation (λ = 0.71073 Å) and a graphite monochromator were used for data collection. The chemical formula and ring labeling system are shown in Figure 2. Crystal data for compound 3: C_{22}H_{21}N_{7}O_{3}S, M_r = 463.520; system, Monoclinic; space group, P2_1/c; a = 11.3957 (3) Å; b = 13.1843 (5) Å; c = 5.1206 (5) Å; α = 90.00°; β = 106.413 (3)°; γ = 90.00°; V = 2179.21 (12) Å³; Z = 4; D_x = 1.413 Mg m⁻³; range for data θ = 2.910–27.485°; μ = 0.190 mm⁻¹; T = 298 K; 16702 measured reflections; 4921 independent reflections; 4921 reflections; R(all) = 0.1595; R(gt) = 0.0623; wR(ref) = 0.2021; wR(gt) = 0.1604; S(ref) = 0.995; 4921 reflections; d/ₐmax = 0.004; dqmax = 0.278 eÅ⁻³; dqmin = -0.346 eÅ⁻³.

Crystallographic data for the structure 5 have been deposited with the Cambridge Crystallographic Data Center (CCDC) under the number 1574927. 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.

3.1.5. General procedure for the synthesis of compounds 4, 5, and 6

A solution of 3 (4.63 g, 10 mmol) and thiosemicarbazide or carbothiohydrazide or cyanacetic acid hydrazide (11 mmol) in a mixture of acetic acid/ethanol (1:1) was refluxed for 6 h. The solid formed on boiling was filtered of, dried and crystallized from acetic acid to afford.

3.1.6. 2-[(3-(1-(4-(N-(dimethylamino)methylene)sulfamoyl)phenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)methylene]hydrazine-1-carbothioamide (4)

Pale yellow crystals; yield (4.60 g, 86%); m.p. 234-236 °C. IR (KBr, cm⁻¹) ν = 3427 (NH), 3329, 3253 (NH2), 1637 (C= N), 1346, 1143 (SO2); ¹H-NMR (500 MHz, d, ppm, DMSO-d₆): δ = 11.55 (s, 1H, NH), 9.29 (s, 1H, pyrazole H-5), 8.74 (s, 1H, CH=N), 8.30 (s, 2H, NH₂), 8.04 (d, 2H, J = 8.5 Hz, Ar-H), 7.91 (d, 2H, J = 8.5 Hz, Ar-H), 7.89 (s, 1H, N=CH), 7.59-7.37 (m, 5H, Ph-H), 3.17 (s, 3H, NCH₃), 2.94 (s, 3H, NCH₃) 2.68 (s, 3H, CH₃–). Anal. Calcd. For. C_{23}H_{24}N_{10}O_{2}S_{2} (536.63): C, 51.58; H, 4.51; N, 26.10%. Found: C, 51.60; H, 4.70; N, 26.20%.

3.1.7. N'-(4-(4-(4-(2-(hydrazinecarbothioyl)hydrazineylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)-1H-5-methyl-1H-1,2,3-triazol-1-yl)phenyl)sulfonyl-N,N-dimethylformimidamine (5)

Pale yellow crystals; yield (4.74 g, 86%); m.p. 202-204 °C. IR (KBr, cm⁻¹) ν = 3232-3138 (2NH, NH2), 1633 (C= N), 1338, 1147 (SO2); ¹H-NMR (500 MHz, ppm, DMSO-d₆): δ = 11.92 (s, 1H, NH), 11.77 (s, 1H, CH=N), 8.79 (s, 1H, pyrazole H-5), 8.29 (s, 1H, CH=N), 8.04 (d, 2H, J = 8.5 Hz, Ar-H), 7.90 (d, 2H, J = 8.5 Hz, Ar-H), 7.87 (s, 1H, N=CH), 7.58-7.40 (m, 5H, Ph-H), 3.17 (s, 3H, NCH₃), 2.94 (s, 3H, NCH₃) 2.69 (s, 3H, CH₃–). Anal. Calcd. For. C_{23}H_{25}N_{11}O_{2}S_{2} (551.65): C, 50.08; H, 4.57; N, 27.93%. Found: C, 50.20; H, 4.70; N, 27.80%.

3.1.8. N'-(4-(4-(4-(2-Cyanoacetyl)hydrazineylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)-1H-5-methyl-1H-1,2,3-triazol-1-yl)phenyl)sulfonyl-N,N-dimethylformimidamine (6)

Colorless crystals; yield (4.18 g, 79%); m.p. 152-154 °C. IR (KBr, cm⁻¹) ν = 3217 (NH), 2250(CN), 1697 (CO), 1627(C= N) (CO), 1344, 1149 (SO2); ¹H-NMR (500 MHz, ppm, DMSO-d₆): δ = 11.81 (s, 1H, NH), 9.10 (s, 1H, pyrazole H-5), 8.74 (s, 1H, CH=N), 8.29 (s, 1H, N=CH), 8.02 (d, 2H, J = 8.6 Hz, Ar-H), 7.89 (d, 2H, J = 8.6 Hz, Ar-H), 7.58-7.37 (m, 5H, Ph-H), 4.25 (s, 2H, CH₂), 3.17 (s, 3H, NCH₃), 2.94 (s, 3H, NCH₃) 2.69 (s, 3H, CH₃–). Anal. Calcd. For. C_{25}H_{24}N_{10}O_{3}S (530.17): C, 56.59; H, 4.56; N, 23.76%. Found: C, 56.30; H, 4.50; N, 23.60%.
3.1.9. Ethyl-2-cyano-3-[3-(1-(4-(N-(-dimethylamino)methylene)sulfamoyl)phenyl)-5-methyl-1H,1,2,3-triazole-4-yl] acrylate (7)

A solution of 3 (10 mmol), ethyl cyanoacetate (1.13 mL, 10 mmol) in the presence of three drops of triethylamine in absolute ethanol (20 mL) was refluxed for 5 h. The solution was cooled and poured onto crushed ice. The resulting solid was filtered, dried, and recrystallized from ethanol to yield 7. Yellow crystals; yield (5.02 g, 90%); m.p. 230-231 °C; IR (KBr, cm⁻¹) ν = 2220 (CN), 1703 (COOEt), 1336, 1151 (SO₂); 1H-NMR (500 MHz, d, pmm, DMSO-d₆): δ = 9.21 (s, 1H, pyrazole H-5), 8.17 (s, 1H, N-CH), 8.00 (s, 1H, CH=C), 7.89 (d, 2H, J = 8.6 Hz, Ar-H), 7.86 (d, 2H, J = 8.6 Hz, Ar-H), 7.56-7.45 (m, 5H, Ph–), 4.29 (q, 2H, J = 7.6 Hz, CH₂, ester), 3.13 (s, 3H, NCH₃), 2.92 (s, 3H, NCH₃) 2.66(s, 3H, CH₃–), 1.27 (t, 3H, J = 7.65 Hz, CH₃–). MS, m/z (%): 558 [M⁺] (100). Anal. Calcd. For. C₂₇H₂₆N₈O₄S (558.62): C, 58.05; H, 4.69; N, 20.06%. Found: C, 58.20; H, 4.80; N, 20.10%.

3.1.10. N₀-[4-(4-(4-(4-(3-Cyano-2-oxo-6-phenyl-1,2-dihydropyridin-4-yl)-1-phenyl-1H-pyrazol-3-yl)-5-methyl-1H-1,2,3-triazol-1-yl)phenyl)sulfonyl]-N,N-dimethylformimidamide (8)

A mixture of 7 (2.79 g, 5 mmol), ammonium acetate (2.73 g, 10 mmol) a acetophenone (5 mmol) in absolute ethanol (50 mL) was refluxed for 12 h. The solid which was precipitated during heating, was filtered, washed with water, dried, and crystallized from acetic acid to afford 8 as pale yellow crystals; yield (5.03, 80%); m.p. 264–266 °C. IR (KBr, cm⁻¹) ν = 3360 (NH), 2218 (CN), 1655 (CO), 1337, 1154 (SO₂); 1H-NMR (500 MHz, d, ppm, DMSO-d₆): δ = 12.54 (brs., 1H, NH), 9.28 (s, 1H, pyrazole H-5), 8.12 (s, 1H, N-CH), 8.00 (d, 2H, J = 8.6 Hz, Ar-H), 7.90 (d, 2H, J = 8.6 Hz, Ar-H), 7.74 (s, 1H, pyridine H-5), 7.56–7.30 (m, 10H, 2 Ph-H), 3.15 (s, 3H, NCH₃), 2.94 (s, 3H, NCH₃) 2.66(s, 3H, CH₃–). Anal. Calcd. For. C₃₃H₂₇N₉O₃S (629.70): C, 62.94; H, 4.32; N, 20.02%. Found: C, 62.80; H, 4.50; N, 20.10%.

3.1.11. General procedure for the synthesis of chalcones 9a,b

To a well stirred solution of acetophenone or 2-acetylthiophene at 0-5 °C, 3 (10 mmol) in alcoholic NaOH (5%, 25 mL) was added gradually. Stirring was continued for 10 h at r.t. the resulting precipitate was filtrated, washed with water, dried, and crystallized from acetic acid to give:

3.1.12. N,N-Dimethyl-N₀-[4-(5-methyl-4-(4-(3-oxo-3-phenylprop-1-en-1-yl)-1-phenyl-1H-pyrazol-3-yl)-1H-1,2,3-triazol-1-yl)phenyl)sulfonyl]formimidamide (9a)

Yellow crystals; yield (4.85 g, 86%); m.p. 190-191 °C. IR (KBr, cm⁻¹) ν = 1678 (CO), 1631 (C=N), 1597 (C=C), 1340, 1163 (SO₂); 1H-NMR (500 MHz, δ, ppm, DMSO-d₆): δ = 9.49 (s, 1H, pyrazole H-5), 8.60 (s, 1H, N=CH), 8.10 (d, 2H, J = 8.5 Hz, Ar-H), 7.92 (d, 2H, J = 8.5 Hz, Ar-H), 7.80 (d, 1H, J = 15.30 Hz, CH=CH), 7.70 (d, 1H, J = 15.30 Hz, CH=CH), 7.59-7.45(m, 10H, 2Ph-H), 3.13 (s, 3H, NCH₃), 2.94 (s, 3H, NCH₃) 2.67 (s, 3H, CH₃–). Anal. Calcd. For. C₃₀H₂₇N₇O₃S (565.65): C, 63.70; H, 4.81; N, 17.33%. Found: C, 63.80; H, 4.70; N, 17.50%.

3.1.13. N,N-Dimethyl-N₀-[4-(5-methyl-4-(4-(3-oxo-3-(thiophen-2-yl)prop-1-en-1-yl)-1-phenyl-1H-pyrazol-3-yl)-1H-1,2,3-triazol-1-yl)phenyl)sulfonyl]formimidamide (9b)

Yellow crystals; yield (5.57 g, 80%); m.p. 166-168 °C. IR (KBr, cm⁻¹) ν = 1643 (CO), 1631 (C=N), 1597 (C=C), 1342, 1159 (SO₂); 1H-NMR (500 MHz, δ, ppm, DMSO-d₆): δ = 9.49 (s, 1H, pyrazole H-5), 8.60 (s, 1H, CH=N), 8.48 (d, 1H, J = 16.70 Hz, CH=CH), 7.94 (d, 2H, J = 8.5 Hz, Ar-H), 7.92 (d, 2H, J = 8.5 Hz, Ar-H), 7.59-7.45(m, 9H, CH=CH, Ph-H, 3 thiophene -H)), 3.16 (s, 3H, NCH₃), 2.90 (s, 3H, NCH₃) 2.66 (s, 3H, CH₃–), MS, m/z (%): 571 [M⁺] (43). Anal. Calcd. For. C₂₉H₂₅N₇O₃S₂ (571.67): C, 58.83; H, 4.41; N, 17.15%. Found: C, 58.70; H, 4.60; N, 17.20%.
3.1.14. 4-(4′-(1′,5-Diphenyl-1′H,2H-[3,4′-bipyrazol]-3′-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzene-
sulfonamide (10)
To a solution of appropriate chalcones 9a (2.78 g, 5 mmol) in ethanol (30 mL), hydrazine hydrate
80% (12 mmol) was added. The reaction mixture was refluxed for 6 h. Left to cool to room tem-
perature. The formed solid product was filtered, dried, and recrystallized from EtOH to afford
10 as colorless crystals; yield (4.28 g, 82%); m.p. 180-182°C. IR (KBr, cm⁻¹) ν = 3218 (NH), 1631
(C=O), 1597 (C=C), 1340, 1163 (SO₂); ¹H NMR (500 MHz, δ, ppm, DMSO-d₆): δ = 11.21 (s, 1H, NH),
9.49 (s, 1H, pyrazole H-5), 8.60 (s, 1H, CH=N), 8.20 (s, 1H, pyrazole- H), 7.94 (d, 2H, J = 8.5 Hz, Ar-H),
7.92 (d, 2H, J = 8.5 Hz, Ar-H), 7.59-7.45 (m, 10H, 2Ph-H), 3.19 (s, 3H, NCH₃), 2.92 (s, 3H, NCH₃),
2.65 (s, 3H, CH₃). Anal. Calcd. For. C₂₇H₂₂N₈O₂S (522.16): C, 62.06; H, 4.24; N, 21.44%. Found: C,
62.20; H, 4.80; N, 21.70%.

3.1.15. General procedure for the synthesis of compounds 11a, 12a, and 12b
To a stirred cold solution of compound 1a or 1b (10 mmol) in acetic acid, a bromine (15 mmol) is add
drop wisely within 1 h and the stirring is continued at room temperature for another 4 h. The reaction mixture was heated at 80°C for another 6 h. The solid which was formed on heating
filtered off, washed with ethanol (10 mL), dried, and crystalized from acetic acid to give:

3.1.16. 4-[4-(2-Bromoacetyl)-5-methyl-1H-1,2,3-triazol-1-yl] benzene sulfonamide (11a)
Colorless crystals; m.p. 230-232°C. IR (KBr, cm⁻¹) ν = 3340, 3194 (NH₂), 1681 (C=O), 1330,
1161 (SO₂). ¹H-NMR (500 MHz, δ, ppm, DMSO-d₆): δ = 8.01 (d, 2H, J = 8.6 Hz, Ar-H), 7.90 (d, 2H,
J = 8.6 Hz, Ar-H), 7.57 (s, 2H, NH₂), 4.66 (s, 2H, CH₂), 2.62 (s, 3H, CH₃). Anal. Calcd for
C₁₁H₁₁BrN₄O₃S (359.20): C, 36.78; H, 3.09; N, 15.60%. Found C, 36.90; H, 3.20; N, 15.70%.

3.1.17. 4-[4-(2,2-Dibromoacetyl)-5-methyl-1H-1,2,3-triazol-1-yl] benzene sulfonamide (12a)
Colorless crystals; yield (3.94 g, 90%); m.p. 222-224°C. IR (KBr, cm⁻¹) ν = 3226, 3103 (NH₂),
1705 (C=O), 1338, 1163 (SO₂). ¹H-NMR (500 MHz, δ, ppm, DMSO-d₆): δ = 8.0 (d, 2H, J = 8.5 Hz, Ar–H),
7.92 (d, 2H, J = 8.5 Hz, Ar–H), 7.62 (s, 2H, NH₂), 4.66 (s, 2H, CH₂), 2.62 (s, 3H, CH₃). ¹⁳C NMR (125 MHz,
δ, ppm, DMSO-d₆) δc 10.09 (CH₃), 41.86 (CH), 126.32, 127.26, 137.02 (CH triazole), 137.42
(CH triazole), 141.58, 145.56, 181.32 (C=O). Anal. Calcd for
C₁₁H₁₀Br₂N₄O₃S (438.09): C, 30.16; H, 2.30; N, 12.79%. Found C, 30.10; H, 2.40; N, 12.90%.

3.1.18. N-[[4-[4-(2,2-Dibromoacetyl)-5-methyl-1H-1,2,3-triazol-1-yl] phenyl] sulfonyl]-N, N-dime-
thylformimidamide (12b)
Colorless crystals; yield (4.50 g, 92%); m.p. 214-216°C. IR (KBr, cm⁻¹) ν = 2991 (CH), 1699(C=O), 1338, 1151 (SO₂). ¹H-NMR (500 MHz, δ, ppm, DMSO-d₆): δ = 8.28 (s, 1H, CH= N),
8.02(d, 2H, J = 8.6 Hz, Ar–H), 7.86 (d, 2H, J = 8.6 Hz, Ar–H), 7.57 (s, 1H, CH), 3.16(s, 3H,
NCH₃), 2.93(s, 3H, NCH₃), 2.62 (s, 3H, CH₃). ¹³C NMR (125 MHz, δ, ppm, DMSO-d₆) δc 10.05
(CH₃), 35.20 (NCH₃), 41.04 (CH), 126.06, 127.50, 136.92 (=CH triazole), 137.42 (=CH triazole),
141.59, 144.60, 150.16 (N=C),181.31 (C=O). MS, m/z (%): 493 [M+H]+(56), 445 [M+H+1(CH₃)]
(4). Anal. Calcd for C₁₄H₁₅Br₂N₅O₃S (493.17): C, 34.10; H, 3.07; N, 14.20%. Found C, 34.20; H,
3.20; N, 14.30%.

3.1.19. General procedure for the synthesis of compounds 13a-d
A solution of 12a or 12b (10 mmol), and thioura or N-phenylthiourea in a mixture of acetic acid/
ethanol (50 mL, 1:1) was refluxed for 10 h. The solid formed on boiling was filtered of, dried and
crystallized from acetone to afford:
3.1.20. 4-[2-Aminothiazol-5-yl]-5-methyl-1H-1,2,3-triazol-1-yl] benzene sulfonamide (13a)
Pale yellow crystals; yield (2.79 g, 83%); m.p. 268-270°C. IR (KBr, cm\(^{-1}\)) \(\nu = 3329, 3228, 2889\) (CH), 1624 (C=N), 1334, 1155 (SO\(_2\)). \(^1\)H-NMR (500 MHz, \(\delta\), ppm, DMSO-d\(_6\)): \(\delta = 8.66\) (brs, 2H, NH\(_2\)), 8.07 (d, 2H, \(J = 8.5\) Hz, Ar–H), 7.90 (d, 2H, \(J = 8.5\) Hz, Ar–H), 7.88 (s, 2H, NH\(_2\)), 7.16 (s, 1H, thiazole- H4), 2.52 (s, 3H, CH\(_3\)). \(^1\)C NMR (125 MHz, ppm, DMSO-d\(_6\)): \(\delta = 9.99\) (CH\(_3\)), 103.89 (thiazole C5), 125.82 (2 C), 127.31 (2 C), 130.11, 133.07 (pyrazole C4), 135.47, 137.62 (thiazole C4), 145.20 (pyrazole C5), 169.99 (thiazole C2). MS, \(m/z\) (%): 336 [M\(^+\)] (22).
Anal. Calcd for C\(_{12}\)H\(_{12}\)N\(_6\)O\(_2\)S (336.39): C, 42.85; H, 3.60; N, 24.98%. Found C, 42.70; H, 3.50; N, 24.90%.

3.1.21. N’-((4-(2-Aminothiazol-5-yl)-5-methyl-1H-1,2,3-triazol-1-yl)phenyl)sulfonyl)-N,N-dimethylformimidamide (13 b)
Yellow crystals; yield (3.20 g, 82%); m.p. 234-236°C. IR (KBr, cm\(^{-1}\)) \(\nu = 3354, 3263\) (NH\(_2\)), 2999 (CH), 1635 (C=N), 1340, 1143 (SO\(_2\)). \(^1\)H-NMR (500 MHz, \(\delta\), ppm, DMSO-d\(_6\)): \(\delta = 8.66\) (brs, 2H, NH\(_2\)), 8.28 (s, 1H, CH=N), 8.01 (d, 2H, \(J = 8.5\) Hz, Ar–H), 7.82 (d, 2H, \(J = 8.5\) Hz, Ar–H), 7.14 (s, 1H, thiazole- H4), 3.16 (s, 3H, NCH\(_3\)), 2.93 (s, 3H, NCH\(_3\)), 2.52 (s, 3H, CH\(_3\)). \(^1\)C NMR (125 MHz, ppm, DMSO-d\(_6\)): \(\delta = 9.9\) (CH\(_3\)), 35.22 (NCH\(_3\)), 41.08 (NCH\(_3\)), 103.9 (thiazole C5), 125.51 (2 C), 127.55 (2 C), 130.1, 132.88 (pyrazole C4), 135.85, 137.61 (thiazole C5), 160.12 (N=CH), 169.90 (thiazole C2). Anal. Calcd for C\(_{15}\)H\(_{17}\)N\(_7\)O\(_2\)S\(_2\) (391.47): C, 46.02; H, 4.38; N, 25.05%. Found C, 46.10; H, 4.20; N, 25.20%.

3.1.22. 4-[5-Methyl-4-(2-(phenylamino) thiazol-5-yl)- 1H-1,2,3-triazol-1-yl] benzene sulfonamide (13c)
Yellow crystals; yield (3.50 g, 85%); m.p. 254-256°C. IR (KBr, cm\(^{-1}\)) \(\nu = 3329, 3242\) (NH\(_2\)), 3147 (NH), 1618 (C=N), 1338, 1166 (SO\(_2\)). \(^1\)H-NMR (500 MHz, \(\delta\), ppm, DMSO-d\(_6\)): \(\delta = 10.51\) (s, 1H, NH), 8.07 (d, 2H, \(J = 8.5\) Hz, Ar–H), 7.93 (d, 2H, \(J = 8.5\) Hz, Ar–H), 7.65 (m, 3H, Ph-H), 7.29 (s, 1H, thiazole- H4), 3.16 (s, 3H, NCH\(_3\)), 2.93 (s, 3H, NCH\(_3\)), 2.52 (s, 3H, CH\(_3\)). \(^1\)C NMR (125 MHz, ppm, DMSO-d\(_6\)): \(\delta = 10.07\) (CH\(_3\)), 104.18 (thiazole C5), 35.22 (NCH\(_3\)), 41.08 (NCH\(_3\)), 103.9 (thiazole C5), 125.51 (2 C), 127.55 (2 C), 130.1, 132.88 (pyrazole C4), 135.85, 137.61 (thiazole C4), 160.12 (N=CH), 169.90 (thiazole C2). Anal. Calcd for C\(_{18}\)H\(_{16}\)N\(_6\)O\(_2\)S\(_2\) (412.49): C, 52.60; H, 4.38; N, 25.05%. Found C, 52.60; H, 4.20; N, 25.20%.

3.1.23. N,N- Dimethyl amino-N’-((4-(5-methyl-4-(2-(phenylamino)thiazol-5-yl)- 1H-1,2,3-triazol-1-yl)phenyl)sulfonyl)-N,N-dimethylformimidamide (13 d)
Pale yellow crystals; yield (3.64 g, 78%); m.p. 265-267°C. IR (KBr, cm\(^{-1}\)) \(\nu = 3263\) (NH), 1635 (C=N), 1340, 1143 (SO\(_2\)). \(^1\)H-NMR (500 MHz, \(\delta\), ppm, DMSO-d\(_6\)): \(\delta = 10.36\) (s, 1H, NH), 8.28 (s, 1H, CH=N), 8.01 (d, 2H, \(J = 8.5\) Hz, Ar–H), 7.84 (d, 2H, \(J = 8.5\) Hz, Ar–H), 7.67 (s, 1H, thiazole- H4), 7.28-6.93 (m, 5H, Ph-H), 3.16 (s, 3H, NCH\(_3\)), 2.93 (s, 3H, NCH\(_3\)), 2.69 (s, 3H, CH\(_3\)). \(^1\)C NMR (125 MHz, \(\delta\), ppm, DMSO-d\(_6\)): \(\delta = 10.06\) (CH\(_3\)), 35.2 (NCH\(_3\)), 41.2 (NCH\(_3\)), 104.15 (thiazole C5), 117.0, 125.56 (2 C), 125.66 (2 C), 127.45 (2 C), 128.99 (2 C), 129.07 (2 C), 139.82, 140.47, 141.06 (pyrazole C5), 142.23, 160.15 (N=CH), 162.55 (thiazole C2), 163.8. Anal. Calcd for C\(_{21}\)H\(_{21}\)N\(_7\)O\(_2\)S\(_2\) (467.57): C, 53.95; H, 4.53; N, 20.97%. Found C, 53.80; H, 4.70; N, 20.80%.
3.2. Molecular docking studies

3.2.1. 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 force field; then partial charges are calculated by Momany Rone method. Furthermore, 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:

\[ E = E_b + E_q + E_f + E_{vdw} + E_{el} + E_{hb} + E_{cr} + E_{cj} \]

where, \( E \) = total energy, \( E_b \) = bond potential energy, \( E_q \) and \( E_f \) = bond angle potential energy, \( E_{vdw} \) = 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.

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 non-bonded interactions which involve van der Waals (vdW) and electrostatics are softened at different levels, except during the final minimization step. Initially, 10 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.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

Authors participated in the idea of this research and they carried out the synthesis, purification and characterization of all compounds by the different spectroscopic techniques. All authors have read and approved the final version submitted.

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