Molecular Diversity
https://doi.org/10.1007/s11030-020-10093-3

ORIGINAL ARTICLE

Design and synthesis of novel (*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl) methylene)-3-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl) thiazolidine-2,4-diones: a potential cytotoxic scaffolds and their molecular modeling studies

N. J. P. Subhashini[1] · Kolluri Prashanth Kumar[1] · Edigi Praveen Kumar[1] · Putta Shravani[2] · Surya Sathyanarayana Singh[2] · Tamalapakula Vani[3] · Manga Vijjulatha[3]

Received: 7 February 2020 / Accepted: 21 April 2020

Abstract

In an effort to discover potential cytotoxic agents, a series of novel (*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione derivatives (**8a**–**n**) were designed and synthesized in various steps with acceptable reaction procedures with quantitative yields and characterized by ^{1}H NMR, ^{13}C NMR, IR, HRMS and ESI–MS spectra. These newly synthesized novel derivatives were screened for their in vitro cell viability/cytotoxic studies against human breast cancer cell line (MCF-7) with various concentrations of 0.625 µM, 1.25 µM, 2.5 µM, 5 µM and 10 µM, respectively. The biological interpretation assay outcome was demonstrated in terms of cell viability percentage reduction and IC_{50} values against standard reference drug cisplatin. Based on these results, most of the derivatives exhibited promising cytotoxic activity. Among them, particularly compounds **8j** (R_1 = OMe and R_3 = NO_2) and **8e** (R_3 = CF_3) demonstrate remarkable cytotoxic activity with IC_{50} values **0.426 µM ± 0.455** and **0.608 µM ± 0.408**, which are even better than the standard drug cisplatin **0.636 µM ± 0.458** and compounds **8m** (R_2 = OMe and R_3 = OMe) and **8c** (R_3 = OMe) exhibited closely equivalent IC_{50} values to the standard drug with IC_{50} values **0.95 µM ± 0.32** and **0.976 µM ± 0.313** and rest of the compounds exhibits moderate cytotoxic activity. Moreover, molecular modeling studies and ADME calculations of the novel synthesized derivatives are in adequate consent with the pharmacological screening results.

Keywords Pyrazole · 2,4-Thiazolidinedione (TZD) · 1,2,3-Triazoles · Cytotoxic activity · Molecular modeling studies

Introduction

Cancer is a lethal disease. The term cancer encompasses more than 100 diseases affecting almost every part of the body, and all are presumably life-threatening. Cancer is a disease in which incongruous cell proliferation and expansion of anomalous cells beyond their conventional outer limits that can impinge on contiguous parts of the body and destroy body tissue affect other organs. The global cancer burden is evaluated to have risen to 18.1 million new cases and 9.6 million deaths in 2018 [1]. Breast cancer is most frequently diagnosed cancer in women (24%, i.e., about one in four of all new cancer cases diagnosed in women worldwide are breast cancer), and it is the most common cancer and also the leading cause of cancer death in women followed by lung cancer and colorectal cancer, approximately 2.1 million diagnoses are estimated in

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11030-020-10093-3) contains supplementary material, which is available to authorized users.

✉ N. J. P. Subhashini
njsubhashini@yahoo.co.in

[1] Department of Chemistry, University College of Science, Osmania University, Hyderabad, Telangana 500007, India

[2] Department of Biochemistry, University College of Science, Osmania University, Hyderabad, Telangana 500 007, India

[3] Molecular Modeling and Medicinal Chemistry Laboratory, Department of Chemistry, University College of Science, Osmania University, Hyderabad, Telangana 500 007, India

Published online: 02 May 2020

2018 [2]. Although the causes of cancer are not completely understood, there was significant progress to decrease cancer percentage in the world. The present cancer therapies, face various limitations and current cancer medicine are not always persuasive, efficient and may often engender hostile effects. Therefore, there is a necessity for the exploration and development of new anticancer drugs with enormous efficiency and low in adverse effects is a major and significant need of research across the world [3–5].

Nitrogen consisting of heterocyclic moieties has always played an extensive role in modern medicinal and agrochemical fields because of their outstanding biological properties which have emanated in various applications. Among them, pyrazole embedded pharmacophores are prominent structural fragments and the essential backbone of various synthetic and natural existing pharmacological active moieties. In recent years, exploration on condensed pyrazole-4-carbaldehyde compounds has gained considerable scientific significance and proven advantageous for cancer treatment. Many pyrazole-containing molecules are in the advancement phase as promising new drugs acting against distinct biological targets. Derivatives of pyrazole compounds have been described for excellent drug-like properties and exhibit a wide range of biological activities which comprise antimalarial [6], antimycobacterial [7], antiviral [8], antitubercular [9], antioxidant [10], anticancer [11, 12], antileishmanial [13] and anti-inflammatory activities [14].

On the other hand, thiazolidinediones are generally called as glitazones after the prototypical medicine ciglitazone used in the treatment of type-2 diabetes that were introduced in the late 1990s and the thiazolidinediones are a broad class of heterocyclic pharmacophores with many extensive pharmacological properties [15]. Among them, 2,4-thiazolidinedione (TZD) was essential and privileged moiety consists of a five-membered C_3NS ring with two carbonyl groups at second and fourth positions, sulfur at the first position, and variable substitution reactions take place on third and fifth positions and possess low molecular weight. Various heterocyclic compounds embedded TZD scaffold were exhibited significant biological activities, and it is bearing a number of clinically used medicines which include rosiglitazone, lobeglitazone, pioglitazone, englitazone, netoglitazone and revoglitazone and a fewer TZD containing drugs; in particular, ciglitazone and troglitazone have shown cytotoxic activity. In recent years, experimental investigation on TZD moiety was attracted extensive scientific attention due to their adaptable, diverse and flexible nature and has shown a wide range of biological activities, which include antiviral [16], antimicrobial [17], anticancer [18, 19], aldose reductase inhibitors [20], antihyperglycemic [21], cytotoxic [22], antioxidant [23], anti-inflammatory [24], antidiabetic [25] and peptide deformylase inhibitors [26].

Moreover, triazoles are an essential heterocyclic structural moieties that are associated with numerous pharmacological activities and privileged motifs in medicinal and agrochemical fields. Among them, 1,2,3-triazole motif is a unique structure and this compound is an impressive option to use it is a fundamental component in the drug design of new molecules because they are exceedingly stable under any conditions (acidic/basic) and exhibit high dipole moment and they have capable of forming hydrogen bonds with various biological targets [27]. 1,2,3-Triazoles have been the subject of considerable research because of their involvement in the regulation of distinctive biological processes, and it is embedded in a number of clinically used medicines such as tazobactam, carboxyamidotriazole, cefatrizine, etc., and exhibit broad-spectrum of pharmacological activities which include antioxidant [28], antitubercular [29], antibacterial [30], antiviral [31], anticancer [32], antimicrobial [33] and anti-inflammatory [34] activities. Some of the proclaimed natural and synthetically developed cytotoxic compounds bearing 2,4-thiazolidinedione, 1,2,3-triazole and pyrazole pharmacophores are displayed in Fig. 1.

Pharmacophore hybridization is a powerful tool to design and development of potentially high active new chemical compounds by covalently incorporating two and more biological active compounds into a novel scaffold. In the view of the above exploration and pharmacological significance of these pharmacophores (pyrazole, 2,4-thiazolidinedione and 1,2,3-triazole), we have made in an attempt to design, develop and synthesize of excellent tumor growth inhibitors with potent cytotoxic activity, high ability and less toxic drugs for the treatment of cancer and designed prototype scaffold based on cytotoxic active compounds which are demonstrated in Fig. 2. Based on these investigations and our ongoing significance on these moieties in the exploration of new pharmacophores with potent cytotoxic activity, we developed and synthesized a series of novel (*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione analogues (**8a**–**n**) and these derivatives were screened for their cell viability/cytotoxic activity against human breast cancer cell line (MCF-7).

Results and discussion

Chemistry

The synthetic approach of desired compounds (*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (**8a**–**n**) was accomplished as demonstrated in Scheme 1. The vital intermediate pharmacophore (*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-(prop-2-yn-1-yl)

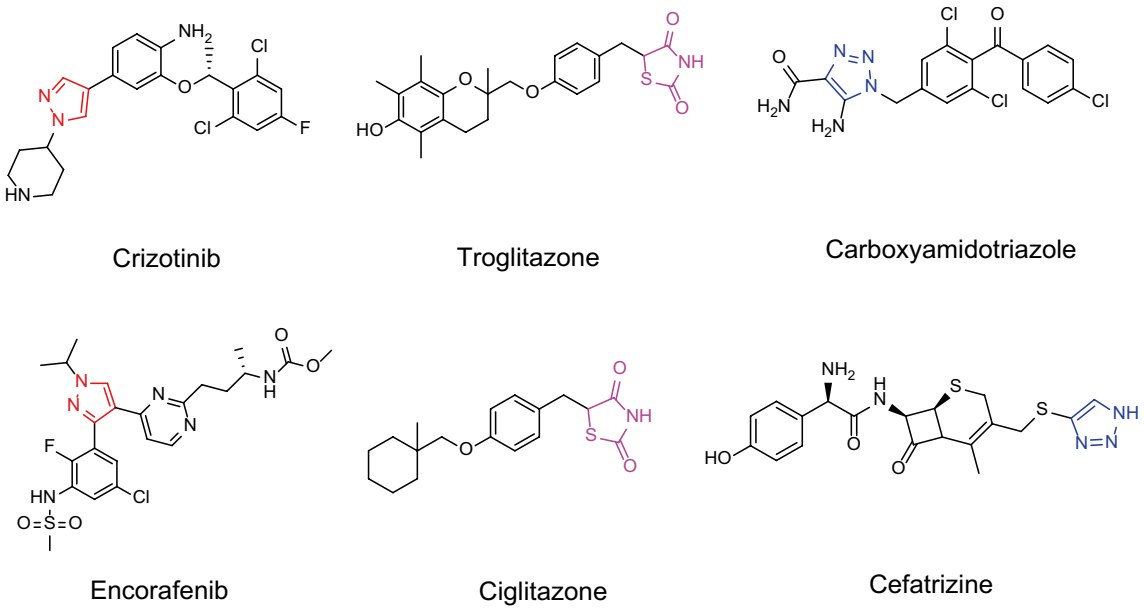


Fig. 1 Pyrazole, 2,4-thiazolidinedione and 1,2,3-triazole based inhibitors reported as cytotoxic agents

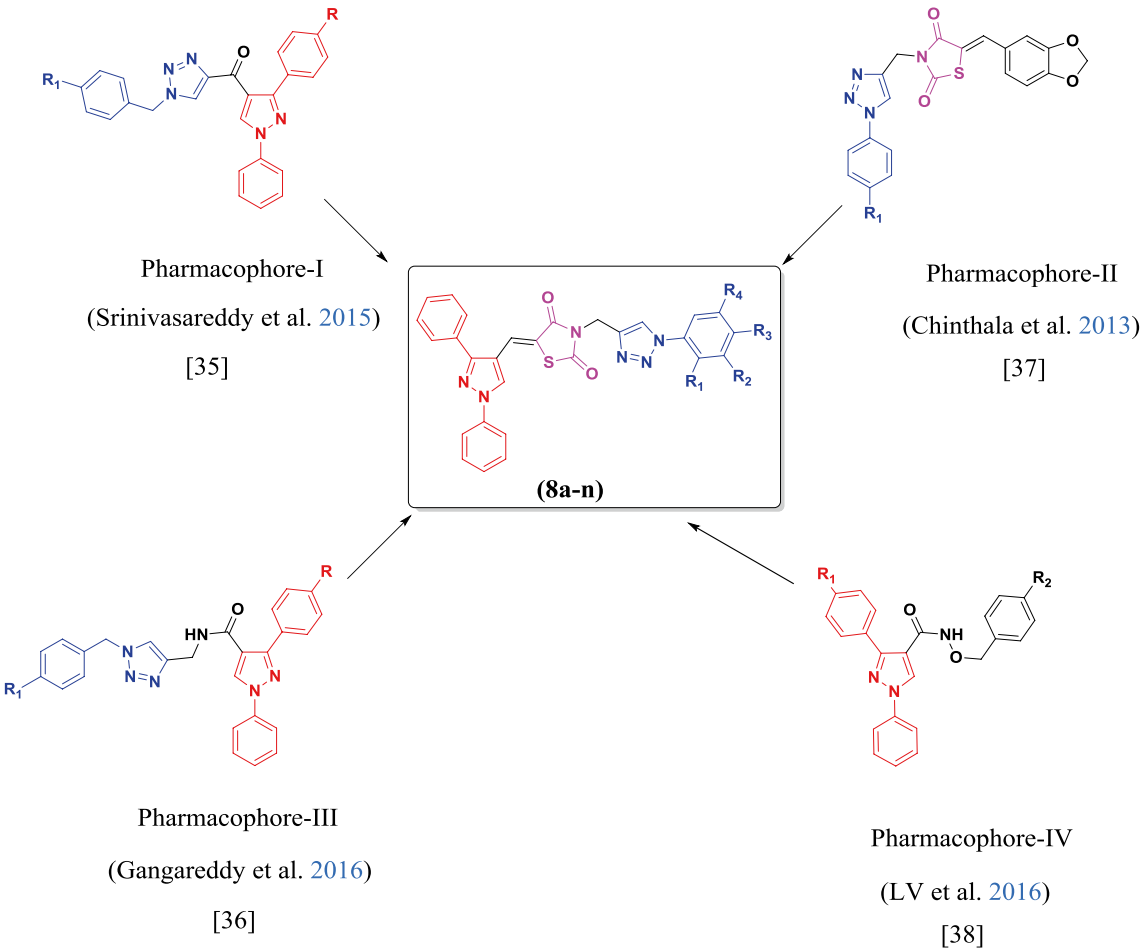
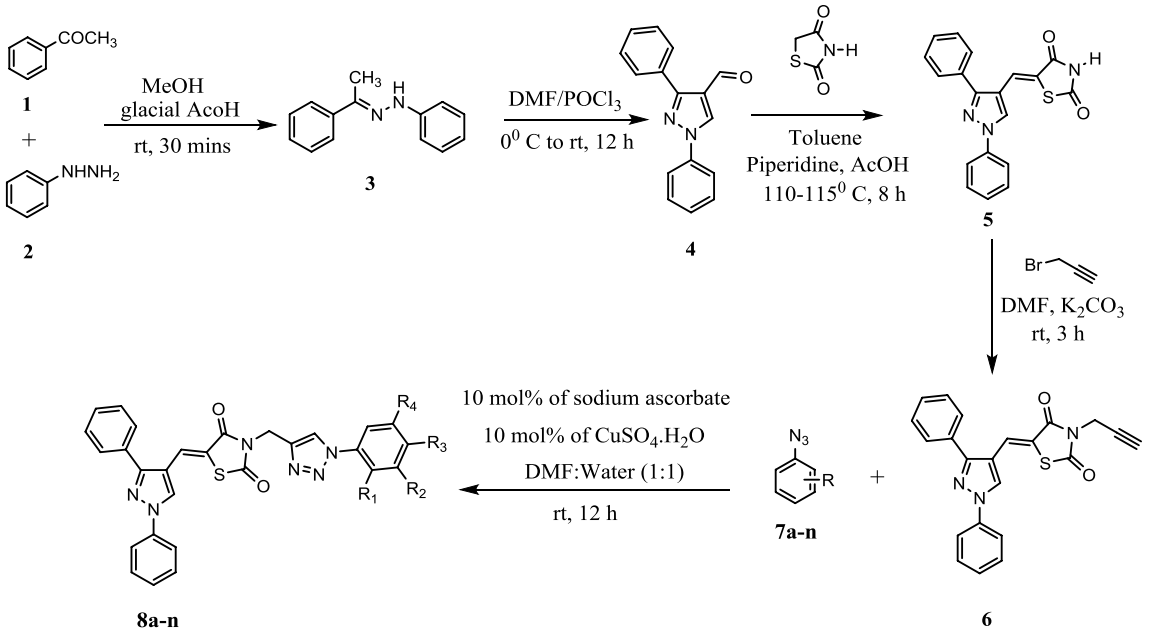


Fig. 2 Designed prototype scaffold based on cytotoxic active pharmacophores



Scheme 1 Synthesis of novel (*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione analogues (**8a–n**)

thiazolidine-2,4-dione (**6**) was synthesized in four steps. First, we have synthesized 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde, as reported by previously published literature, concisely, condensation reaction of acetophenone (**1**) and phenyl hydrazine (**2**) gives corresponding phenyl hydrazone (**3**). Subsequently, these compounds (**3**) underwent Vilsmeier–Haack cyclization reaction using DMF/$POCl_3$ as a solvent/reagent to produce corresponding compound (**4**) [39]. In the third step, the desired compound (**5**) was achieved from 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde with 2,4-thiazolidinedione involving Knoevenagel condensation using a few drops of glacial acetic acid and a catalytic amount of piperidine in toluene yielded required compound (**5**) [40] that upon treating with propargyl bromide in the presence of DMF using K_2CO_3 as a base to afford intermediate (**6**). Finally, the desired final derivatives were acquired by employing click reaction of compound (**6**) with various substituted phenyl azides (**7a–n**) in DMF by using 10 mol% of sodium ascorbate and 10 mol% copper sulfate provided final derivatives (**8a–n**) in reasonable to significant yields and entire physical data of final derivatives are depicted in Table 1.

All these newly synthesized moieties (**8a–n**) were confirmed by ^{1}H NMR, ^{13}C NMR, IR, HRMS and ESI–MS spectra. In ^{1}H NMR, the characteristic pyrazole proton was appeared as a singlet at 8.42–8.16 ppm region, the triazole proton was appeared at 8.04–7.98 ppm as a singlet and characteristic arylidene proton was appeared in preferably either as singlet or multiplet at deshielded region of 7.96–7.81 ppm as expected from *Z*-form, comparatively to the shielded proton of *E*-from (6.22–6.46 ppm) thus proving that all the synthesized derivatives were obtained exclusively in *Z*-form and *Z*-isomer was thermodynamically more stable due to intramolecular hydrogen bond that can be formed between the hydrogen bond of arylidene proton and oxygen atom of carbonyl group in 2,4-thiazolidinedione [41–43] and the nitrogen attached methylene protons (N–CH_2) was appeared as a singlet at 5.07–5.15 ppm. In ^{13}C NMR spectra, the two carbonyl carbons of 2,4-thiazolidine ring were appeared at 165.2–164.2 ppm and 166.6–165.3 ppm region. The nitrogen attached methylene carbon (N–CH_2) was appeared at 37.3–36.3 ppm, and remaining all protons and carbons were resonating at expected region. Additionally, it is also confirmed by HRMS and ESI–MS spectra of the analogues.

Cell viability assay/cytotoxic activity

All these newly synthesized (*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (**8a–n**) analogues were screened for their in vitro cell viability/cytotoxic activity against MCF-7 cell line (Source: National Centre for Cell Science-Pune). The standard MTT assay was employed for cytotoxic activity, and the standard drug used was cisplatin [44, 45]. Cell viability analysis of final derivatives was conducted with MCF-7 cell line at five distinct concentrations of 0.625; 1.25; 2.5; 5; and 10 µM, respectively, and final cell viability assay summary is demonstrated in Table 2 and

Table 1 Physical data of final derivatives (**8a–n**)

S. no.	R_1	R_2	R_3	R_4	M.F (M.Wt)	M.P (°C)	Time (h)	Yield (%)
8a	H	H	F	H	$C_{28}H_{19}FN_6O_2S$ (522.1)	208–210	12	68
8b	H	H	Br	H	$C_{28}H_{19}BrN_6O_2S$ (582.1)	240–242	12	71
8c	H	H	OCH_3	H	$C_{29}H_{22}N_6O_3S$ (534.2)	244–246	12	73
8d	H	H	$COCH_3$	H	$C_{30}H_{22}N_6O_3S$ (546.2)	252–254	12	65
8e	H	H	CF_3	H	$C_{29}H_{19}F_3N_6O_2S$ (572.2)	212–214	12	63
8f	H	H	NO_2	H	$C_{28}H_{19}N_7O_4S$ (549.2)	228–230	12	62
8g	H	OH	H	H	$C_{28}H_{20}N_6O_3S$ (520.2)	232–234	12	66
8h	H	H	Cl	H	$C_{28}H_{19}ClN_6O_2S$ (538.2)	238–240	12	72
8i	H	Cl	H	H	$C_{28}H_{19}ClN_6O_2S$ (538.2)	248–250	12	74
8j	OCH_3	H	NO_2	H	$C_{29}H_{21}N_7O_5S$ (579.2)	218–220	12	61
8k	H	H	H	H	$C_{28}H_{20}N_6O_2S$ (504.2)	242–244	12	75
8l	H	H	I	H	$C_{28}H_{19}IN_6O_2S$ (630.1)	220–222	12	69
8m	H	OCH_3	OCH_3	H	$C_{30}H_{24}N_6O_4S$ (564.2)	210–212	12	61
8n	H	H	CH_3	H	$C_{29}H_{22}N_6O_2S$ (518.1)	256–258	12	70

M.F, molecular formula; M.Wt, molecular weight; M.P (°C), melting points in degrees centigrade
Isolated yield

Table 2 Cell viability evaluation of novel synthesized derivatives (**8a–n**)

S. no.	Compound	Concentrations				
		0.625 µM	1.25 µM	2.5 µM	5 µM	10 µM
1	**8a**	33% ± 4.866	45.25% ± 0.64	38.09% ± 2.58	35.43% ± 3.77	32.18% ± 5.23
2	**8b**	235.01% ± 3.4	24.66% ± 1.22	25.81% ± 0.76	31.89% ± 2.02	19.62% ± 3.47
3	**8c**	33.67% ± 2.33	39.96% ± 5.17	30.46% ± 0.93	19.01% ± 4.19	18.82% ± 4.27
4	**8d**	51.93% ± 0.527	48.09% ± 2.24	47.95% ± 2.3	51.14% ± 0.877	66.45% ± 5.96
5	**8e**	38.67% ± 2.3	32.9% ± 4.88	42.58% ± 0.59	58.2% ± 6.42	46.84% ± 1.36
6	**8f**	45.61% ± 3.58	31.57% ± 2.69	28.4% ± 4.1	45.18% ± 3.39	37.23% ± 0.16
7	**8g**	26.15% ± 3.134	33.07% ± 1.38	36.13% ± 1.32	34.88% ± 0.79	35.6% ± 1.09
8	**8h**	46.85% ± 2.88	34.51% ± 2.63	43.82% ± 1.59	35.42% ± 2.22	41.42% ± 0.46
9	**8i**	21.79% ± 2.18	22.92% ± 1.66	34.53% ± 3.51	31.59% ± 2.2	22.56% ± 2.28
10	**8j**	47.26% ± 5.48	39.2% ± 1.878	25.95% ± 4.04	45.19% ± 4.55	38.43% ± 1.53
11	**8k**	44.41% ± 2.56	40.46% ± 0.85	34.47% ± 1.88	42.96% ± 1.91	31.05% ± 3.40
12	**8l**	40.31% ± 2.46	37.85% ± 1.37	31.98% ± 1.25	24.87% ± 4.43	38.9% ± 1.84
13	**8m**	45.33% ± 3.25	40.88% ± 1.26	47.05% ± 4.04	34.54% ± 1.56	22.46% ± 6.97
14	**8n**	23.54% ± 2.64	26.2% ± 1.45	26.71% ± 1.22	32.52% ± 1.36	38.37% ± 3.98
15	Cisplatin	51.45% ± 7.56	40.27% ± 2.56	34.30% ± 0.1	28.17% ± 2.85	18.53% ± 7.16

Fig. 3. The cell viability percentage was calculated by using the following formula:

Cell viability percentage

= Absorbance of treated cells/

Absorbance of untreated cells × 100

The percentage of cell viability of synthesized derivatives (**8a**–**n**) subjected to the MCF-7 cell line was evaluated, and from Table 2, a standard clustered column graph was plotted between the concentration of synthesized compounds on *x*-axis and percentage of cell viability was subjected to compounds on *y*-axis. A series of response data for concentrations and growth inhibition percentages were needed for switching to Table 3. The *x*–*y* graph was plotted for determination of IC_{50} values. From formula $y = ax + b$, the plot *x*–*y* with a linear regression was studied. Then, IC_{50} values of synthesized derivatives were evaluated employing formula $IC_{50} = 0.5 - b/a$, which are depicted in Table 3. The standard deviation for Table 2 was calculated from values of percentage of cell viability of every sample of various concentrations and for Table 3 was calculated from IC_{50} values.

A close investigation of results from Table 3 and Fig. 4 clearly illustrated that all the synthesized derivatives exhibited in vitro cytotoxic efficiency with IC_{50} values ranging

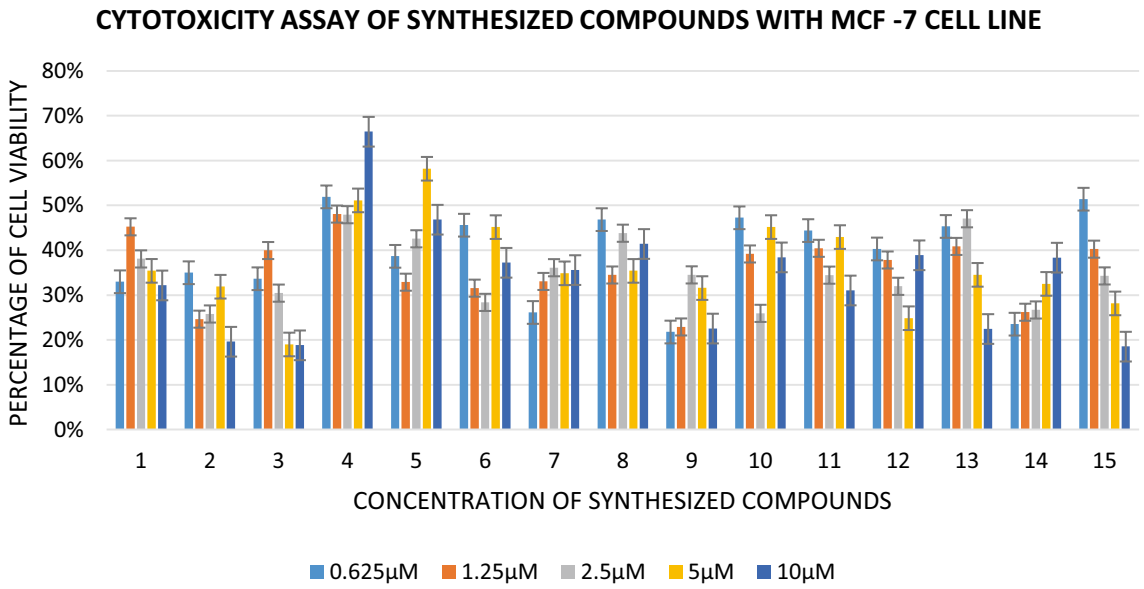


Fig. 3 Cell viability evaluation of novel synthesized derivatives (**8a–n**) measured by MTT assay

Table 3 Cytotoxic assay of novel synthesized derivatives (**8a–n**) in terms of [a]IC_{50} values

S. no.		IC_{50} values (μM) MCF-7
1	**8a**	2.056 μM ± 0.034
2	**8b**	2.284 μM ± 0.0212
3	**8c**	0.976 μM ± 0.313
4	**8d**	1.54 μM ± 0.167
5	**8e**	0.608 μM ± 0.408
6	**8f**	1.589 μM ± 0.157
7	**8g**	2.38 μM ± 0.049
8	**8h**	4.943 μM ± 0.71
9	**8i**	4.827 μM ± 0.68
10	**8j**	0.426 μM ± 0.455
11	**8k**	2.043 μM ± 0.037
12	**8l**	3.126 μM ± 0.241
13	**8m**	0.95 μM ± 0.32
14	**8n**	1.366 μM ± 0.212
15	Cisplatin[b]	0.636 μM ± 0.458

[a]IC_{50} values are the concentration that cause 50% inhibition of cancer cell growth. Data represent as mean values ± standard deviation and are displayed in micromolar concentrations (μM)

[b]Positive control

from 0.426 to 4.943 μM, respectively; among them, most of the derivatives have shown excellent cytotoxic activity compared to that of standard reference drug and some of the derivatives exhibited reasonable activity. Based on these conclusions, some of the representative analogues exceptionally derivatives **8j** and **8e** exhibited greater capability compared to that of standard reference drug and derivatives **8m** and **8c** exhibited approximately comparable IC_{50} values compared to standard reference drug and derivatives **8n**, **8d** and **8f** showed promising activity and the remaining derivatives have shown reasonable cytotoxic activity.

The structure activity relationship (SAR) of these (*Z*)-5-((1, 3-diphenyl-1*H*-pyrazol-4-yl) methylene)-3-((1-phenyl-1*H*-1, 2, 3-triazol-4-yl) methyl) thiazolidine-2, 4-dione derivatives (**8a–n**) was explored. These synthesized derivatives consist of pyrazole moiety embedded two phenyl rings and one triazole phenyl ring system, all the synthesized compounds have a same pyrazole system, and SAR of these final derivatives was examined by differing the substitutions attached to the triazole phenyl ring; we have synthesized various final derivatives by placing an electron-withdrawing and electron-donating groups. The SAR study reveals that the derivatives embedded electron-donating and electron-withdrawing groups (R_1 = OMe and $R_3 = NO_2$; **8j**) and electron-withdrawing group ($R_3 = CF_3$; **8e**) exhibited more potential cytotoxic activity compared to standard with IC_{50} values **0.426 μM ± 0.455** and **0.608 μM ± 0.408.** When cell viability percentage is observed in Table 2 and Fig. 3 for compounds **8j** and **8e**, the cell viability percentage is independent of its concentration and most of the triazole precursors bearing electron-donating groups increased the cytotoxic activity; among them, particularly 3,4-dimethoxy compound (R_2 = OMe and R_3 = OMe; **8m**) showed excellent activity with IC_{50} value **0.95 μM ± 0.32;** when moving to Table 2 and Fig. 3, the cell viability of **8m** compound is concentration dependent from 0.625 to 2.5 μM, and then, decreasing in concentration is seen from with increasing in concentration from 2.5 μM, 5 μM and 10 μM. Removal of one methoxy group at R_2 position of triazole phenyl

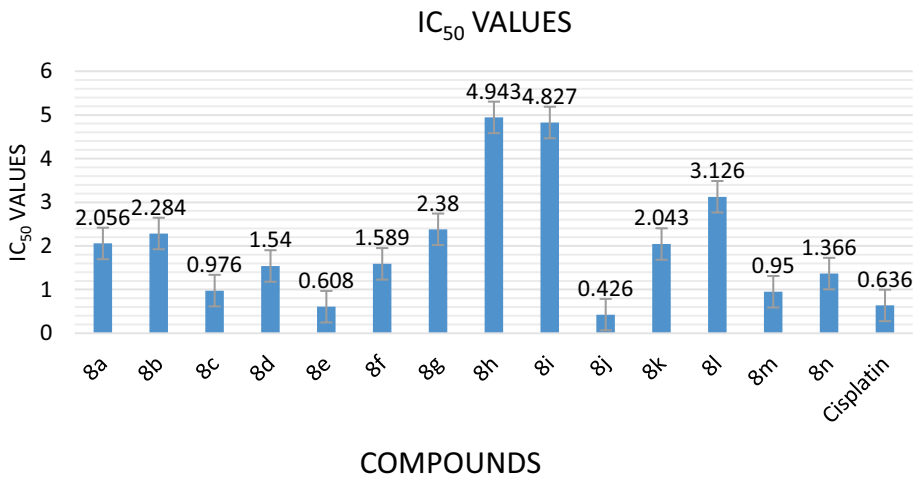


Fig. 4 IC_{50} values of novel synthesized derivatives (**8a–n**)

ring system from compound **8m** resulted in compound **8c** (R_3 = OMe; **8c**) which exhibited slightly lower cytotoxic activity with IC_{50} **0.976 µM ± 0.313**, and in Table 2 and Fig. 3, it has been observed that the cell viability percentages are increasing from 33.67% at concentration 0.625 µM to 39.96% at concentration 1.25 µM, and after 1.25 µM concentration, gradually the cell viability percentage is decreasing with increasing in concentration. Further, compound consists of methyl group (R_3 = Me; **8n**) and acetyl group ($R_3 = COCH_3$; **8d**) at fourth position exhibited promising cytotoxic activity with IC_{50} values **1.366 µM ± 0.212** and **1.54 µM ± 0.167**. On observing data in Table 2 and Fig. 3 due to the presence of methyl group in compound **8n**, the cell viability percentage is increasing with increase in concentration, and for compound **8d**, the cell viability percentage is concentration dependant due to adding of acetyl group. Moreover, the compounds bearing different halo substituents at different positions on the triazole phenyl ring (**8a**, **8b**, **8l**, **8i** and **8h**) exhibit lesser cytotoxic activity compared to other substituted compounds. So, finally, it was determined that compounds bearing electron-donating groups on the triazole phenyl ring enhanced the cytotoxic activity and some of the analogues with their IC_{50} values are displayed in Fig. 5.

Molecular modeling studies

Cisplatin, the positive control in the current work, acts by interfering with DNA replication by aquation process [47]. In this process, water molecule in cisplatin gets displaced by nucleotide bases of DNA preferentially Guanine [48, 49]. To assess the formation of cisplatin–DNA adducts along

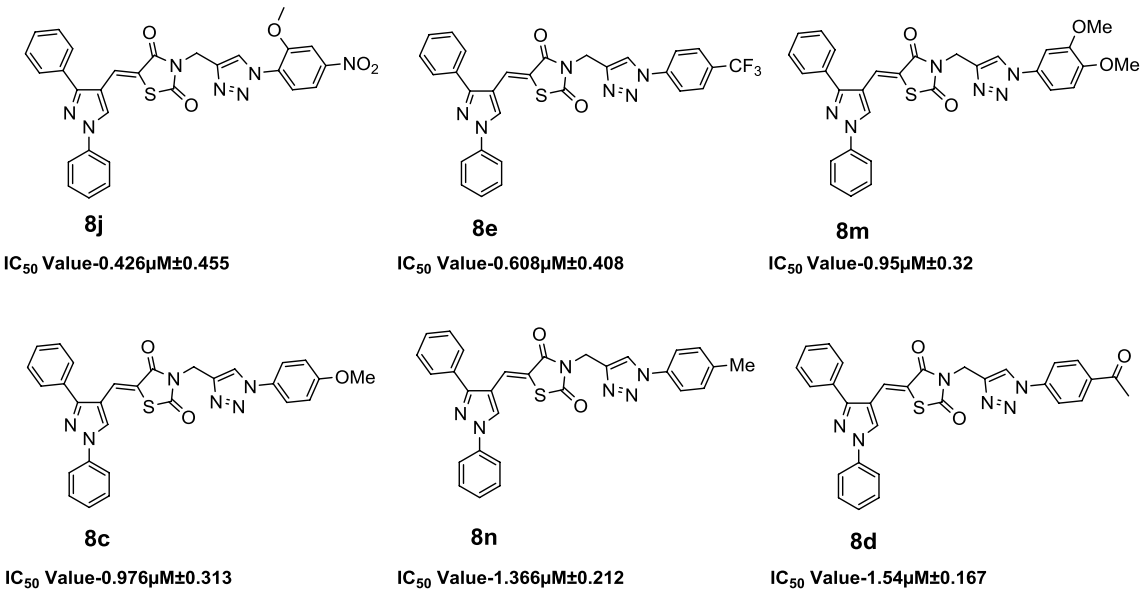


Fig. 5 IC_{50} values of some of the representative compounds

with the binding mode of the newly synthesized derivatives, docking studies have been carried out in Schrodinger. Two homologous DNA sequences with **PDB ID/3LPV** [50] and **1A2E** [51] have been retrieved from protein data bank, respectively. The cisplatin-induced apoptosis was associated with the formation of intra in addition to interchain cross-links with nucleotides principally DG-5, DC-6, DT-7 from A-chain and DG-15, DC-16, DG-17 and DA-18 from B-chain (54). The newly synthesized derivatives along with positive control have been docked into the active site and found that cisplatin has formed intramolecular adduct with DG-6 and DG-7 of A-Chain in **3LPV** protein, while intermolecular adduct with DG-5, DT-7 of A-Chain and DG-15 of B-Chain in **1A2E** protein is depicted in Fig. 6 (A) and (B). Hence, docking has been carried out on both proteins for the above synthesized compounds initially.

The docking studies reveal that highest active compound **8j** has displayed similar intermolecular adduct formation with DG-5 of A-Chain and DG-18 of B-Chain as that of positive control in **1A2E** protein as illustrated in Fig. 7, while **3LPV** has not succeeded in displaying neither intra- nor intermolecular adduct, thereby further docking has been carried out exclusively on **1A2E** itself. The compounds **8c**, **8g**, **8i** and **8k** are forming single hydrogen-bonding interactions with DG-13 (green) of the B-Chain, while compounds **8f**, **8l**, **8m** are forming two hydrogen-bonding interactions with DG-5 (blue) of A-Chain as shown in Fig. 8. The lowest active compound **8h** along with **8a**, **8b**, **8d**, **8e** and **8n** has not shown any interactions with DNA. This might be due to the higher electronegativity of fluorine (**8a)** and trifluoromethyl (**8e)** groups which requires more dissociation energy to displace with nucleotide of DNA which has been clearly confirmed with the binding energies that are tabulated in Table 4. The binding energies of lowest active **8h** are found to be **−30.88** which is far greater than positive control cisplatin binding energy **−8.381**, respectively. This demonstrates that those compounds possessing high ΔG could form molecular adduct with DNA and hence shows less activity. Dock scores along with the ΔG are tabulated in Table 4.

ADME properties

It is always preferable to analyze the ADME profile of newly synthesized derivatives, which have significant impact on a good drug. The fundamental ADME properties were determined by using QikProp module version 3.4 [52] and scrutinized for drug-likeness by applying Lipinski rule of five. QikProp module aids in enumerating pharmacodynamics (study of the biochemical and physiological effects of drugs) and pharmacokinetics (study of how the organism affects the drug) of the molecules by accessing drug-like properties. Notably, all these novel synthesized derivatives have shown significant percentage of human oral absorption exclude compound **8n**, QPPMDCK cell permeability in nm/s values appeared as agreeable limits, some of the derivatives have shown excellent values, and remaining compounds have shown moderate values. Blood–brain barrier permeability values (QPlogBB) appeared as acceptable limits,

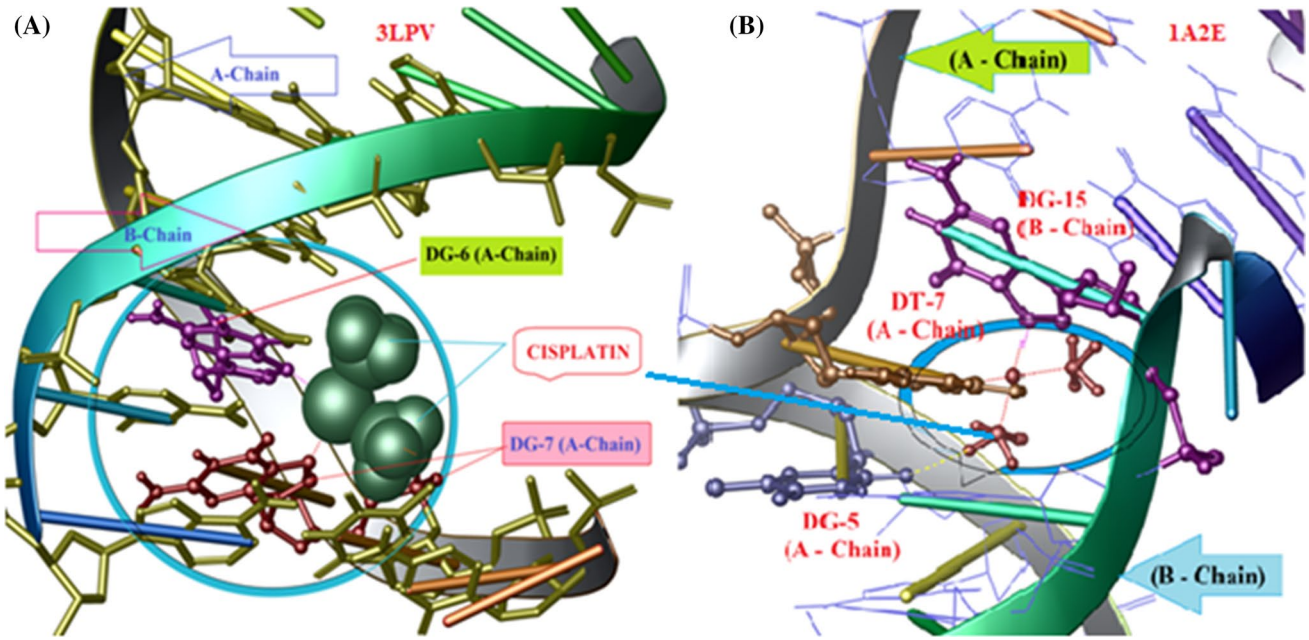


Fig. 6 Dock poses of positive control drug cisplatin demonstrating intramolecular cross-linking with DG-6 and DG-7 of A-Chain in **3LPV** protein (**a**), and intermolecular cross-linking with DG-5, DT-7 of A-Chain and DG-15 of B-Chain in the protein **1A2E** (**b**)

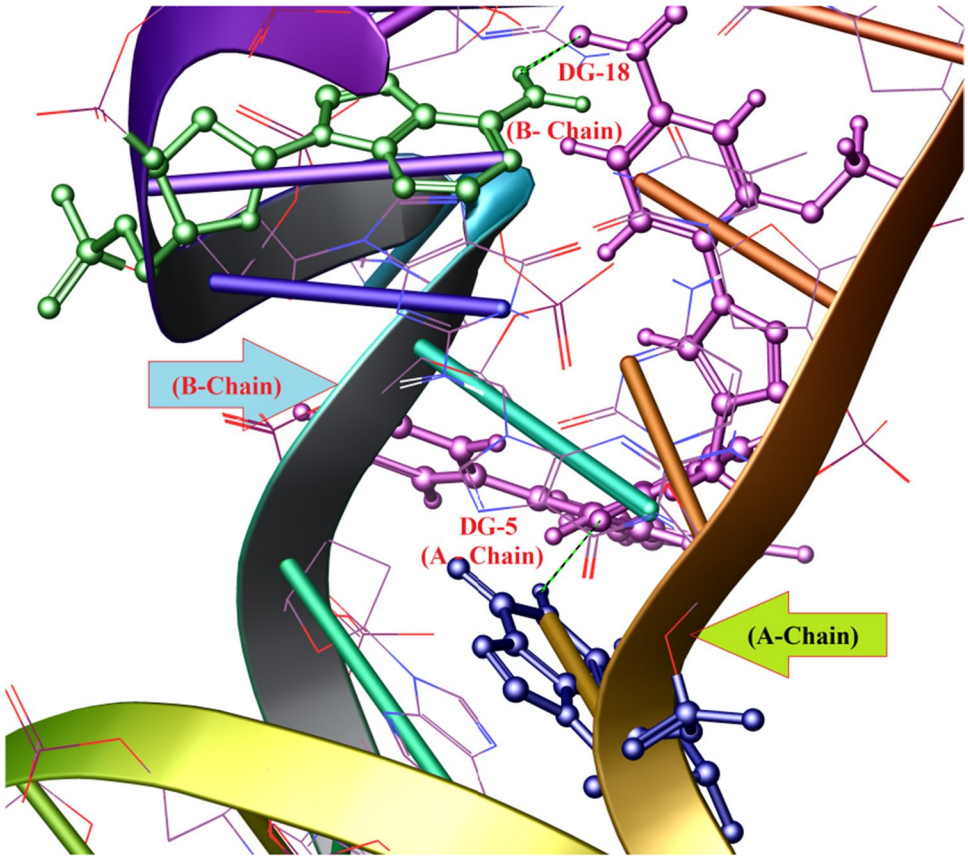


Fig. 7 Dock pose of highest active compound (**8j**) displaying intermolecular hydrogen bond interactions with DG-5 of A-Chain and DG-18 of B-Chain in the protein **1A2E**

and all remaining properties are in an acceptable ranges as displayed in Table 5. All these novel synthesized analogues exhibit drug-likeness properties and can be further optimized for better cytotoxic activity.

Experimental

Materials and methods

All the reagents, chemicals and solvents were acquired from Sigma-Aldrich, Merck and Avra and were used without further purification. Reactions were monitored by thin-layer chromatography on silica gel plate (60 f_{254}. 0.2 mm), visualization was done by exposing UV light, and column chromatography was done by using silica gel (60–120 mesh) and eluting with distilled petroleum ether/ethyl acetate. Melting points were recorded on melting point apparatus and are uncorrected. The IR spectra were determined in the Shimadzu FTIR-8400S spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance II 400 MHz spectrometer using TMS (Tetramethylsilane) as standard and using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shift values are presented in ppm, and spin multiplicities are described as s (singlet); d (doublet); dd (doublet of doublet); td (triplet of doublet); t (triplet); and m (multiplets), and coupling constants are presented in hertz. Mass spectra were recorded on GCMS-QP 1000 EX mass spectrometer.

General procedure for the synthesis of (*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl) methylene)-3-(prop-2-yn-1-yl) thiazolidine-2,4-dione (6)

A mixture of (*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)thiazolidine-2,4-dione (**5**) (1 mmol) and anhydrous K_2CO_3 (2 mmol) in dry DMF solution was stirred under N_2 atmosphere at rt for 10–15 min. Then, to the above reaction mixture, propargyl bromide (1 mmol) was added and the reaction was stirred for 3 h. After completion of the reaction (TLC analyses), the resulting reaction mixture was poured into a beaker contained crushed ice. The resultant solid product was filtered and collected under suction pump.

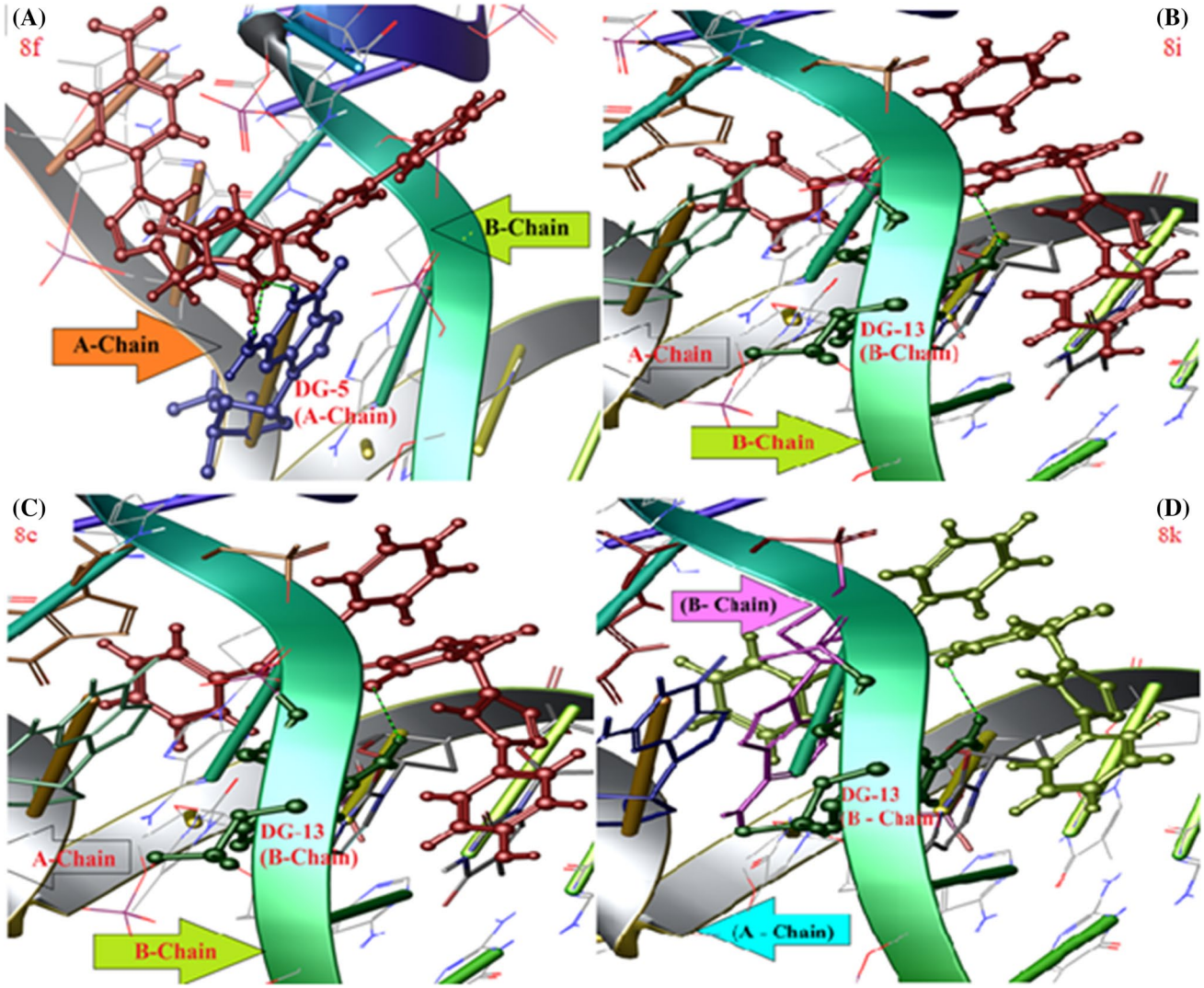


Fig. 8 Dock poses of intramolecular hydrogen-bonding interaction in A-chain (**a**, **8f**) as well as B-Chain (**b**, **8i**) (**c**, **8c**) and (**d**, **8k**)

(*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl) methylene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (6)

Light yellow colored solid; M.F: $C_{22}H_{15}N_3O_2S$; Yield: 81%; M.P: 216–218 °C; IR (KBr cm^{-1}):2312, 1739, 1687, 1531, 1367, 1215; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20 (s, 1H, Pyrazole-H), 7.98 (s, 1H, Arylidene-H), 7.83–7.79 (m, 2H, Ar–H), 7.69–7.65 (m, 2H, Ar–H), 7.56–7.50 (m, 6H, Ar–H), 4.53 (d, $J = 3.022$ Hz, 2H, Propinyl-CH_2), 2.30 (t, $J = 3.022$ Hz, 1H, Propynyl-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.0, 164.2, 153.7, 138.6, 131.1, 129.5, 129.0, 128.9, 128.7, 128.3, 127.5, 124.0, 119.5, 119.4, 115.2, 77.2, 74.5, 30.5; MS (ESI mass) *m/z* $[M + H]^+$: 386.1; Anal. Calcd for $C_{22}H_{15}N_3O_2S$: C-68.56, H-3.92, N-10.90; Found: C-68.58, H-3.94, N-10.86.

General procedure for the synthesis of compound (8a–n)

Compound (*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl) methylene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (6) (1 mmol) was dissolved in dimethylformamide (DMF) to this a solution of 10 mol% sodium ascorbate, and 10 mol% copper sulfate was added. Then, to the above reaction mixture, various substituted phenyl azides (1 mmol) in DMF were added slowly to the reaction mixture and stirred for 12 h at rt under nitrogen atmosphere. After the completion of the reaction by using TLC, the resulting crude was diluted with ice-cold water and was extracted with DCM (20 ml × 3 times) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by using column chromatography on silica gel eluting with petroleum ether/

Table 4 Binding energies (ΔG), dock scores and PIC_{50} values of newly synthesized derivatives (**8a–n**)

S. no.	Compound	IC_{50} values (μM)	PIC_{50} (μM)	Dock scores	Binding energies (ΔG)
1	**8a**	2.056 μM ± 0.034	5.686	− 6.420	− 28.30
2	**8b**	2.284 μM ± 0.0212	5.641	− 6.266	− 27.09
3	**8c**	0.976 μM ± 0.313	6.010	− 6.105	− 26.13
4	**8d**	1.54 μM ± 0.167	5.812	− 6.240	− 17.60
5	**8e**	0.608 μM ± 0.408	6.216	− 6.313	− 24.24
6	**8f**	1.589 μM ± 0.157	5.798	− 5.457	− 27.40
7	**8g**	2.38 μM ± 0.049	5.623	− 6.668	− 22.93
8	**8h**	4.943 μM ± 0.71	5.305	− 6.921	− 30.88
9	**8i**	4.827 μM ± 0.68	5.316	− 6.126	− 28.76
10	**8j**	0.426 μM ± 0.455	6.370	− 6.799	− 19.37
11	**8k**	2.043 μM ± 0.037	5.689	− 5.964	− 21.01
12	**8l**	3.126 μM ± 0.241	5.505	− 7.021	− 18.98
13	**8m**	0.95 μM ± 0.32	6.022	− 6.331	− 14.99
14	**8n**	1.366 μM ± 0.212	5.864	− 6.014	− 20.68
15	Cisplatin	0.636 μM ± 0.458	6.196	− 7.008	− 8.381

More negative indicates higher binding energies

Table 5 ADME properties of the novel synthesized derivatives (**8a–n**)

S. no.	Compound	M.Wt	QPlogPo/w[a]	QPlogS[b]	QPPCaco[c]	QPlogBB[d]	QPPMDCK[e]	% of human oral absorption[f]
1	**8a**	630.462	7.016	− 9.62	641.023	− 0.878	1365.754	92.346
2	**8b**	539.01	6.886	− 9.568	596.749	− 0.962	1085.666	91.029
3	**8c**	579.589	5.542	− 8.421	74.067	− 2.398	38.886	53.984
4	**8d**	520.564	5.673	− 8.861	155.084	− 1.944	99.542	73.455
5	**8e**	522.555	6.539	− 9.184	498.384	− 1.118	634.197	87.599
6	**8f**	564.617	6.421	− 8.852	603.417	− 1.269	432.226	88.393
7	**8g**	572.563	7.303	− 10.172	582.819	− 0.888	1833.096	93.29
8	**8h**	583.461	6.883	− 9.622	567.736	− 0.989	1071.833	90.622
9	**8i**	546.602	5.683	− 8.685	192.036	− 1.873	124.997	75.175
10	**8j**	539.01	6.784	− 9.463	546.851	− 1.011	956.458	89.754
11	**8k**	534.591	6.37	− 8.884	584.601	− 1.222	417.278	87.848
12	**8l**	518.592	6.619	− 9.261	603.123	− 1.136	431.424	89.547
13	**8m**	504.565	6.294	− 8.652	603.97	− 1.101	431.73	87.657
14	**8n**	549.563	5.511	− 8.779	57.718	− 2.507	34.37	51.864

[a]Foreseened octanol/water partition coefficient log *p* (agreeable range 2.0–6.5)

[b]Foreseened aqueous solubility in mol/L (agreeable range 6.5–0.5)

[c]Foreseened caco cell permeability in nm/s (agreeable range < 25 is poor and > 500 is excellent)

[d]Foreseened blood–brain barrier permeability (agreeable range 3–1.2)

[e]Foreseened apparent MDCK cell permeability in nm/s (agreeable range < 25 is poor and > 500 is excellent)

[f]Percentage of human oral absorption (agreeable range < 25% is poor and > 80% is excellent)

ethyl acetate to afford desired final derivatives (**8a**–**n**) with excellent yields.

(*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (8a) Light yellow colored solid; M.F: $C_{28}H_{19}FN_6O_2S$; M.P: 208–210 °C; Yield: 68%; IR (KBr cm^{-1}): 2310, 1737, 1691, 1531, 1367, 1222; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 (s, 1H, Pyrazole-H), 8.02 (s, 1H, Triazole-H), 7.96 (s, 1H, Arylidene-H), 7.80 (t, $J = 1.6$ Hz, 1H, Ar–H), 7.79–7.78 (m, 1H, Ar–H), 7.71–7.68 (m, 2H, Ar–H), 7.67–7.66 (m, 1H, Ar–H), 7.65–7.64 (m, 1H, Ar–H), 7.51 (m, 5H, Ar–H), 7.42–7.37 (m, 1H, Ar–H), 7.24–7.19 (m, 2H, Ar–H), 5.12 (s, 2H, N–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 165.2, 142.4, 139.1, 131.5, 131.3, 129.7, 129.1, 128.9, 127.7, 127.3, 125.5, 122.7, 122.6, 121.8, 119.6, 119.3, 116.8, 116.6, 116.1, 36.5; MS (ESI mass) *m/z* $[M+H]^+$: 523.1; Anal. Calcd for $C_{28}H_{19}FN_6O_2S$: C-64.36, H-3.67, N-16.08; Found: C-64.33, H-3.69, N-16.09.

(*Z*)-3-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)thiazolidine-2,4-dione (8b) Light yellow colored solid; M.F: $C_{28}H_{19}BrN_6O_2S$; M.P: 240–242 °C; Yield: 71%; IR (KBr cm^{-1}): 2312, 1737, 1683, 1531, 1234; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 (s, 1H, Pyrazole-H), 8.05 (s, 1H, Triazole-H), 7.96 (s, 1H, Arylidene-H), 7.80 (t, $J = 1.6$ Hz, 1H, Ar–H), 7.78 (d, $J = 0.9$ Hz, 1H, Ar–H), 7.67–7.62 (m, 6H, Ar–H), 7.53–7.48 (m, 5H, Ar–H), 7.39 (dd, $J = 9.2$, 5.7 Hz, 1H, Ar–H), 5.12 (s, 2H, N–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 165.2, 155.0, 142.5, 139.1, 135.8, 132.9, 131.3, 129.7, 129.1, 128.9, 127.8, 127.3, 125.6, 122.6, 122.0, 121.4, 119.6, 119.3, 116.1, 36.5; HRMS $(ESI)^+$ calcd for $C_{28}H_{20}BrN_6O_2S$ $[M+H]^+$: 583.05492 and found: 583.05463; Anal. Calcd for $C_{28}H_{19}BrN_6O_2S$: C-57.64, H-3.28, N-14.40; Found: C-57.68, H-3.26, N-14.38.

(*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (8c) Light yellow colored solid; M.F: $C_{29}H_{22}N_6O_3S$; M.P: 244–246 °C; Yield: 73%; IR (KBr cm^{-1}): 2312, 1685, 1598, 1521, 1303, 1246; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20–8.17 (s, 1H, Pyrazole-H), 7.98 (s, 1H, Triazole-H), 7.96 (s, 1H, Arylidene-H), 7.81–7.78 (m, 2H, Ar–H), 7.67–7.64 (m, 2H, Ar–H), 7.62–7.59 (m, 2H, Ar–H), 7.53–7.49 (m, 5H, Ar–H), 7.39 (m, 1H, Ar–H), 7.01 (m, 1H, Ar–H), 7.00–6.98 (m, 1H, Ar–H), 5.12 (s, 2H, N–CH_2), 3.86 (s, 3H, O–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 165.3, 159.9, 155.0, 142.1, 139.2, 131.4, 130.3, 130.2, 129.8, 129.7, 129.6, 129.0, 128.9, 127.7, 127.5, 127.3, 125.4, 122.3, 121.7, 119.6, 119.5, 119.5, 116.1, 114.7, 55.6, 36.6; HRMS $(ESI)^+$ calcd for $C_{29}H_{23}N_6O_3S$ $[M+H]^+$: 535.15452 and found: 535.15469; Anal. Calcd for $C_{29}H_{22}N_6O_3S$: C-65.16, H-4.15, N-15.72; Found: C-65.18, H-4.17, N-15.68.

(*Z*)-3-((1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)thiazolidine-2,4-dione (8d) Light yellow colored solid; M.F: $C_{30}H_{22}N_6O_3S$; M.P: 252–254 °C; Yield: 65%; IR (KBr cm^{-1}): 2308, 1739, 1689, 1527, 1369, 1215; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.18 (s, 1H, Pyrazole-H), 8.15 (s, 1H, Triazole-H), 8.12 (d, $J = 8.8$ Hz, 2H, Ar–H), 7.97 (s, 1H, Arylidene-H), 7.88 (d, $J = 2.1$ Hz, 1H, Ar–H), 7.86 (d, $J = 2.1$ Hz, 1H, Ar–H), 7.82–7.78 (m, 2H, Ar–H), 7.66 (dd, $J = 8.0$, 1.5 Hz, 2H, Ar–H), 7.54–7.49 (m, 5H, Ar–H), 7.39 (m, 1H, Ar–H), 5.14 (s, 2H, N–CH_2), 2.65 (s, 3H, Acetyl-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.4, 165.2, 164.6, 155.0, 142.7, 139.8, 139.1, 136.9, 131.3, 130.1, 129.7, 129.5, 129.4, 129.1, 128.9, 128.8, 127.8, 127.3, 125.6, 121.4, 120.1, 119.7, 119.6, 119.2, 116.1, 36.6, 26.7; MS (ESI mass) *m/z* $[M+H]^+$: 547.2; Anal. Calcd for $C_{30}H_{22}N_6O_3S$: C-65.92, H-4.06, N-15.38; Found: C-65.90, H-4.04, N-15.42.

(*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (8e) Light yellow colored solid; M.F: $C_{29}H_{19}F_3N_6O_2S$; M.P: 212–214 °C; Yield: 63%; IR (KBr cm^{-1}): 2310, 1739, 1691, 1531, 1371, 1215; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 (s, 1H, Pyrazole-H), 8.14 (s, 1H, Triazole-H), 7.97 (s, 1H, Arylidene-H), 7.82–7.78 (m, 3H, Ar–H), 7.69–7.64 (m, 4H, Ar–H), 7.53–7.48 (m, 6H, Ar–H), 7.42–7.38 (m, 1H, Ar–H), 5.14 (s, 2H, N–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.5, 165.2, 155.0, 142.8, 139.1, 131.3, 130.6, 130.2, 130.1, 129.7, 129.1, 129.0, 128.9, 127.8, 127.7, 127.3, 125.6, 125.6, 123.7, 121.6, 119.6, 119.2, 116.1, 36.5; MS (ESI mass) *m/z* $[M+H]^+$: 573.2; Anal. Calcd for $C_{29}H_{19}F_3N_6O_2S$: C-60.83, H-3.34, N-14.68; Found: C-60.81, H-3.32, N-14.72.

(*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (8f) Light yellow colored solid; M.F: $C_{28}H_{19}N_7O_4S$; M.P: 228–230 °C; Yield: 62%; IR (KBr cm^{-1}): 2312, 1739, 1689, 1531, 1317; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.42 (s, 1H, Pyrazole-H), 8.40 (s, 1H, Triazole-H), 8.19 (d, $J = 2.1$ Hz, 2H, Ar–H), 7.98–7.96 (m, 2H, Ar–H), 7.80 (m, 1H, Ar–H), 7.79 (m, 1H, Ar–H), 7.67–7.66 (m, 1H, Ar–H), 7.65 (d, $J = 1.4$ Hz, 1H, Ar–H), 7.55–7.49 (m, 6H, Ar–H), 7.39 (m, 1H, Ar–H), 5.15 (s, 2H, N–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.7, 165.2, 143.2, 129.7, 129.7, 129.1, 128.97, 128.96, 127.8, 127.3, 126.8, 125.8, 125.5, 125.5, 121.5, 120.6, 119.69, 119.67, 116.0, 36.4; HRMS $(ESI)^+$ calcd for $C_{28}H_{20}N_7O_4S$ $[M+H]^+$: 550.13015 and found: 550.12920; Anal. Calcd for $C_{28}H_{19}N_7O_4S$:

C-61.20, H-3.18, N-17.84; Found: C-61.27, H-3.14, N-17.81.

(*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-(3-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (8g) Light yellow colored solid; M.F: $C_{28}H_{20}N_6O_3S$; M.P: 232–234 °C; Yield: 66%; IR (KBr cm^{-1}): 3024, 2310, 1737, 1531, 1367, 1222; ^{1}H NMR (400 MHz, DMSO) δ (ppm): 10.04 (s, 1H, Ar–OH), 8.81 (s, 1H, Pyrazole-H), 8.77 (s, 1H, Triazole-H), 8.05 (d, $J = 7.7$ Hz, 2H, Ar–H), 7.74 (s, 1H, Ar–H), 7.66 (dd, $J = 8.1$, 1.4 Hz, 2H, Ar–H), 7.61–7.52 (m, 6H, Ar–H), 7.43 (m, 1H, Ar–H), 7.39–7.34 (m, 1H, Ar–H), 7.30–7.26 (m, 2H, Ar–H), 4.97 (s, 2H, N–CH_2); ^{13}C NMR (100 MHz, DMSO) δ (ppm): 166.6, 164.9, 153.7, 142.0, 138.7, 137.39, 137.37, 131.2, 130.7, 129.6, 129.0, 128.9, 128.7, 128.2, 127.5, 123.5, 121.6, 120.1, 119.4, 115.6, 115.3, 110.3, 106.9, 36.4; MS (ESI mass) *m/z* $[M + H]^+$: 521.2; Anal. Calcd for $C_{28}H_{20}N_6O_3S$: C-64.60, H-3.87, N-16.14; Found: C-64.58, H-3.85, N-16.19.

(*Z*)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)thiazolidine-2,4-dione (8h) Light yellow colored solid; M.F: $C_{28}H_{19}ClN_6O_2S$; M.P: 238–240 °C; Yield: 72%; IR (KBr cm^{-1}): 2310, 1739, 1531, 1367, 1220; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.21–8.20 (s, 1H, Pyrazole-H), 8.07 (s, 1H, Triazole-H), 7.98 (s, 1H, Arylidene-H), 7.82 (m, 2H, Ar–H), 7.71 (d, $J = 2.1$ Hz, 1H, Ar–H), 7.68 (m, 3H, Ar–H), 7.52 (m, 7H, Ar–H), 7.42 (m, 1H, Ar–H), 5.14 (s, 2H, N–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 165.2, 155.0, 142.5, 139.1, 135.3, 134.7, 131.3, 129.9, 129.7, 129.7, 129.6, 129.1, 128.9, 127.7, 127.3, 121.7, 121.5, 119.6, 119.3, 116.1, 36.4; HRMS $(ESI)^+$ calcd for $C_{28}H_{20}ClN_6O_2S$ $[M + H]^+$: 539.10593 and found: 539.10515; Anal. Calcd for $C_{28}H_{19}ClN_6O_2S$: C-62.39, H-3.55, N-15.59; Found: C-62.35, H-3.60, N-15.58.

(*Z*)-3-((1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)thiazolidine-2,4-dione (8i) Light yellow colored solid; M.F: $C_{28}H_{19}ClN_6O_2S$; M.P: 248–250 °C; Yield: 74%; IR (KBr cm^{-1}): 2312, 1687, 1527, 1244; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 (s, 1H, Pyrazole-H), 8.07 (s, 1H, Triazole-H), 7.97 (s, 1H, Arylidene-H), 7.82–7.76 (m, 3H, Ar–H), 7.65 (m, 3H, Ar–H), 7.56–7.47 (m, 6H, Ar–H), 7.41 (m, 2H, Ar–H), 5.13 (s, 2H, N–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 165.2, 155.0, 142.5, 139.1, 137.6, 135.6, 131.3, 130.8, 129.7, 129.1, 129.0, 128.9, 127.8, 127.3, 125.6, 120.8, 119.6, 119.3, 118.6, 116.1, 36.5; MS (ESI mass) *m/z* $[M + H]^+$: 539.2; Anal. Calcd for $C_{28}H_{19}ClN_6O_2S$: C-62.39, H-3.55, N-15.59; Found: C-62.35, H-3.58, N-15.60.

(*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-(2-methoxy-4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (8j) Light yellow colored solid; M.F: $C_{29}H_{21}N_7O_5S$; M.P: 218–220 °C; Yield: 61%; IR (KBr cm^{-1}): 2316, 1685, 1523, 1309, 1247; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.38 (s, 1H, Pyrazole-H), 8.20–8.17 (s, 1H, Triazole-H), 8.10 (d, $J = 8.8$ Hz, 1H, Ar–H), 8.02–7.98 (m, 1H, Ar–H), 7.96 (d, $J = 2.5$ Hz, 2H, Ar–H), 7.81–7.76 (m, 2H, Ar–H), 7.67–7.63 (m, 2H, Ar–H), 7.51 (m, 5H, Ar–H), 7.39 (m, 1H, Ar–H), 5.14 (s, 2H, N–CH_2), 4.06 (s, 3H, O-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 165.2, 154.9, 150.6, 148.1, 139.1, 131.3, 130.7, 129.7, 129.5, 129.4, 129.1, 128.9, 127.8, 127.3, 125.5, 125.4, 125.2, 119.6, 119.4, 116.7, 116.1, 107.7, 56.8, 36.4; HRMS $(ESI)^+$ calcd for $C_{29}H_{22}N_7O_5S$ $[M + H]^+$: 580.14066 and found: 580.13976; Anal. Calcd for $C_{29}H_{21}N_7O_5S$: C-60.10, H-3.65, N-16.92; Found: C-60.15, H-3.62, N-16.89.

(*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (8k) Light yellow colored solid; M.F: $C_{28}H_{20}N_6O_2S$; M.P: 242–244 °C; Yield: 75%; IR (KBr cm^{-1}): 2312, 1739, 1691, 1531, 1373, 1219; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 (s, 1H, Pyrazole-H), 8.05 (s, 1H, Triazole-H), 7.96 (s, 1H, Arylidene-H), 7.79 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.67 (t, $J = 8.0$ Hz, 4H, Ar–H), 7.55–7.47 (m, 8H, Ar–H), 7.39 (m, 1H, Ar–H), 5.12 (s, 2H, N–CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.4, 165.2, 142.5, 139.1, 139.0, 138.3, 135.3, 129.9, 129.7, 129.1, 128.9, 127.8, 127.3, 125.6, 121.7, 121.5, 119.8, 119.6, 119.3, 116.1, 36.4; MS (ESI mass) *m/z* $[M + H]^+$: 505.2; Anal. Calcd for $C_{28}H_{20}N_6O_2S$: C-66.65, H-4.00, N-16.66; Found: C-66.61, H-4.05, N-16.65.

(*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-(4-iodophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (8l) Light yellow colored solid; M.F: $C_{28}H_{19}IN_6O_2S$; M.P: 220–222 °C; Yield: 69%; IR (KBr cm^{-1}): 2310, 1739, 1689, 1531, 1367, 1220; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20–8.17 (s, 1H, Pyrazole-H), 8.16 (s, 1H, Triazole-H), 7.97–7.94 (s, 1H, Arylidene-H), 7.93–7.89 (m, 2H, Ar–H), 7.86–7.84 (m, 1H, Ar–H), 7.83–7.78 (m, 3H, Ar–H), 7.67–7.63 (m, 2H, Ar–H), 7.54–7.49 (m, 5H, Ar–H), 7.42–7.37 (m, 1H, Ar–H), 5.14 (s, 2H, N–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.8, 164.6, 142.5, 139.19, 139.18, 138.8, 131.3, 129.7, 129.1, 129.1, 128.9, 127.8, 127.38, 127.36, 125.7, 125.6, 124.7, 124.6, 122.1, 119.6, 36.6; MS (ESI mass) *m/z* $[M + H]^+$: 631.1; Anal. Calcd for $C_{28}H_{19}IN_6O_2S$: C-53.34, H-3.04, N-13.33; Found: C-53.37, H-3.06, N-13.28.

(*Z*)-3-((1-(3,4-dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl) methyl)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)thiazolidine-2,4-dione (8m) Light yellow colored solid; M.F: $C_{30}H_{24}N_6O_4S$; M.P: 210–212 °C; Yield: 61%; IR (KBr cm^{-1}): 2312, 1739, 1685, 1527, 1244; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.21 (s, 1H, Pyrazole-H), 7.98 (s,1H, Triazole-H), 7.81 (dd, $J = 8.6$, 1.1 Hz, 2H, Ar–H), 7.68–7.65 (m, 2H, Ar–H), 7.55–7.48 (m, 6H, Ar–H), 7.42–7.38 (m, 1H, Ar–H), 7.08–7.04 (m, 1H, Ar–H), 6.98 (m, 2H, Ar–H), 5.07 (s, 2H, N–CH_2), 3.96 (s, 3H, O-CH_3), 3.91 (s, 3H, O-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.5, 165.3, 155.0, 150.4, 149.2, 145.5, 139.2, 131.4, 129.7, 129.5, 129.5, 129.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.9, 127.7, 127.3, 125.4, 119.7, 119.5, 118.7, 116.2, 110.7, 109.7, 56.2, 56.1, 37.3; MS (ESI mass) m/z $[M+H]^+$: 565.2; Anal. Calcd for $C_{30}H_{24}N_6O_4S$: C-63.82, H-4.28, N-14.88; Found: C-63.80, H-4.32, N-14.86.

(*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (8n) Light yellow colored solid; M.F: $C_{29}H_{22}N_6O_2S$; M.P: 256–258 °C; Yield: 70%; IR (KBr cm^{-1}): 2308, 1739, 1689, 1531, 1369, 1217; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 (s, 1H, Pyrazole-H), 8.03 (s, 1H, Triazole-H), 7.96 (s, 1H, Arylidene-H), 7.80 (t, $J = 1.6$ Hz, 1H, Ar–H), 7.80–7.78 (m, 1H, Ar–H), 7.67–7.64 (m, 2H, Ar–H), 7.60–7.57 (m, 2H, Ar–H), 7.54–7.48 (m, 5H, Ar–H), 7.42–7.37 (m, 1H, Ar–H), 7.30 (d, $J = 8.1$ Hz, 2H, Ar–H), 5.12 (s, 2H, N–CH_2), 2.41 (s, 3H, Tolyl-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 165.3, 155.0, 142.1, 139.1, 139.0, 134.6, 131.5, 131.4, 130.2, 129.7, 129.0, 128.9, 127.7, 127.7, 127.3, 125.4, 121.6, 120.5, 119.6, 119.5, 119.5, 116.1, 36.6, 21.1; MS (ESI mass) m/z $[M+H]^+$: 519.2; Anal. Calcd for $C_{29}H_{22}N_6O_2S$: C-67.17, H-4.28, N-16.21; Found: C-67.20, H-4.31, N-16.11.

Cell viability assay/cytotoxic activity of newly synthesized derivatives toward MCF-7 cell line

Materials and method

MTT (3-(4, 5-dimethyl thiazol-2yl)-2, 5-di phenyl tetrazolium bromide) assay was carried out as a standard assay for determining in vitro cytotoxicity assay of the MCF-7 tumor cell line subjected to synthesized compounds. Under sterile conditions, the MCF-7 tumor cells were seeded in 96-well microassay, culture plate at a density of 3×10^3 cells per well in 200 µl in Dulbecco's modified eagles medium (DMEM) (Gibco NY, USA) supplemented with 10% Fetal bovine serum (FBS) (Bio cell, CA, USA) and 1 × antibiotic–antimycotic solution(contains Penicillin, Streptomycin, Amphotericin-D) and were grown exponentially for 24 h in a humidified 5% CO_2 incubator at 37 °C to test the growth inhibition of synthesized compounds. The 10 mM stocks were prepared initially by diluting the synthesized compounds and standard cisplatin in DMSO. The different concentrations of 25 µM, 50 µM, 100 µM, 200 µM, 500 µM were prepared from 10 mM stocks diluted in DMSO. After seeding of cells for 24 h in 96-well plate, 5 µl of given synthesized compounds and standard cisplatin of respective concentrations 25 µM, 50 µM, 100 µM and 200 µM, 500 µM were added to each well in duplicates having MCF 7 cells to reach the final concentration of 0.625 µM, 1.25 µM, 2.5 µM, 5 µM and 10 µM, respectively. The culture medium (DMEM) was added to wells containing only MCF 7 cells for control, and also culture medium (DMEM) was added to each well without cells for blank prepared in duplicates. After treatment, the plates were incubated in humidified 5% CO_2 incubator for 24 h at 37 °C. Upon completion of 24 h, 20 µl stock MTT dye solution (5 mg/ml) was added to each well and incubated at 37 °C in humidified 5% CO_2 incubator for 4 h. After incubation of 4 h, an MTT dye solution was aspirated and 100 µl of DMSO was added to solubilize the MTT formazan crystals. This formazan is directly proportional to the number of viable cells and inversely proportional to the degree of cytotoxicity. After 1 h, the absorbance of each well at 490 nm was measured on microplate spectrophotometer. IC_{50} values were calculated by plotting the graph between the concentration of synthesized compounds at which 50% of cells remain viable to the control on x-axis (0.625 µM, 1.25 µM, 2.5 µM, 5 µM and 10 µM) and percentage of cell viability on y-axis. The cell viability percentage can be calculated from the following formula:

$$\text{Cell viability percentage} = \text{Absorbance of treated cells} / \text{Absorbance of untreated cells} \times 100.$$

Conclusion

In summary, we have designed and synthesized a series of novel (*Z*)-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl)methyl) thiazolidine-2,4-dione hybrids (**8a-n**). These synthesized derivatives were confirmed by ^{1}H NMR, ^{13}C NMR, IR, HRMS and ESI–MS spectra and screened for their in vitro cell viability assay/cytotoxic activity. Overall, this biological assay outcome clearly illustrated that most of the synthesized derivatives showed moderate-to-excellent cytotoxic activity. These findings described that derivatives embedded electron-donating groups have shown remarkable cytotoxic activity. Among the series, lead analogues **8j** ($R_1 = OMe$ and $R_3 = NO_2$) and **8e** ($R_3 = CF_3$) have shown excellent

cytotoxic activity with IC_{50} values **0.426 µM ± 0.455** and **0.608 µM ± 0.408**, which are even better than the standard drug cisplatin **0.636 µM ± 0.458**. Noticeably, compounds bearing different halo substituents at different positions on the triazole phenyl ring (**8a**, **8b**, **8l**, **8i** and **8h**) showed lesser cytotoxic activity compared to other substituted analogues. Based on these analyses, all the novel synthesized hybrids have potential cytotoxic activity and further structural modification of these derivatives may produce significant cytotoxic agents.

Supplementary

^{1}H NMR, ^{13}C NMR, IR, HRMS and ESI–MS spectra of all these synthesized novel hybrids were provided in supplementary.

Acknowledgements The authors thank the Head, Department of Chemistry, Osmania University, Hyderabad for providing laboratory facilities. Kolluri Prashanth Kumar is thankful to UGC, New Delhi, for providing fellowship. One of the authors N. J. P. Subhashini is grateful to OU-DST PURSE-II/60/2018-2019 and SAP program, Department of Chemistry, Osmania University, Hyderabad, for providing financial assistance. We thank the CFRD analytical department for providing spectral analysis facilities.

Compliance with ethical standards

Conflict of interest The authors have declared no conflict of interest.

References

1. World Health Organization (2019) Global cancer report. http://www.who.int/cancer/publications/global_report/en. Accessed 2 Dec 2019
2. Siegel R, Desantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S, Hachey M, Kirch R, Jemal A, Ward E (2012) Cancer treatment and survivorship statistics. CA Cancer J Clin 62:220–241. https://doi.org/10.3322/caac.21149
3. Senwar KR, Sharma P, Reddy TS, Jeengar MK, Nayak VL, Naidu VGM, Kamal A, Shankaraiah N (2015) Spirooxindole-derived morpholine-fused-1,2,3-triazoles: design, synthesis, cytotoxicity and apoptosis inducing studies. Eur J Med Chem 102:413–424. https://doi.org/10.1016/j.ejmech.2015.08.017
4. Fox JL, MacFarlane M (2016) Targeting cell death signalling in cancer: minimising 'Collateral damage'. Br J Cancer 115:5–11. https://doi.org/10.1038/bjc.2016.111
5. Senwar KR, Reddy TS, Thummuri D, Sharma P, Naidu VGM, Srinivasulu G, Shankaraiah N (2016) Design, synthesis and apoptosis inducing effect of novel (Z)-3-(3′-methoxy-4′-(2-amino-2-oxoethoxy)-benzylidene)indolin-2-ones as potential antitumour agents. Eur J Med Chem 118:34–46. https://doi.org/10.1016/j.ejmech.2016.04.025
6. Bekhit AA, Saudi MN, Hassan AMM, Fahmy SM, Ibrahim TM, Ghareeb D, El-Seidy AM, Nasralla SN, Bekhit AM (2019) Synthesis, in silico experiments and biological evaluation of 1,3,4-trisubstituted pyrazole derivatives as antimalarial agents. Eur J Med Chem 163:353–366. https://doi.org/10.1016/j.ejmech.2018.11.067
7. Taban IM, Elshihawy H, Torun B, Zucchini B, Williamson CJ, Altuwairigi D, Ngu AST, McLean KJ, Levy CW, Sood S, Marino LB, Munro AW, de Carvalho LPS, Simons C (2017) Novel aryl substituted pyrazoles as small molecule inhibitors of cytochrome P450 CYP121A1: synthesis and antimycobacterial evaluation. J Med Chem 60:10257–10267. https://doi.org/10.1021/acs.jmedchem.7b01562
8. Cox BD, Prosser AR, Sun Y, Li Z, Lee S, Huang MB, Bond VC, Snyder JP, Krystal M, Wilson LJ, Liotta DC (2015) Pyrazolopiperidines exhibit dual inhibition of CCR5/CXCR4 HIV entry and reverse transcriptase. ACS Med Chem Lett 6:753–757. https://doi.org/10.1021/acsmedchemlett.5b00036
9. Pathak RB, Chovatia PT, Parekh HH (2012) Synthesis, antitubercular and antimicrobial evaluation of 3-(4-chlorophenyl)-4-substituted pyrazole derivatives. Bioorg Med Chem Lett 22:5129–5133. https://doi.org/10.1016/j.bmcl.2012.05.063
10. Dias D, Pacheco BS, Cunico W, Pizzuti L, Pereira CM (2015) Recent advances on the green synthesis and antioxidant activities of pyrazoles. Mini Rev Med Chem 14:1078–1092. https://doi.org/10.2174/1389557515666150101102606
11. Kamal A, Shaik AB, Jain N, Kishor C, Nagabhushana A, Supriya B, Kumar GB, Chourasiya SS, Suresh Y, Mishra RK, Addlagatta A (2015) Design and synthesis of pyrazole–oxindole conjugates targeting tubulin polymerization as new anticancer agents. Eur J Med Chem 92:501–513. https://doi.org/10.1016/j.ejmech.2013.10.077
12. Shi JB, Tang WJ, Li R, Liu XH (2015) Novel pyrazole-5-carboxamide and pyrazole–pyrimidine derivatives: synthesis and anticancer activity. Eur J Med Chem 90:889–896. https://doi.org/10.1016/j.ejmech.2014.12.013
13. Bekhit AA, Hassan AMM, Abd El Razik HA, El-Miligy MMM, El-Agroudy EJ, Bekhit DA (2015) New heterocyclic hybrids of pyrazole and its bioisosteres: design, synthesis and biological evaluation as dual acting antimalarial-antileishmanial agents. Eur J Med Chem 94:30–44. https://doi.org/10.1016/j.ejmech.2015.02.038
14. Mohammed KO, Nissan YM (2014) Synthesis, molecular docking, and biological evaluation of some novel hydrazones and pyrazole derivatives as anti-inflammatory agents. Chem Biol Drug Des 84:473–488. https://doi.org/10.1111/cbdd.12336
15. Naim MJ, Alam MJ, Ahmad S, Nawaz F, Shrivastava N, Sahu M, Alam O (2017) Therapeutic journey of 2,4-thiazolidinediones as a versatile scaffold: an insight into structure activity relationship. Eur J Med Chem 129:218–250. https://doi.org/10.1016/j.ejmech.2017.02.031
16. Bahare RS, Ganguly S, Choowongkomon K, Seetaha S (2015) Synthesis, HIV-1 RT inhibitory, antibacterial, antifungal & binding mode studies of some novel N-substituted 5-benzylidine-2,4-thiazolidinediones. DARU J Pharm Sci 23:1–5. https://doi.org/10.1186/s40199-014-0086-1
17. Aneja DK, Lohan P, Arora S, Sharma C, Aneja KR, Prakash O (2011) Synthesis of new pyrazolyl-2, 4-thiazolidinediones as antibacterial and antifungal agents. Org Med Chem Lett 1:1–15. https://doi.org/10.1186/2191-2858-1-15
18. de Melo Rêgo MJ, Galdino-Pitta MR, Pereira DT, da Silva JC, Rabello MM, de Lima MD, Hernandes MZ, da Rocha Pitta I, Galdino SL, da Rocha Pitta MG (2014) Synthesis study of new disubstituted thiazolidinedione derivatives. Med Chem Res 23:3220–3226. https://doi.org/10.1007/s00044-013-0902-z
19. Nagarapu L, Yadagiri B, Bantu R, Kumar CG, Pombala S, Nanubolu J (2014) Studies on the synthetic and structural aspects of benzosuberones bearing 2, 4-thiazolidenone moiety as

potential anti-cancer agents. Eur J Med Chem 71:91–97. https://doi.org/10.1016/j.ejmech.2013.10.078
20. Maccari R, Ottanà R, Curinga C, Vigorita MG, Rakowitz D, Steindl T, Langer T (2005) Structure-activity relationships and molecular modelling of 5-arylidene-2,4-thiazolidinediones active as aldose reductase inhibitors. Bioorg Med Chem 13:2809–2823. https://doi.org/10.1016/j.bmc.2005.02.026
21. Jawale DV, Pratap UR, Rahuja N, Srivastava AK, Mane RA (2012) Synthesis and antihyperglycemic evaluation of new 2,4-thiazolidinediones having biodynamic aryl sulfonylurea moieties. Bioorg Med Chem Lett 22:436–439. https://doi.org/10.1016/j.bmcl.2011.10.110
22. Sharma P, Reddy TS, Thummuri D, Senwar KR, Kumar NP, Naidu VG, Bhargava SK, Shankaraiah N (2016) Synthesis and biological evaluation of new benzimidazole-thiazolidinedione hybrids as potential cytotoxic and apoptosis inducing agents. Eur J Med Chem 124:608–621. https://doi.org/10.1016/j.ejmech.2016.08.029
23. Begum AB, Begum M, Ranganatha VL, Prashanth T, Zameer F, Hegdekatte R, Khanum SA (2014) Synthesis, antioxidant, and xanthine oxidase inhibitory activities of 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione derivatives. Arch Pharm (Weinh) 347:247–255. https://doi.org/10.1002/ardp.201300319
24. Ma L, Pei H, Lei L, He L, Chen J, Liang X, Peng A, Ye H, Xiang M, Chen L (2015) Structural exploration, synthesis and pharmacological evaluation of novel 5-benzylidenethiazolidine-2,4-dione derivatives as iNOS inhibitors against inflammatory diseases. Eur J Med Chem 92:178–190. https://doi.org/10.1016/j.ejmech.2014.12.036
25. Day C (1999) Thiazolidinediones: a new class of antidiabetic drugs. Diabet Med 16:192. https://doi.org/10.1046/j.1464-5491.1999.00023.x
26. Khan FAK, Patil RH, Shinde DB, Sangshetti JN (2016) Design and synthesis of 4′-((5-benzylidene-2,4-dioxothiazolidin-3-yl) methyl)biphenyl-2-carbonitrile analogues as bacterial peptide deformylase inhibitors. Chem Bio Drug Des 88:938–944. https://doi.org/10.1111/cbdd.12817
27. Kolluri PK, Gurrapu N, Edigi PK, Subhashini NJP, Putta S, Singh SS (2019) Design, synthesis of (Z)-3-benzyl-5-((1-phenyl-3-(3-((1- substituted phenyl-1H-1,2,3-triazol-4-yl)methoxy) phenyl)-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione analogues as potential cytotoxic agents. J Heterocyclic Chem 2019:1–13. https://doi.org/10.1002/jhet.3720
28. Mady MF, Awad GE, Jorgensen KB (2014) Ultrasound-assisted synthesis of novel 1,2,3-triazoles coupled diaryl sulfone moieties by the CuAAC reaction, and biological evaluation of them as antioxidant and antimicrobial agents. Eur J Med Chem 84:433–443. https://doi.org/10.1016/j.ejmech.2014.07.042
29. Shaikh MH, Subhedar DD, Arkile M, Khedkar VM, Jadhav N, Sarkar D, Shingate BB (2016) Synthesis and bioactivity of novel triazole incorporated benzothiazinone derivatives as antitubercular and antioxidant agent. Bioorg Med Chem Lett 26:561–569. https://doi.org/10.1016/j.bmcl.2015.11.071
30. Tan L, Li Q, Wang H, Liu Y, Zhang J, Dong F, Guo Z (2016) Synthesis, characterization, and antibacterial property of novel starch derivatives with 1,2,3-triazoles. Carbohyd Polym 142:1–7
31. Ouahrouch A, Taourirte M, Schols D, Snoeck R, Andrei G, Engels JW, Lazrek HB (2016) Design, synthesis, and antiviral activity of novel ribonucleosides of 1,2,3-triazolylbenzyl-aminophosphonates. Arch Pharm (Weinheim) 349:30–41. https://doi.org/10.1002/ardp.201500292
32. Penthala NR, Madhukuri L, Thakkar S, Madadi NR, Lamture G, Eoff RL, Crooks PA (2015) Synthesis and anti-cancer screening of novel heterocyclic-(2H)-1,2,3-triazoles as potential anti-cancer agents. MedChemComm 6:1535–1543. https://doi.org/10.1039/C5MD00219B
33. Kant R, Kumar D, Agarwal D, Gupta RD, Tilak R, Awasthi SK, Agarwal A (2016) Synthesis of newer 1,2,3-triazole linked chalcone and flavone hybrid compounds and evaluation of their antimicrobial and cytotoxic activities. Eur J Med Chem 113:34–49. https://doi.org/10.1016/j.ejmech.2016.02.041
34. Kim TW, Yong Y, Shin SY, Jung H, Park KH, Lee YH, Lim Y, Jung KY (2015) Synthesis and biological evaluation of phenyl-1H-1,2,3-triazole derivatives as anti-inflammatory agents. Bioorg Chem 59:1–11. https://doi.org/10.1016/j.bioorg.2015.01.003
35. Srinivasa Reddy T, Kulhari H, Ganga Reddy V, Subba Rao AV, Bansal V, Kamal A, Shukla R (2015) Synthesis and biological evaluation of pyrazolo–triazole hybrids as cytotoxic and apoptosis inducing agents. Organ Biomol Chem 13:10136–10149. https://doi.org/10.1039/c5ob00842e
36. Ganga Reddy V, Srinivasa Reddy T, Lakshma Nayak V, Prasad B, Reddy AP, Ravikumar A, Taj S, Kamal A (2016) Design, synthesis and biological evaluation of *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,3-diphenyl-1*H*-pyrazole-4-carboxamides as CDK1/Cdc2 inhibitors. Eur J Med Chem 122:164–177. https://doi.org/10.1016/j.ejmech.2016.06.011
37. Chinthala Y, Kumar Domatti A, Sarfaraz A, Singh SP, Kumar Arigari N, Gupta N, Satya SKVN, Kotesh Kumar J, Khan F, Tiwari AK, Paramjit G (2013) Synthesis, biological evaluation and molecular modeling studies of some novel thiazolidinediones with triazole ring. Eur J Med Chem 70:308–314. https://doi.org/10.1016/j.ejmech.2013.10.005
38. Lv XH, Ren ZL, Zhou BG, Li QS, Chu MJ, Liu DH, Mo K, Zhang LS, Yao XK, Cao HQ (2016) Discovery of N-(benzyloxy)-1,3-diphenyl-1H-pyrazole-4-carboxamide derivatives as potential antiproliferative agents by inhibiting MEK. Bioorg Med Chem 24:4652–4659. https://doi.org/10.1016/j.bmc.2016.08.002
39. Samia MR, Manal NSS, Amal MY, Madiha AH (2009) Synthesis and biological evaluation of the pyrazole class of cyclooxygenase-2-inhibitors. Lett Org Chem 6:282–288. https://doi.org/10.2174/157017809788489909
40. Sridhar SNC, Bhurta D, Kantiwal D, George G, Monga V, Paul AT (2017) Design, synthesis, biological evaluation and molecular modelling studies of novel diaryl substituted pyrazolyl thiazolidinediones as potent pancreatic lipase inhibitors. Bioorg Med Chem Lett 27:3749–3754. https://doi.org/10.1016/j.bmcl.2017.06.069
41. Andleeb H, Tehseen Y, Ali Shah SJ, Khan I, Iqbal J, Hameed S (2016) Identification of novel pyrazole–rhodanine hybrid scaffolds as potent inhibitors of aldose reductase: design, synthesis, biological evaluation and molecular docking analysis. RSC Adv 6:77688–77700. https://doi.org/10.1039/C6RA14531K
42. Mohanty S, Roy AK, Kumar VKP, Reddy SG, Karmakar AC (2014) Acetic anhydride-promoted one-pot condensation of 2,4-thiazolidinedione with bisulfite adducts of aldehydes. Tetra Lett 55:4585–4589. https://doi.org/10.1016/j.tetlet.2014.06.082
43. Pratap UR, Jawale DV, Waghmare RA, Lingampalle DL, Mane RA (2011) Synthesis of 5-arylidene-2,4-thiazolidinediones by Knoevenagel condensation catalyzed by baker's yeast. New J Chem 35:49–51. https://doi.org/10.1039/C0NJ00691B
44. Mosmann T (1983) Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J Immunol Methods 65:55–63. https://doi.org/10.1016/0022-1759(83)90303-4
45. Van Meerloo J, Kaspers GJL, Cloos J (2011) Cell sensitivity assays: the MTT assay. In: Cree I (ed) Cancer Cell culture. Methods in molecular biology (methods and protocols), vol 731. Humana Press, Totowa, pp 237–245. https://doi.org/10.1007/978-1-61779-080-5_20
46. Kolluri PK, Gurrapu N, Subhashini NJP, Putta S, Singh SS, Vani T, Manga V (2020) Design, synthesis of novel (Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)

methyl)-1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-N-arylacetamide derivatives: evaluation of cytotoxic activity and molecular docking studies. J Mol Structure 1202:127300. https://doi.org/10.1016/j.molstruc.2019.127300
47. IUPAC (1997) Compendium of chemical terminology, 2nd edn. (the "Gold Book") compiled by A. D. McNaught and A. Wilkinson. http://doi.org/10.1351/goldbook
48. Wang D, Lippard SJ (2005) Cellular processing of platinum anticancer drugs. Nat Rev Drug Discovery 4:307–320. https://doi.org/10.1038/nrd1691
49. Johnstone TC, Suntharalingam K, Lippard SJ (2016) The next generation of platinum drugs: targeted Pt(II) agents, nanoparticle delivery, and Pt(IV) prodrugs. Chem Rev 116:3436–3486. https://doi.org/10.1021/acs.chemrev.5b00597
50. Todd RC, Lippard SJ (2010) Structure of duplex DNA containing the cisplatin 1,2-{Pt (NH3)2}2+-d(GpG) cross-link at 1.77 Å resolution. J Inorg Biochem 104:902–908. https://doi.org/10.1016/j.jinorgbio.2010.04.005
51. Coste F, Malinge JM, Serre L, Shepard W, Roth M, Leng M, Zelwer C (1999) Crystal structure of a double-stranded DNA containing a cisplatin interstrand cross-link at 1.63 A resolution: hydration at the platinated site. Nucl Acids Res 27:1837–1846. https://doi.org/10.1093/nar/27.8.1837
52. Qik Prop (2011) Version 3.4, Schrödinger, LLC, New York