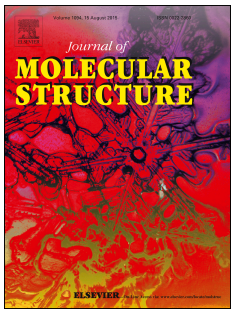

Design, synthesis of novel (*Z*)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-*N*-arylacetamide derivatives: Evaluation of cytotoxic activity and molecular docking studies

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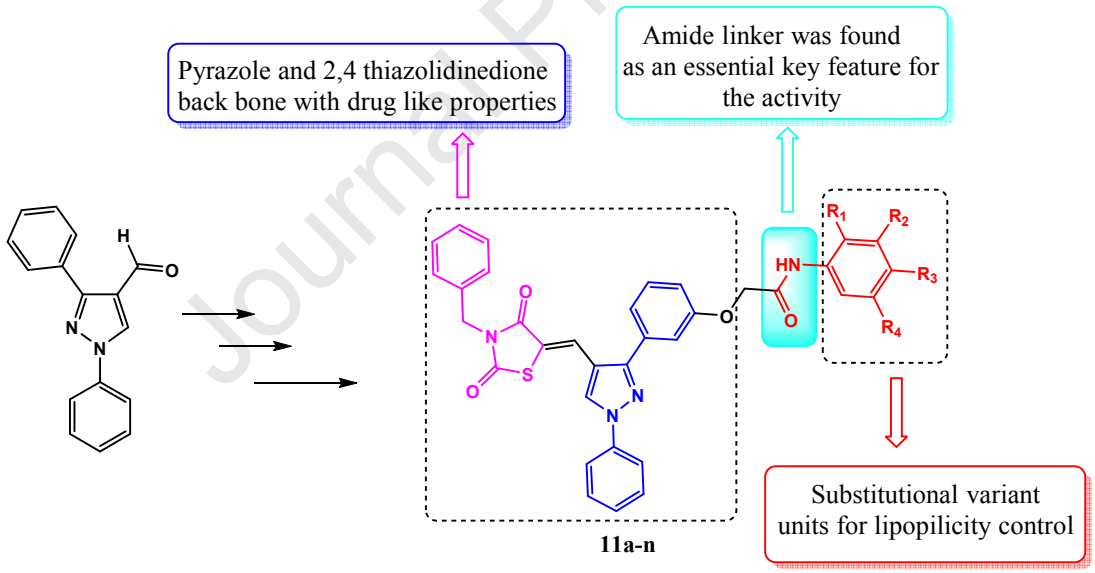
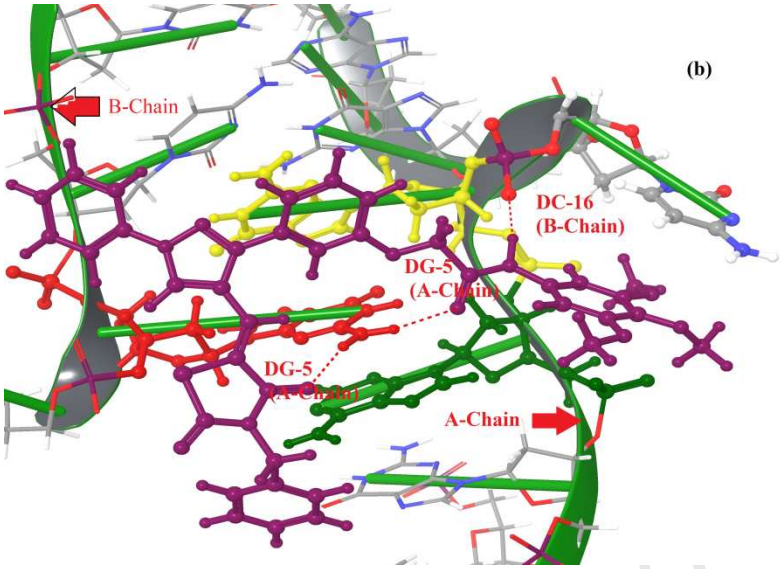
Graphical abstract:





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

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Abstract: In an attempt to discover potential cytotoxic agents, a series 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 **11a-n** were synthesized in varied steps with acceptable reaction procedures with good yields and characterized by ^{1}H NMR, ^{13}C NMR, IR and ESI-MS spectra. All the novel synthesized derivatives were assessed for their cytotoxic activity against human breast cell line (MCF-7) with different concentration of 0.625µM, 1.25µM, 2.5µM, 5µM and 10µM respectively. Biological evaluation assay results were displayed in terms of percentage of cell viability reduction and IC_{50} values. Most of the screened derivatives demonstrated moderate to promising cytotoxic activity. Some of the derivatives, particularly compound **11d** and **11n** have shown promising cytotoxic activity with IC_{50} values 0.604µM and 0.665µM compared to standard drug cisplatin and compounds **11a**, **11e** and **11g** also have shown considerable cytotoxic activity and the rest of the derivatives have shown moderate activity. Furthermore, molecular docking calculations and ADME properties of the synthesized molecules are in effective compliance with the cytotoxic evaluation results.

Keywords: Pyrazole, 2,4-thiazolidinedione (TZD), *N*-aryl acetamide, Knoevenagel condensation, cytotoxic activity.

1. Introduction: Cancer is a generic term for a massive group of diseases (most common types are Lung, prostate, colorectal, liver and breast cancer) described by uncontrolled

growth and spread of abnormal cells beyond their usual boundaries that can encroach adjacent parts of the body and transmitted to other organs. Cancer affects everyone and is one of the leading causes of deaths in the world. Breast cancer is most frequently occurring cancer in women and second most common cancer overall, there were over 2 million new cases in 2018 [1-2]. Although the causes of cancer are not completely understood and there was reasonable progress to diminish cancer percentage in the world. The current anticancer drugs face several boundaries and may often cause negative influences. Therefore, to overcome all these problems endless exploration and discovery of novel, safe anticancer drugs with low in toxicity and high efficiency is still significant program in anticancer drug research and development in the world [3-5].

Heterocyclic pharmacophores play an outstanding role as a potential moieties in cancer drug design and development in medicinal chemistry. Among them, pyrazole compounds are leading structural fragments and integral part of many natural occurring moieties and play crucial role in synthetic and medicinal chemistry and various other fields due to their broad-spectrum of biological activities such as anti-inflammatory, antimicrobial, antioxidant, antimycobacterial, antiviral, anticonvulsant, antidepressant and anticancer activities [6-14]. The condensed moieties of pyrazole-4-carbaldehyde are important active structural scaffolds in drug design and taken significant positions in medical and agrochemical research and development.

On the other hand, 2,4-thiazolidinedione (TZD) scaffold is an essential heterocyclic ring system and privileged moiety in diverse biological active fields. In the recent years, research on TZD has attracted considerable scientific attention because of their unique structure, and they have low molecular weight and changeable substitution reactions happen at 3 and 5 positions [15]. The TZD moiety is especially seen in glitazone family drugs which include revoglitazone, netoglitazone, englitazone, rosiglitazone, lobeglitazone and pioglitazone etc. Some of the TZD representative drugs in particular, troglitazone and ciglitazone drugs exhibited moderate anticancer activities. 2,4-thiazolidinedione occupy significant position in medicinal chemistry due to their distinct and adaptable nature exhibit a vast range of pharmacological activities including antidiabetic, antileishmanial, antimicrobial, antioxidant, anti-inflammatory and anticancer agents [16-24].

Moreover, the presence of the *N*-aryl acetamide derivatives containing hetero cyclic compounds exhibit outstanding biological activities because these amide linkages were

discovered as a significant key feature for activity and the presence of the amide group improve the polarity of the compounds, which is advantageous for their solubility and prohibits amalgamation [25-27]. Some of the reported synthetic developed anticancer active compounds embedded pyrazole, 2,4-thiazolidinedione and amide linkage pharmacophores were depicted in **Figure 1**.

In the view of above scrutiny and biological significance of above moieties we have made an effort to synthesize excellent therapeutic agents with less perniciousness and more efficiency drugs for the treatment of cancer. Therefore, the idea is combination of these three biological active moieties (pyrazole-4-carbaldehyde, 2,4-thiazolidinedione and *N*-aryl acetamide derivatives) into a novel scaffold seems to be a significant hybrid pharmacophore with considerable biological activities were demonstrated in **Figure 2**. Based on these observations and our ongoing research and development program, we synthesized a series 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 **11a-n** and these compounds were explored for their cytotoxic activity against human breast cancer cell line (MCF-7).

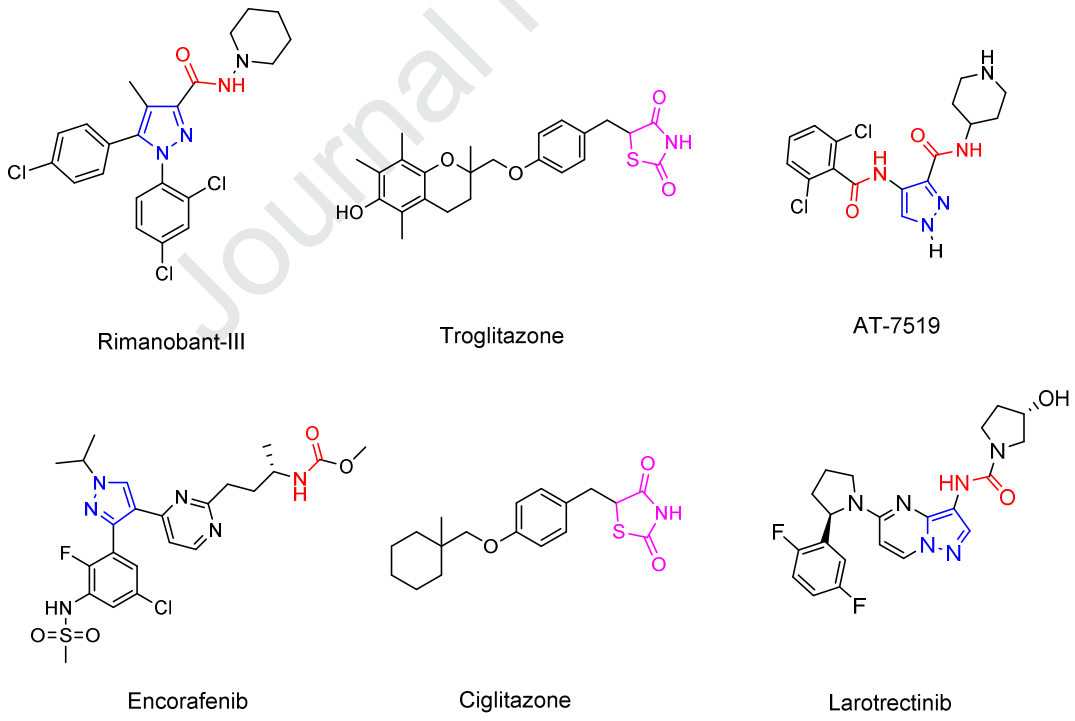


Figure 1. Structures of a few synthetic and reported cytotoxic active compounds consist of pyrazole, 2,4-thiazolidinedione and amide linkage moieties.

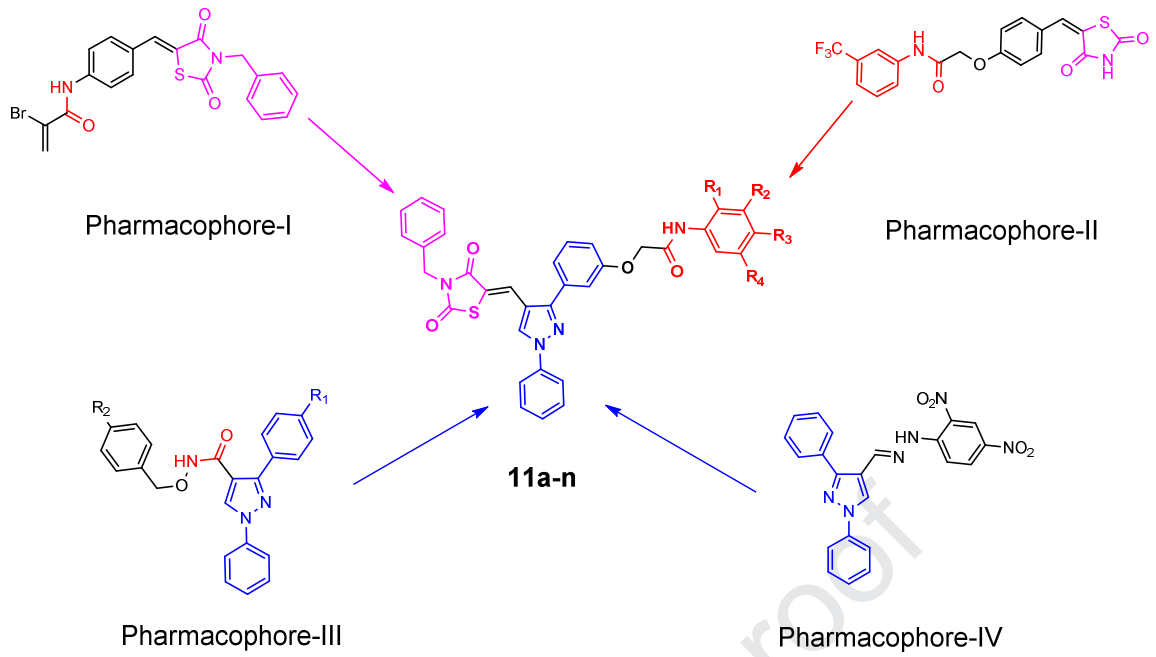


Figure 2. Design strategy of scaffold based on cytotoxic active pharmacophores.

2. Results and discussion

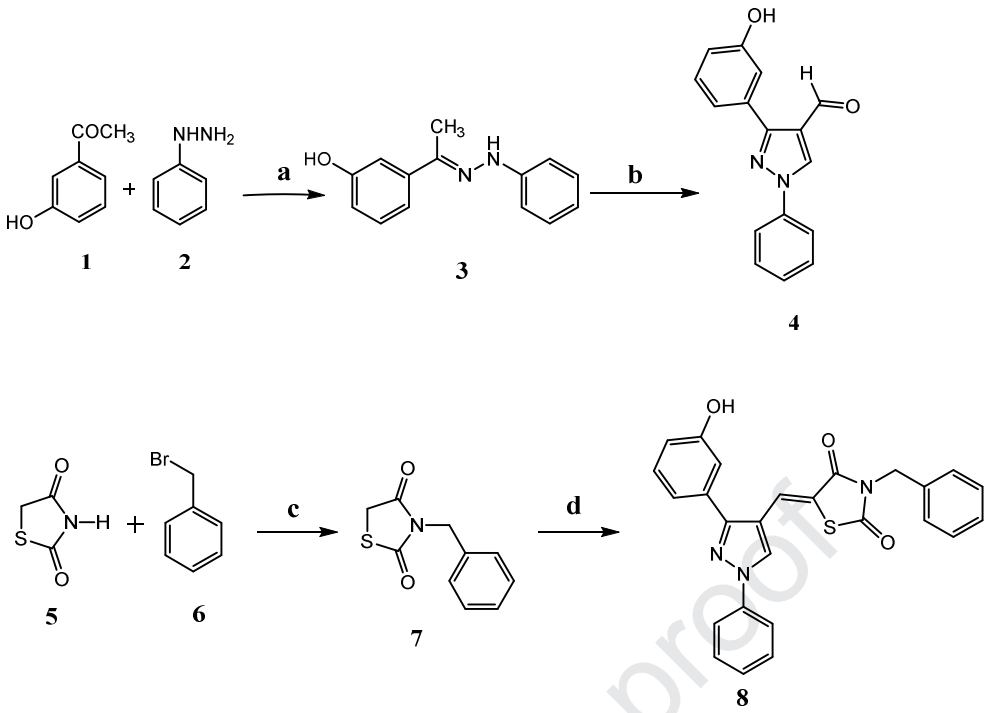
2.1. Chemistry

The synthetic route of target analogues (*Z*)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-*N*-arylacetamide derivatives (**11a-n**) were illustrated in **scheme 1, scheme 2** and **scheme 3**. The key intermediate compound (**8**) was synthesized in four steps as described in **scheme 1,** according to previous literature. Briefly condensation of 3-hydroxy acetophenone (**1**) and phenyl hydrazine (**2**) produce required phenyl hydrazone (**3**). This phenyl hydrazone underwent Vilsmeier-Haack cyclization in the presence of DMF/$POCl_3$ to afford pyarazole-4-carbaldehyde moiety (**4**) [28-30]. Subsequently, 2,4-thiazolidinedione (**5**) was reacted with benzyl bromide (**6**) in DMF solvent K_2CO_3 used as a base yielded 3-benzylthiazolidine-2,4-dione (**7**) [31-32] that upon condensation with pyarazole-4-carbaldehyde in toluene using a few drops of glacial acetic acid and a catalytic amount of piperidine (Knoevenagal condensation) provided required intermediate compound (**8**). On the other side, different substituted anilines (**9a-n**) were treated with bromo acetyl bromide in DCM using Et_3N as a base to give 2-bromo-*N*-arylacetamides (**10a-n**) compounds were outlined in **scheme 2** [33]. Thus, obtained

intermediate (**8**) was allowed to react with different synthesized 2-bromo-*N*-arylacetamides (**10a-n**) in the presence of K_2CO_3 in DMF at room temperature to furnish desired products (**11a-n**) in moderate to excellent yields were displayed in **scheme 3** and complete physical constants of the compounds was displayed in **Table 1**.

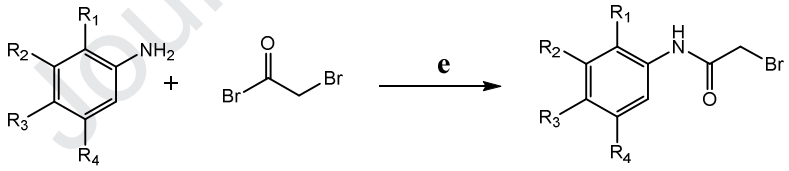
All the synthesized derivatives were characterized by ^{1}H NMR, ^{13}C NMR, IR and ESI-MS spectra. Derivatives (**11a-n**) were confirmed by their representative peaks in ^{1}H NMR, characteristic singlets appeared at 8.25-8.63, 8.14-8.23 and 7.91-7.96 ppm due to amide proton, pyrazole proton and arylidene (=CH) protons. The arylidene (=CH) proton appeared in preferably either as a singlet or multiplet at deshielded region of 7.91-7.96 ppm as expected in *Z*-form, relative to the shielded proton of the E-form (6.21-6.45 ppm) thus confirming that all the derivatives were obtained particularly in *Z*-form and *Z*-isomer is thermodynamically more stable because of intramolecular hydrogen bond that can be formed between the hydrogen bond of arylidene-H and oxygen atom of carbonyl group in TZD [34-37] and O-CH_2 and N-CH_2 protons appeared as singlets at 5.18-5.29 and 4.69-4.87 ppm. ^{13}C NMR spectra of derivatives (**11a-n**) showed characteristic signals of three carbonyl carbons (amide carbon and two TZD rind carbonyl carbons) displayed three singlets at 165.4-166.7 ppm region and carbons of methylene attached oxygen and nitrogen atoms showed two singlets at 61.9-62.4 and 44.8-45.6 ppm. Moreover, it is also proved by ESI-MS spectrum of the derivatives.

Scheme 1: Synthesis of (*Z*)-3-benzyl-5-((3-(3-hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)thiazolidine-2,4-dione (**8**).



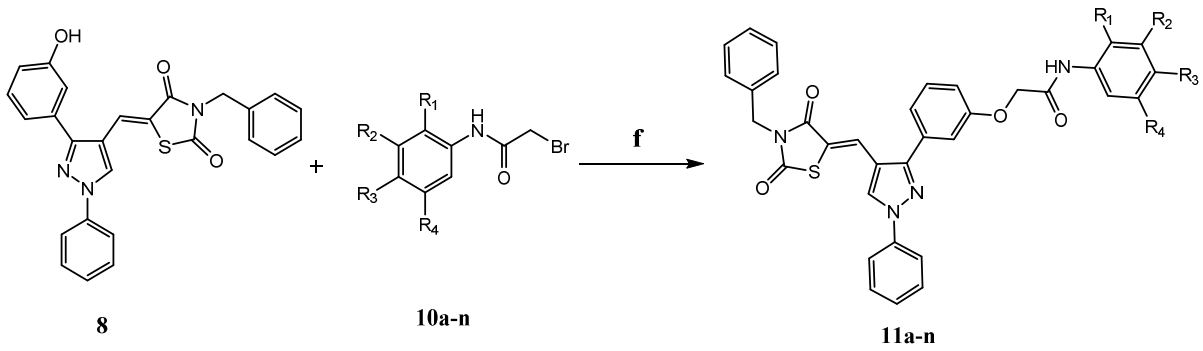
Reagents and conditions: (a) MeOH, glacial AcOH; (b) DMF/$POCl_3$, 0^0C to rt, 12 h; (c) K_2CO_3, DMF, rt, 3 h; (d) 3-(3-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4), toluene, piperidine, glacial AcOH, reflux, 8 h.

Scheme 2: Synthesis of 2-bromo-*N*-arylacetamide compounds (**10a-n**).



Reagents and conditions: (e) Et_3N, DCM, 0^0C to rt, 30 mins.

Scheme 3: 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 (**11a-n**).



Reagents and conditions: (f) K_2CO_3, DMF, rt, 5 h.

Table 1. Physical data of the compounds **11a-n**

S.No	R_1	R_2	R_3	R_4	M.F[a]	M.Wt[b]	M.P (^{0}C)[c]	Yield[d] (%)
11a	H	H	F	H	$C_{34}H_{25}FN_4O_4S$	604.16	256-258^{0}C	63%
11b	H	H	H	H	$C_{34}H_{26}N_4O_4S$	586.17	224-226^{0}C	72%
11c	H	H	Br	H	$C_{34}H_{25}BrN_4O_4S$	664.08	218-220^{0}C	68%
11d	H	H	OCH_3	H	$C_{35}H_{28}N_4O_5S$	616.18	178-180^{0}C	65%
11e	H	H	NO_2	H	$C_{34}H_{25}N_5O_6S$	631.15	>300^{0}C	61%
11f	H	H	CH_3	H	$C_{35}H_{28}N_4O_4S$	600.18	238-240^{0}C	76%
11g	H	OCH_3	OCH_3	H	$C_{36}H_{30}N_4O_6S$	646.19	>300^{0}C	63%
11h	H	CF_3	H	H	$C_{35}H_{25}F_3N_4O_4S$	654.15	186-188^{0}C	60%
11i	H	H	I	H	$C_{34}H_{25}IN_4O_4S$	712.06	204-206^{0}C	69%

11j	H	Cl	H	H	$C_{34}H_{25}ClN_4O_4S$	620.13	228-230^{0}C	75%
11k	H	H	Cl	H	$C_{34}H_{25}ClN_4O_4S$	620.13	>300^{0}C	73%
11l	H	CH_3	H	H	$C_{35}H_{28}N_4O_4S$	600.18	>300^{0}C	70%
11m	H	H	$COCH_3$	H	$C_{36}H_{28}N_4O_5S$	628.18	232-234^{0}C	63%
11n	H	OCH_3	OCH_3	OCH_3	$C_{37}H_{32}N_4O_7S$	676.20	>300^{0}C	66%

[a]Molecular formula

[b]Molecular weight

[c]Melting points in degrees centigrade

[d]Isolated yield

2.2. Cell viability assay/cytotoxic activity

All the synthesized novel (*Z*)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-*N*-arylacetamide derivatives **11a-n** were investigated for their cell viability assay or cytotoxic activity against human breast cancer cell line (MCF-7) were assessed by performing standard MTT assay and cis platin was used as a standard drug [38-41]. The compounds were treated with MCF-7 cell line at five different concentrations (0.625µM, 1.25µM, 2.5µM, 5µM and 10µM) and cell viability or cytotoxic activity results was summarized in **Table 2** and **Figure 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 standard clustered column graph was plotted after determining the cell viability percentage of compounds treated with MCF-7 cell line from **Table 2.** The graph between cell viability percentage of treated compounds on y-axis and the synthesized compounds concentration on x-axis was plotted. For switching to table 3 a series of concentrations and growth inhibition percentages response data were needed. For determination of IC_{50} values the x-y graph was plotted. The plot x-y with a linear regression was studied from formula y= ax + b. Then IC_{50} values were estimated using formula

IC_{50}=0.5-b/a and the IC_{50} values are presented in **Table 3**. The standard deviation for table 2 was calculated from values of cell viability percentage for each sample of different concentrations for table 3 was calculated from IC_{50} values.

$s = \frac{\sqrt{(x-\bar{x})^2}}{\sqrt{(n-1)}}$Where *s=standard deviation; x=sample value;* $\bar{x}$*=Mean of samples; n=number of samples*

The results were clearly demonstrated that all the synthesized compounds have shown moderate to significant cytotoxic activity with IC_{50} values ranging from 0.604µM to 6.355µM respectively. So, it was confirmed that all the novel synthesized derivatives exhibited cytotoxic activity. Based on these results, some of the corresponding compounds in particular compound **11d** exhibited remarkable cytotoxic activity comparable to standard drug and compounds **11n** and **11a** have shown nearly equivalent values to the standard drug. Compounds **11g** and **11e** have shown promising cytotoxic activity.

The structure activity relationship (SAR) of these compounds was studied by changing the substituents attached to the amide phenyl ring system. Several final derivatives were synthesized by placing an electron withdrawing or electron donating groups. The SAR study explains that the compounds bearing an electron donating groups, particularly methoxy substituent at the para position (**11d**), 3,4 dimethoxy (**11g**) and 3,4,5 trimethoxy (**11n**) derivatives have shown extraordinary cytotoxic activity with IC_{50} values (**Table 3)** 0.604µM, 1.057µM and 0.665µM respectively. When cell viability percentage readings for **11d, 11g** and **11n** was observed in **Table 2** and **Figure 2** the activity of compounds on MCF-7 cell line were active at lower concentrations compared to higher concentrations which explains that the proliferation of MCF-7 cells at lower concentration was lower than higher concentrations. Moreover, the compounds embedded electron withdrawing groups, especially fluoro substituent at the para position (**11a**) and nitro substituent at the para position (**11e**) exhibited significant cytotoxic activity with IC_{50} values 0.802µM and 1.309µM. For fluoro substituent at the para position (**11a**), the Cell viability percentage readings **Table 2** and **Figure 2** decreases with increasing of concentrations which clearly explains that the compound is concentration dependent. By analyzing SAR data, it was observed that compounds which have methyl and chloro substituents at different position have shown lesser activity when compared with other derivatives and remaining compounds showed moderate cytotoxic activity.

Table 2. Cell viability assay/Cytotoxic activity of novel synthesized derivatives (**11a-n**)

S.No	Compound	Concentrations				
		0.625µM	1.25µM	2.5µM	5µM	10µM
1	11a	84.98%±6.60	76.62%±2.86	65.47%±2.12	63.62%±2.94	60.37%±4.4
2	11b	53.71%±0.48	35.60%±7.61	53.25%±0.27	60.37%±3.46	60.21%±3.39
3	11c	60.52%±1.13	63.77%±0.31	58.20%±2.17	67.18%1.84	65.63%±1.14
4	11d	59.59%±3.0	63%±1.48	63.46%±1.27	67.18%±0.38	78.32%±5.37
5	11e	75.85%±0.93	77.08%±0.38	63.31%±6.54	80.49%±1.13	93.06%±6.75
6	11f	63.46%±1.55	54.17%2.60	57.58%±1.07	60.68%0.30	64.08%±1.82
7	11g	55.57%±3.97	61.60%±1.23	60.68%±1.64	68.42%±1.81	75.55%±5.0
8	11h	59.90%±1.55	60.06%±1.48	56.96%±2.86	73.06%±4.33	66.87%±1.56
9	11i	67.95%±2.34	71.98%±0.54	70.89%±1.02	73.39%±0.09	81.73%±3.82
10	11j	80.80%±0.12	76%±2.02	77.08%±1.53	85.75%±2.33	82.97%±1.09
11	11k	55.26%±2.38	52.32%±1.06	34.36%±6.96	64.39%±6.46	43.34%±2.95
12	11l	44.89%±0.914	48.60%±2.57	38.39%±1.99	36.53%±2.82	45.82%±1.33
13	11m	39.31%±0.76	38.85%±0.96	33.12%±3.53	48.76%±3.46	45.04%±1.79
14	11n	31.88%±6.75	40.86%±2.74	44.58%±1.07	56.65%±4.31	60.99%±6.26
15	Cisplatin	51.45%±7.56	40.27%±2.56	34.30%±0.1	28.17%±2.85	18.53%±7.16

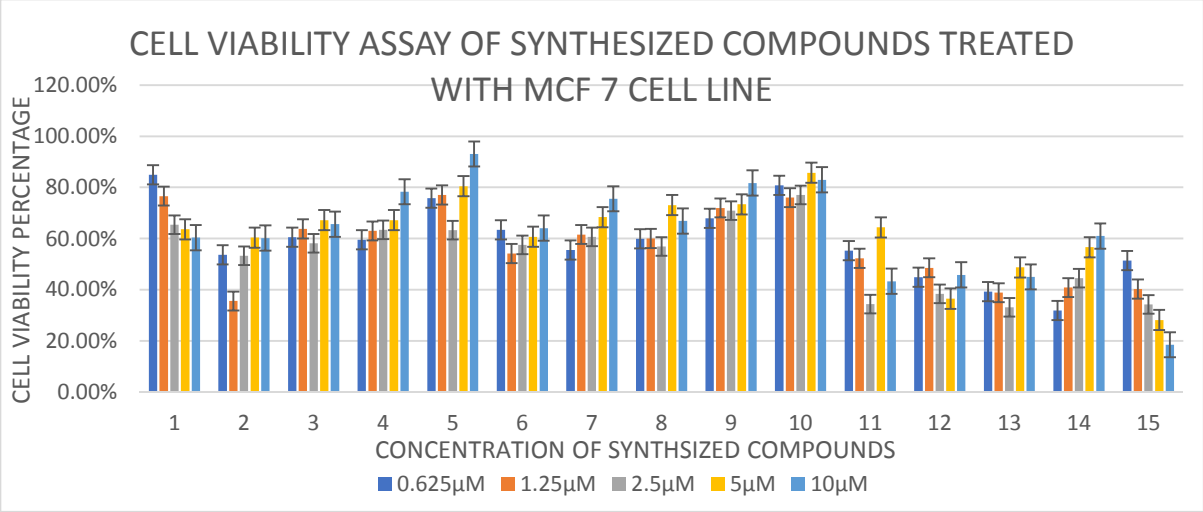


Figure 3. Cell viability assay of screened derivatives (**11a-n**) measured by MTT assay

Table 3. [a]IC_{50} values of the tested derivatives (**11a-n**) against MCF-7 cell line

S.No	Compound	IC_{50} Values (µM) MCF-7
1	**11a**	0.802µM±0.41
2	**11b**	2.661µM±0.06
3	**11c**	3.646µM±0.32
4	**11d**	0.604µM±0.46
5	**11e**	1.309µM±0.28
6	**11f**	6.355µM±1.01
7	**11g**	1.057µM±0.34
8	**11h**	1.842µM±0.146
9	**11i**	1.711µM±0.18
10	**11j**	3.529µM±0.28
11	**11k**	4.197µM±0.46
12	**11l**	4.856µM±0.63
13	**11m**	2.305µM±0.02
14	**11n**	0.665µM±0.45
15	**Cisplatin**[b]	0.636.µM±0.458
	Mean of IC_{50} values for standard deviation	2.411

[a]IC_{50} values are the concentration that cause 50% inhibition of cancer cell growth. Data represent the mean values ±, standard deviation.

[b]Positive control.

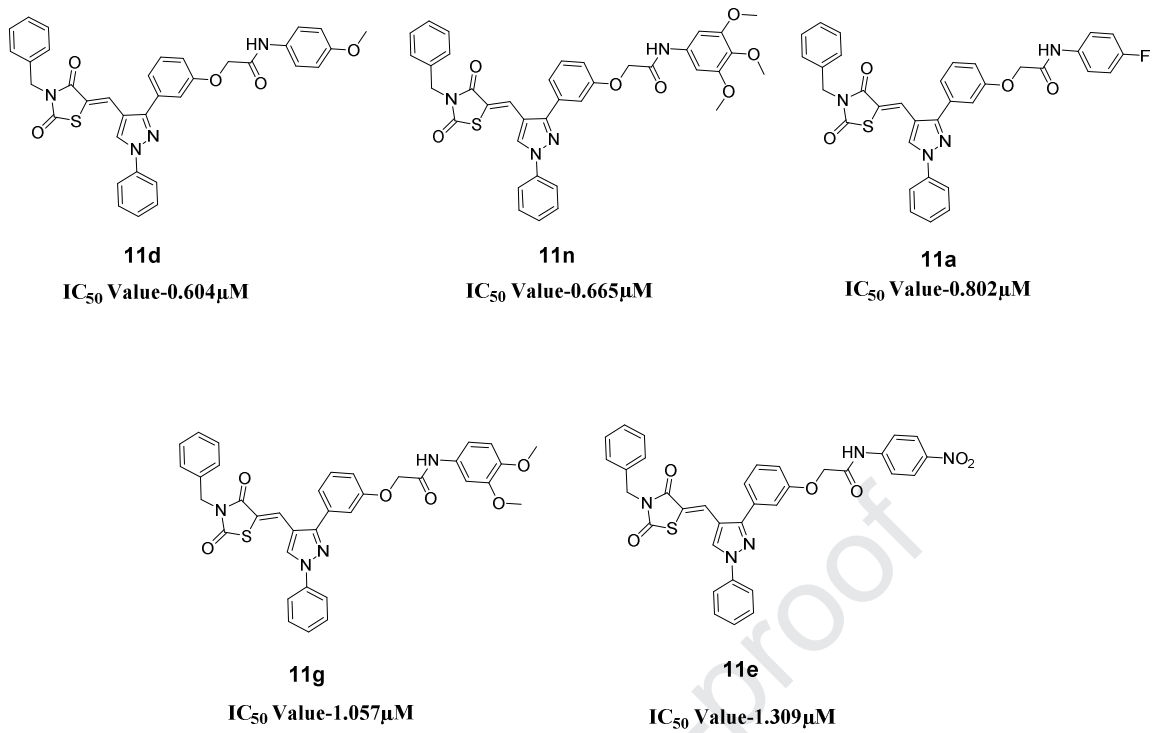


Figure 4. Some of the representative derivatives with their IC_{50} values.

2.3 Molecular docking studies

Cisplatin an ubiquitous chemotherapeutic agent is likely to exhibit its cytotoxic effect as by inhibiting DNA replication a result of forming cisplatin-DNA adducts and inducing apoptosis [42-44]. The binding mode of the newly synthesized compounds with DNA has been characterized using Glide docking in Schrodinger [45]. The intercalation of DNA was associated with the formation of intra as well as inter chain cross links with nucleotides especially DG-5, DC-6, DT-7 from A-chain and DG-15, DC-16, DG-17 and DA-18 from B-chain. All the synthesized compounds along with the standard were docked into the above specified nucleotide active site (**PDB ID: 1A2E**) [46]. The compounds 11a, 11b, 11c, 11f, 11i, 11j, 11k, 11l has shown single H-bond interaction with the DG-5 of A-chain, while **11d**, **11h**, **11n** has shown three H-bond interactions. Among them, the highest active compound **11d** has shown two hydrogen bonding interactions with DG- 5 of A-chain and one additional hydrogen bond with DC-16 of B-chain, while the standard has shown two hydrogen bonding interactions with DG- 5 of A-chain and DG-15 of B-chain. The formation of hydrogen bonding with two different chains in the DNA clearly specifies the probability of intercalation. The additional hydrogen bonding is probably due to the electron donating methoxy substitution with is para directing. The binding energies of the compounds 11a, 11b, 11c, 11f, 11l and 11i are more than the standard. It is probably because of electron

withdrawing substitutions. However, increase in substitution of electron donating groups decreases the binding energies as shown in 11n. Intermolecular hydrogen bond interactions and Intramolecular hydrogen bond interactions of the molecules were depicted in **Fig 5** and **Fig 6**. The binding energies along with the dock score has been tabulated in **Table 4.**

Table 4. Dock scores and binding energies for the synthesized compounds (**11a-n**)

S.No	Compound	IC_{50} Values(μM)	PIC_{50} (μM)	Dock scores	Binding energies(ΔG)
1	**11a**	0.802±0.41	6.095	-5.751	-24.717
2	**11b**	2.661±0.06	5.574	-5.297	-22.895
3	**11c**	3.646±0.32	5.438	-6.585	-26.827
4	**11d**	0.604±0.46	6.218	-5.801	-27.72
5	**11e**	1.309±0.28	5.883	-6.473	-15.713
6	**11f**	6.355±1.01	5.196	-6.110	-32.423
7	**11g**	1.057±0.34	5.975	-6.296	-15.96
8	**11h**	1.842±0.146	5.734	-5.865	-6.907
9	**11i**	1.711±0.18	5.766	-6.106	-29.573
10	**11j**	3.529±0.28	5.452	-5.840	-16.294
11	**11k**	4.197±0.46	5.377	-6.163	-30.10
12	**11l**	4.856±0.63	5.313	-5.891	-30.131
13	**11m**	2.305±0.02	5.637	-5.497	-17.754
14	**11n**	0.665±0.45	6.177	-5.497	-6.848
15	**Cisplatin**	0.636±0.458	6.196	-7.008	-8.381

Note: More negative indicates higher binding energies.

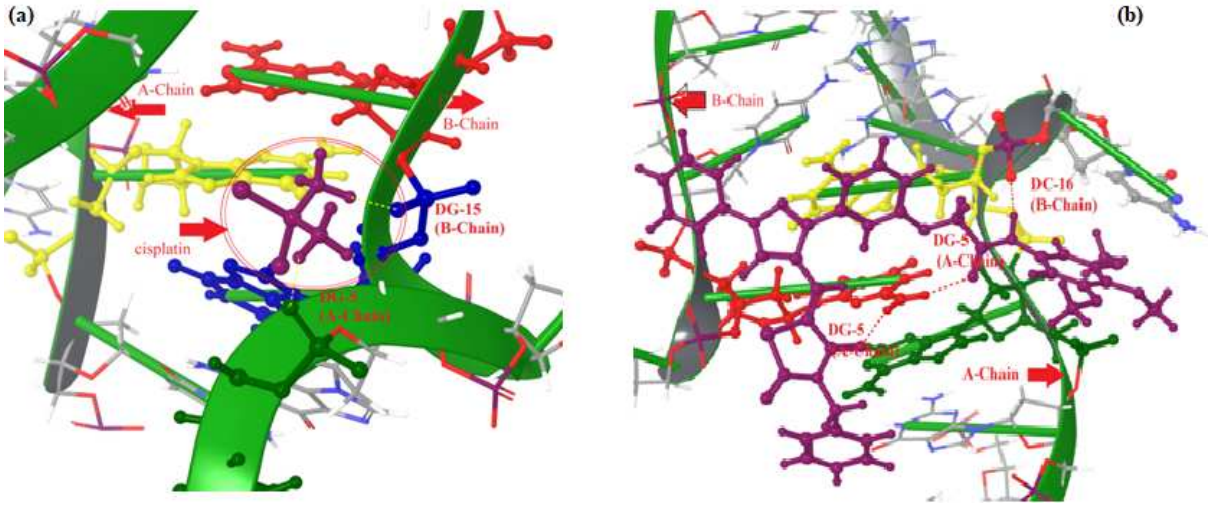


Fig 5. (a) Dock pose of standard drug (**cisplatin**) showing intermolecular hydrogen bond interaction with DG-5 of A-chain and DG-15 of B-chain. (b) Dock pose of highest active compound **11d** exhibiting three intermolecular hydrogen bond interactions, two H- bond interactions with DG-5 of A-chain and one H-bond with DC-16 of B-chain.

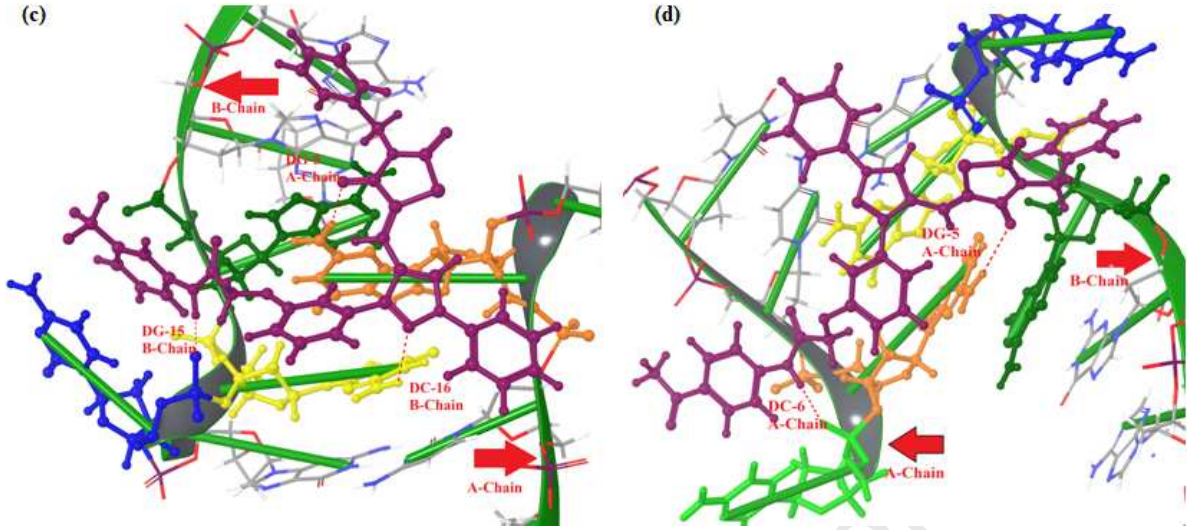


Fig 6. (c) Interchain H-bond interaction with DG-5 of A-chain and DG-15, DC-16 of B-chain in **11h** compound. (d) Intrachain H-bond interaction with DG-5, DC-6 of A-Chain in **11m**.

2.4. ADME properties

Enhancement of the ADME properties of the drug molecule is often the most difficult and challenging part of the whole drug discovery process in medicinal chemistry. The ADME profile also have a considerable impact on the possibility of success of a drug. The essential ADME properties were calculated by using QikProp module (2011) version 3.4 [47] and explored for drug-likeness by utilizing Lipinski rule of five. ADME analyses about Absorption, Distribution, Metabolism and Excretion of drug molecules. QikProp module helps in explaining pharmacodynamics and pharmacokinetics of the molecules by accessing drug like properties. All the synthesized compounds exhibit excellent percentage of human oral absorption except compound 11e, QPPMDCK cell permeability in nm/s values appeared as acceptable ranges, QPlogBB (blood brain barrier permeability) values occurred as agreeable range and all remaining properties are in an acceptable range as shown in **Table 5**. The ADME calculation results of all the synthesized derivatives have drug-likeness properties and can be additionally enhanced for better activity.

Table 5. Drug likeness properties (ADME) for the synthesized compounds.

S.No	Compound	M.Wt	QPlogPo/w[a]	QPlogS[b]	QPPCaco[c]	QPlogBB[d]	QPPMDCK[e]	% of human oral absorption[f]
1	11a	604.16	7.768	-10.683	601.687	-1.386	772.013	96.26
2	11b	586.17	7.536	-10.442	572.364	-1.545	398.775	94.512
3	11c	664.08	8.15	-11.333	592.987	-1.359	1126.085	100

4	**11d**	616.18	7.489	-10.226	598.108	-1.557	418.558	94.58
5	**11e**	631.15	6.659	-10.293	57.118	-2.996	32.822	58.505
6	**11f**	600.18	7.84	-10.841	642.071	-1.494	429.701	100
7	**11g**	646.19	7.748	-10.157	924.426	-1.353	658.782	100
8	**11h**	654.15	8.573	-11.89	522.201	-1.344	1644.623	100
9	**11i**	712.06	8.088	-11.075	606.924	-1.295	1224.702	100
10	**11j**	620.13	8.062	-11.169	572.036	-1.384	991.553	100
11	**11k**	620.13	7.919	-10.82	611.663	-1.308	1061.074	100
12	**11l**	600.18	7.92	-11.177	549.84	-1.609	393.361	96.444
13	**11m**	628.18	6.848	-10.406	144.531	-2.471	93.345	79.787
14	**11n**	676.20	7.764	-11.071	429.439	-1.994	300.975	80.657

Note: [a]foreseened octanol/water partition co-efficient 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 & >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 & >500 is excellent)

[f]percentage of human oral absorption (agreeable range: <25% is poor & >80% is excellent)

3. Experimental

Materials and methods

All the chemicals, solvents and reagents were purchased from Sigma Aldrich, Merk and Avra and were used without additional purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer using Tetramethyl silane as an internal standard and using DMSO-d_6 and $CDCl_3$ as a solvents. All chemical shift values are displayed as ppm and spin multiplicities are indicated as singlet (s); doublet (d); doublet of doublet (dd); triplet (t); multiplets (m); and coupling constants are shown in hertz. Thin layer chromatography (TLC) was performed on aluminium sheets coated with silica gel 60F254 (Merk, 0.2mm) and the spots were visualized by using UV light. The IR spectra were recorded on the Shimadzu FTIR-8400S spectrometer. Mass spectra were recorded on the GCMS-QP-1000EX mass spectrometer. Melting points were determined in melting point instruments and are uncorrected and presented in degrees centigrade.

General procedure for the synthesis of 3-(3-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4)

The fundamental beginning compound 3-(3-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**4**) was prepared according to their previous approaches. Condensation

between 3-Hydroxy acetophenone (**1**) (1 mmol) and phenyl hydrazine (**2**) (1 mmol) in the presence of a few drops of acetic acid in methanol produce required Schiff base (**3**). This imine (**3**) underwent Vilsmeier-Haack cyclization using ice cold solution of DMF (8 mmol) and $POCl_3$ (4 mmol) stirred at room temperature for 12 h. The completion of the reaction was monitored by using TLC, the resulting mixture was poured into ice cold water and was neutralized using sodium bicarbonate solution and the formed precipitate was filtered under suction pump. The resulting solid was dried and recrystalized from methanol.

General procedure for the synthesis of (*Z*)-3-benzyl-5-((3-(3-hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl) methylene) thiazolidine-2,4-dione (8)

To a solution of 3-benzylthiazolidine-2,4-dione (**7**) (1 mmol), a few drops of glacial acetic acid and catalytic amount of piperidine in anhydrous toluene was stirred for 10 mins under nitrogen atmosphere and to the above solution 3-(3-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**4**) (1 mmol), was added and the reaction mixture was stirred at reflux condition for 8 h, the completion of reaction by using TLC, the resulting reaction mixture was cooled to normal temperature. The resulting light yellow coloured solid was washed with petroleum ether and solid was collected by using a suction pump.

(Z)-3-benzyl-5-((3-(3-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione (8)

M.F: $C_{26}H_{19}N_3O_3S$; Light yellow coloured solid; Yield: 77%; M.P: 178-180^{0}C, IR (KBr cm^{-1}): 3520, 3304, 1730, 1681, 1504; ^{1}H NMR (400 MHz DMSO-d_6) δ (ppm): 9.79 (s, 1 H, Ar-OH), 8.77 (s, 1 H, Pyrazole-H), 8.02 (d, *J* = 7.7 Hz, 2 H, Ar-H), 7.76 (s, 1H, Arylidene-H), 7.58 (t, *J* = 7.8 Hz, 2 H, Ar-H), 7.43 (t, *J* = 7.4 Hz, 1 H, Ar-H), 7.38 – 7.34 (m, 3 H, Ar-H), 7.33 – 7.30 (m, 3 H, Ar-H), 7.06-7.03 (m, 2 H, Ar-H), 6.94-6.90 (m, 1 H, Ar-H), 4.83 (s, 2 H, N-CH_2); ^{13}C NMR (100 MHz DMSO-d_6) δ (ppm): 166.9, 165.2, 157.7, 153.7, 138.6, 135.5, 132.3, 130.0, 129.6, 128.6, 128.2, 127.8, 127.6, 127.5, 123.8, 119.8, 119.3, 116.0, 115.3, 115.2, 44.6; MS (ESI mass) m/z $[M+H]^+$: 454.11.

General procedure for the synthesis of 2-bromo-*N*-phenylacetamide derivatives (10a-n)

To a solution of substituted anilines (**9a-n**) (1 mmol) in DCM and triethyl amine (1 mmol) was used as a base was cooled to 0^0-5^0 C in ice bath was magnetically stirred for 5 mins. Then to the above cool solution bromo acetyl bromide (1 mmol) was added slowly, then the reaction mixture was stirred for 30 mins, the completion of the reaction was checked by TLC.

The resulting mixture was diluted with ice cold water and was extracted with dichloro methane. The combined organic layer was dried over sodium sulphate and the solvent was removed under reduced pressure to afford required acetamide derivatives (**10a-n**).

General procedure for the synthesis of (*Z*)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene) methyl)-1-phenyl-1*H*-pyrazol-3-yl) phenoxy)-*N*-phenyl acetamide derivatives (11a-n)

To a mixture of (*Z*)-3-benzyl-5-((3-(3-hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl) methylene) thiazolidine-2,4-dione (**8**) (1 mmol) and anhydrous K_2CO_3 (2 mmol) in DMF was magnetically stirred at room temperature under N_2 atmosphere for 12 mins. To the above solution substituted 2-bromo-*N*-phenylacetamide derivatives (**10a-n**) (1 mmol) were added and stirred for 5 h. After completion of the reaction (TLC analyses), the resulting reaction mixture was diluted with ice cold water and was extracted with ethyl acetate, the combined organic layer was washed with brine solution, dried over sodium sulphate the solvent was removed using reduced vacuum. The crude was purified by column chromatography on silica mesh eluting with petroleum ether and ethyl acetate as solvents to produce required compounds (**11a-n**).

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(4-fluorophenyl)acetamide11(a)

M.F: $C_{34}H_{25}FN_4O_4S$; Light yellow coloured solid; yield: 63%; M.P: 256-258^{0}C; IR (KBr cm^{-1}): 3539, 3375, 1737, 1676, 1602, 1533; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.32 (s, 1H, Amide-NH), 8.17 (d, *J* = 11.0 Hz, 1H, Pyrazole-H), 7.92 (s, 1H, Arylidene), 7.79 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.58 (dd, *J* = 8.7, 4.8 Hz, 2H, Ar-H), 7.53 – 7.49 (m, 2H, Ar-H), 7.44 (d, *J* = 6.6 Hz, 3H, Ar-H), 7.33 (s, 6H, Ar-H), 7.09 – 7.03 (m, 3H, Ar-H), 4.89 (s, 2H, O-CH_2), 4.69 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.6, 166.0, 165.7, 160.9, 158.5, 157.2, 154.0, 139.0, 135.1, 133.3, 130.5, 129.7, 128.9, 128.7, 128.3, 127.9, 127.4, 124.5, 123.2, 122.1, 122.1, 120.1, 119.7, 116.2, 115.9, 115.6, 115.4, 115.2, 67.5, 45.4; MS (ESI mass) m/z $[M+H]^+$: 605.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-phenylacetamide11(b)

M.F: $C_{34}H_{26}N_4O_4S$; Light yellow coloured solid; yield: 72%; M.P: 224-226^{0}C; IR (KBr cm^{-1}): 3375, 3061, 2920, 1735, 1678, 1597; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.32 (s, 1H,

Amide-NH), 8.18 (s, 1H, Pyrazole-H), 7.93 (s, 1H, Arylidene-H), 7.79 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.63 – 7.60 (m, 2H, Ar-H), 7.52 (dd, *J* = 12.9, 4.6 Hz, 3H, Ar-H), 7.46 – 7.43 (m, 3H, Ar-H), 7.36 – 7.31 (m, 7H, Ar-H), 7.18 – 7.14 (m, 1H, Ar-H), 7.09 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar-H), 4.89 (s, 2H, O-CH_2), 4.70 (s, 2H, N-CH_2); ^{13}C NMR (100MHz, $CDCl_3$) δ (ppm): 166.6, 166.0, 165.6, 157.3, 154.0, 139.0, 136.7, 135.1, 133.3, 130.5, 130.2, 129.7, 129.1, 128.9, 128.7, 128.3, 127.9, 127.7, 127.4, 127.3, 124.9, 124.5, 123.1, 121.1, 120.2, 120.1, 119.7, 119.6, 116.2, 115.4, 115.2, 67.6, 45.4; MS (ESI mass) m/z $[M+H]^+$: 587.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(4-bromophenyl)acetamide(11c)

M.F: $C_{34}H_{25}BrN_4O_4S$; Light yellow coloured solid; yield: 68%; M.P: 218-220^{0}C; IR (KBr cm^{-1}): 3066, 2922, 1735, 1681, 1606, 1539; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.35 (s, 1H, Amide-NH), 8.17 (s, 1H, Pyrazole), 7.91 (s, 1H, Arylidene), 7.78 (dd, *J* = 8.5, 1.0 Hz, 2H, Ar-H), 7.52 (ddd, *J* = 11.4, 7.2, 2.9 Hz, 5H, Ar-H), 7.47 (s, 1H, Ar-H), 7.46 – 7.44 (m, 2H, Ar-H), 7.42 – 7.35 (m, 2H, Ar-H), 7.35 – 7.30 (m, 5H, Ar-H), 7.09 – 7.05 (m, 1H, Ar-H), 4.88 (d, *J* = 3.5 Hz, 2H, O-CH_2), 4.67 (s, 2H, N-CH_2); ^{13}C NMR (100MHz, DMSO-d_6) δ (ppm): 166.9, 166.5, 165.1, 158.0, 157.7, 153.2, 138.6, 138.6, 137.7, 135.4, 132.5, 132.3, 131.5, 130.1, 130.0, 129.5, 128.6, 128.3, 127.8, 127.6, 123.7, 121.6, 120.1, 119.8, 119.3, 115.4, 115.0, 67.1, 44.6; MS (ESI mass) m/z $[M+H]^+$: 665.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(4-methoxyphenyl)acetamide(11d)

M.F: $C_{35}H_{28}N_4O_5S$; Light yellow coloured solid; yield: 65%; M.P: 178-180^{0}C; IR (KBr cm^{-1}): 3304, 2920, 1737, 1683, 1610, 1537; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.24 (s, 1H, Amide-NH), 8.18 (s, 1H, Pyrazole-H), 7.92 (s, 1H, Arylidene-H), 7.79 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.56 – 7.49 (m, 5H, Ar-H), 7.42 (dd, *J* = 12.8, 7.0 Hz, 3H, Ar-H), 7.35 – 7.30 (m, 5H, Ar-H), 7.08 (dd, *J* = 8.2, 2.2 Hz, 1H, Ar-H), 6.89 (d, *J* = 8.9 Hz, 2H, Ar-H), 4.89 (s, 2H, O-CH_2), 4.68 (s, 2H, N-CH_2), 3.80 (s, 3H, Methoxy-H); ^{13}C NMR (100MHz, $CDCl_3$) δ (ppm): 166.6, 165.8, 165.6, 157.4, 156.8, 139.1, 135.1, 133.3, 130.4, 129.8, 129.7, 128.9, 128.7, 128.3, 127.8, 127.4, 127.3, 124.5, 123.1, 122.1, 120.1, 119.7, 116.2, 115.4, 115.2, 114.2, 67.6, 55.4, 45.4; MS (ESI mass) m/z $[M+H]^+$: 617.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(4-nitrophenyl)acetamide(11e)

M.F: $C_{34}H_{25}N_5O_6S$; Light yellow coloured solid; yield: 61%; M.P: >300^{0}C; IR (KBr cm^{-1}): 3383, 3240, 1732, 1678, 1600, 1494; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.63 (s, 1H,

Amide-NH), 8.26 (d, *J* = 2.0 Hz, 1H, Ar-H), 8.25 – 8.23 (m, 1H, Ar-H), 8.18 (s, 1H, Pyrazole-H), 7.91 (s, 1H, Arylidene-H), 7.86 – 7.82 (m, 2H, Ar-H), 7.79 (dd, *J* = 7.5, 1.3 Hz, 2H, Ar-H), 7.55 – 7.51 (m, 2H, Ar-H), 7.44 (dd, *J* = 10.3, 3.9 Hz, 3H, Ar-H), 7.33 (dd, *J* = 8.9, 4.3 Hz, 6H, Ar-H), 7.09 (dd, *J* = 7.9, 2.1 Hz, 1H, Ar-H), 4.89 (d, *J* = 2.7 Hz, 2H, O-CH_2), 4.73 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 167.4, 166.9, 165.2, 158.0, 157.7, 153.7, 144.5, 142.4, 138.6, 135.5, 132.5, 132.3, 130.1, 130.0, 129.6, 128.6, 128.3, 128.2, 127.8, 127.6, 127.5, 127.5, 124.9, 123.8, 121.7, 120.1, 119.8, 119.4, 119.3, 115.2, 67.1, 44.6; MS (ESI mass) m/z $[M+H]^+$: 632.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(p-tolyl)acetamide(11f)

M.F: $C_{35}H_{28}N_4O_4S$; Light yellow coloured solid; yield: 76%; M.P: 238-240^{0}C; IR (KBr cm^{-1}): 3522, 3300, 1732, 1676, 1600, 1531; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.27 (s, 1H, Amide-NH), 8.18 (s, 1H, Pyrazole-H), 7.92 (s, 1H, Arylidene-H), 7.79 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.52 – 7.47 (m, 4H, Ar-H), 7.44 (dd, *J* = 8.7, 2.2 Hz, 3H, Ar-H), 7.36 – 7.30 (m, 6H, Ar-H), 7.16 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.09 (dd, *J* = 8.1, 2.2 Hz, 1H, Ar-H), 4.89 (d, *J* = 2.7 Hz, 2H, O-CH_2), 4.68 (s, 2H, N-CH_2), 2.33 (s, 3H, Tolyl-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.6, 165.8, 165.6, 157.4, 139.1, 135.1, 134.6, 134.2, 133.3, 130.4, 129.7, 129.6, 129.5, 128.9, 128.7, 128.3, 127.8, 127.4, 124.5, 123.1, 120.3, 120.1, 119.7, 119.6, 116.2, 115.4, 115.2, 67.6, 45.4, 20.9; MS (ESI mass) m/z $[M+H]^+$: 601.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(3,4-dimethoxyphenyl)acetamide(11g)

M.F: $C_{36}H_{30}N_4O_6S$; Light yellow coloured solid; yield: 63%; M.P: >300^{0}C; IR (KBr cm^{-1}): 3385, 1734, 1683, 1602, 1514; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.24 (s, 1H, Amide-NH), 8.18 (s, 1H, Pyrazole-H), 7.92 (s, 1H, Arylidene-H), 7.81 – 7.76 (m, 2H, Ar-H), 7.55 – 7.48 (m, 3H, Ar-H), 7.46 – 7.39 (m, 3H, Ar-H), 7.32 (ddd, *J* = 8.7, 7.9, 3.5 Hz, 6H, Ar-H), 7.06 (ddd, *J* = 23.8, 8.4, 2.3 Hz, 2H, Ar-H), 6.84 (d, *J* = 8.7 Hz, 1H, Ar-H), 4.89 (s, 2H, O-CH_2), 4.68 (s, 2H, N-CH_2), 3.90 (s, 3H, Methoxy-H), 3.87 (s, 3H, Methoxy-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.6, 165.7, 165.6, 157.4, 154.0, 149.1, 146.3, 139.1, 135.1, 133.3, 130.4, 130.3, 129.7, 129.5, 128.9, 128.7, 128.3, 127.9, 127.4, 124.5, 123.1, 120.1, 119.7, 116.2, 115.5, 115.2, 112.4, 111.3, 105.1, 67.6, 56.1, 56.0, 45.4; MS (ESI mass) m/z $[M+H]^+$: 647.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(4-(trifluoromethyl)phenyl)acetamide(11h)

M.F: $C_{35}H_{25}F_3N_4O_4S$; Light yellow coloured solid; yield: 60%; M.P: 186-188^{0}C; IR (KBr cm^{-1}): 3369, 3240, 1737, 1681, 1602; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.47 (s, 1H, Amide-NH), 8.18 (d, *J* = 6.9 Hz, 1H, Pyrazole-H), 7.95 – 7.91 (m, 2H, Ar-H), 7.86 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.79 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.56 – 7.49 (m, 4H, Ar-H), 7.43 (t, *J* = 7.5 Hz, 4H, Ar-H), 7.36 – 7.31 (m, 5H, Ar-H), 7.10 (dd, *J* = 8.2, 2.2 Hz, 1H, Ar-H), 4.90 (s, 2H, O-CH_2), 4.71 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.6, 166.2, 165.7, 157.1, 156.2, 154.0, 139.0, 137.3, 135.1, 133.4, 131.3, 130.5, 129.7, 129.6, 128.9, 128.7, 128.3, 127.9, 127.4, 124.5, 123.3, 123.2, 120.1, 119.7, 116.8, 116.8, 116.2, 115.4, 115.2, 67.5, 45.4; MS (ESI mass) m/z $[M+H]^+$: 655.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(4-iodophenyl)acetamide(11i)

M.F: $C_{34}H_{25}IN_4O_4S$; Light yellow coloured solid; yield: 69%; M.P: 204-206^{0}C; IR (KBr cm^{-1}): 3388, 3240, 1730, 1683, 1670, 1521; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.32 (s, 1H, Amide-NH), 8.17 (s, 1H, Pyrazole-H), 7.91 (s, 1H, Arylidene-H), 7.80 – 7.76 (m, 2H, Ar-H), 7.68 – 7.64 (m, 2H, Ar-H), 7.55 – 7.48 (m, 3H, Ar-H), 7.45 – 7.40 (m, 5H, Ar-H), 7.33 (tt, *J* = 6.8, 3.4 Hz, 5H, Ar-H), 7.07 (dd, *J* = 8.0, 2.1 Hz, 1H, Ar-H), 4.88 (d, *J* = 5.7 Hz, 2H, O-CH_2), 4.67 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.6, 166.0, 165.6, 157.2, 154.0, 139.1, 138.0, 136.6, 135.1, 133.3, 130.5, 129.7, 129.6, 128.9, 128.8, 128.3, 127.9, 127.4, 124.5, 123.2, 122.0, 120.2, 119.7, 119.6, 116.2, 115.4, 115.2, 88.2, 67.6, 45.4; MS (ESI mass) m/z $[M+H]^+$: 713.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(3-chlorophenyl)acetamide(11j)

M.F: $C_{34}H_{25}ClN_4O_4S$; Light yellow coloured solid; yield: 75%; M.P: 228-230^{0}C; IR (KBr cm^{-1}): 3381, 3294, 1734, 1685, 1591; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.34 (s, 1H, Amide-NH), 8.18 (s, 1H, Pyrazole-H), 7.92 (s, 1H, Arylidene-H), 7.77 (dt, *J* = 3.7, 1.5 Hz, 3H, Ar-H), 7.52 (dd, *J* = 16.8, 8.4 Hz, 4H, Ar-H), 7.46 – 7.40 (m, 3H, Ar-H), 7.35 – 7.27 (m, 6H, Ar-H), 7.16 – 7.12 (m, 1H, Ar-H), 7.08 (dd, *J* = 8.1, 2.1 Hz, 1H, Ar-H), 4.89 (d, *J* = 4.2 Hz, 2H, O-CH_2), 4.69 (s, 2H, N-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.6, 166.0, 165.6, 157.2, 154.0, 139.1, 137.9, 135.1, 134.7, 133.3, 130.5, 130.1, 129.7, 128.9, 128.7, 128.3, 127.9, 127.4, 124.9, 124.5, 123.2, 120.2, 120.1, 119.7, 118.1, 116.2, 115.4, 115.2, 67.6, 45.4; MS (ESI mass) m/z $[M+H]^+$: 621.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(4-chlorophenyl)acetamide(11k)

M.F: $C_{34}H_{25}ClN_4O_4S$; Light yellow coloured solid; yield: 73%; M.P: >300^{0}C; IR (KBr cm^{-1}): 3369, 2918, 1735, 1674, 1531; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.33 (s, 1H, Amide-NH), 8.18 (s, 1H, Pyrazole-H), 7.92 (s, 1H, Arylidene-H), 7.78 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.58 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.55 – 7.48 (m, 3H, Ar-H), 7.46 – 7.41 (m, 3H, Ar-H), 7.32 (dt, *J* = 8.0, 3.3 Hz, 7H, Ar-H), 7.08 (dd, *J* = 8.3, 2.0 Hz, 1H, Ar-H), 4.89 (s, 2H, O-CH_2), 4.70 (s, 2H, N-CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.6, 166.0, 165.6, 157.2, 139.1, 135.4, 135.1, 133.3, 130.5, 129.9, 129.7, 129.6, 129.1, 128.9, 128.7, 128.3, 127.9, 127.4, 124.5, 123.2, 121.4, 120.2, 119.7, 119.6, 116.2, 115.4, 115.2, 67.6, 45.4; MS (ESI mass) m/z $[M+H]^+$: 621.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(m-tolyl)acetamide(11l)

M.F: $C_{35}H_{28}N_4O_4S$; Light yellow coloured solid; yield: 70%; M.P: >300^{0}C; IR (KBr cm^{-1}): 3066, 2922, 1735, 1681, 1606; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.27 (s, 1H, Amide-NH), 8.18 (s, 1H, Pyrazole-H), 7.93 (s, 1H, Arylidene-H), 7.79 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.53 (t, *J* = 7.9 Hz, 2H, Ar-H), 7.47 – 7.38 (m, 6H, Ar-H), 7.35 – 7.29 (m, 5H, Ar-H), 7.23 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.09 (dd, *J* = 8.2, 2.4 Hz, 1H, Ar-H), 6.98 (d, *J* = 7.6 Hz, 1H, Ar-H), 4.89 (s, 2H, O-CH_2), 4.68 (s, 2H, N-CH_2), 2.36 (s, 3H, Tolyl-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.6, 165.9, 165.6, 157.3, 154.0, 139.1, 139.0, 136.7, 135.1, 133.3, 130.4, 129.7, 128.9, 128.7, 128.3, 127.8, 127.4, 125.7, 124.5, 123.1, 120.8, 120.1, 119.7, 117.3, 116.2, 115.4, 115.2, 67.7, 45.4, 21.4; MS (ESI mass) m/z $[M+H]^+$: 601.

(Z)-N-(4-acetylphenyl)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)acetamide(11m)

M.F: $C_{36}H_{28}N_4O_5S$; Light yellow coloured solid; yield: 63%; M.P: 232-234^{0}C; IR (KBr cm^{-1}): 3240, 3055, 1737, 1681, 1604; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.51 (s, 1H, Amide-NH), 8.18 (s, 1H, Pyrazole-H), 7.98 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.92 (s, 1H, Arylidene-H), 7.81 – 7.72 (m, 4H, Ar-H), 7.52 (dd, *J* = 15.4, 7.5 Hz, 3H, Ar-H), 7.47 – 7.39 (m, 3H, Ar-H), 7.37 – 7.29 (m, 5H, Ar-H), 7.10 (dd, *J* = 8.0, 2.6 Hz, 1H, Ar-H), 4.90 (s, 2H, O-CH_2), 4.71 (s, 2H, N-CH_2), 2.59 (s, 3H, Acetyl-H), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 191.3, 166.6, 165.9, 165.3, 157.3, 154.1, 139.1, 137.2, 135.2, 134.7, 133.3, 132.9, 129.7, 129.1, 128.6, 127.9, 127.3, 124.6, 123.3, 120.4, 119.9, 119.2, 118.6, 116.5, 115.4, 115.1, 67.4, 45.4, 23.3; MS (ESI mass) m/z $[M+H]^+$: 629.

(Z)-2-(3-(4-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)-N-(3,4,5-trimethoxyphenyl)acetamide(11n)

M.F: $C_{37}H_{32}N_4O_7S$; Light yellow coloured solid; yield: 66%; M.P: >300^{0}C; IR (KBr cm^{-1}): 3383, 3240, 1735, 1683, 1597; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.27 (s, 1H, Amide-NH), 8.17 (s, 1H, Pyrazole-H), 7.92 (d, *J* = 7.0 Hz, 1H, Ar-H), 7.78 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.57 – 7.37 (m, 7H, Ar-H), 7.32 (ddd, *J* = 22.3, 13.9, 8.5 Hz, 6H, Ar-H), 7.09 (dd, *J* = 8.2, 2.3 Hz, 1H, Ar-H), 4.88 (s, 2H, O-CH_2), 4.67 (s, 2H, N-CH_2), 3.87 (s, 6H, Methoxy-H), 3.83 (s, 3H, Methoxy-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.5, 165.9, 165.6, 157.3, 154.0, 153.4, 139.1, 135.2, 135.1, 133.3, 132.9, 130.4, 129.7, 128.8, 128.7, 128.3, 127.9, 127.4, 124.4, 123.2, 120.2, 119.7, 116.2, 115.6, 115.1, 97.9, 67.7, 60.9, 56.2, 45.4; MS (ESI mass) m/z $[M+H]^+$: 677.

3.1. Cell Viability assay and cytotoxic activity of synthesized compounds towards breast cancer cell line (MCF-7)

Materials and method:

MTT (3-(4, 5-dimethyl thiazol-2yl)-2, 5-di phenyl tetrazolium bromide) assay were 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 micro assay, culture plate at a density of 3×10^3 cells per well in 200µl in Dulbecco's modified eagles medium (DMEM) (Gibco NY,USA)supplemented with 10% Fetal bovine serum (FBS)(Bio cell, CA,USA)and 1x antibiotic- anti-mycotic solution(contains Penicillin, Streptomycin, Amphotericin-D) and were grown exponentially for 24hrs in a humidified 5% CO_2 incubator at 37^{0}C to test the growth inhibition of synthesized compounds. The 10mM stocks were prepared initially by diluting the synthesized compounds and standard Cisplatin in DMSO. The different concentrations of 25µM, 50µM, 100µM, 200µM, 500µM were prepared from 10mM stocksdiluted in DMSO. After seeding of cells for 24hrs in 96well plate, 5µl of given synthesized compounds and standard cisplatin of respective concentrations 25µM, 50µM, 100µM, and200µM, 500µM were added to each well in duplicates having MCF 7 cells to reach the final concentration of 0.625µM, 1.25µM, 2.5µM, 5µM and 10µM 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 24hrs at 37^{0}C. Upon completion of 24hrs, 20µL stock MTT dye solution (5mg/ml) was added to each well and incubated at 37^{0}C in humidified 5% CO_2 incubator for 4hrs. After incubation of 4hrs, an MTT dye solution was aspirated and 100µl 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 hr the absorbance of each well at 490nm 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 (0.625µM, 1.25µM, 2.5µM, 5µM and 10µM) and percentage of cell viability on y-axis. The cell viability percentage can be calculated from the following formula:

Cell viability percentage = Absorbance of treated cells / Absorbance of untreated cells × 100

4. Conclusion

In conclusion, we have developed and synthesized a series 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 (**11a-n**) and evaluated for their cytotoxic activity. All the novel synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, IR and MS spectra. The biological assay results demonstrate that all the derivatives exhibit moderate to remarkable cytotoxic activity. However, some of the derivatives consist of electron donating groups have display extensive cytotoxic activity. Among all the synthesized compounds, particularly compounds **11d** and **11n** has shown promising cytotoxic activity with IC_{50} values 0.604µM and 0.665µM compared to standard drug cisplatin. Noticeably compounds **11a**, **11e** and **11g** also have shown significant cytotoxic activity. By close examination of these results proves that all the synthesized derivatives have potential cytotoxic efficiency and could be recognized as significant moieties for the discovery and development of novel therapeutic cytotoxic drugs.

5. Supplementary

^{1}H NMR, ^{13}C NMR, IR and ESI-MS spectra of all the novel synthesized compounds were provided in supplementary.

6. Conflict of interest

The authors have declared no conflict of interest

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Highlights of manuscript are:

- The newly synthesized compounds were screened for their cytotoxic activity against human breast cancer cell line (MCF-7) at different concentrations of 0.625µM, 1.25µM, 2.5µM, 5µM and 10µM respectively.
- Among the series, compound **11d** and **11n** have shown promising cytotoxic activity with IC_{50} values 0.604µM and 0.665µM compared to standard drug cisplatin and compounds **11a**, **11e** and **11g** also have shown considerable cytotoxic activity.
- *In-Silico* molecular docking studies were performed using Schrodinger software. (**PDB ID: 1A2E**) compounds **11d**, **11h** and **11n** have shown three H-bond interactions, while the standard cisplatin has shown two H-bond interactions.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.