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Graphical Abstract

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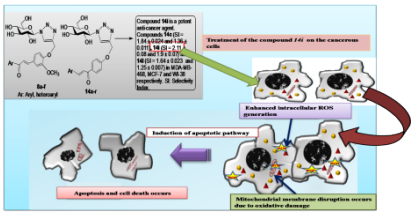

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Anti-cancer potential of novel glycosylated 1,4-substituted triazolylchalcone derivatives

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ABSTRACT

A series of glycosylated 1,4-substituted triazolyl chalcone derivatives (**8a-f** and **14a-r**) were synthesized in high yield using 1,3-cycloaddition (Click chemistry) of D-glucosyl azides with a variety of propargylated chalcone derivatives followed by de-*O*-acetylation. The synthesized compounds were evaluated for their cytotoxic potential against the human breast carcinoma cell lines and non-cancerous cells. The MTT assay identified three promising cytotoxic compounds (**14c**, **14i** and **14l**) and further biochemical and microscopic studies were carried out with the best compound **14i** among the active compounds.

Cancer is one of the most deadly diseases known to mankind, which remains a global healthcare issue for a long time. It still continues to be a major threat in the developing countries like India with limited awareness of the disease. Among the various interventions used therapeutically against cancer, chemotherapy along with radiotherapy has been the most widely used and potential strategies for treating this disease.[1,2] Over the last few decades, several bio-molecular interactions have been identified through different biochemical techniques. Protein-protein interactions, [3,4] Protein-DNA[5] and RNA interactions [6] have given enormous idea about their decisive role in oncogenic transformation, tumor progression and metastasis. [7] All together the genomic, proteomic and structural information has provided several new targets and opportunities for future drug discovery against cancer. Chemotherapy is unable to provide complete protection against cancer, regardless of remarkable advancement in modern medical research. Most of the chemotherapeutic agents have been found to be associated with poor prognosis, largely owing to their cytotoxicity on normal cells.[8,9] Additionally, high toxicities and undesirable side-effects associated with some cancer chemotherapy drugs increase the need for novel anti-tumor drugs, with fewer side-effects and greater therapeutic efficacy.[10] Therefore, targeting the molecular mechanism that contributes to the hallmarks of cancer through small molecule from synthetic or natural source can be an useful tool for future cancer therapeutics.

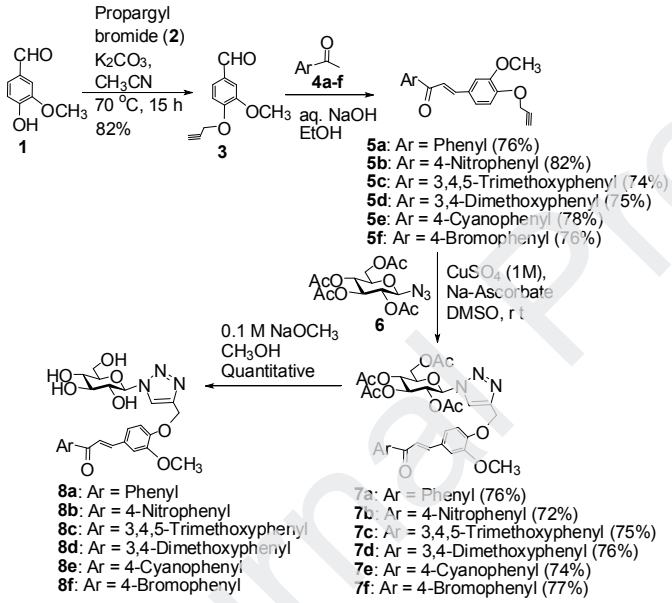
1,3-Diaryl-2-propenones namely, chalcones are important class of molecules [11,12] to act as precursors of the medicinally important heterocyclic compounds such as, pyrazolines, quinoxalines, flavones, flavanones, isoxazolines, pyrimidines to name a few. Conventionally, chalcones are prepared by Claisen-Schmidt condensation of aryl aldehyde and acetophenone derivatives in the presence of a base. [13] Chalcones possess a wide range of therapeutic potential, which include antitumor, antiviral, antitubercular, antifungal, enzyme inhibitor, antiplatelet and many more.[14, 15]

In another aspect, glycosylated 1,2,3-triazole derivatives are privileged class of compounds[16,17] showing wide variety of pharmacological properties such as anticancer, anti-tubercular, enzyme inhibitors, reverse transcriptase inhibitors, β-lactum antibiotics etc. Because of their remarkable synthetic utility 1,2,3-triazole derivatives have been extensively studied by medicinal chemists.[18] Conventionally, they have been prepared under copper mediated click chemistry condition.[19-21]

Molecular hybridization of multiple pharmacophores for the development of a single molecule with enhanced biological activities has become an attractive area in medicinal chemistry. Several reports have appeared in the literature on the synthesis of hybrid class of molecules containing triazole and chalcone moieties having significant improvement in the medicinal properties, which include chalcone-triazole derivatives,[22] chalcone-β-lactum-triazole derivative,[23] chalcone-pyrrolo-[2,1-c][1,4]-benzodiazepine conjugate[24] and their anticancer potential against a variety of cancer cells. Taking cues from the earlier reports, it was decided to design hybride class of molecules incorporating chalcone, triazole and carbohydrate in them to develop more potent anti-cancer agents. It is envisioned that presence of carbohydrate moiety could improve the bioavailability of the compound by improving its solubility in

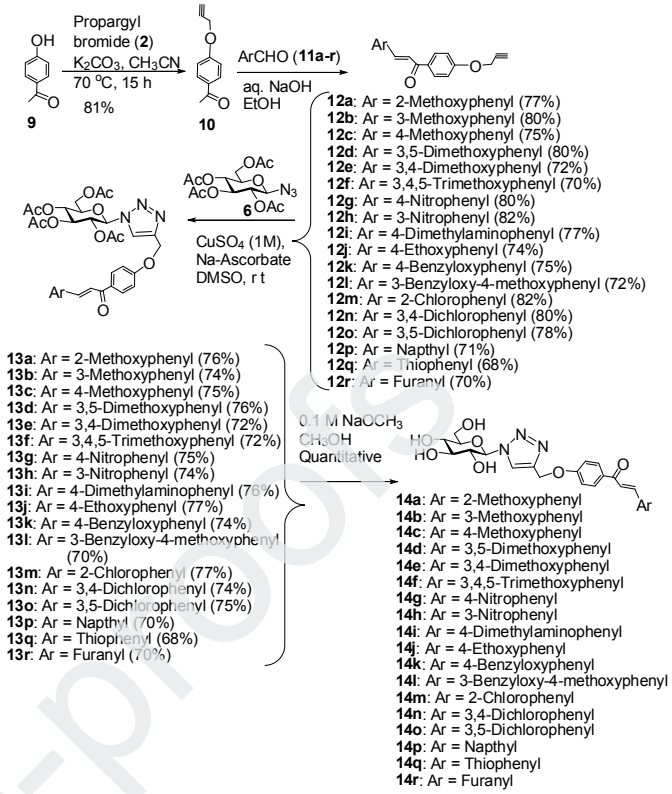
ac... de-*O*-substituted triazolyl chalcone derivatives and their evaluation as anti-proliferative agent against human breast carcinoma cell lines is presented here. Several biochemical and microscopic experiments were also been executed to demonstrate the potential of the most promising compound as anti-cancer agent.

In order to prepare the chalcone derivatives containing a propargyl functionality two starting materials were selected. Vaniline (**1**) was treated with propargyl bromide (**2**) in the presence of potassium carbonate at 70 °C to give compound **3** in 82% yield. Compound **3** was treated with a series of acetophenone derivatives (**4a-f**) in the presence of aq. sodium hydroxide [25] in ethanol to furnish a series of chalcone derivatives (**5a-f**) in satisfactory yield. It is noteworthy that the chalcone derivatives (**5a-f**) were obtained exclusively as *trans*-olefins. Compounds (**5a-f**) allowed to react with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**6**) [21] using "Click chemistry" in the presence of a combination of copper(II) sulphate and sodium L-ascorbate[21] to give glycosylated 1,4-substituted triazolylmethyl chalcone derivatives (**7a-f**) in satisfactory yield. Exclusive formation of 1,4-substituted 1,2,3-triazole derivatives (**7a-f**) was observed under the reaction conditions, which was confirmed from the NMR spectral analysis. Finally, de-*O*-acetylation of compounds **7a-f** using sodium methoxide furnished compounds **8a-f** with free hydroxyl groups in the sugar moieties in quantitative yield (Scheme 1).



Scheme 1: Synthesis of glycosylated 1,4-substituted triazolylmethyl chalcone derivatives (**8a-8f**). Isolated yield is presented in parenthesis.

In another experiment, 4-hydroxyacetophenone (**9**) was treated with propargyl bromide (**2**) in the presence of potassium carbonate at 70 °C to give compound **10** in 81% yield. Compound **10** was treated with a series of aromatic aldehyde derivatives (**11a-r**) in the presence of aq. sodium hydroxide in ethanol[25] to furnish a series of chalcone derivatives (**12a-r**) as exclusively *trans*-olefin in satisfactory yield. The chalcone derivatives (**12a-r**) were allowed to react with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**6**) [21] using "Click chemistry" in the presence of a combination of copper(II) sulphate and sodium L-ascorbate[21] to give glycosylated 1,4-substituted triazolylmethyl chalcone derivatives (**13a-r**) in satisfactory yield. Exclusive formation of 1,4-substituted 1,2,3-triazole derivatives (**13a-r**) was observed under the reaction conditions, which was confirmed from the NMR spectral analysis. Finally, de-*O*-acetylation of compounds **13a-r** using sodium methoxide furnished compounds **14a-r** with free hydroxyl groups in the sugar moieties in quantitative yield (Scheme 2).



Scheme 2: Synthesis of glycosylated 1,4-substituted triazolylmethyl chalcone derivatives (**14a-14r**). Isolated yield is presented in parenthesis.

Selective cytotoxicity of synthesized compounds towards the cancer cells

Primarily, 24 synthesized compounds (**8a-f** and **14a-r**) along with etoposide and paclitaxel were assessed for their cytotoxic ability on MDA-MB-468 cells [human triple negative (ER-, PR- and HER2-) breast cancer cells], MCF-7 [human (ER+, PR+ and HER2-) breast cancer cells] and WI-38 cells (non-cancerous lung fibroblast cell). For this experiment, cells were treated with varying concentrations of the compounds (0-50 μM) and cell cytotoxicity was measured by MTT assay.[26] The cytotoxicity of the tested compounds in terms of LD_{50} were presented in Table 1. From the MTT assay it was observed that three compounds, **14c**, **14i** and **14l** showed significantly higher efficacy in MDA-MB-468 cells with LD_{50} values of (39 ± 1.87; 28 ± 1.9 and 64 ± 3.8 μM) respectively. Similar efficacy of **14c**, **14i** and **14l** was found in MCF-7 cells with LD_{50} values of (53 ± 1.13; 31 ± 2.3 and 84 ± 3.4 μM) respectively. Subsequently, when the selectivity index (SI) of the compounds were calculated by comparing the cytotoxic LD_{50} value of the compound in normal cell (WI-38) versus cancer cells (MDA-MB-468 and MCF-7), it was found that compound **14i** possessed higher SI (SI = 2.11 ± 0.08 and 1.9 ± 0.07) as compared to compound **14c** (1.84 ± 0.024 and 1.36 ± 0.011) and compound **14l** (SI = 1.64 ± 0.023 and 1.25 ± 0.007). Considering the MTT data, compound **14i** was found as a potent cytotoxic agent against cancer cells in comparison to non-cancerous cells based on its highest selectivity index (SI) (Figure 1).

T cancer cell lines (Data for active compounds are mentioned in bold).

Compd.	MDA-MB 468	MCF-7	WI38	S.I.(WI38/ MDA-MB 468)	S.I.(WI38/ MCF-7)
8a	89 ± 3.2	123 ± 3.59	98 ±1.89	1.10 ± 0.02	0.80 ± 0.01
8b	68 ± 2.3	76 ± 1.6	75 ± 2.9	1.02 ± 0.09	0.99 ± 0.014
8c	73 ± 3.2	87 ± 2.49	67 ± 1.89	0.92 ± 0.016	0.77 ±0.0002
8d	67±2.5	66 ± 2.17	96 ± 3.63	1.43 ± 0.004	1.45 ± 0.01
8e	82 ± 3.1	78± 1.65	88± 1.78	1.07 ± 0.02	1.13 ± 0.003
8f	65 ± 1.7	99 ± 2.4	89 ±2.9	1.37 ± 0.008	0.90 ± 0.006
14a	79 ± 3.8	97 ± 1.9	103 ± 2.6	1.3 ± 0.025	1.06 ±0.008
14b	77 ±1.6	63 ± 1.3	73 ± 1.8	0.94 ± 0.01	1.16 ± 0.003
14c	**39 ± 1.87**	**53 ± 1.13**	**72 ± 2.23**	**1.84 ± 0.024**	**1.36 ± 0.011**
14d	33 ± 2.3	72 ± 2.65	52 ± 1.8	1.56 ± 0.04	0.72 ± 0.009
14e	88 ± 2.4	115 ± 1.43	95 ± 2.25	1.08 ± 0.004	0.83 ± 0.005
14f	51 ± 2.4	84 ± 1.68	54 ± 2.39	1.06 ± 0.04	0.64 ±0.018
14g	43 ± 3.4	54 ± 1.9	64 ± 2.34	1.49 ± 0.06	1.19 ± 0.003
14h	64 ± 3.1	59 ± 2.3	69 ± 1.6	1.07 ± 0.018	1.17 ± 0.04
14i	**28 ± 1.9**	**31 ± 2.3**	**59 ± 1.8**	**2.11 ± 0.08**	**1.9 ± 0.07**
14j	74± 1.5	68 ± 4.7	78 ± 2.7	1.05 ± 0.019	1.15 ± 0.04
14k	57 ± 3.13	79 ±2.9	68 ± 4.5	1.19 ± 0.016	0.86 ± 0.025
14l	**64 ± 3.8**	**84 ± 3.4**	**105 ± 3.6**	**1.64 ± 0.023**	**1.25 ± 0.007**
14m	64 ± 2.9	72 ±2.5	68 ±3.5	1.06 ± 0.009	0.94 ± 0.02
14n	59± 3.5	65±2.4	55± 3.12	0.93 ± 0.0008	0.85 ± 0.012
14o	62 ± 3.1	74 ± 2.9	64 ±3.9	1.03 ± 0.01	0.86 ± 0.023
14p	65 ± 3.7	69 ±2.4	69 ± 1.7	1.06 ± 0.03	1.00 ±0.01
14q	76 ± 2.8	92 ± 2.7	88 ± 3.7	1.16 ± 0.004	0.96 ± 0.008
14r	89 ± 3.5	83 ±1.7	87 ±2.9	0.98 ± 0.008	1.05 ± 0.01
Etoposide	34 ± 2.7	38 ±2.2	36 ±1.2	1.06 ± 0.19	0.95 ± 0.025
Paclitaxel	27 ± 1.8	29 ±2.6	35 ±1.9	1.29 ± 0.21	1.20 ± 0.042

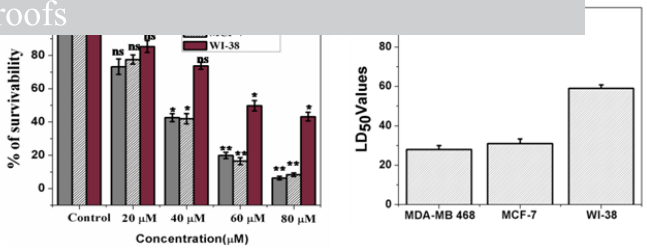


Figure 1: (a) Cytotoxicity assay of compound **14i** on cancer (MDA-MB-468 and MCF-7) and non-cancerous cells (WI-38); (b) LD_{50} values of compound **14i** in cancer (MDA-MB-468 and MCF-7) and non-cancerous cells (WI-38).

Induction of apoptosis with the treatment of compound 14i in cancer cells

In order to study the mechanism of action of the cytotoxicity of the most promising compound **14i** against the cancer cells the induction of apoptosis was measured using Annexin V-FITC/PI staining.[27] After the treatment of MDA-MB-468, MCF-7 and WI38 cells with different concentrations of compound **14i** (0, 20, 40 and 60 µM) for 24 h and staining with Annexin V-FITC/PI, the flow cytometry analysis showed significant induction of apoptosis in a concentration dependent manner in the cancer cells in comparison with the non-cancer cells (WI38). Quite evidently, compound **14i** was able to induce nearly 60% apoptosis in MDA-MB-468 cells and 63% in MCF-7 cells at 60 µM dose (Figure 2). From the Annexin V-FITC/PI staining on the cancer cells (MDA-MB-468 and MCF-7) and non-cancer cell lines (WI38), it was observed that there was no substantial apoptosis in the case of the non-cancer cells treated with compound **14i,** while in case of the cancer cells the percentage of apoptosis was quite high. Moreover, compound **14i** was found comparatively non-toxic to the non-cancerous cells in comparison to cancerous cells. Hence, this experiment confirmed that the compound **14i** kills the cancerous cells via apoptosis sparing any adverse effects on the non-cancerous cells. Therefore, it was decided to identify the mechanism of the induction of apoptosis in cancer cells by compound **14i** employing different types of biochemical and microscopic analysis.

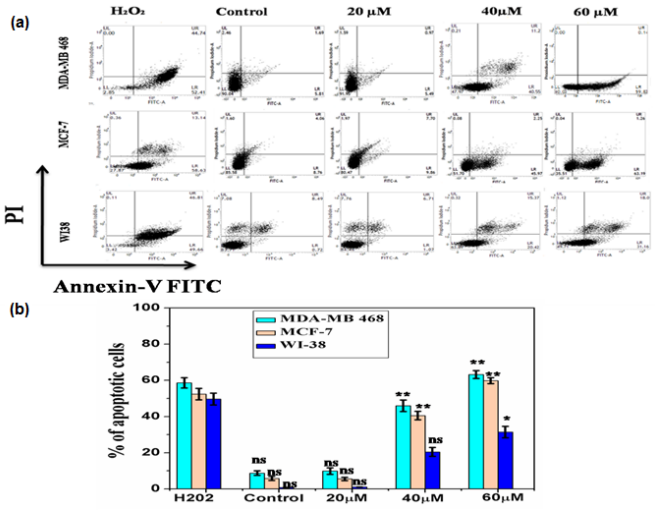


Figure 2: Annexin V-FITC/PI analysis after 24 h of different concentrations of compound **14i** treatment in cancer cells and normal cells. (a) Dot plot of Annexin V-FITC/PI for evaluation of apoptosis in MDA-MB 468, MCF-7 and WI-38 cells treated with the compound **14i**; (b) Quantification of apoptotic cells for evaluation of apoptosis in these cells treated with the compound **14i** at doses 20µM, 40 µM, 60 µM.

mitochondrial permeability transition (MPT) in cancer cells

Since the generation of reactive oxygen species (ROS) is a critical phenomenon linked with several anti-proliferative processes,[28] the ROS production in response to the treatment with compound **14i** was measured using the DCFDA method.[29] Briefly, cells were treated with varying doses (0, 20, 40 and 60 µM) of compound **14i** for 12 h followed by microscopic analysis after staining with DCFDA (100 µM) for 30 min. The photomicrographs demonstrated concentration dependent increase in the intensity of the green color in response to compound **14i** suggesting significant induction of ROS generation by compound **14i** in MDA-MB-468 and MCF-7 cells as shown in Figure 3. Hydrogen peroxide (H_2O_2) has been used as a positive control to confirm the generation of ROS induced by compound **14i** (Figure 3). Moreover, it has been confirmed that compound **14i** induced oxidative damage of the cancer cells through the production of ROS. Compound **14i** induce pro-oxidant activity leading to ROS generation as well as cancer cell apoptosis, which was confirmed from the above experiment.

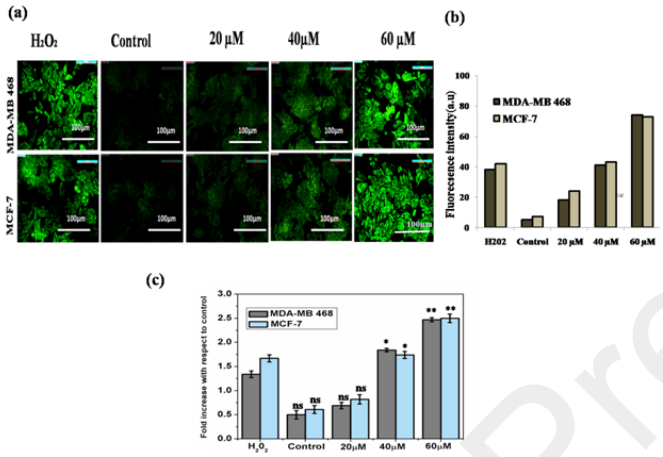


Figure 3: Assessment of ROS generation following treatment with compound **14i** and H_2O_2 in cancer cells. (a) Fluorescence microscopic image of treated cells ; (b) Quantitative analyses of Fluorescence microscopic images; (c) Spectrophotometric fluorescence intensity measurement which indicates the enhancement of ROS in cells treated with the compound **14i** at doses 40 µM, 60 µM.

Since ROS plays a critical role in changing the mitochondrial permeability transition (MPT)[28] therefore, the effect of compound **14i** on mitochondrial damage was investigated by JC-1 staining, which showed a drastic alteration of the redox status of cellular mitochondria in response to compound **14i** in a concentration dependent manner (Figure 4). The shift of fluorescence from red to green or a decrease in the red/green ratio indicated the increase in the mitochondrial permeability in response to compound **14i**. Altogether this result implies that compound **14i** mediated generations of ROS may have decisive role in the mitochondrial permeability transition. Hydrogen peroxide (H_2O_2) has also been used as a positive control (Figure 4). Thus from the above results we can conclude that the exposure to the compound **14i** is responsible for inducing intracellular ROS generation which subsequently results in the mitochondrial membrane potential disruption.

Furthermore, the mitochondrial ROS production in response to compound **14i** was measured by the treatment with MitoSOX™ Red reagent,[28] which permeates live cells selectively targeting mitochondria. MitoSOX™ Red can be rapidly oxidized by superoxide anions and the oxidized product emits high red

study, treated with different concentrations of compound **14i** (40 µM and 60 µM) as well as H_2O_2 (positive control) (Figure 5). Therefore, it can be concluded that compound **14i** mediated cancer cell apoptosis was observed due to the increased generation of mitochondrial ROS. Altogether these results imply that **14i** mediated generation of mitochondrial ROS may have decisive role in the mitochondrial permeability transition.

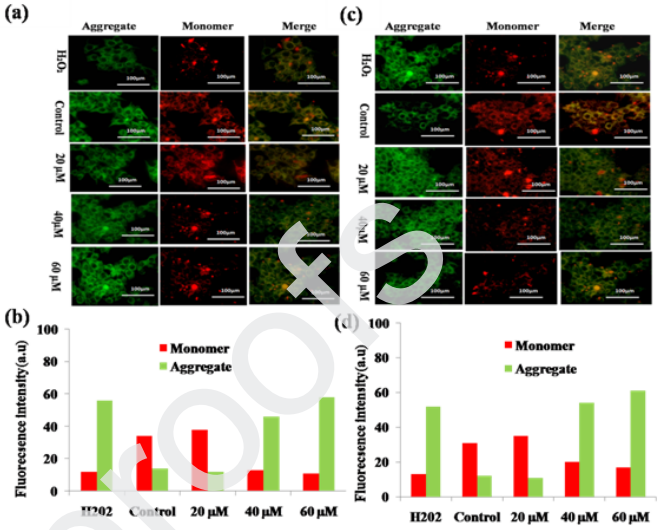


Figure 4: Mitochondrial permeability transition (MPT) determination by JC-1 dye in (a) MDA-MB-468 cells and (b) Quantitative analysis of red to green transition in MDA-MB 468 cells; (c) MPT determination by JC-1 dye in MCF-7 cells and (d) Quantitative analysis of red to green transition in MCF-7 cells.

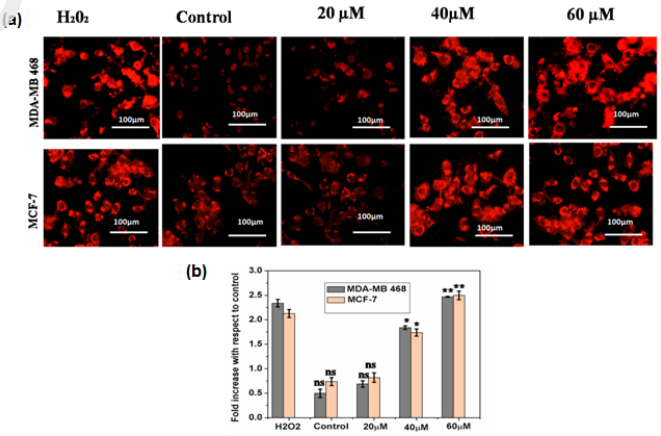


Figure 5: Measurement of mitochondrial ROS generation using MitoSOX™ Red in response to the treatment with compound **14i** (a) Fluorescence microscopic image of treated cells and (b) Spectrophotometric fluorescence intensity measurement which indicates the enhancement of mitochondrial ROS in cells treated with the compound **14i** at doses 40 µM, 60 µM.

Treatment of compound 14i induces DNA fragmentation and Cell cycle arrest in cancer cells.

Several reports suggested [28] that ROS generation and change in MPT are linked with cell cycle arrest and DNA damage induced apoptosis, which is an imperative process that controls cellular growth. Therefore, the effects of compound **14i** on cell cycle analysis and DNA damage were assessed. Treatment of MDA-MB-468 and MCF-7 cells with different doses of compound **14i** (20 µM, 40 µM and 60 µM), significantly increased the percentage (%) of sub G1 cells populations up to 62% for MDA-MB-468 cells and 67% for MCF-7 cells (in 60

polynuclear fragmentation and apoptosis in comparison to the untreated cells (Figure 7). The quantitative analysis confirmed around 72% and 78% apoptotic cells in MDA-MB-468 and MCF-7 cells respectively following the treatment with 60 µM compound **14i**, which were highly significant compared to corresponding control cells as mentioned in Figure 7. Hydrogen peroxide (H_2O_2) has also been used as a positive control. Hence, we can conclude that compound **14i** induces cell cycle arrest, DNA fragmentation and apoptosis in cancer cells without affecting the non-cancerous cells.

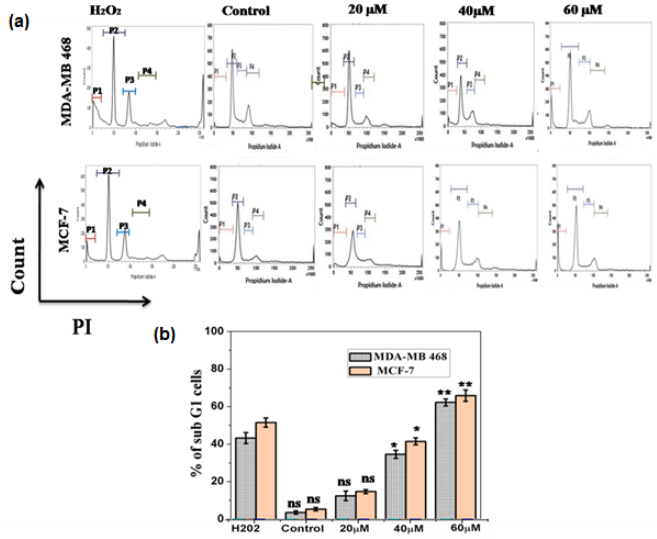


Figure 6: (a) Cell cycle analysis following the treatment of compound **14i** in cancer cells (MDA-MB 468 and MCF-7); (b) bar diagram of the quantification of the sub G1 cells in the cell cycle which is the indication of cellular apoptosis.

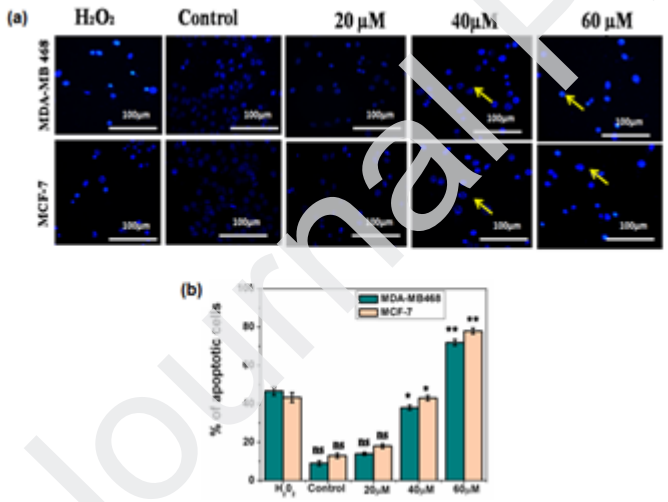


Figure 7: (a) Apoptotic nuclear morphology study by DAPI staining of cancer cells (MDA-MB 468 and MCF-7); (b) Bar diagram showing the quantification data of the apoptotic cells.

Treatment of compound 14i induces caspase mediated apoptosis

The western blot analysis of MDA-MB-468 cells treated with compound **14i** showed increase in the expression of pro-apoptotic protein Bax, whereas the expression of anti-apoptotic protein Bcl-2 was decreased significantly.[30] Moreover, treatment with compound **14i** showed cleavage mediated activation of caspase-3, which suggesting caspase mediated apoptosis. Therefore, these

mediated cancer cell apoptosis (Figure 8).

In summary, a series of glycosylated 1,4-substituted triazolyl chalcone derivatives (**8a-f** and **14a-r**) were synthesized using a generalized reaction condition in satisfactory yield. The synthesized compounds (**8a-f** and **14a-r**) were evaluated against human breast cancer cells (MDA-MB-468 and MCF-7 cells) and non-cancer cells (WI38). Three compounds (**14c**, **14i** and **14l**) were found promising in terms of the cytotoxic activities against cancer cells and less cytotoxic against non-cancer cells (WI38). Among three active compounds, compound **14i** has been considered as the best based on the selectivity index. Further, a number of microscopic experiments and fluorescence activated cell sorter (FACS) studies confirmed that compound **14i** exhibits anti-cancer activities against several cancer cells following apoptotic pathway.

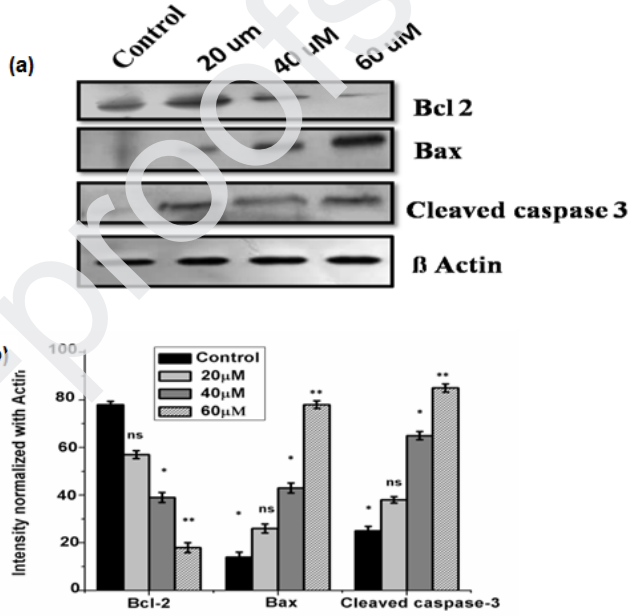


Figure 8: (a) Western blot of apoptotic protein cleaved Caspase-3, Bax and Bcl2 which suggests the upregulation of apoptic pathway upon treatment of the MDA-MB 468 cells (b) Bar diagram of the quantitative analysis of the band intensity**.**

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Supplementary Material

Detailed experimental conditions for the synthesis of compounds and their analytical data. Copies of the NMR spectra of s

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A one derivatives

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Research highlights:

- Glycosylated 1,4-substituted triazolylchalcone derivatives were prepared.
- "Click chemistry" condition has been used to prepare compounds in high yield.
- Synthetic compounds were evaluated for their potential as anticancer agents.
- Three compounds showed promising cytotoxicity against human breast cancer.
- Biochemical and microscopic experiments were carried out using the best compound.