Biological Forum – An International Journal **15(5a): 463-468(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Synthesis, Anticancer Activity and Molecular Docking Study of Some Novel 1,3,5-Triazine Derivatives

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(Received: 06 April 2023; Revised: 25 April 2023; Accepted: 03 May 2023; Published: 15 May 2023)
(Published by Research Trend)

ABSTRACT: A crucial field of medical research is the study of cancer medications. New medications that can target and cure various forms of cancer are constantly being developed by researchers and pharmaceutical firms. A series of some novel triazine derivatives has been synthesized and screened them for cancer activity against human breast (MCF-7), cervical cancer (C33A), oral (KB) and prostrate (DU-145). The structures of the synthesized compounds were confirmed bn IR, Mass and ^{1}H NMR Sectra. The compounds showed 1b 1e, 1f, 1h and 1j showed significant anticancer activity. The docked compounds 1e, 1f, and 1j (-8.4, -8.4, -8.5) that had the highest binding affinity against the PDB ID: 1XKK. This can possibly lead to emergence of new anticancer agents.

Keywords: Triazines, Anticancer, Molecular Docking, human breast (MCF-7,), cervical cancer (C33A), oral (KB) and prostrate (DU-145)

INTRODUCTION

Cancer has a significant impact on the world, affecting millions of lives each year. It leads to loss of lives, strains healthcare systems, and has economic implications due to treatment costs and reduced productivity (Lunenfeld and Stratton 2013). Efforts are ongoing to advance research, improve early detection, and develop better treatment options to mitigate its effects. Research on cancer drugs is a critical area of medical science (Dancey and Eisenhauer 1996; Arive *et al*., 2017). Scientists and pharmaceutical companies continually work to develop new drugs that can target and treat various types of cancer (Tinkle *et al*., 2014; Lasri *et al*., 2021). These drugs aim to inhibit the growth and spread of cancer cells, while minimizing damage to healthy cells (Begg *et al*., 2011; Maliszewski & Drozdowska 2022). Clinical trials are conducted to test the effectiveness and safety of these drugs before they can be approved for widespread use. Advances in cancer drug research have led to improved treatment options and increased survival rates for many cancer patients (Velihina *et al*., 2021). Some triazine derivatives have been investigated for their ability to inhibit certain enzymes or pathways that are involved in cancer cell growth and proliferation (De Cian *et al*., 2008; Maliszewski and Drozdowska 2022; Yan *et al*., 2018; Refaat *et al*., 2022). Interestingly, there are numerous clinically accepted triazine- based anticancer drugs with potent EGFR-TK inhibitory activity such as Altretamine (Damia and D'lncalci 1995), Oteracil (Kobayakawa and Kojima 2011), Enasidenib (Fathi *et al*., 2018) and Tretamine (Michelmann *et al*., 1975).

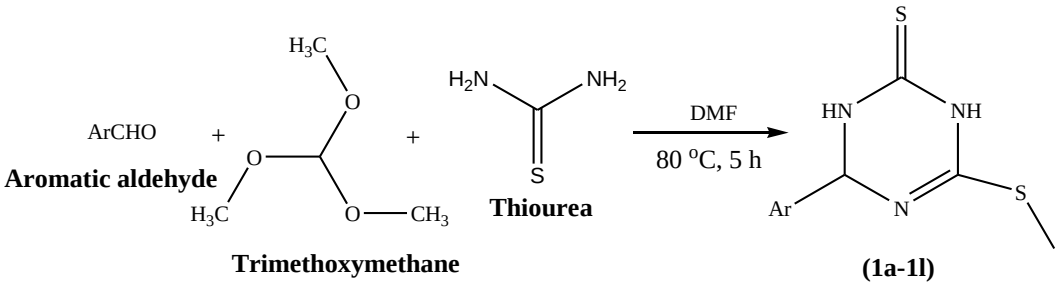
In this research work we attempted to synthesize some novel triazine derivatives as potent anti-cancer agents.

MATERIAL AND METHODS

All the triazines synthesized from earlier reported method were followed with or without modification appropriately as and when required and melting points reported were determined by open capillary tube method and are uncorrected. The synthesis and analytical studies of the compounds were carried out using laboratory grade and analytical grade. Elemental analysis (C, H and N) was undertaken with a Perkin-Elmer model 240C analyzer, and all analyses were consistent with theoretical values (within 0.4%) unless indicated. IR absorption spectra were recorded on Bruker alpha. ^{1}H NMR spectra were recorded on the Bruker DPX-400 instrument at 400 MHz. The ^{1}H chemical shifts are reported as parts per million (ppm) downfield from TMS (Me4Si). The LC mass spectra of the compounds were recorded on Shimadzu 8201PC spectrometer. The homogeneity of the compounds was monitored by ascending thin-layer chromatography (TLC) on silica gel G (Merck)-coated aluminum plates, visualized by iodine vapor.

Chemistry

General procedure for synthesis of substituted triazines (Scheme 1): A mixture of 1g (1eq) of substituted heterocyclic aldehyde, 1.30g (2.5eq) of Thiourea and 0.75ml trimethyl orthoformate in 10 mL of DMF was stirred at 80^{o}C for 5 h. The mixture was cooled to room temperature and the desired compound was extracted using chloroform. The chloroform was evaporated to get solid final compounds (**1a-1l**) which was further washed using pentane.



Scheme 1. Synthesis of Substituted triazines

4-(1*H*-indol-3-yl)-6-(methylthio)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (**1a**)

Melting Point: 230-234ºC; Yield: 80 %; R_f value: 0.56; Solvent system: Benzene: Methanol (9.5: 0.5); Anal. Calcd. for $C_{12}H_{12}N_4S_2$(276.38): C, 52.15; H, 4.38; N, 20.27. Found: C, 52.85; H, 4.78; N, 20.07; IR (υ_{max}, cm^{-1}): 3416(N-H), 3061 (Ar. C−H), 2932 (C–H aliphatic), 1558 (C=N), 1535, 1474 (Ar. C=C), 1231 (C–N), 1025 (C=S), 697(C-S); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.53 (s, 3H, CH_3), 6.98-7.25 (m, 5H, Ar-H), 7.37 (s, 1H, CH,), 7.43 (s, 1H, NH,), 8.46 (s, 1H, NH,), 8.96 (s, 1H, NH,); LCMS (m/z): $[M]^+$; 276.05.

4-(1*H*-indol-4-yl)-6-(methylthio)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (**1b**)

Melting Point: 222-224ºC; Yield: 81 %; R_f value: 0.65; Solvent system: Benzene: Methanol (9.5: 0.5); Anal. Calcd. for $C_{12}H_{12}N_4S_2$(276.38): C, 52.15; H, 4.38; N, 20.27. Found: C, 52.67; H, 4.89; N, 19.98; IR (υ_{max}, cm^{-1}): 3413(N-H), 3026 (Ar. C−H), 2928 (C–H aliphatic), 1554 (C=N), 1462 (Ar. C=C), 1177 (C–N), 1041 (C=S), 692 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.68 (s, 3H, CH_3), 6.89-7.40 (m, 5H, Ar-H), 7.44 (s, 1H, CH,), 7.51 (s, 1H, NH,), 8.48 (s, 1H, NH,), 8.88 (s, 1H, NH,); LCMS (m/z): $[M]^+$; 276.05.

4-(1*H*-indol-5-yl)-6-(methylthio)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione(1c)

Melting Point: 228-232ºC; Yield: 79 %; R_f value: 0.56; Solvent system: Benzene: Methanol (9.5: 0.5); Anal. Calcd. for $C_{12}H_{12}N_4S_2$ (276.38): C, 52.15; H, 4.38; N, 20.27. Found: C, 52.20; H, 4.52; N, 20.02; IR (υ_{max}, cm^{-1}): 3420 (N-H), 3032 (Ar. C−H), 2935 (C–H aliphatic), 1560 (C=N), 1468 (Ar. C=C), 1170 (C–N), 998 (C=S), 698 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.42 (s, 3H, CH_3), 3.29 (s, 1H, CH,), 6.89-7.40 (m, 5H, Ar-H), 7.38 (s, 1H, NH,), 8.31 (s, 1H, NH,), 8.76 (s, 1H, NH,); LCMS (m/z): $[M]^+$; 276.05.

4-(1*H*-indol-6-yl)-6-(methylthio)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione(1d)

Melting Point: 232-236ºC; Yield: 77 %; R_f value: 0.64; Solvent system: Benzene: Methanol (9.5: 0.5); Anal. Calcd. for $C_{12}H_{12}N_4S_2$(276.38): C, 52.15; H, 4.38; N, 20.27. Found: C, 52.28; H, 4.47; N, 20.39; IR (υ_{max}, cm^{-1}): 3415 (N-H), 3029 (Ar. C−H), 2934 (C–H aliphatic), 1566 (C=N), 1477 (Ar. C=C), 1176 (C–N), 1011 (C=S), 705 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.54 (s, 3H, CH_3), 6.85-7.53 (m, 5H, Ar-H), 7.11 (s, 1H, CH,), 7.31 (s, 1H, NH,), 8.28 (s, 1H, NH,), 8.79 (s, 1H, NH,); LCMS (m/z): $[M]^+$; 276.05.

6-(methylthio)-4-(quinolin-2-yl)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (1e)

Melting Point: 220-224ºC; Yield: 79 %; R_f value: 0.66; Solvent system: Benzene: Methanol (9.5: 0.5); Anal. Calcd. for $C_{13}H_{12}N_4S_2$ (288.39): C, 54.14; H, 4.19; N, 19.43. Found: C, 54.04; H, 4.29; N, 32.43; IR (υ_{max}, cm^{-1}): 3406 (N-H), 3075 (Ar. C−H), 2921 (C–H aliphatic), 1579 (C=N), 1461 (Ar. C=C), 1144 (C–N), 999 (C=S), 738 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.62 (s, 3H, CH_3), 6.14 (s, 1H, CH,), 7.47-8.15 (m, 6H, Ar-H), 8.33 (s, 1H, NH,), 8.84 (s, 1H, NH,); LCMS (m/z): $[M]^+$; 288.05.

6-(methylthio)-4-(quinolin-3-yl)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (1f)

Melting Point: 232-236ºC; Yield: 76 %; R_f value: 0.72; Solvent system: Benzene: Methanol (9.5: 0.5); Anal. Calcd. for $C_{13}H_{12}N_4S_2$ (288.39): C, 54.14; H, 4.19; N, 19.43. Found: C, 54.07; H, 4.23; N, 19.32; IR (υ_{max}, cm^{-1}): 3347 (N-H), 2992 (Ar. C−H), 2940 (C–H aliphatic), 1514 (C=N), 1487 (Ar. C=C), 1155 (C–N), 1032 (C=S), 712 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.58 (s, 3H, CH_3), 6.62 (s, 1H, CH,), 7.20-8.14 (m, 6H, Ar-H), 8.33 (s, 1H, NH,), 8.91 (s, 1H, NH,); LCMS (m/z): $[M]^+$; 288.05.

6-(methylthio)-4-(quinolin-6-yl)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (1g)

Melting Point: 226-228ºC; Yield: 80 %; R_f value: 0.67; Solvent system: Benzene: Methanol (9.5: 0.5); Anal. Calcd. for $C_{13}H_{12}N_4S_2$ (288.39): C, 54.14; H, 4.19; N, 19.43. Found: C, 54.26; H, 4.21; N, 19.36; IR (υ_{max}, cm^{-1}): 3420 (N-H), 3042 (Ar. C−H), 2939 (C–H aliphatic), 1553 (C=N), 1468 (Ar. C=C), 1123 (C–N), 1002 (C=S), 696 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.48 (s, 3H, CH_3), 5.72 (s, 1H, CH,), 7.29-7.93 (m, 6H, Ar-H), 8.38 (s, 1H, NH,), 8.70 (s, 1H, NH,); LCMS (m/z): $[M]^+$; 288.05.

6-(methylthio)-4-(quinolin-8-yl)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (1h)

Melting Point: 218-222ºC; Yield: 77 %; R_f value: 0.59; Solvent system: Benzene: Methanol (9.5: 0.5); Anal. Calcd. for $C_{13}H_{12}N_4S_2$ (288.39): C, 54.14; H, 4.19; N, 19.43. Found: C, 54.21; H, 4.27; N, 19.47; IR (υ_{max}, cm^{-1}): 3426 (N-H), 3023 (Ar. C−H), 2943 (C–H aliphatic), 1569 (C=N), 1483 (Ar. C=C), 1181 (C–N), 972 (C=S), 693 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.42 (s, 3H, CH_3), 5.81 (s, 1H, CH,), 7.33-7.78 (m, 6H, Ar-H), 8.41 (s, 1H, NH,), 8.69 (s, 1H, NH); LCMS (m/z): $[M]^+$; 288.05.

4-(isoquinolin-1-yl)-6-(methylthio)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (1i)

Melting Point: 224-226ºC; Yield: 79 %; R_f value: 0.72; Solvent system: Benzene: Methanol (9.5: 0.5); Anal.

Calcd. for $C_{13}H_{12}N_4S_2$ (288.39): C, 54.14; H, 4.19; N, 19.43; Found: C, 54.19; H, 4.09; N, 19.39; IR (υ_{max}, cm^{-1}): 3421 (N-H), 3032 (Ar. C−H), 2927 (C–H aliphatic), 1546 (C=N), 1481 (Ar. C=C), 1166 (C–N), 994 (C=S), 687 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.58 (s, 3H, CH_3), 7.12 (s, 1H, CH,), 7.21-8.01 (m, 6H, Ar-H), 8.43 (s, 1H, NH,), 8.91 (s, 1H, NH,); LCMS (m/z): $[M]^+$; 288.05

4-(isoquinolin-3-yl)-6-(methylthio)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (1j)

Melting Point: 220-222ºC; Yield: 76 %; R_f value: 0.55; Solvent system: Benzene: Methanol (9.5: 0.5); Anal. Calcd. for $C_{13}H_{12}N_4S_2$ (288.39): C, 54.14; H, 4.19; N, 19.43. Found: C, 54.19; H, 4.39; N, 19.57; IR (υ_{max}, cm^{-1}): 3348 (N-H), 3041 (Ar. C−H), 2941 (C–H aliphatic), 1603 (C=N), 1508, 1464 (Ar. C=C), 1161 (C–N), 985 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.59 (s, 3H, CH_3), 6.54 (s, 1H, CH,), 7.24-8.11 (m, 6H, Ar-H), 8.38 (s, 1H, NH,), 8.82 (s, 1H, NH); LCMS (m/z): $[M]^+$; 288.05.

4-(isoquinolin-4-yl)-6-(methylthio)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (1k)

Melting Point: 228-230ºC; Yield: 79 %; R_f value: 0.62; Solvent system: Benzene: Methanol (9.5: 0.5); Anal. Calcd. for $C_{13}H_{12}N_4S_2$ (288.39): C, 54.14; H, 4.19; N, 19.43. Found: C, 54.01; H, 4.33; N, 19.50; IR (υ_{max}, cm^{-1}): 3404 (N-H), 3063 (Ar. C−H), 2928 (C–H aliphatic), 1549 (C=N), 1470 (Ar. C=C), 1172 (C–N), 981 (C=S), 691 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.52 (s, 3H, CH_3), 7.15 (s, 1H, CH,), 7.31-7.89 (m, 6H, Ar-H), 8.32 (s, 1H, NH,), 8.94 (s, 1H, NH,); LCMS (m/z): $[M]^+$; 288.05.

4-(isoquinolin-5-yl)-6-(methylthio)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (1l)

Melting Point: 234-236ºC; Yield: 80 %; R_f value: 0.69; Solvent system: Benzene: Methanol (9.5: 0.5); Anal. Calcd. for $C_{13}H_{12}N_4S_2$ (288.39): C, 54.14; H, 4.19; N, 19.43. Found: C, 54.29; H, 4.11; N, 19.35; IR (υ_{max}, cm^{-1}): 3399 (N-H), 3034 (Ar. C−H), 2939 (C–H aliphatic), 1553 (C=N), 1482 (Ar. C=C), 1179 (C–N), 978 (C=S), 689 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.57 (s, 3H, CH_3), 7.04 (s, 1H, CH,), 7.22-7.89 (m, 6H, Ar-H), 8.21 (s, 1H, NH,), 8.82 (s, 1H, NH); LCMS (m/z): $[M]^+$; 288.05

***In vitro* Anticancer activity.** The anticancer activity of the synthesized compounds was evaluated against four cancerous cell lines; human breast (MCF-7,), cervical cancer (C33A), oral (KB) and prostrate (DU-145) using (SRB) colorimetric assay. Doxorubicin and Erlotinib were included in the experiments as reference cytotoxic compounds for all the tested cell lines. The results were expressed as median growth inhibitory concentration (IC_{50}) values, which represent the concentration of a drug that is required for 50% inhibition of cell growth after 48 h of incubation, compared to untreated controls (Ismail *et al*., 2019).

Molecular Docking Study. The molecular docking studies of the synthesized peptides was performed on Windows 10 (64-bit) operating systems with 64 GB RAM and AMD Ryzen 9 5950X 16-Core Processor 3.40 GHz.

The crystallographic 3D structure of EGFR kinase domain complexed with a quinazoline inhibitor-GW572016 was accessed from Protein Data Bank (PDB ID: 1XKK). The resolution of the XRD structure of this model enzyme is 2.80 Å. The structure of PDB ID: 1XKK complex was downloaded from RCSB database and protein preparation was carried out using the Autodock Wizard by deleting attached water molecules, bound heteroatoms/ligand, adding polar hydrogens, kollman charges, spreading charge equally over all atoms and checking for missing atoms on residues. The PDB files were then converted to the PDBQT format for executing the next step (Janani *et al*., 2022).

The 2D structures were drawn by Chemdraw and converted into 3D format. The ligands were minimized by MMFF94 Force Field and converted to PDBQT format by openbabel in PyRx tool. For carrying out docking between prepared receptors and ligands, grid was generating by taking the center on attached ligand. The grid dimensions for PDB ID: 1XKK was number of points as 20.18, 20.18, 20.18 in X,Y,Z direction 16.8550, 32.5486, 39.05 respectively with default spacing. Docking was performed to obtain a population of possible conformations and orientations for the ligand at the binding site. Binding sites and docking run of target protein with ligand was analyzed by using the PyRx, AutoDock Vina option based on scoring functions. The conformations for each ligand were analysed and best conformations were taken keeping binding affinity as criteria. The 3D and 2D interaction diagrams were created using Maestro Visualizer (Ashraf *et al*., 2014; Bommu *et al*., 2017; Dallakyan and Olson 2015; Idris *et al*., 2021; Perike *et al*., 2022; Veeranna *et al*., 2022).

RESULTS AND DISCUSSION

A simple and efficient method for the synthesis of substituted triazine, the one-pot reaction of substituted aldehydes, thiourea, and trimethyl orthoformate in DMF solvent at 80ºC for 5hr.

The structures of the synthesized compounds were confirmed by IR, Mass and NMR Sectra (Idris *et al*., 2021).

The *in vitro* anticancer activity of the synthesized compounds was evaluated against four cancerous cell lines; human breast (MCF-7,), cervical cancer (C33A), oral (KB) and prostrate (DU-145) using (SRB) colorimetric assay and most of synthesized compounds exhibited moderate to high anticancer activities against five human tumor cell lines including human breast (MCF-7,), cervical cancer (C33A), oral (KB) and prostrate (DU-145) using (SRB) colorimetric assay (Ismail *et al*., 2019). The compounds showed **1b 1e, 1f, 1h, 1j** showed significant activity as compared to others (Table 1).

Table 1: *In vitro* anticancer activity of Compounds (1a-1l).

Compound	IC_{50} (µg/ml)			
	DU 145	MCF7	C33A	KB
1a	14.8	23.9	21.6	15.2
1b	3.5	1.9	1.2	3.0
1c	20.1	27.8	24.4	22.1
1d	9.2	4.8	3.1	3.6
1e	0.9	1.3	4.0	1.5
1f	2.7	3.4	3.5	5.9
1g	10.5	5.7	4.6	4.9
1h	5.4	4.9	3.1	5.9
1i	13.3	23.9	16.8	11.8
1j	0.8	1.8	3.8	2.1
1k	15.8	23.4	21.7	15.6
1l	23.2	32.4	19.8	22.8
Doxorubicin	2.3	0.9	1.4	1.2
Erlotinib	2.4	1.2	1.3	1.5

Molecular Docking Study. The docked compounds **1e**, **1f**, and **1j** (-8.4, -8.4, -8.5) that had the highest binding affinity were found by the results of our study (Table 2). When we look at the protein-ligand interaction, compound **1e** forms some hydrophobic bond interaction with MET766, LEU777, LEU788, VAL726, LEU718, GLY719, GLY721 and one hydrogen bond with ASP855. It forms some polar interactions with ASN842 and THR854 (Fig. 1, Table 2). Compound **1f** showed some hydrophobic bond interaction MET766, LEU777, LEU788, VAL726, LEU792, MET793, LEU844, ARG841, THR854. It forms some polar interactions with ASP855 and THR790 respectively (Fig. 2, Table 2). Compound **1j** showed some hydrophobic bond interaction with LEU788, LEU777, VAL726, LEU718, GLY719, GLY721 and one hydrogen bond with ASP855. It forms some polar interactions with THR790, ASN842 and THR854 (Fig. 3, Table 2).

Table 2: Molecular Docking Results of Compounds 1a-1l.

Compound	Binding Affinity	Hydrophobic interactions	H-bond
1a	-7.8	LEU788, THR790, LEU792, MET793, LEU844, ARG841, CYS797, VAL726, THR854, ASP855	-
1b	-7.6	MET766, LEU777, LEU788, THR790, MET793, LEU844, VAL726, ASP855, THR854	-
1c	-7.8	LEU777, MET766, THR790, LEU788, VAL726, LEU718, GLY719, ASN842, THR854	ASP855
1d	-8	MET766, LEU858, LEU788, THR790, LEU844, LEU792, MET793, GLY796, VAL726, LEU718, THR854	ASP855
1e	**-8.4**	MET766, LEU777, LEU788, VAL726, LEU718, GLY719, GLY721, ASN842, THR854	**ASP855**
1f	**-8.4**	MET766, LEU777, LEU788, THR790, VAL726, LEU792, MET793, LEU844, ARG841, ASP855, THR854	-
1g	-8.1	LEU788, THR790, LEU844, MET793, GLY796, LEU718, VAL726, ASP855, THR854, MET766	-
1h	-8.1	MET766, LEU777, LEU788, THR790, LEU718, LEU844, VAL726, THR854, ASP855	-
1i	-8.2	LEU788, THR790, LEU844, LEU718, VAL726, ASP855, THR854	-
1j	**-8.5**	LEU788, LEU777, THR790, VAL726, LEU718, GLY719, GLY721, ASN842, THR854	**ASP855**
1k	-8.3	LEU788, THR790, LEU792, MET793, LEU844, CYS797, VAL726, ASP855, THR854	-
1l	-7.8	MET766, LEU777, LEU788, THR790, MET793, LEU844, VAL726, THR854, ASP855	

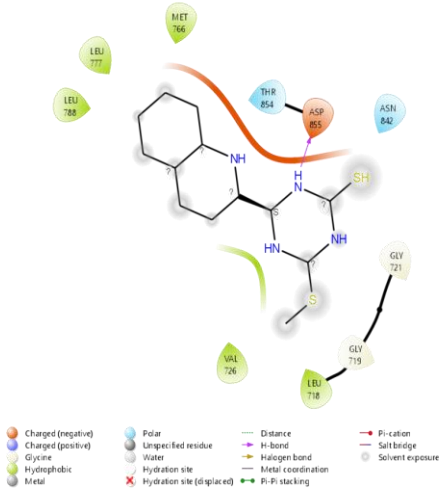


Fig. 1. Binding Pattern of **1e** with PDB id: 1xkk

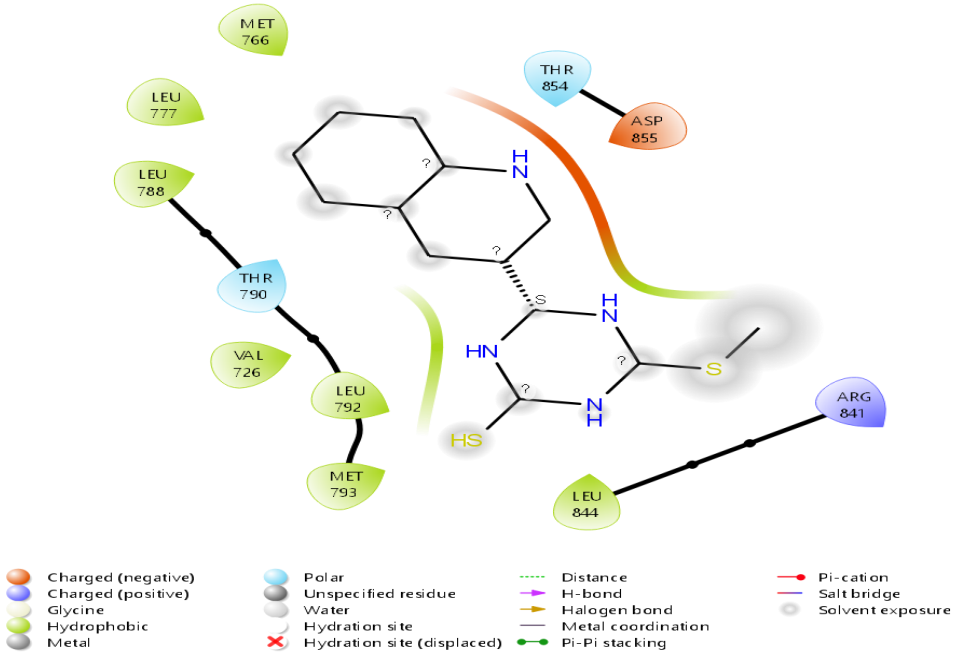


Fig. 2. Binding Pattern of **1f** with PDB id: 1xkk.

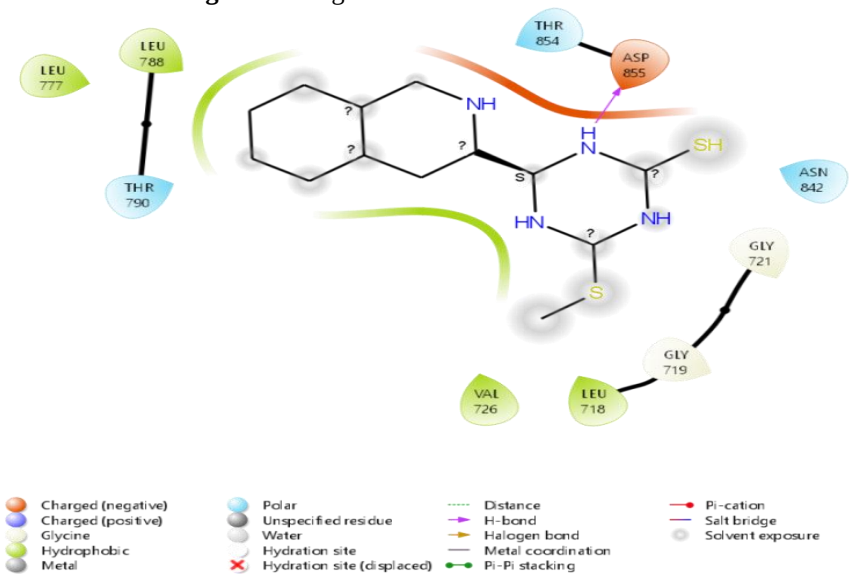


Fig. 3. Binding Pattern of **1j** with PDB id: 1xkk.

CONCLUSIONS

A novel and simple method for the synthesis of triazine derivatives has been developed. Some of the synthesized compounds produced cytotoxic activity against cell lines; human breast (MCF-7,), cervical cancer (C33A), oral (KB) and prostrate (DU-145) in particular, the compounds 6-(methylthio)-4-(quinolin-2-yl)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (**1e**), 6-(methylthio)-4-(quinolin-3-yl)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (**1f**) and 4-(isoquinolin-3-yl)-6-(methylthio)-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione (**1j**) were found as promising compounds and could serve as leads for further modification to develop clinically useful anticancer agents.

FUTURE SCOPE

The new findings might be useful for scientist in future research and development of triazine nucleus as newer anti- breast cancer agents.

Acknowledgement. The authors deeply appreciate the assistance of the Department of Chemistry, Bhupal Nobles' University, Udaipur-313001, India.
Conflict of Interest. None.

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How to cite this article: Ridhima Chauhan and Girdhar Pal Singh (2023). Synthesis, Anticancer Activity and Molecular Docking Study of Some Novel 1,3,5-Triazine Derivatives. *Biological Forum – An International Journal*, *15*(5a): 463-468.