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Design, Synthesis and Molecular Modeling of New 1,3,5-Triazine Derivatives as Anticancer Agents

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ABSTRACT

A new series of 1,3,5-triazine analogues were designed, synthesized and in vitro screened by the US National Cancer Institute (NCI) for their ability to inhibit 60 different human tumor cell lines. Compound 6 the most active member in this study, showing effectiveness toward numerous cell lines belonging to different tumor cell lines that reach to 60.13% inhibition in renal cancer (CAKI-1) cell line, also it has good inhibitory activity against PI3Kγ (IC_{50}=6.90 μM) closer activity to reference wortmannin (IC_{50}=3.19 μM). Molecular docking reveal that compound 6 occupied the same pocket of the active site of PI3Kγ and these, consistent with biological results.

Keywords: Anticancer activity, Cyanuric chloride, 1,3,5-triazine, PI3K, Molecular docking.

INTRODUCTION

Cancer or in other expression uncontrolled cellular proliferation resulted from the genetic alterations of three main types of genes; proto-oncogenes, tumor suppressor genes, and DNA repair genes, lies at the core of cancer as a pathological process [1]. Phosphatidylinositol 3-kinases (PI3Ks) are lipid kinases, which phosphorylate the 3-hydroxyl group of the inositol ring of phosphoinositides. As the most important phosphorylated product, phosphatidylinositol 3, 4, 5-trisphosphate (PIP3) works as a second messenger that plays leading roles in substantial cellular responses such as cell growth, survival, motility and metabolism. Alterations in the phosphatidylinositol 3-kinases (PI3K) pathway are known to play a sizable role in the buildup of cancer and provide a possible target for new therapies [2,3]. Many 1,3,5- triazines derivatives were found to be PI3K inhibitors as ZSTK474 compound I and AMG 511 compound II [4,5]. 1,3,5-triazine derivatives typify one of the most effective categories having diverse biological activity [6-11]. Altretamine III 1,3,5- triazine derivative drug that is used in treatment of ovarian cancer [12-15], also a variety of substituted 1,3,5-triazine derivatives have been synthesized and exhibited inhibitory activities against various cell lines [16,17], as compound IV (Figure 1) [18].

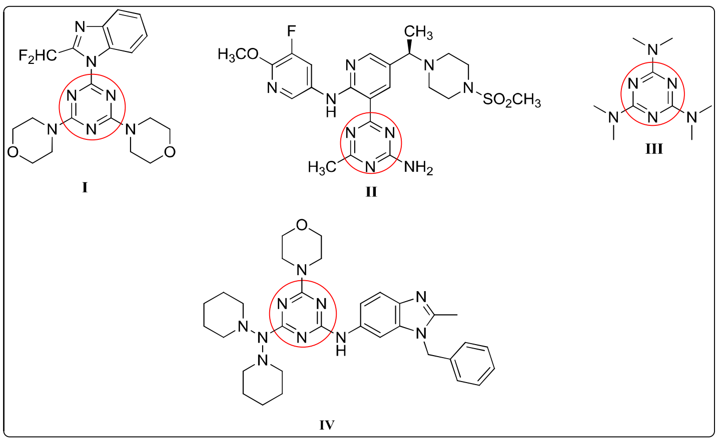


Figure 1: 1,3,5-triazine containing anti-tumor drugs

Based on the previous information, a series of new mono, di, and trisubstituted 1,3,5-triazine containing compounds were designed and synthesized. (Figure 2) 1,3,5-triazine moiety was used as a scaffold that coupled with piperidine or morpholine as heterocyclic ring or o-disubstituted phenol as illustrated in Figure 2. Moreover varying the substitution pattern at 1,3,5-triazine moiety was made with either phenyl ring attached through amine linkage or ether linkage, or heterocyclic ring through amine linkage hoping to enhance the biological activity as a result of these hybridizations.

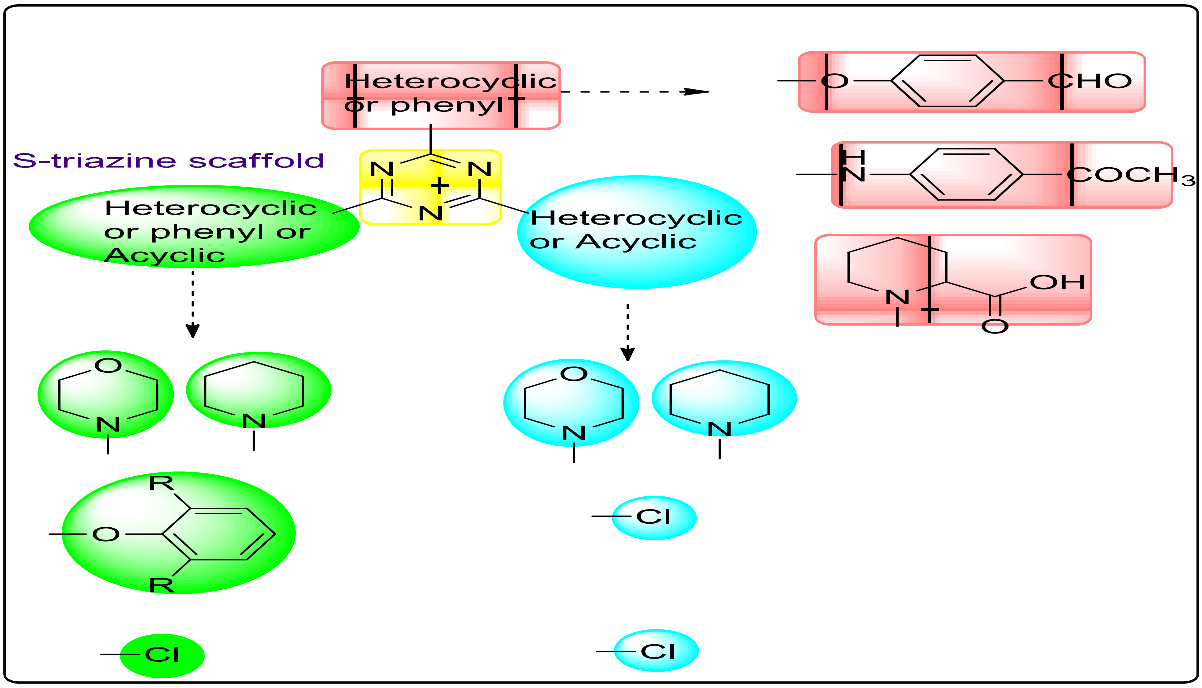


Figure 2: Structure of the designed target compounds

MATERIALS AND METHODS

Chemistry

Melting points (ºC) were recorded using *Fisher-John* melting point apparatus and are uncorrected. Microanalyses were performed at the microanalytical unit, Cairo University. IR spectra were recorded on Mattson 5000 FT-IR spectrometer (υ in cm^{-1}) using KBr disk. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker Ac 400 FT NMR spectrometer (400 MHZ), Faculty of Pharmacy, Mansoura University**.** The chemical shifts in ppm are expressed in δ units using tetramethylsilane (TMS) as internal standard. MS analyses were performed on JOEL JMS-600H spectrometer in Cairo University. Reaction times were determined using TLC technique on Silica gel plates 60 F245 E. Merk, and the spots were visualized by U.V. (366 nm). Compound 1 and 4 were synthesized according to the reported method [19,20].

General procedure for preparation of compounds 2 and 3

A solution of 4-(4,6-dichloro-1,3,5-triazin-2-yloxy)benzaldehyde (1) (2.7 g, 0.01 mol) in dry DMF and amine (0.023 mol) and potassium carbonate (2.76 g, 0.02 mol) was heated at 70°C for 24 h. On completion of the reaction, the reaction mixture teeming in crumbled ice and obtained precipitate was filtered, dried and crystallized from methanol.

4-(4,6-di(piperidin-1-yl)-1,3,5-triazin-2-yloxy)benzaldehyde (2): Yield 60%; MP >300°C; IR: 1701 (C=O), 2851, 2934 (H-C=O). ^{1}H-NMR: δ 1.45-1.46 (m, 12H, 6X (CH_2- piperidine -3, -4, and -5)), 3.62-3.69 (m, 8H, 4X (CH_2- piperidine -2, and -6)), 7.41 (d, *J*=8.5 Hz, 2H, Ar-H), 7.96 (d, *J*=8.5 Hz, 2H, Ar-H), 9.99 (s, 1H, CHO). MS: m/z 367 **[**M^+], 368 [M^++1). Anal. calcd for $C_{20}H_{25}N_5O_2$: C, 65.37; H, 6.86; N, 19.06. Found: C, 65.66; H, 6.53; N, 19.21.

4-(4,6-dimorpholino-1,3,5-triazin-2-yloxy)benzaldehyde (3): Yield 69%; MP >300°C; IR: 1711 (C=O), 2849, 2930 (H-C=O). ^{1}H-NMR: δ 3.68-3.74 (m, 16H, 8X (CH_2- morpholine H)), 7.42 (d, *J*=8.5 Hz, 2H, Ar-H), 7.96 (d, *J*=8.6 Hz, 2H, Ar-H), 9.99 (s, 1H, CHO). MS: m/z 371 **[**M^+], 372 [M^++1). Anal. calcd for $C_{18}H_{21}N_5O_4$: C, 58.21; H, 5.70; N, 18.86. Found: C, 58.55; H, 5.42; N, 18.77.

General procedure for preparation of compounds 5 and 6

A solution of 1-(4-(4,6-dichloro -1,3,5-triazin-2-ylamino)phenyl)ethanone (4) (2.83 g, 0.01 mol) in 1,4-dioxane, 2,6-disubstitutedphenol (0.01 mol) and potassium carbonate (1.38 g, 0.01 mol) was whiskered for 12 h at 25ºC, therewith teeming in crumbled ice. The formative precipitate filtered, washed with water and crystallized from acetone.

1-(4-(4-chloro-6-(2,6-dichlorophenoxy)-1,3,5-triazin-2-ylamino)phenyl)ethanone (5): Yield 76%; MP 232-234°C; IR: 1704 (C=O), 3500 (NH); ^{1}H-NMR: δ 3.35 (s, 3H, CH_3-CO), 7.46-7.48 (m, 3H, (dichlorophenoxy)), 7.65 (d, *J*=7.8 Hz, 2H, Ar-H), 7.70 (d, *J*=7.9 Hz, 2H, Ar-H), 10.99 (s, 1H, NH, D_2O-exchangeable); ^{13}C-NMR: 26.9, 120.1, 128.4, 128.9, 129.4, 129.7, 132.5, 142.5, 144.5, 166.3, 171.05, 171.4, 196.9. MS: m/z 409.5 **[**M^+]. Anal. calcd for $C_{17}H_{11}Cl_3N_4O_2$: C, 49.84; H, 2.71; N, 13.68. Found; C, 50.14; H, 2.90; N, 13.88.

1-(4-(4-chloro-6-(2,6-diisopropylphenoxy)-1,3,5-triazin-2-ylamino)phenyl)ethanone (6): Yield 70%; MP 85-87°C; IR: 1708 (C=O), 3515 (NH); ^{1}H-NMR: δ 1.11 (d, *J*=6.4 Hz, 12H, 4X (CH_3-diisopropyl)), 2.79-2.89 (m, 2H, 2X (CH-diisopropyl)), 3.95 (s, 3H, CH_3-CO), 7.27 (s, 3H, (diisopropylphenoxy)), 7.58 (d, *J*=7.8 Hz, 2H, Ar-H), 7.94 (d, *J*=7.9 Hz, 2H, Ar-H), 10.61 (s, 1H, NH, D_2O-exchangeable). MS: m/z 424.5 **[**M^+]. Anal. calcd for $C_{23}H_{25}ClN_4O_2$: C, 65.01; H, 5.93; N, 13.19. Found: C, 65.31; H, 5.63; N, 13.49.

procedure for preparation of 1-(4,6-dichloro-1,3,5-triazin-2-yl)piperidine-2-carboxylic acid (7): pipecolic acid (1.29 g, 0.01 mol) in acetone was added slowly to cyanuric chloride (1.84 g, 0.01 mol) in acetone with constant stirring for 18 h in crumbled ice-cold at 0 to 5ºC. Periodically, sodium carbonate solution (0.53 g, 0.005 mol, in 10 ml water) was added dropwise to neutralized HCl evolved during the reaction, therewith the reaction mixture was teemed in crumbled ice. The formative precipitate filtered, washed with water and crystallized from tetrahydrofurane: Yield 69%, M.P >300ºC; IR cm^{-1}: 1714 (C=O), 3424 broad (OH-C=O); ^{1}H-NMR: (DMSO-d_6), δ: 1.24-1.29 (m, 6H, 3X (CH_2- piperidine -3, -4, and -5), 2.15-2.22 (m, 2H, (CH_2- piperidine -6), 3.72 (t, 1H, (CH-piperidine -2), 10.68 (s, 1H, OH-C=O, D_2O exchangeable). MS: m/z 277 [M^+]. Anal. Calcd for $C_9H_{10}Cl_2N_4O_2$: C, 39.01; H, 3.64; N, 20.22 Found: C, 39.22; H, 3.75; N, 20.13.

Biology

Cytotoxicity screening

Specifics of the procedure for the NCI 60 cell line screening are obtainable at http://dtp.nci.nih.gov/branches/btb/ivclsp.html. Substantially, for 24 h the cells were expanded in supplemented RPM1 1640 medium. The checking compound was thawed in DMSO and brood with cells at wanted concentrations. With regard to the five dose study, the compound was thawed in five concentrations with 10-fold dilutions (10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8}) M. Extension of cold trichloroacetic acid finished the assay, then the cells were fixed and soiled with sulforhodamine B. The restricted stain was thawed, and the absorbance was read by an automated plate reader. The cytostatic parameters, 50% growth inhibition (GI_{50}), were matured from time zero, monitoring growth, and the absorbance of the five concentration levels. Inhibitory concentrations (LC_{50}), symbolizes the average of two independent experiments. The evaluation of the compound versus the 60 humanitarian tumor cell lines with a single dose of 10 µM is done by following the same procedure as that applied for the five-dose screening. The compounds that display more than 60% of growth inhibition in at least eight tumor cell lines are only chosen for the five dose testing [21-23].

Enzyme activity inhibition assay

The kit was based on ELISA technology. Assay principle depend on that PI3 Kinase phosphorylates PI(3,4)P2 (PIP2) converting it to PI(3,4,5)P3 (PIP3). The PH domain of the protein GRP-1 set bounds to PIP3 with high affinity and specificity. This recombinant protein is included in the kit that is used as the capture protein that links to the glutathione plate and captures either the PIP3 generated as part of the kinase reaction or the biotinylated-PIP3 tracer included in the kit. Using streptavidin-HRP conjugate, the captured biotinylated-PIP3 is revealed and a colorimetric read out. The lower the signal, the higher the PI3 Kinase activity. Assay protocol state that firstly, the reaction mixture is prepared according to the manufacturer instructions with the following reagents (5X reaction buffer, PIP2 (50 µm), kinase, Wortmannin or customer compound, distilled H_2O).

The PI3 Kinase reaction is setup in the Glutathione-coated strips/plate for inhibitor reaction by firstly, preincubating the kinase and inhibitor for 10 min prior to adding PIP2 substrate, then adding 5 µl/well of 5X kinase reaction buffer after that adding 5 µl/well of PIP2 substrate. Finally, adding distilled H_2O to each well to make up to a final 25 µl/well. Incubate at room temperature for 1 h. 25 µl/well of Biotinylated-PIP3/EDTA working solution is added excluding the buffer control wells. 25 µl/well 1XTBS is added to the buffer control wells. 50 µl/well of GRP1 working solution is added to all wells. Incubate at chamber temperature for 1 h. The wells 4 times are rinsed with 200 µl/well 1XTBST. 50 µl/well SA-HRP working solution is added, incubate at chamber temperature for 1 h. The wells are rinsed 3 times with 200 µl of 1X TBST per well, then 2 times with 200 µl of 1X TBS per well. 100 µl of the Substrate TMB is added per well, develop in the dark for 5-20 min. Monitor the appearance of the blue color to avoid over-development. The reaction is stopped by adding 100 µl of the stop solution per well. Read at 450nm. The lower the signal, the higher the PI3 Kinase activity.

Molecular docking

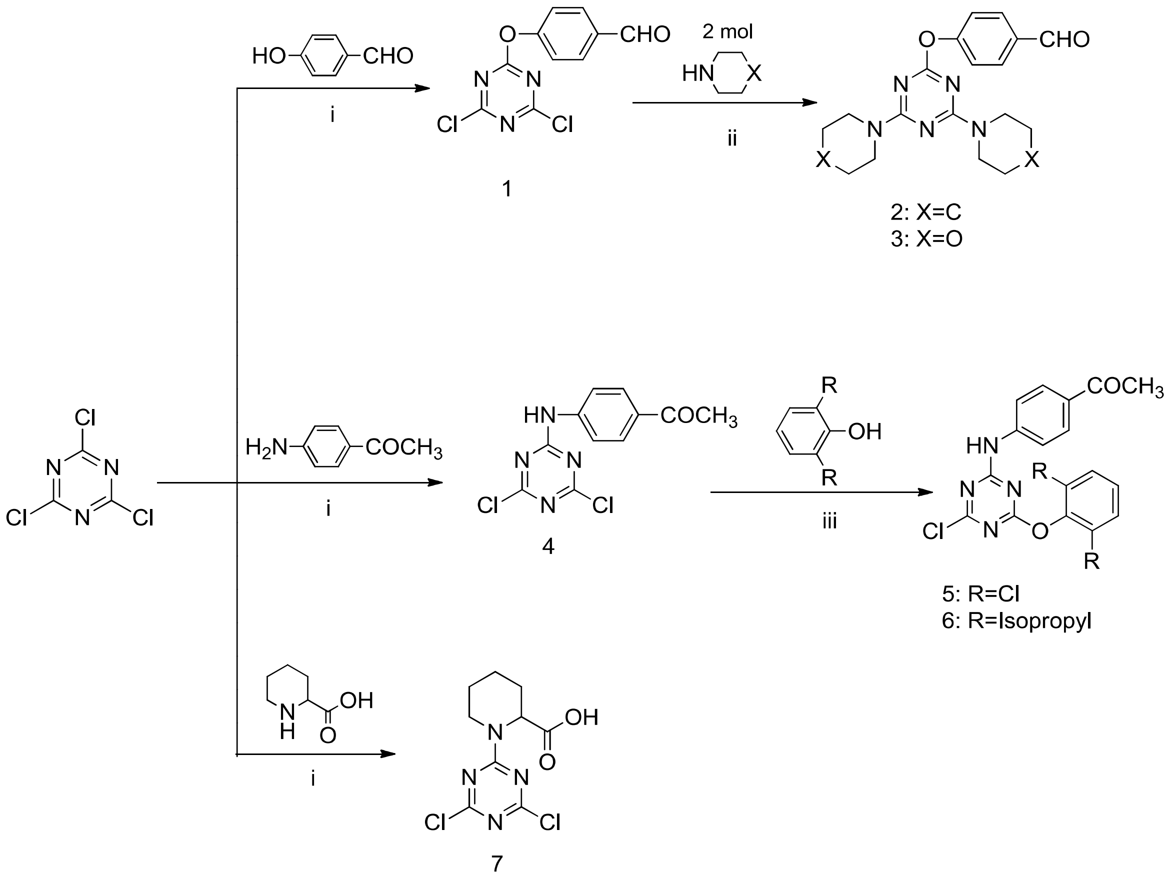
Molecular modeling calculations and docking studies were carried out using molecular operating environment (MOE) software version 2014.09 (Chemical Computing Group Inc., Montreal, Quebec, Canada). The file representing the crystal structure of PI3Kγ with wortmannin was obtained from protein data bank (PDB ID: 1E7U) http://www.rscb.org. All water molecules in PDB were ignored and hydrogen atoms were added to the protein, the energy minimized using MMFF94x force field and the conformers generated were docked into the PI3Kγ receptor with MOE-DOCK using the triangle matcher placement method and the London dG scoring function. The validated docking protocol in the active site was then used to study the ligand-receptor interactions for the novel compounds to predict their binding mode and binding affinity.

RESULTS AND DISCUSSION

Chemistry

According to the reported procedure, compounds (1) and (4) were obtained. [19,20] Nucleophilic substitution of the first Cl of cyanuric chloride with -OH group in 4-hydroxybenzaldehyde and –NH group in 1-(4-aminophenyl)ethanone was carried out in acetone at 0-5ºC with gradual addition of sodium carbonate solution to neutralized HCl evolved during the reaction to get the desired compounds 4-(4,6-dichloro-1,3,5-triazin-2-yloxy)benzaldehyde (1) and 1-(4-(4,6-dichloro -1,3,5-triazin-2-ylamino)phenyl)ethanone (4), respectively. Compound (1) was reacted with 2 moles of piperidine or morpholine with heating at 70ºC in dry DMF in the presence of potassium carbonate to get 4-(4,6-di(piperidin-1-yl)-1,3,5-triazin-2-yloxy)benzaldehyde (2) and 4-(4,6-dimorpholino-1,3,5-triazin-2-yloxy)benzaldehyde (3), respectively.

Equimolar amount of compound (4) and 2,6-disubstitutedphenol were allowed to react using 1,4-dioxane solvent/ anhydrous K_2CO_3 to give the new titled compounds1-(4-(4-chloro-6-(2,6-dichlorophenoxy)-1,3,5-triazin-2-ylamino)phenyl)ethanone (5) and 1-(4-(4-chloro-6-(2,6-diisopropylphenoxy)-1,3,5-triazin-2-ylamino)phenyl)ethanone (6). Finally, stirring of a solution of pipecolic acid with cyanuric chloride in acetone at 0-5ºC with gradual addition of sodium carbonate solution yielded 1-(4,6-dichloro-1,3,5-triazin-2-yl)piperidine-2-carboxylic acid (7) (Scheme 1).



Scheme 1: The synthesis of 1–7: (i) Acetone, aq. Na_2CO_3, 0-5°C; (ii) DMF, K_2CO_3, 70°C; (iii) 1,4-dioxane, K_2CO_3, stirring

Biological screening (anticancer activities)

Cytotoxicity screening

The National Cancer Institute (NCI, USA) for *in vitro* anticancer assay evaluated the anticancer activity of the synthesized compounds. In the NCI 60 cell lines, a single dose (10 µM) of the check compounds were utilized which involved nine tumor subpanels; namely, leukemia, colon, non-small cell lung, melanoma, CNS, renal, ovarian, breast, and prostate cancer cells. The growth percentage of *in vitro* subpanel tumor cell lines of the synthesized compounds showed in Table 1. Compounds 5 and 6 exhibited the highest activity, being compound 6 the most active member in this study, showing effectiveness toward numerous cell lines belonging to different tumor cell lines that reach to 60.13% inhibition in renal cancer (CAKI-1) cell line. In addition, it exhibited the strongest activity against all breast cancer and non-small cell lung cancer cell lines with 12.52 to 42.49% and 12.37 to 46.51% inhibition, respectively. Compound 6 also showed good activity against Leukemia (MOLT-4), colon (HCT-116 and HT29) and CNS (SF-295) with 32.23, 33.56, 35.70 and 40.05% inhibition. By 41.88 and 40.30%, it inhibited melanoma (UACC-62) and prostate cancer (PC-3) cell lines, respectively. It showed good to moderate activity against ovarian cancer and CNS cancer cell lines. With regard to this results, outcropped that compound 6 is the most active member in this study.

Table 1: Growth percentage of *in vitro* subpanel tumor cell lines at 10-µM concentration of the synthesized compounds

Cancer cell lines	**Growth percentage of cell lines in NCI 60**				
	2	**3**	**5**	**6**	**7**
Leukemia					
CCRF-CEM	101.94	107.64	90.98	84.24	104.53
HL-60(TB)	98.11	95.8	97.83	88.77	97.77
K-562	99.9	100.05	82.47	77.7	102.59
MOLT-4	101.61	100.59	77.06	67.77	103.68
RPMI-8226	106.01	102.18	70.01	80.24	108.98
SR	111.9	110.66	82.3	103.55	118.3
Non-small cell lung cancer					
A549/ATCC	96.89	97.76	83.8	65.07	100.67
EKVX	91.35	99.54	77.15	71.09	99.83
HOP-62	99.7	97.68	100.85	80.41	101.13

HOP-92	90.3	101.54	81.21	53.49	105.82
NCI-H226	93.9	88.14	74.87	59.46	89.08
NCI-H23	97.5	95.23	92.27	77.39	98.86
NCI-H322M	100.59	101.02	103.53	87.63	105.57
NCI-H460	101.71	98.51	79.91	92.38	104.72
NCI-H522	94.93	93.77	64.42	74.82	93.32
Colon Cancer					
COLO 205	105.56	106.47	99.72	83.25	106.35
HCC-2998	99.85	100.29	106.21	88.79	100.84
HCT-116	105.54	101.22	84.85	66.42	111.17
HCT-15	97.45	102.02	89.67	79.42	102.29
HT29	101.19	103.41	73.57	64.3	105.82
KM12	106.35	106.38	98.04	87.88	111.37
SW-620	104.96	101.41	88.58	90.81	100.69
CNS Cancer					
SF-268	100.84	95.4	91.33	72.34	99.23
SF-295	97.37	97.58	89.63	59.95	100.72
SF-539	89.11	104.46	90.37	86.48	92.61
SNB-19	97.76	95.36	81.88	75.32	101.84
SNB-75	-	90	74.97	71.04	-
U251	99.84	97.88	76.93	77.38	103.64
Melanoma					
LOX IMVI	92.61	92.09	87.93	76.11	95.79
MALME-3M	102.34	94.97	83.2	97.82	108.15
M14	104.79	111.53	101.09	93.92	107.64
MDA-MB-435	-	101.83	89.86	89.85	-
SK-MEL-2	103.44	105	97.05	90.11	103.9
SK-MEL-28	-	-	-	-	-
SK-MEL-5	98.11	97.02	79.06	90.01	97.28
UACC-257	109.22	104.02	95.41	95.78	100.39
UACC-62	108.6	94	80.57	58.12	99.78
Ovarian Cancer					
IGROV1	101.13	100.67	89.14	60.51	105.77
OVCAR-3	107.8	105.68	90.88	79.69	107.84
OVCAR-4	-	100.05	67.21	71.66	-
OVCAR-5	101.46	101.33	105.34	91.83	105.14
OVCAR-8	103.01	100.08	92.54	82	99.26
NCI/ADR-RES	96.36	103.65	93.57	87.24	101.26
SK-OV-3	100.49	102.41	100.28	82.61	99.87
Renal Cancer					
786-0	101.16	100.4	100.44	81.44	105.2
A498	98	88.09	69.26	90.83	89.97
ACHN	106.21	100.59	98.3	78.89	112.56
CAKI-1	-	100.25	85.45	39.87	-
RXF 393	106	109.55	100.81	72.53	113.09
SN12C	104.15	97.79	93.07	91.01	102.87
TK-10	96.21	93.44	115.12	98.13	102.94
UO-31	88.75	90.9	77.82	62.44	98.1

Prostate Cancer					
PC-3	97.71	101.01	72.52	59.7	99.25
DU-145	104.7	104.06	91.12	97.82	106.54
Breast Cancer					
MCF7	93.52	93.45	74.92	69.05	99.96
MDA-MB-231/ATCC	103.8	99.53	80.02	57.51	110.45
HS 578T	98.16	93.09	74.35	74.33	102.94
BT-549	97.35	91.2	84.7	87.48	103.42
T-47D	90.83	99.91	79.79	63.86	98.98
MDA-MB-468	98.72	104.89	93.33	82.81	102.05

Enzyme inhibition assay

Compound 6 was tested for its phosphatidylinositol 3-kinase gamma PI3Kγ and alphasubunite PI3Kα inhibition activity to evaluate the mode of action of the synthesized compounds as anticancer agents. As shown in Table 2, compound 6 exhibited inhibitory activity against PI3Kγ with (IC_{50}=6.90 µM), that is closer activity to wortmannin (IC_{50}=3.19 µM) as a reference drug. In addition, it exhibited a weak inhibitory activity towards PI3Kα (IC_{50}=0.87 µM) in comparison to Idelalisib (IC_{50}=0.18 µM). This result indicates that PI3Kγ may be a possible target for the designed compounds for their antitumor activity.

Table 2: Inhibitory activities (IC_{50} µM) against PI3Kγ and PI3Kα

compound	**IC_{50} (µM)**	
	PI3Kγ	**PI3Kα**
6	6.9	0.87
Wortmannin	3.19	--
Idelalisib	--	0.18

Molecular modeling

In order to ravel out the pattern of interaction between the target compounds and PI3Kγ receptor (PDB ID: 1E7U) in complex with wortmannin, docking studies were performed for compound 6, which showed the highest *in vitro* activity through examining its binding mode with the key amino acids (hot spots) in the PI3Kγ active site. Examination of the protein ligand interaction for 1E7U revealed that the key amino acids of the active site were Lys (833) and Val (882) (Figure 3) [4,24].

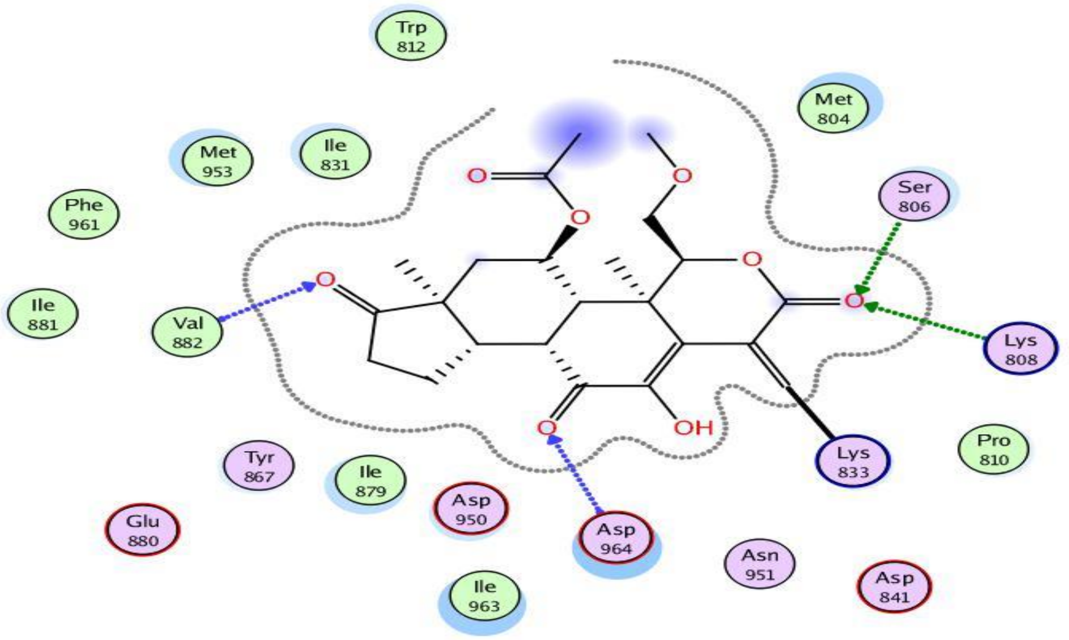


Figure 3: 2D binding of wortmannin with PI3Kγ receptor active site (PDB code 1E7U)

Compound 6 occupied the same pocket of the active site of the protein and formed one hydrogen bond between backbone Val (882) residue and carbonyl group within the target pocket, demonstrating significant binding similarity with wortmannin (Figure 4). The docking results consistent with the biological scores, confirming the PI3Kγ inhibitory activity of compound 6.

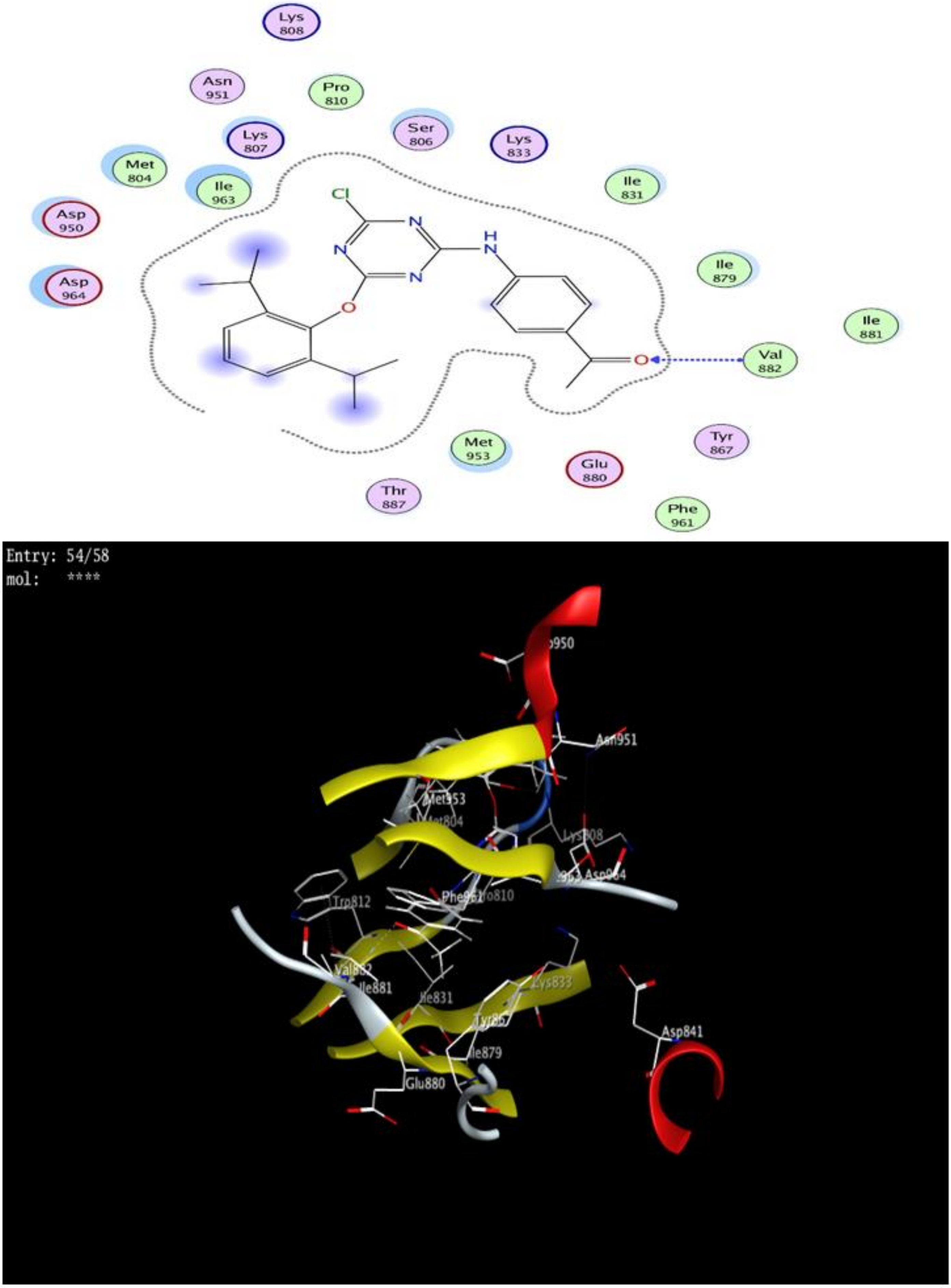


Figure 4: 2D and 3D binding of compound 6 with the PI3Kγ receptor active site

CONCLUSION

Novel series of 1,3,5-triazine analogues were synthesized and *in vitro* screened by the US National Cancer Institute (NCI) for their ability to inhibit 60 different human tumor cell lines. Compound 6 displaying remarkable activity against most of the human tumor cell lines. Also, it has a PI3Kγ inhibitory activity close to that of wortmannin that match with its docking results. It is expected that the target compounds ant proliferative activity may be due to inhibition of PI3Kγ activity.

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