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SYNTHESIS AND MOLECULAR DOCKING STUDIES OF NOVEL SUBSTITUTED 1,3,4-OXADIAZOLO- [3,2-a]-1,3,5-TRIAZINE AND 1,3,4-THIADIAZOLO-[3,2- a]-1,3,5-TRIAZINE DERIVATIVES: A RATIONAL APPROACH TO ANTICANCER DRUG DESIGN

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ABSTRACT

A series of compounds 1,3,4-oxadiazolo-[3,2-a]-1,3,5-triazine and 1,3,4-thiadiazolo-[3,2-a]-1,3,5-triazine derivatives were synthesized in good yield by four different scheme under standard reaction condition. Their structures were confirmed by spectral analysis (IR, NMR & Mass). Molecular docking of title compounds were done using V-Life MDS docking software on breast cancer protein BRCA1 (PDB: 2IOK) and their protein receptor interaction study has done to identify potential anticancer compound based on dock score.

Keywords: 1,3,5-Triazine, Molecular docking, Dock score, Breast cancer protein BRCA1, V-Life MDS, Anticancer activity.

INTRODUCTION

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions. Docking is frequently used to predict the binding orientation of small molecule drug compounds to their protein targets in order to predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs.[1-2] The application of computational methods to study the formation of intermolecular complexes has been the subject of intensive research during the last decade. It is widely

accepted that drug activity obtained through the molecular binding of one molecule (the ligand) to the pocket of another, usually larger molecule (the receptor), which is commonly a protein, in their binding conformations, the molecules exhibit geometric and chemical complementarities, both of which are essential for successful drug activity.[3-4]

Cancer is one of the most prominent human diseases which has enthused scientific and commercial interest in the discovery of newer anticancer agents from synthesized derivatives.[5-6]

In the race of synthesis of new anticancer drugs 1,3,5-triazine derivatives have attracted a great deal of attention amongst the scientific community due to their several reported therapeutic uses.[7-13] The 1,3,5-triazine nucleus is also the core structure of a great number of cancer growth inhibitors.[14-16]

In the present work, we propose to synthesis a series of 1,3,4-oxadiazolo-[3,2-a]-1,3,5-triazine and 1,3,4-thiadiazolo-[3,2-a]-1,3,5-triazine derivatives, confirm their structures by spectral analysis, molecular docking studies of the title compounds to ascertain their anticancer activity and will try to correlate the same with anticancer activity.

Experimental section

A series of compounds 1,3,4-oxadiazolo-[3,2-a]-1,3,5-triazine and 1,3,4-thiadiazolo-[3,2-a]-1,3,5-triazine derivatives were synthesized in good yield by four different scheme under standard reaction condition. All the chemicals used were laboratory grade. Melting points determined in open capillary tubes and were found uncorrected. TLC performed to monitor the progress of reactions. The Purity of all the compounds was checked by thin layer chromatography (TLC) on Precoated silica gel-G. Iodine chamber and UV lamp was used for the visualization of TLC spots. IR spectra recorded on FT-IR Spectrometer using KBr disc method. ^{1}H-NMR spectra recorded on Bruker avance-400 MHz NMR spectrometer in DMSO, $CDCl_3$. Mass spectra recorded on LC-MSD-Tranp-SL2010A Shimadzu.

Docking studies of the title compounds was done on V-Life docking software on breast cancer protein BRCA1 (PDB: 2IOK). Docking score of all synthesized compounds was determined and reported in table.

Docking studies

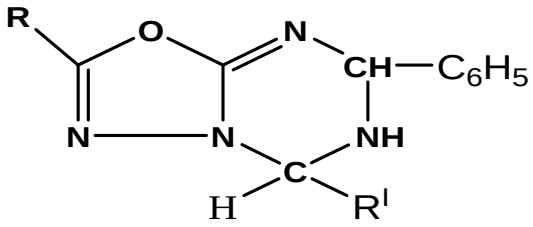
The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and related orientation between protein and ligand such that the free energy of the

overall system minimized. In the fields of computational chemistry and molecular modeling, scoring functions are fast approximate mathematical methods used to predict the strength of the non-covalent interaction (also referred to as binding affinity) between two molecules after they have been docked. Most commonly one of the molecules is a small organic compound such as a drug and the second is the drug's biological target such as a protein receptor. Scoring functions have also been developed to predict the strength of other types of intermolecular interactions, for example between two proteins or between protein and DNA. The ideal scoring is to have lowest energy pose be the one with the lowest energy pose be the one with the lowest RMSD relative to experimental pose.[17-19]

Docking studies of the synthesized compounds 1,3,5-triazine derivatives was done on breast cancer protein BRCA1 (PDB: 2IOK) by V-Life Science MDS docking software to ascertain anticancer activity.

Docking study and dock score

1,3,5-Triazine derivatives from scheme-1



2,5-substituted aryl-7-phenyl-[1,3,4]-oxadiazolo-[3,2-a][1,3,5]-triazine (Compounds :1a-1n & 2a-2n)

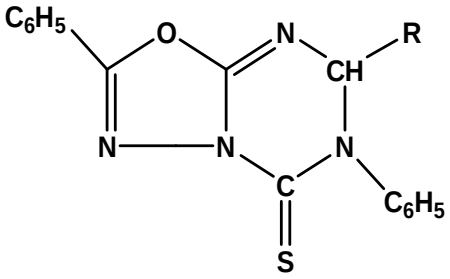
Table No: 01 - Compound 1a-1n

S. No.	Code	R	R^I	Dock score
1.	1a	C_6H_5	C_6H_5	-43.77
2.	1b	C_6H_5	o- OHC_6H_4	-65.07
3.	1c	C_6H_5	m-OHC_6H_4	-64.04
4.	1d	C_6H_5	p- OHC_6H_4	-70.93
5.	1e	C_6H_5	o- $NO_2C_6H_4$	-61.49
6.	1f	C_6H_5	m-$NO_2C_6H_4$	-54.95
7.	1g	C_6H_5	p- $NO_2C_6H_4$	-45.89
8.	1h	C_6H_5	o- ClC_6H_4	-53.64
9.	1i	C_6H_5	p- ClC_6H_4	-61.93
10.	1j	C_6H_5	4- $N(CH_3)_2C_6H_4$	-63.07
11.	1k	C_6H_5	3,4,5-$OCH_3C_6H_2$	-45.62
12.	1l	C_6H_5	4-$OCH_3C_6H_4$	-46.26
13.	1m	C_6H_5	4-OH-3-OCH_3-C_6H_3	-36.64
14.	1n	C_6H_5	2,5- ClC_6H_3	-39.80

Table No 02 - Compound 2a-2n

S. No.	Code	R	R^1	Dock score
1.	2a	p-OHC_6H_4	C_6H_5	-60.55
2.	2b	p-OHC_6H_5	o- OHC_6H_4	-73.00
3.	2c	p-OHC_6H_5	m-OHC_6H_4	-79.12
4.	2d	p-OHC_6H_5	p- OHC_6H_4	-79.12
5.	2e	p-OHC_6H_5	o- $NO_2C_6H_4$	-57.90
6.	2f	p-OHC_6H_5	m-$NO_2C_6H_4$	-46.28
7.	2g	p-OHC_6H_5	p- $NO_2C_6H_4$	-64.61
8.	2h	p-OHC_6H_5	o- ClC_6H_4	-57.60
9.	2i	p-OHC_6H_5	p- ClC_6H_4	-74.68
10.	2j	p-OHC_6H_5	4- $N(CH_3)_2C_6H_4$	-60.47
11.	2k	p-OHC_6H_5	3,4,5-$OCH_3C_6H_2$	-7.00
12.	2l	p-OHC_6H_5	4-$OCH_3C_6H_4$	-76.83
13.	2m	p-OHC_6H_5	4-OH-3-OCH_3-C_6H_3	-64.80
14.	2n	p-OHC_6H_5	2,5- ClC_6H_3	-49.17

1,3,5-Triazine derivatives from scheme-2

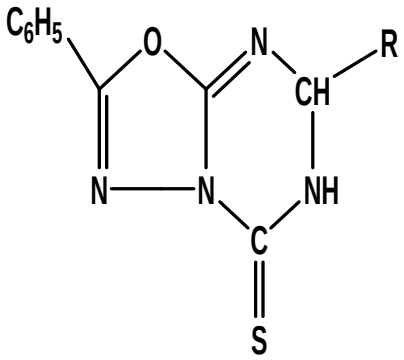


7- substituted aryl-2,6-diphenyl-5-thioxo-[1,3,4]-oxadiazolo-[3,2-a][1,3,5]-triazine (Compounds : 3a-3n)

Table No 03 - Compound 3a-3n

S. No.	Code	R	Dock score
1.	3a	C_6H_5	-61.13
2.	3b	o- OHC_6H_4	-44.89
3.	3c	m-OHC_6H_4	-61.79
4.	3d	p- OHC_6H_4	-50.47
5.	3e	o- $NO_2C_6H_4$	-43.68
6.	3f	m-$NO_2C_6H_4$	-63.08
7.	3g	p- $NO_2C_6H_4$	-82.52
8.	3h	o- ClC_6H_4	-71.08
9.	3i	p- ClC_6H_4	-60.68
10.	3j	4- $N(CH_3)_2C_6H_4$	-57.42
11.	3k	3,4,5-$OCH_3C_6H_2$	-15.43
12.	3l	4-$OCH_3C_6H_4$	-20.89
13.	3m	4-OH-3-OCH_3-C_6H_3	-73.09
14.	3n	2,5- ClC_6H_3	-40.15

1,3,5-Triazine derivatives from scheme-3

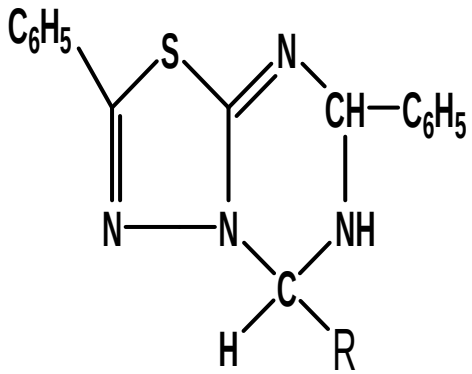


7-substituted aryl-2-phenyl-5-thioxo-[1,3,4]-oxadiazolo-[3,2-a][1,3,5]-triazine
(Compounds : 4a-4n)

Table No 04 - Compound 4a-4n

S. No.	Code	R	Dock score
1.	4a	C_6H_5	-62.18
2.	4b	o- OHC_6H_4	-66.59
3.	4c	m-OHC_6H_4	-65.37
4.	4d	p- OHC_6H_4	-67.62
5.	4e	o- $NO_2C_6H_4$	-66.72
6.	4f	m-$NO_2C_6H_4$	-65.28
7.	4g	p- $NO_2C_6H_4$	-70.24
8.	4h	o- ClC_6H_4	-61.67
9.	4i	p- ClC_6H_4	-65.64
10.	4j	4- $N(CH_3)_2C_6H_4$	-57.25
11.	4k	3,4,5-$OCH_3C_6H_2$	-58.96
12.	4l	4-$OCH_3C_6H_4$	-69.68
13.	4m	4-OH-3-OCH_3-C_6H_3	-65.14
14.	4n	2,5- ClC_6H_3	-54.47

1,3,5-Triazine derivatives from scheme-4



5-substituted aryl-2,7-diphenyl-[1,3,4]-thiadiazolo-[3,2-a][1,3,5]-triazine
(Compounds :5a-5n)

Table No 05 - Compound 5a-5n

S. No.	Code	R	Dock score
1.	5a	C_6H_5	-69.90
2.	5b	o- OHC_6H_4	-65.53
3.	5c	m-OHC_6H_4	-66.96
4.	5d	p- OHC_6H_4	-73.11
5.	5e	o- $NO_2C_6H_4$	-50.90
6.	5f	m-$NO_2C_6H_4$	-33.65
7.	5g	p- $NO_2C_6H_4$	-62.67
8.	5h	o- ClC_6H_4	-55.55
9.	5i	p- ClC_6H_4	-69.31
10.	5j	4- $N(CH_3)_2C_6H_4$	-44.29
11.	5k	3,4,5-$OCH_3C_6H_2$	-56.27
12.	5l	4-$OCH_3C_6H_4$	-53.92
13.	5m	4-OH-3-OCH_3-C_6H_3	-30.98
14.	5n	2,5- ClC_6H_3	-51.48

List of compound showing maximum and minimum dock value are further subject to biological evaluation as anticancer study

Table No: 06 -

High dock score			Low dock score		
S. No.	**Compound Code**	**Dock score**	**S. No.**	**Compound Code**	**Dock score**
1	1b	-65.07	**1**	1m	-36.64
2	1d	-70.93	**2**	1n	-39.80
3	2c	-79.12	**3**	2f	-46.28
4	2d	-79.12	**4**	2k	-7.00
5	3g	-82.52	**5**	3k	-15.43
6	3h	-71.08	**6**	3l	-20.89
7	4g	-70.24	**7**	4j	-57.25
8	4l	-69.68	**8**	4n	-54.47
9	5a	-69.90	**9**	5f	-33.65
10	5d	-73.11	**10**	5m	-30.98

Compounds having high dock score and its receptor interaction

Receptor interaction between synthesized compounds and receptor

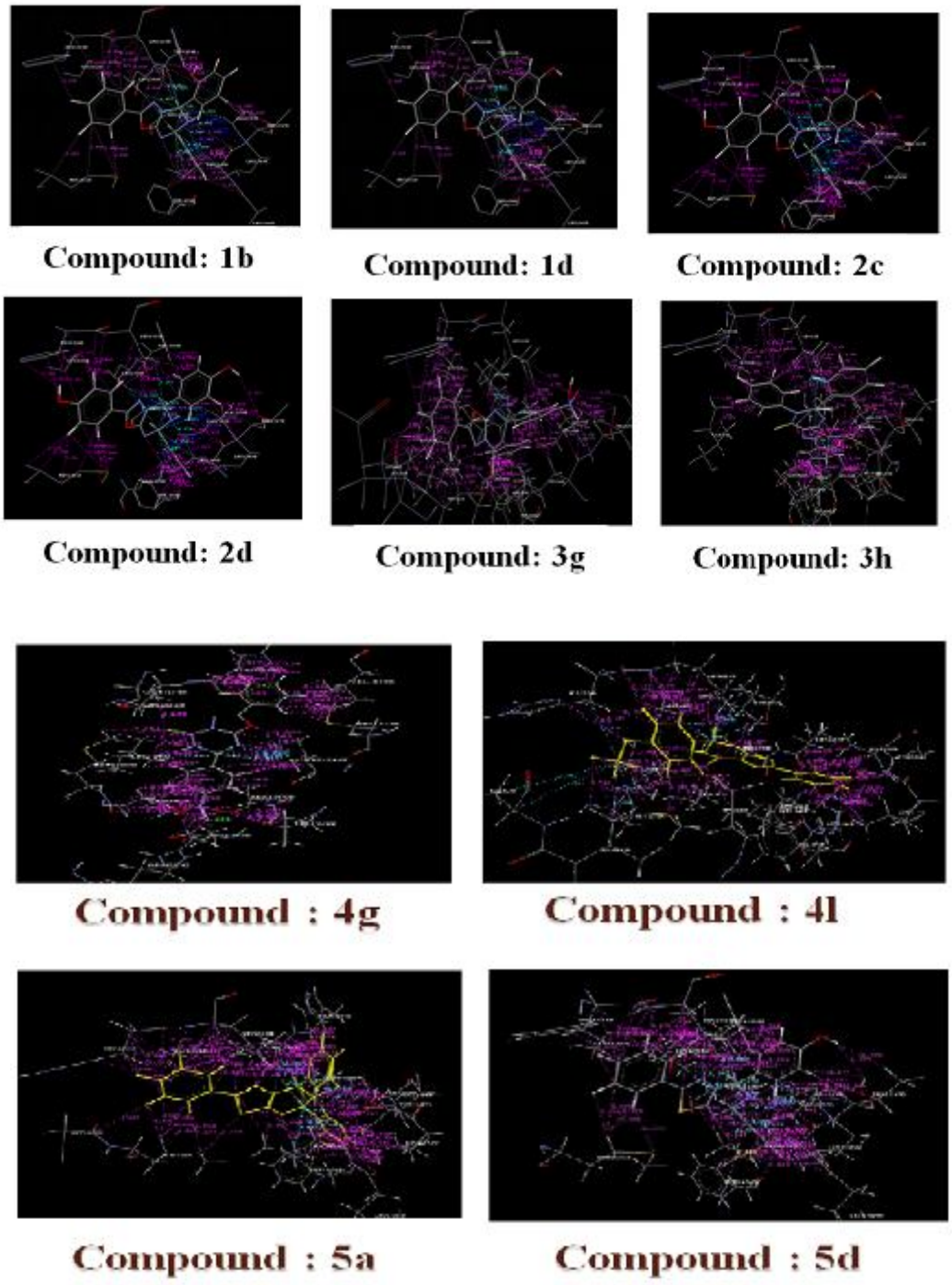


Figure: 01- Binding-site analysis and its graphical interpretation

RESULTS AND DISCUSSION

The present study reported the synthesis of novel substituted 1,3,4-oxadiazolo-[3,2-a]-1,3,5-triazine and 1,3,4-thiadiazolo-[3,2-a]-1,3,5-triazine derivatives. The synthesized compounds were recrystallized and identified by TLC. The melting point were found uncorrected. The difference in the R_f value and melting point show the change in the structure between the molecules. All Physical data of the compounds were recorded and reported.

IR Spectra were recorded in KBr on FT-IR instrument. All the compounds show characteristic peaks of different functional group presence in synthesized compounds. ^{1}NMR was recorded on Bruker Avance-400 MHz NMR spectrometer chemical shift was measured at part per million downfield from tetra methyl silane. Compounds show characteristic peaks and confirmed the structure of synthesized compounds. Mass spectra were recorded on LC-MSD-Trap-SL which show characteristic molecular ion, base peak and further confirmed the synthesized compounds.

Docking studies of the title compounds was done on V-Life docking software on breast cancer protein BRCA1 (PDB: 2IOK) and dock score were correlated with anti-cancer activity. The docking of the title compounds yielded scores ranging from -7.00 to -79.12. The docking study revealed that the title compounds have good interaction with protein BRCA1 (PDB: 2IOK) and compounds 1b, 1d, 2c, 2d, 3g, 3h, 4g, 4l, 5a and 5d are potential derivatives as a anticancer agent because of the highest negative dock score (-79.12 and -65.07). Compounds bind with protein BRCA1 (PDB: 2IOK) by forming hydrogen bond interaction, hydrophobic interaction with amino acid residues. Comparison of docked complexes provides shown the activity patterns of various 1,3,5-derivatives in terms of effective hydrogen-bonding and hydrophobic interactions. The detailed results of dock score are given in Table 01 to 06 and figures-01 represent the interaction patterns of highly active compounds.

CONCLUSION

A series of novel heterocyclic compounds 1,3,4-oxadiazolo-[3,2-a]-1,3,5-triazine and 1,3,4-thiadiazolo-[3,2-a]-1,3,5-triazine derivatives has been successfully synthesized. Compounds contain bioactive heterocyclic rings 1,3,5-triazine, 1,3,4-oxadiazole and 1,3,4-thiadiazole. The molecular docking of synthesized compounds were studied on breast cancer protein BRCA1 (PDB: 2IOK) by V-Life Science MDS docking software. Newly synthesized compounds have shown promising dock value. To strengthen the current investigation, further evidences both in vitro and in vivo are needed so as to use this approach effectively for cancer treatment.

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