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Molecular Docking Studies of Tyrosine Kinase-inhibiting New Styryl-Coumarin derived Aminothiozoles

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ABSTRACT

Coumarins are the enormous type of 1-benzopyran derivatives, which have vast biological importance like antimicrobial, anti-inflammatory, anti-cancer, anti-HIV, anti-oxidant, Anti-coagulant, Anti-tubercular, anti-psychotic and anti-malarial activities. Thiazoles are most intensively investigated classes of aromatic five-membered heterocycles with bacteriostatic, antibiotic, CNS regulants, high ceiling diuretics, anthelmintic, anti-inflammatory, anti-hypertension and anti-HIV activities. Present work describes in-silico pharmacological evaluation of some new hybrid molecules of styrylcoumarin derived aminothiazoles. Since the coumarin and thiazole derivatives were proved with anticancer activity studies, an attempt was made to dock the hybrid molecular libraries of these compounds through in-silico docking techniques using the crystal structure of Protein tyrosine kinase (PDB ID: 2src) to recognize the hypothetical binding mode of the ligands with the receptor for their possible anticancer activity. The title compounds were docked by using Schrodinger Maestro 9.8 Glide 5.8 XP. Thiazole nucleus showed good interaction with Methionine 341 amino acid and forms strong hydrogen bond interaction with OH of molecules. Tyrosine 340 has good interaction with benzene in acetophenone portion. Among all the compounds, SCT 2, SCT 6 and SCT 10 showed good binding interactions with the target site.

Keywords: Styrylcoumarin derived chalcone, Docking, Anti-cancer.

INTRODUCTION

In the current scenario of medical treatment, cancer is the second burning issue after the cardiovascular disease which leads to human death. However, the cancer has been treated by huge medical strategies (like chemotherapy), it was not irradiated completely. So, there is a compulsion to track down the highly potent drug molecules with fewer side effects to treat the cancer. Medicinal chemistry is the branch of science, which includes incredible aspects like discovery, development, identification and explanation of Pharmacological action active compounds at molecular level for synthesis of new drugs with potent therapeutic activity [1]. Till date several anticancer agents (tyrosine kinase inhibitors) were developed, still there is a requisite to effective lead discovery and develop of new tyrosine kinase inhibitors which can be achieved by employing *in-silico* drug design tools. Prudent drug design assist to promote and fasten the drug designing process which includes multiple methods to identify new compounds [2]. One such method is the *in-silico* docking of the ligands with the proteins (target). Docking is the technique that explains the interaction between ligands and proteins when they contact in 3D space [3]. Molecular docking tries to predict the types of bonds, orientation and binding energy of the intermolecular complex [4].

Coumarin, an oxygen heterocyclic compound, shows vital role in the domain of natural products and synthetic organic chemistry. Coumarins belong to 1-benzopyran category and they are generally oxygenated at C-7. Coumarins are spontaneously found in plants. Thiazoles contain aromatic five-membered heterocycles. At first thiozoles were described by Hantzsch and Weber in 1887 [5]. Thiazoles are generally present in many of the natural products. Thiazole and its derivatives have importance in drug discovery. However, thiazoles are also synthetic intermediates various pharmacologically active compounds [6].

Review of literature reveals that the coumarin and its derivatives possess antimicrobial [7-9], anti-inflammatory [10-13], anticancer [14-17], anti-HIV [18-20], antioxidant [21-23], Anticoagulant [24,25], Anti-tuberculosis [26,27], anti-psychotic [28] and anti-malarial [29] activities. Thiazole derivatives also possess a wide variety of applications like bacteriostatics, antibiotics, CNS regulants and high selling diuretics [30]. Thiazole system has found broad application in drug development for the treatment of inflammation, hypertension and HIV infections [31]. Aminothiazoles are known to be ligands of estrogen receptors as well as a novel class of adenosine receptor antagonists [32]. Other analogues are used as fungicides, inhibiting *in vivo* growth of *Xanthomonas*, as an ingredient of herbicides or as schisto-somicidal and anti-helmintic drugs.

By combining the coumarin derivatives with aminothiazoles through chemical reactions may lead to intensify the pharmacological activity of the derived compounds. The present work explains the attempt was made to design, synthesis, characterization and biological evaluation of some styrylcoumarin derived aminothiazoles.

MATERIALS AND METHODS

The molecular docking studies were performed using Schrodinger 9.8 software XP Glide 5.8 Software. Tyrosine kinase was selected as target protein for this study. The crystal structure of tyrosine kinase (2src) was obtained from protein data bank (http://www.rscb.org/pdb). Occasionally the crystal structures to be modified according to our docking requirements. Schrodinger has required tools (like maestro) to convert proteins into compatible file formats to run the docking studies.

The Schrodinger tool, LigPrep used to minimize the energy and convert the ligands into compatible formats. GLIDE (Grid-based Ligand Docking with Energetics) can able to detect the binding interactions between ligands and protein. It changes the position and orientation of ligand interaction with protein at active binding sites and filter the effective position and orientation interaction between the ligands and protein. Finally it generates the Glide (G) score based on the bond type, binding energies, bond length, bond angles and bond orientation. The best Glide (G) Score is assigned for highly active ligands with most negative value and are listed in descending order.

RESULTS AND DISCUSSION

Molecular docking studies for designed coumarin aminothiazole compounds were carried out with the crystal structure of tyrosine kinase active binding site. The analogues showed good binding interactions with the target site. Thiazole nucleus has a good interaction with Methionine 341 amino acid and a strong hydrogen bond interaction with a water molecule. Tyrosine 340 has good interaction with benzene in acetophenone portion. Amine substituted pyrazole compounds forms the amine linkage between amine group of pyrazole and SER 342. Nitro compounds forms the bond with PHE 406 (Figures 1 and 2).

The designed compounds SCT 2, SCT 6, and SCT 10 were showing the low Glide (G) score when compared to other designed compounds. If lower the G-score, then higher the binding efficiency of compounds to active binding sites. SCT 2, SCT 6, and SCT 10 were found to accommodate the binding pocket of the receptor showing the effective interactions with all the crucial amino acid residues (Table 1).

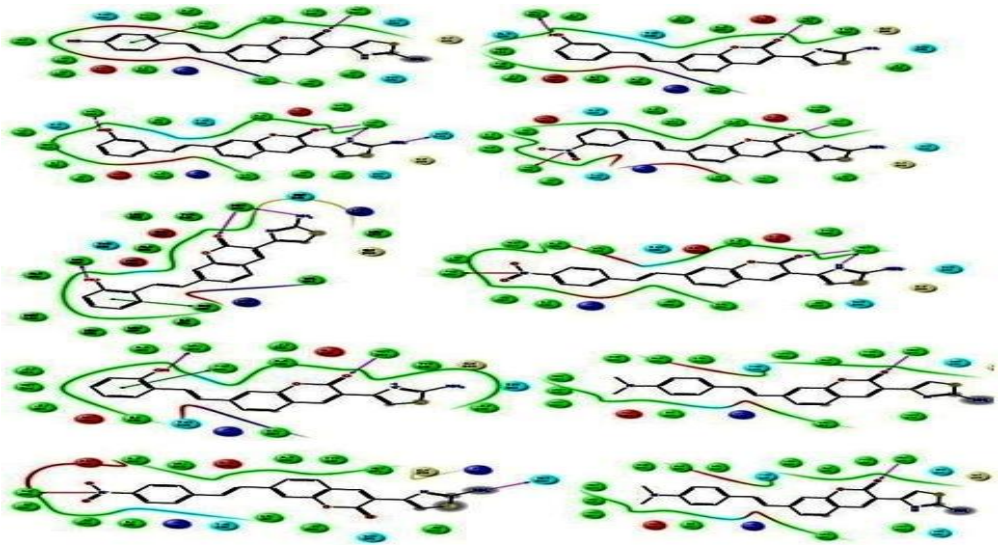

Figure 1: 2D representation of compounds interaction with protein amino acids at active site.

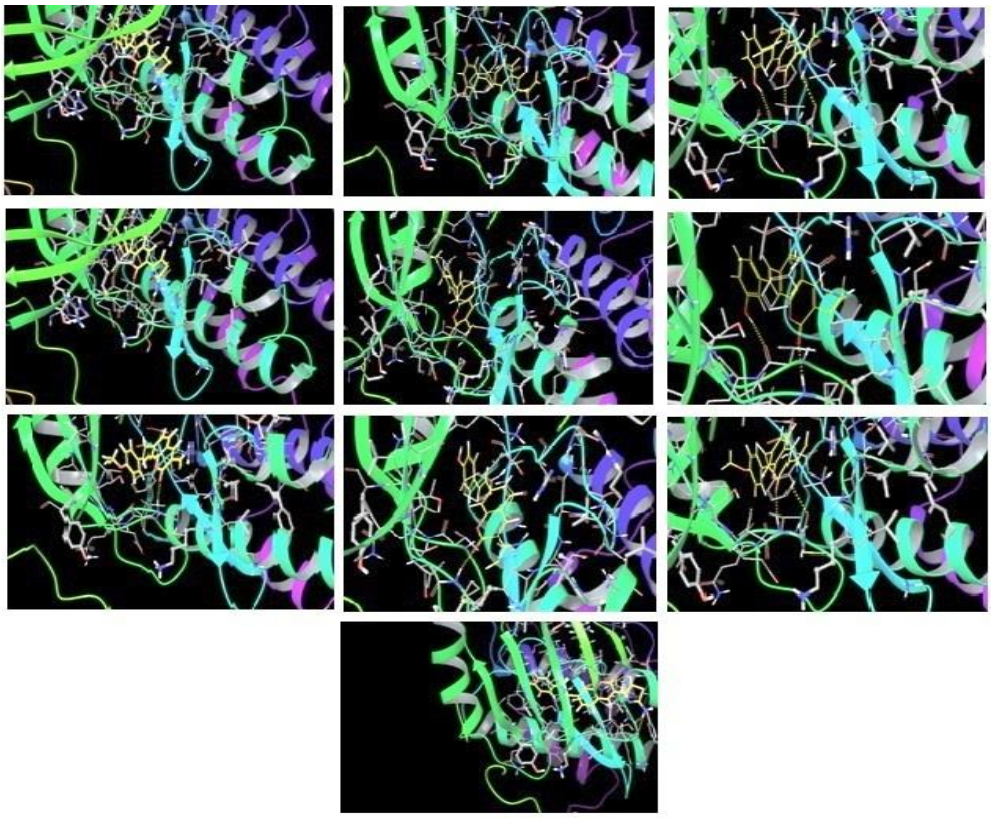

Figure 2: 3D representation of compounds interaction with protein amino acids at active site.

Table 1: Docking Studies of the title compounds with 2Src Protein in GLIDE.

Compound Code	Glide lignum	Glide ligand efficiency	XP G Score	Glide g score	Glide energy	Docking score
SCT 2	3	-2.03	-8.65	-8.65	-52.166	-8.643
SCT 6	7	-1.943	-8.281	-8.281	-52.492	-8.275
SCT 10	16	-1.783	-7.664	-7.664	-52.646	-7.658
SCT 4	5	-1.589	-6.888	-6.888	-35.514	-6.882
SCT 8	11	-1.553	-6.743	-6.743	-53.343	-6.729
SCT 2	4	-1.381	-8.573	-8.573	-52.608	-5.879
SCT 7	9	-1.291	-5.601	-5.601	-48.12	-5.595
SCT 3	2	-1.292	-8.195	-8.195	-48.166	-5.502
SCT 3	1	-1.264	-5.387	-5.387	-52.267	-5.381
SCT 10	17	-1.135	-7.567	-7.567	-38.875	-4.874
SCT 9	15	-1.133	-7.518	-7.518	-46.167	-4.825
SCT 9	14	-1.127	-4.806	-4.806	-52.584	-4.8
SCT 4	6	-1.028	-7.147	-7.147	-36.369	-4.454
SCT 8	13	-0.902	-6.608	-6.608	-53.22	-3.907
SCT 6	8	-0.72	-5.758	-5.758	-51.774	-3.065
SCT 7	10	-0.681	-5.642	-5.642	-45.699	-2.949
SCT 8	12	-0.59	-5.111	-5.111	-51.906	-2.558

CONCLUSION

Molecules prepared for the biological testing do not always turn out as potential new compounds but may be intended to serve as models for evaluation of hypothesis. The present work evaluates the *in-silico* anticancer activitie of some styrylcoumarin derived aminothiazoles. The designed compounds were screened for *In-silico* anti-cancer activity. *In-silico* Molecular docking investigations were carried out using Schrodinger 9.8 software XP Glide 5.8. The Glide (G) Score obtained (which indicates the binding affinity of the molecules towards the protein) from the software indicates that the most negative value and the most active ligands. The compound SCT 2, SCT 6 and SCT 10 showed good binding interactions with the target site.

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