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Potential inhibitors of xanthene derivatives by molecular docking study

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ABSTRACT

In the present study, we prepared new xanthene derivatives for the conventional method, and the derivatives are confirmed by the IR, NMR and mass spectral techniques. In the present scenario, numerous people have been affected by the virus for the past two years in the world. Xanthene derivatives in prediction of molecular docking for new compounds and docking studies were performed to investigate the hypothetical binding mode of the target compounds. The lowest binding energy like -5.43, -5.57, -6.25, -5.99 and -5.47 kcal/mol confirmed by protein binding to the molecules. The hydrogen bonding interactions are confirmed by suitable binding confirmation for the docking.

1. Introduction

Molecular docking defined as an optimization problem, which would describe the "best-fit" orientation of a ligand that binds to a particular protein of interest and is used to predict the structure of the intermolecular complex formed between two or more molecules. The most interesting case is the protein-ligand interaction, because of its applications in medicines.[1] Modern drug designing, molecular docking is routinely used for understanding drug-receptor interaction. Invasive microbial infections are major problems around the world, especially in immuno compromised patients. The development of antimicrobial resistance has increased in this century and there is a need for developing new antimicrobial agents which will be more selective, potent and less toxic compared to the existing drugs in clinical treatment. Heterocycles containing an azole ring system are found to exhibit a wide spectrum of biological activities, including antibacterial and antifungal properties.[2] Imidazole derivatives possess a broad spectrum of pharmacological activities such as, anti-inflammatory, analgesic, anti-convulsant, antitubercular, antimicrobial, and anticancer activities.[3-5] Pyrazole derivatives have been showed significant biological activities, a great impetus to the search for potential pharmacologically active drugs carrying pyrazole substituents.[6-11] Antimicrobial activity of various types of compounds indicated that, the presence of certain pharmacophore such as imidazole/pyrazole.[12,13] Docking studies of the biologically active six moieties are better understanding of drug-receptor interaction. Molecular docking studies were carried out to predict the predominant binding modes of the ligand with protein. The Molecular docking studies of the compounds were explored and discussed in order to discover potent scaffolds that can further be developed into drugs.

2. Experimental

2.1. Synthetic route of xanthene derivatives

A mixture of 5,5-dimethylcyclohexane-1,3-dione, substituted benzaldehyde, acetic acid medium. The reaction mixture was refluxed for 6 hours and the completion of the reaction was monitored by TLC technique using benzene and ethyl acetate (9:1) as the eluent. The resultant material was purified by column chromatography. The schematic representation of

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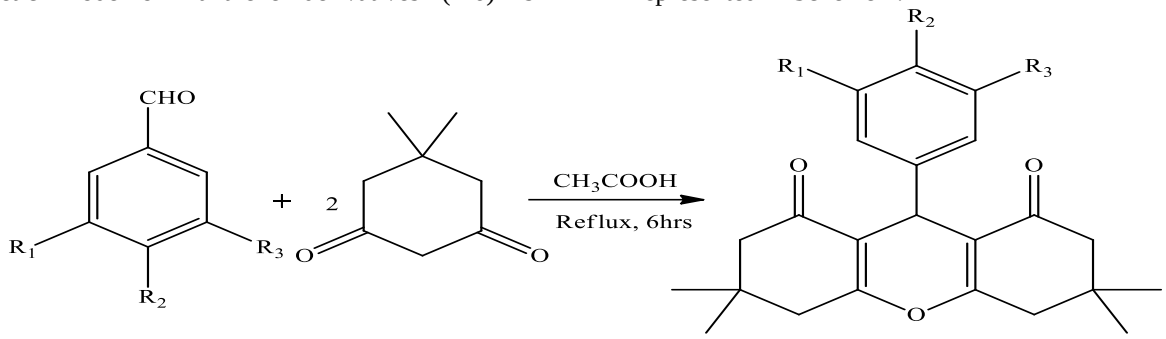
synthetic mode of xanthene derivatives (1-6) is represented in Scheme 1.



R_1 = H, $-OCH_3$, H, $-OCH_3$, H and H
R_2 = $-CH_3$, -OH, $-OCH_3$, $-OCH_3$, -Cl and $-N-(CH_3)_2$
R_3 = H, $-OCH_3$, -OH, $-OCH_3$, H and H

Scheme 1. Synthetic route of xanthene derivatives

2.2. Spectral Measurements

The ^1H and ^{13}C NMR spectra of the synthesized compounds in DMSO were recorded on a Bruker AMX 400 MHz NMR spectrometer. Infrared spectra were recorded on a JASCO FT-IR-5300 Spectrometer in the range 4000 – 400 cm^{-1} using KBr pellets.

2.3. Molecular docking Studies

Molecular docking simulation was performed with the Argus Lab 4.0. The prepared 3D structures were downloaded from the protein data bank and binding site was made by choosing "Making binding site for this protein" option. The ligand was then introduced and docking calculation was allowed to run using shape-based search algorithm and a score scoring function. The scoring function is responsible for evaluating the energy between the ligand and protein target.

Flexible docking was allowed by constructing grids over the binding sites of the protein and energy based rotation is set for that ligand group of atoms that do not have rotatable bonds. The best docking model was selected according to the lowest binding energy calculated by arguslab and the most suitable binding conformation was selected on the basis of hydrogen bond interaction between the ligand and protein near the substrate binding site. The lowest energy poses indicate the highest binding affinity as high energy produces the unstable conformations. The resulting receptor model was saved to Brookhaven PDB file from the file the 2D and 3D interactions are viewed in discovery studio 4.5 versions.

3. Result and Discussion

3.1. Spectral Data

3,3,6,6-tetramethyl-9-(p-tolyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (1)

M.F.: $C_{24}H_{28}O_3$: IR (cm^{-1}); 1663.60 (C=O); 3037.87 – 2874.79 (Aromatic C-H); 1625.26 (C=C) (Figure 1). ^1H NMR (DMSO, ppm); δ: 7.04 (dd, 9.20 MHz, 4H), 0.89 (s, 6H), 1.03 (s, 6H), 2.23 (s, 3H (C23 Protons)), 2.08 (s, 4H), 2.51 (s, 4H), 4.47 (s, 1H) (Figure 2). ^{13}C NMR (DMSO, ppm); δ: 20.95, 26.74, 29.14, 31.22, 32.27, 38.93, 50.45, 114.96, (128.38, 128.93, 135.78, 141.75, 163.52 for aromatic carbons), 197.06 (C=O) (Figure 3).

9-(4-hydroxy-3,5-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (2)

M.F.: $C_{25}H_{30}O_6$: IR (cm^{-1}); 1661.67 (C=O); 3012.74 – 2871.98 (Aromatic C-H); 1617.09 (C=C). ^1H NMR (DMSO, ppm); δ: 0.87 (s, 6H, CH_3), 1.00 (s, 6H, CH_3), 2.07 (s, 4H), 2.50 (s, 4H), 3.64 (s, 1H), 4.01 (s, 6H for methoxy groups), 6.34 (s, 1H (C23 – for OH - group)), 8.38 (s, 12H for aromatic protons) ^{13}C NMR (DMSO, ppm); δ: 26.69, 29.26, 31.19, 32.31, 50.54, (56.42 for methoxy carbons (C21, 22)), 106.17, 115.04, (134.63, 134.99, 147.94, 163.22, Aromatic carbons), 196.66 (C=O).

9-(3-hydroxy-4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3)

M.F.: $C_{24}H_{28}O_5$: IR (cm^{-1}); 1666.00 (C=O); 2955.56 – 2896.74 (Aromatic C-H); 1626.13 (C=C). ^1H NMR (DMSO, ppm); δ: 0.92 (s, 6H), 1.03 (s, 6H), 2.28 (s, 2H), 2.10 (s, 2H), 2.51 (s, 4H), 3.68 (s, 3H), 4.38 (s, 1H), 6.64 (d, J=1.6Hz, 1H), 6.73 (d, J=8.4Hz, 1H), 8.80 (s, 1H for hydroxyl group). ^{13}C NMR (DMSO, ppm); δ: 26.97, 29.16, 30.72, 32.32, 50.54, (55.93 for $-OCH_3$ carbon (C23)), 112.05, 115.15, 116.22, 118.90, (137.43, 146.23, 146.40, 163.03 for aromatic carbons), 196.57 (C=O).

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3,3,6,6-tetramethyl-9-(3,4,5-trimethoxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (4)

M.F.: $C_{26}H_{32}O_6$: IR (cm^{-1}); 1667.68 (C=O); 2954.84 – 2876.42 (Aromatic C-H); 1625.29 (C=C). ^{1}H NMR (DMSO, ppm); δ: 0.92 (s, 6H), 1.04 (s, 6H), 2.07 (s, 4H), 2.25 (s, 4H), 3.67 (s, 9H for -OCH_3 protons), 4.46 (s, 1H), 6.72 (s, 2H). ^{13}C NMR (DMSO, ppm); δ: 27.5, 32.3, 38.9, 39.6, 51.5, 56.1, 60.8, 106.4, 113.9, 136.2, 136.5, 152.8, 155.0, 198.9.

9-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (5)

M.F.: $C_{23}H_{25}ClO_3$: IR (cm^{-1}); 1661.59 (C=O); 2953.05 – 2875.23 (Aromatic C-H); 1626.18 (C=C). ^{1}H NMR (DMSO, ppm); δ: 0.89 (s, 6H), 1.03 (s, 6H), 2.05 (s, 2H), 2.25 (s, 2H), 2.51 (s, 4H), 4.49 (s, 1H), 7.18 (d, J=8.4Hz, 2H), 7.28 (d, J=8.4Hz, 2H). ^{13}C NMR (DMSO, ppm); δ: 26.94, 29.07, 31.41, 32.32, 50.43, 114.42, (128.30, 130.39, 131.19, 143.72 for aromatic carbons), 163.60, 196.65 (C=O).

9-(4-(dimethylamino)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (6)

M.F.: $C_{25}H_{31}NO_3$: IR (cm^{-1}); 1660.70 (C=O); 2965.62 – 2872.99 (Aromatic C-H); 1611.07 (C=C). ^{1}H NMR (DMSO, ppm); δ: 0.89 (s, 6H), 1.03 (s, 6H), 2.08 (s, 4H), 2.51 (s, 4H), 3.06 (s, 6H for –CH_3 protons), 4.47 (s, 1H), 6.94 (d, J=8.0Hz, 2H), 7.14 (d, J=9.5Hz, 2H). ^{13}C NMR (DMSO, ppm); δ: 26.34, 28.08, 32.62, 45.86, 50.43, 112.05, 113.31, (120.56, 136.33, 146.40 for aromatic carbons), 163.03, 189.17 (C=O).

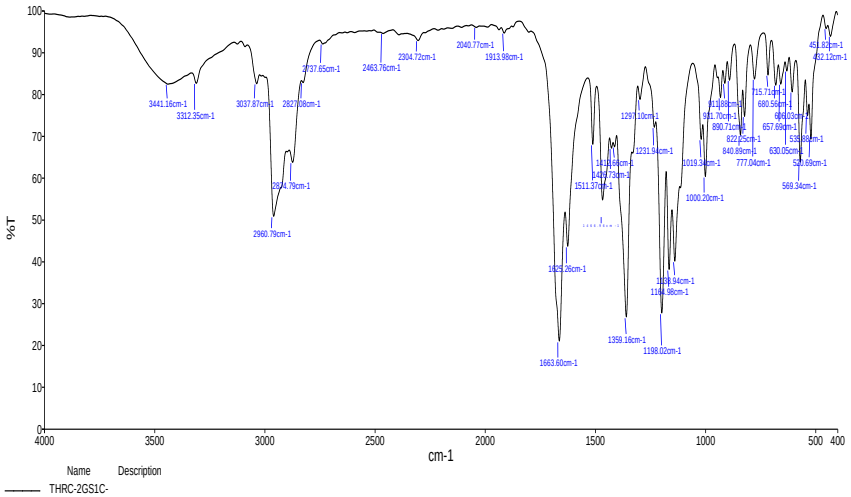

Figure 1. Representative FT-IR spectrum of compound **1**

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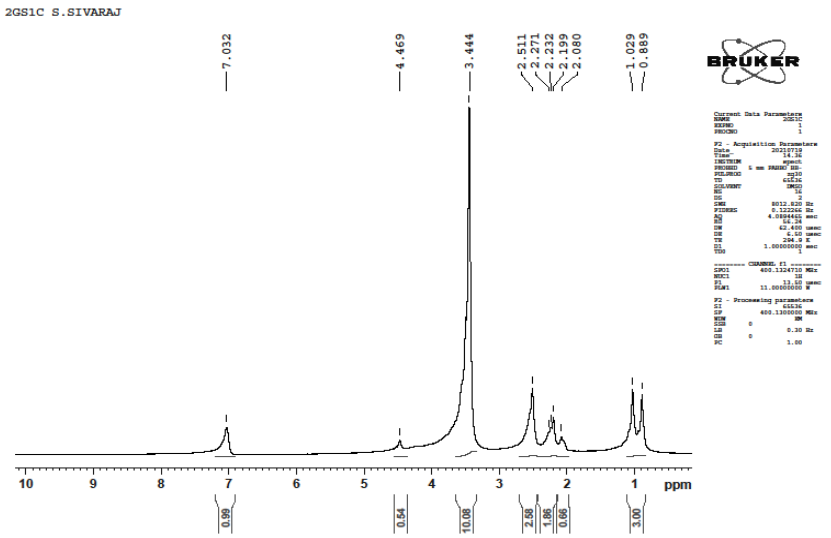

Figure 2. Representative ^{1}H NMR spectrum of compound **1**

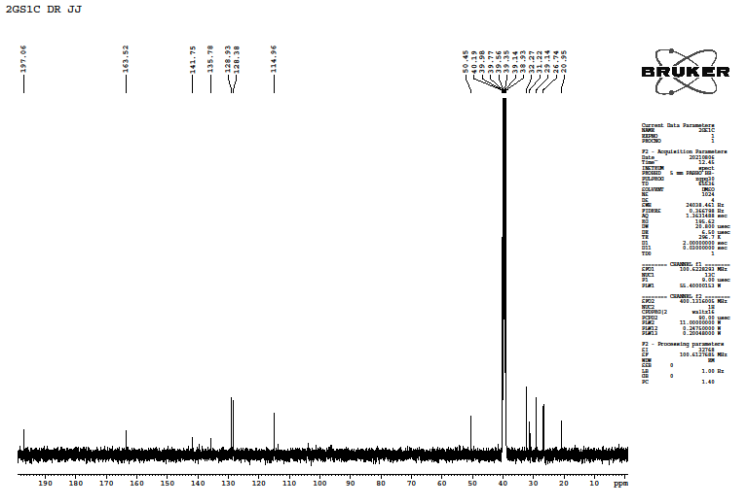

Figure 3. Representative ^{13}C NMR spectrum of compound **1**

3.2. Molecular Docking studies

The entire docking calculations perform flexible protein-ligand docking and searches for favorable interactions between one typically small ligand molecules a typically larger protein molecule. Docking process is divided into three steps. Primary glide docking, wherein protein preparation inhibited refinement is carried out with a maximum of 20 poses. Prime induced fit, wherein the side chains are optimized and refinement of residues takes place, if the ligand poses are within 5.0 Å. It consists of the glide re-docking step by means of standard precision mode. The best docked structure was chosen by three criteria: glide score function, glide energy and the number of amino acids matches (hydrogen bonds) with the standard drug. Binding interaction of the compound (Figure 4) with active site residues (Crystal Structure of NSP1 from SARS-CoV-2 (PDB ID: 7K3N). Molecular analysis of compound 3 indicated the presence of hydrogen bond, hydrophobic and mild polar interactions are the three major interactions incorporating the attachment of this ligand to SARS-CoV-2 acceptor. The hydrophilic and hydrophobic 2D interactions are shown in Figure 5. The two-dimensional interaction diagram of docked compound 3 revealed that the ligand is surrounded by

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hydrophobic residues such as HISA:101 and CYSA:42. This observation concluded that the hydrophobic interactions and de-solvation effects involved in the binding process. Further the hydrophilic residues like THRA:41, GLYA:40, PROA:10, ASPA:39, SERA:8, LEUA:37 are situated around the surface of the target ligand 3. Hence binding affinities also enhanced by these hydrophilic residues. In compound 3, the binding interactions are further surprisingly enhanced by π-π stacking interactions between protein and ligand binding site residue. Among the synthesized compounds 1-6, the *para*-methoxy substituted compound 3 showed good docking score -6.25 and binding energy -4.60 kcal/mol. It is indicated that the compound 3 has better ligand-protein interactions and the remaining moieties are exhibit in the moderate activities of docking studies. Docking score, H – bonding energy, hydrophilic and hydrophobic interactions of protein with the compounds 1-6 are given in Table 1.

Table 1. Docking score, H – bonding energy, Binding energy, hydrophilic and hydrophobic interaction of compounds **1-6**

Compds.	Docking score	H – bonding energy (kcal/mol)	Binding energy (kcal/mol)	Hydrophobic interaction residues	Hydrophilic interaction residues
1	-5.43	-4.82	-5.13	LYSA:63, GLNA:87	THRA:94, GLUA:93, GLYA:92, VALA:47, PHEA:61, LEUA:52, GLUA:82
2	-5.59	-3.51	-3.48	HISA:101	THRA:41, CYSA:42, GLUA:40, ASPA:39, SERA:8, LEUA:37, LEUA:7
3	-6.25	-5.28	-4.60	HISA:101, CYSA:42	THRA:41, GLYA:40, PROA:10, ASPA:39, SERA:8, LEUA:37
4	-5.69	-4.72	-4.85	HISA:101,	THRA:41, GLYA:40, PROA:106, ASPA:39, SERA:8, LEUA:37
5	-5.99	-3.80	-3.43	THRA:94, LYSA63, GLNA:87	GLYA:85, GLUA:82, LEUA:52
6	-5.47	-5.15	-5.17	GLUA:46	GLUA:93, LEUA:95, THRA:94, GLYA:96, ARGA:110

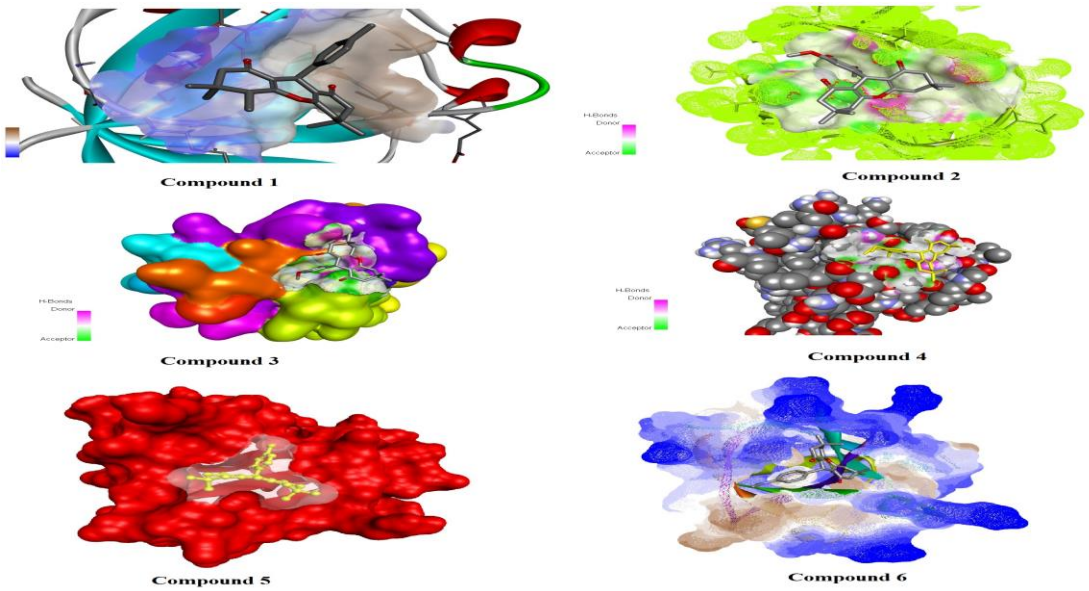

Figure 4. 3D Binding interactions of 1-6 with active site residues of 7K3N receptor

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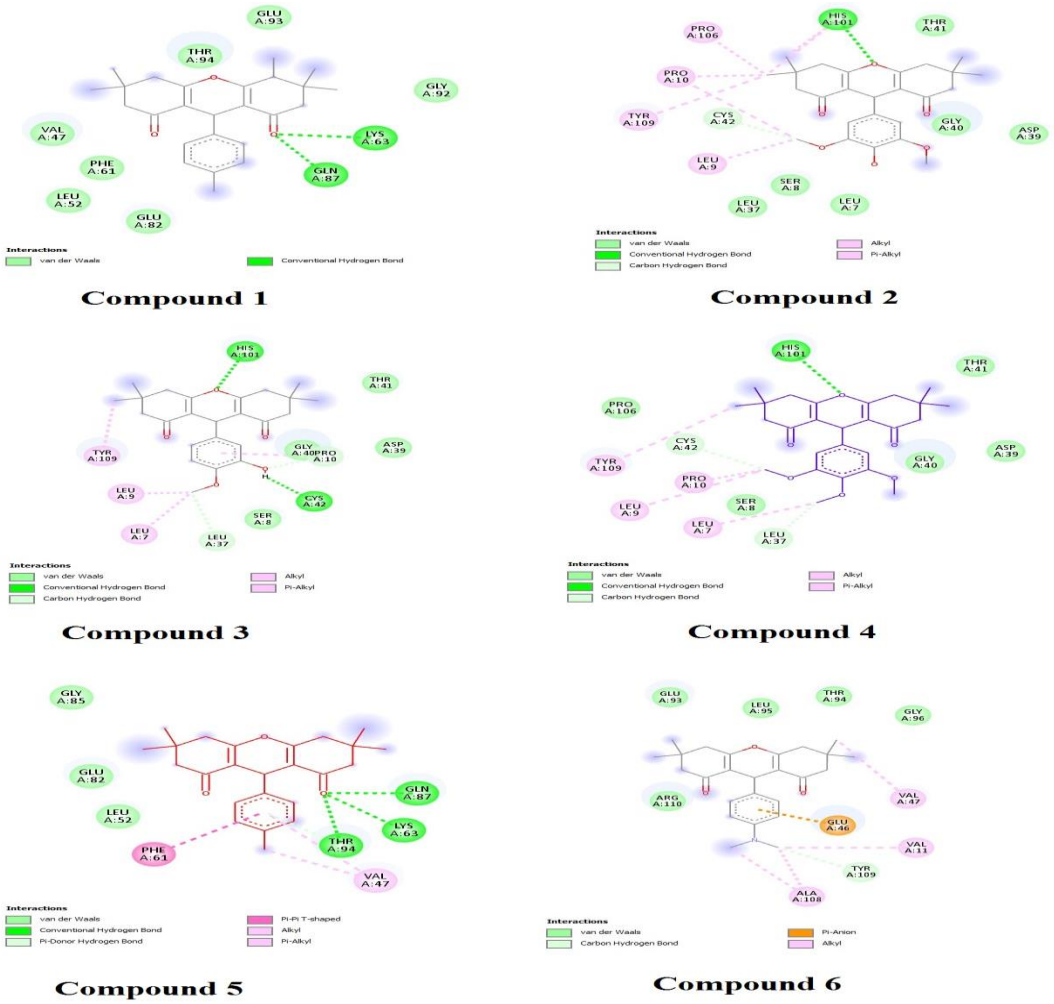

Figure 5. Hydrophilic and hydrophobic interactions of the compound 1-6

4. Conclusion

Six new xanthene compounds were synthesized and characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry, and IR spectral techniques. Molecular docking studies of the synthesized compounds were carried out and the results were reported. It is revealed that all the synthesized compounds **3** have relatively lesser binding energy as compared to the standard drug and may be considered as a good inhibitor of some viruses.

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Conflict of Interests

The authors declare that there is no conflict of interests.

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