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R E S E A R C H A R T I C L E

Synthesis, Characterization and Biological Evaluation of 2-styrylchromone Derivatives

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A B S T R A C T

In this present study of the Design, Synthesis and molecular docking studies of 2-styrylchromone derivatives as novel antioxidant agents was considered chromone as basic fundamental pharmacophore in order to show antioxidant properties. We have performed molecular docking studies of synthesized compounds to check the ligand interactions with target protein. In addition, ADMET studies and molecular simulations studies also performed to know the toxicity and other parameters of synthesized molecules. Finally, through molecular modelling studies it is concluded that the synthesized molecules follows Lipinski rule of five.

Keywords: 2-styrylchromone, Antioxidant, Molecular docking, Molecular modelling, Lipinski rule

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Naturally occurring chromones (1-benzopyran-4-ones) are widely distributed throughout the plant kingdom. These compounds have attracted a great deal of attention due to their substantial activities, including antioxidative and anticancer effects. Accordingly, many synthesized chromone derivatives have been extensively studied for the development of novel anticancer agents. Molecular mechanisms of anticancer effects mediated by chromones such as flavonoids could be attributed to antiproliferation, induction of apoptosis, cell cyclearrest, promotion of differentiation, inhibition of angiogenesis, and modulation of multidrug resistance. Among these chromone derivatives, flavopiridol has been identified as a cyclin-dependent kinase (CDK) inhibitor and it has entered in Phase II clinical trial. 2-Styrylchromones are a small group of chromones with only two natural 2-styrylchromones hormothamnione (II) and 6-desmethoxyhormothamnione (III) are known. Chromone derivatives are abundant in

nature and exhibit a wide range of pharmacological activity like anti-bacterial, anti-fungal, anti-cancer, anti-oxidant, anti-HIV, anti-ulcers, immunostimulators, biocidal, wound healing, anti-inflammatory, and immune-stimulatory. Many chromone derivatives are also photoactive and can be used easily in various photoinduced reactions affording diverse heterocyclic compounds. Chromone derivatives are also active at benzodiazepine receptors and on lipoxygenase and cyclooxygenase.

The antioxidant properties of 2-SC have been shown in cellular and non-cellular systems. In the first case, the authors evaluated the possible protective activity of six synthetic polyhydroxylated 2-SC against the tert-butylhydroperoxide (t-BHP)-induced prooxidant hepatotoxicity in freshly isolated rat hepatocytes. All the studied 2-SC exhibited hepatoprotective activity, which was reflected on the preservation of the integrity of the plasma membrane. It was evident that the 3',4'-dihydroxy (styrylcatechol) derivatives were much more potent than the 4'-hydroxy (styrylphenol) derivatives. The differences between the two groups of compounds were also observed in the qualitative and quantitative preservation of biochemical homeostasis.

2. Materials and Method

Synthetic scheme

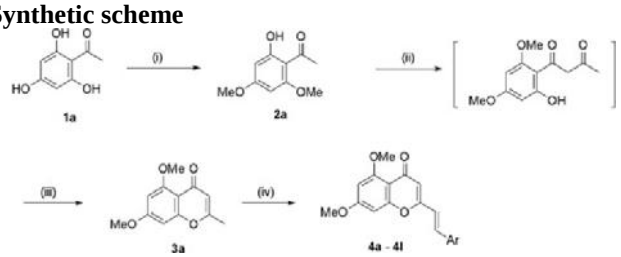

Fig 1: Scheme 1. Reagents and conditions: (i) Me2SO4/K2CO3, acetone; (ii) Na/EtOAc; (iii) conc. HCl/MeOH; (iv) MeONa/ArCHO/MeOH

Experimental procedure

Computer aided drug design:

Computer-aided drug design uses computational chemistry to discover, enhance, or study drugs and related biologically active molecules. Over the last 40 years, computational technologies for drug R & D have evolved rapidly, gaining popularity in implementation and application, especially in the recent decades with the unprecedented development of biology, biomedicine, and computer capabilities. The process of binding of the small molecules can be predicted through docking them to the target protein by employing the use of computational software's. we can also filter the small molecule based on their properties through Lipisnki rule of 5 (drug like properties) and finally simulations can be done by creating an environment same as the biological system.

Molecular docking:

Molecular modeling, a part of computer aided drug design, plays a major role in the designing of drugs based on target (protein) which involves the optimization of various small molecules using different tools available to filter the small molecules based on their interactions and properties. This approach reduces the cost and time involved in SAR studies or screening diverse molecules against the target.

Computational calculations:

Maestro 11.1(Schrödinger suite) was used to carry out computational studies. The designed molecules were docked to identify interactions with the protein. Steps involved in molecular docking:

Protein Preparation: The X - ray crystal structure of the protein was downloaded and subjected to the protein preparation wizard from workflows option implemented in the Schrodinger package. The X - ray crystal structure of the protein with the PDB ID: 1RLU was downloaded and subjected to the protein preparation wizard from workflows option implemented in the Schrodinger package. This preparation included:

- Addition of hydrogen
- assigning bond orders
- creating disulfide bonds
- zero order bonds to metal
- Addition of missing atoms
- Deletion of all water molecules
- Orientation of hydroxyl groups, amide groups of Asn and Gln
- Optimization of charge state of His residues

Ligand Preparation:

The designed molecules were sketched to estimate the number of conformers that could be generated. This may be helpful to understand which conformer shows higher activity in comparison with the other. Ligand preparation also sets bond lengths and bond angles, thereby cleaning the structure and converting it to three-dimensions (3D).

Receptor grid generation:

The receptor grid was generated using glide receptor grid generation tool with X,Y,Z coordinates(X-8.65, Y-36.89, Z-6.39) taking GSP as co-crystal ligand/centre.

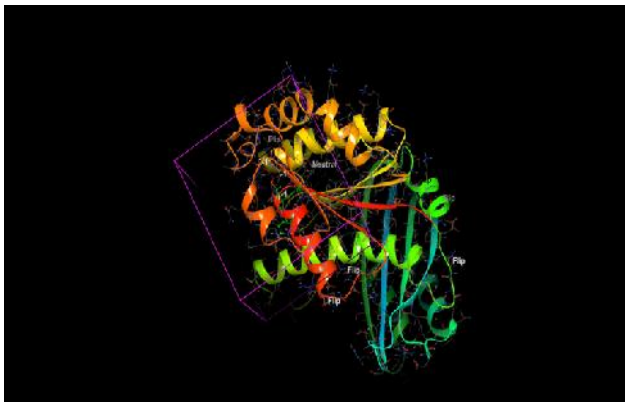

Figure 2

Ligand Docking:

In present study, Glide SP docking was performed and confirmed the conformation which shows binding affinity towards the protein by docking score and ligand interaction patterns. Molecules with more negative scores were selected as they imply greater and stronger interaction with the concerned protein. A molecule containing indole moiety with three fused rings was chosen by manual observation of all structures.

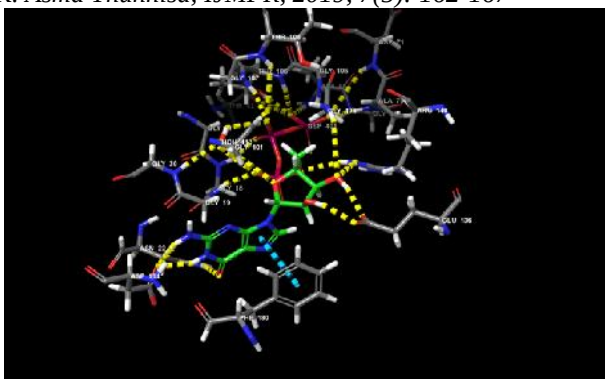

Fig 3: Ligand interaction diagram

ADMET properties and Drug likeness

Computational processes help calculate or evaluate ADMET parameters beforehand. In silico screening of drug likeness is done by using Qikprop 4.2 module in the Schrödinger suite 2017-1. This module has a number of characters for accessing the ADME parameters for good drugs.

Molecular Dynamics and Simulations

The molecular dynamic simulation was performed. Information about binding mode of and stability of protein-ligand complex was obtained by this study. The root mean square deviation (RMSD) is used to measure average change in displacement of a selection of atoms for a particular frame with respect to the reference frame. 'Lig fit Prot' shows the RMSD of a ligand when the protein-ligand complex is first aligned on the protein backbone of the reference and then the RMSD of the ligand heavy atoms is measured. Results show that ligand RMSD tends to be stable and fluctuate around 4.0 Å till 6.5 ns which further undergoes a large conformational change. Additionally, The Ligand Root Mean Square Fluctuation (L-RMSF) is useful for characterizing changes in the ligand atom positions. Although fluctuations are observed from 12-17, lesser fraction is observed in other atoms.

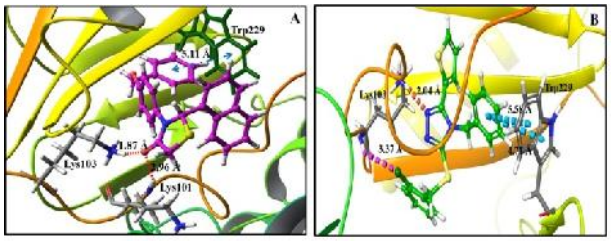

Fig 4: Molecular dynamic stimulation

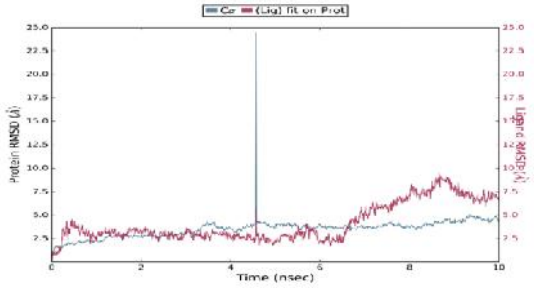

Fig 5: Plot of RMSD evolution of protein (left Y-axis) and Ligand RMSD (right Y-axis) against time in sec

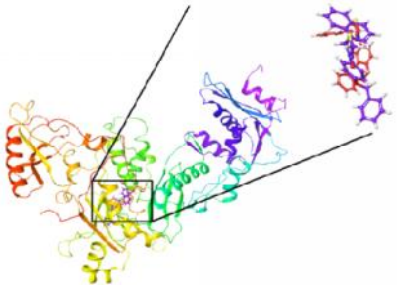

Fig 6: Alignment of initial structure (red) and MD structure (purple) of protein ligand complex. The protein was shown in ribbon and ligand in ball and stick model

3. Results and Discussion

Chemistry: Chemical reagents and organic solvents were purchased from TCI and Alfa Aesar unless otherwise mentioned. Melting points were determined by Fargo MP-2D. Nuclear magnetic resonance spectra (1H NMR) were measured on a Bruker AC-300 instrument. Chemical shifts (δ) are reported in parts per million relative to the TMS peak. Mass spectra were obtained by FAB on a Jeol JMS-700 instrument. Flash column chromatography was performed with silica gel (230–400 mesh). Elemental Analysis was carried out on a Heraeusvario EL-III C, H, N analyzer.

1-(2-Hydroxy-4,6-dimethoxy phenyl)ethanone (2a): To a solution of 2′,4′,6′-trihydroxyacetophenone (1a, 5.0 g, 30.0 mmol), Me2SO4 (5.3 ml, 56 mmol), and anhydrous K2CO3 (8.2 g, 56 mmol) in acetone (90 ml) was stirred at room temperature for 18 h. The reaction mixture was filtered and evaporated in vacuo, followed by recrystallization from ether–hexane to afford 2a (4.9 g, 83%) as a yellowish solid. M.p. 78–80 °C (lit [32] 78.5–79.5 °C). 1H NMR (300 MHz, CDCl3)d 3.96 (s, 3H), 3.941 (s, 3H), 6.896 (s, 3H), 6.924 (d, J = 2.4 Hz, 1H), 7.245 (d, J = 2.3 Hz, 1H), 9.538 (s, 1H) ppm. 13C NMR (75MHz, CDCl3)d 32.9, 56.0, 111.5, 111.9, 115.5, 50.4, 172.9ppm, MASS(311.1550, 415.2176) FTIR(3325.77,2920.22,1611.84,1376.36,1168.10,801.60,619.08,515.82) HRMS (M)+ calcd for C14H14O4 291.3319; found 291.1039. Anal. Calcd for C14H14O4: C, 69.01; H, 3.23. Found: C, 69.89; H, 3.23.

5,7-Dimethoxy-2-methyl-4H-chromen-4-one (3a):

A solution of 2a (3.92 g, 20.0 mmol) in dry ethyl acetate (30 ml) was added sodium (2.76 g, 120 mmol), the reaction mixture was stirred at room temperature for 18 h. Cold 0.5 N HCl (30 ml) was added and the aqueous layer was separated, the remained organic layer was dried and evaporated in vacuo to obtain the crude diketone. A solution of the crude diketone with couple drops of concentrated HCl in methanol (50 ml) was stirred at room temperature for 4 h. The methanol was removed in vacuo to get the residue, followed by the addition of ethyl acetate (50 ml) and washed with brine (50 ml). The organic layer was dried, evaporated in vacuo and purified with silica gel chromatography to obtain 3a (2.95 g, 67% in two steps). M.p. 120–121°C. 1H NMR (300 MHz, CDCl3)d 3.944 (s, 3H), 3.96 (s, 3H), 5.14 (s, 3H), 5.19 (s, 1H), 6.51 (d, J = 2.3 Hz, 1H), 6.54,7.29,7.45 (d, J = 2.3 Hz, 1H) ppm.13CNMR (125MHz,CDCl3)δ74.7,111.2,128.1,128.2,128.6,136.0,192.

4ppm.MASS(545.00,375.049,297.138,143.00,84.9.FTIR(3465.25,2918.92,1735.09,1629.38,1436.10,1198.26,836.30,587.01) HRMS (M)+ calcd for C17H15O4 302.294; found 302.289. Anal. Calcd for C17H15O4: C, 53.01; H, 4.12. Found: C, 73.89; H, 4.12.

(E)-5,7-Dimethoxy-2-styryl-4H-chromen-4-one (4a): Sodium (0.69 g, 30.0 mmol) was gradually added to dry methanol (30 ml) and the mixture was stirred until the solution reached room temperature. 3a (1.1 g, 5.0 mmol) and benzaldehyde (0.64 g, 6.0 mmol) were added and the resulting mixture was allowed to stir at reflux for 18 h. After this period, the solution was poured into iced water and the pH was adjusted to 4 with HCl. The yellow solid was removed by filtration, taken up in DCM and purified with silica gel chromatography (eluent DCM:ethyl acetate = 4:1) to give 4a (1.1 g, 71%) as a white solid. M.p. 186–188 °C. 1H NMR (300 MHz, CDCl3) δ 3.91 (s, 3H), 3.95 (s, 3H), 5.2 (s, 1H), 6.52 (d, J = 2.3 Hz, 1H), 6.94 (d, J = 2.3 Hz, 1H), 6.96 (d, J = 16.2 Hz, 1H), 7.19 (m, 3H), 7.21 (d, J = 16.2 Hz, 1H), 7.25 (m, 2H) ppm. 13C NMR (125.7MHz, CDCl3) δ 56.1, 60.7, 70.9, 71.6, 102.7, 128.0, 128.6, 136.6, 136.7, 136.9ppm. MASS(507.2288,357.1609,297.1391) FTIR(2920.3,1737.61,1632.53,1441.47,1161.32,830.01,644.29) HRMS (M)+ calcd for C19H16O4 308.3279; found 308.1039. Anal. Calcd for C19H16O4: C, 74.01; H, 5.23. Found: C, 73.89; H, 5.32.

(E)-5,7-Dimethoxy-2-(2-pyridin-4-yl-vinyl)-chromen-4-one (4b): Compound 4b was synthesized from the procedure described for compound 4a. M.p. 212–213 °C. 1H NMR (300 MHz, CDCl3)d 3.78 (s, 3H), 3.96 (s, 3H), 5.22 (s, 1H),5.27 (d, J = 16.0 Hz, 1H), 6.9 (d, J = 2.3 Hz, 1H), 7.10 (d, J = 2.3 Hz, 1H), 7.29 (d, J = 16.0 Hz, 1H), 7.47 (m, 2H), 7.9 (m, 2H) ppm. 13C NMR (75 MHz, CDCl3)d 55.8, 56.0, 71.4, 75.7, 100.3, 100.9, 115.9, 120.8, 121.6, 124.0, 127.4, 128.3, 144.7, 148.9, 150.0, 172.8ppm. MASS (419.176, 335.11, 313.135, 230.117, 143.0018) FTIR (3326.77, 2920.22, 1611.84, 1376.36, 1201.00, 1168.0, 831.46, 515.82) HRMS (M)+ calcd for C18H15NO4 309.1001; found 309.0994. Anal. Calcd for C18H15NO4: C, 69.89; H, 4.89. Found: C, 69.76; H, 4.81.

2-[2-(4-Fluoro-phenyl)-vinyl]-5,7-dimethoxy-chromen-4-one (4c): Compound 4c was synthesized from the procedure described for compound 4a. M.p. 169–171°C. 1H NMR (300 MHz, CDCl3)d 3.9 (s, 3H), 4.0 (s, 3H), 5.27 (s, 1H), 5.28 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 2.3 Hz, 1H), 7.04 (d, J = 16.0 Hz, 1H), 7.05 (m, 2H), 7.07 (d, J = 16.0 Hz, 1H), 7.08 (m, 2H) ppm. 13C NMR (75 MHz, CDCl3)d 56.5, 61.5, 70.8, 71.1,110.0, 113.9, 114.1, 115.6, 120.8ppm. MASS(497.16,399.0987,303.0957,201.0429)FTIR(2930.05,1686.22,1611.83,1454.32,1359.94,1035.31,758.10.HRMS(M+1)+calcd for C19H15FO4 326.0954; found 326.0952. Anal. Calcd for C19H15FO4: C, 69.93; H, 4.63. Found: C, 69.04; H, 4.58.

2-[2-(4-Chloro-phenyl)-vinyl]-5,7-dimethoxy-chromen-4-one (4d): Compound 4d was synthesized from the procedure described for compound 4a. M.p. 171–172 °C. 1H NMR (300 MHz, CDCl3)d 3.84 (s, 3H), 3.85 (s, 3H), 6.93 (s, 1H), 6.96 (d, J = 2.3 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 7.17 (d, J = 16.0 Hz, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 16.0 Hz, 1H), 7.87 (d, J = 8.5 Hz, 2H) ppm. 13C NMR(75 MHz, CDCl3) d56.0, 111.5, 111.9, 114.4, 115.5,121.8,124.5,133.0,137.8,144.8,146.4,150.4ppm,MASS(945.534,473.271,340.1819,134.0965,FTIR(2924.08,1614.12,1515.37,1452.23,1153.73,1074.91,831.34,527.04HRMS (M)+ calcd for C19H15ClO4 342.0659; found 342.0660. Anal. Calcd for C19H15ClO4: C, 66.58; H, 4.41. Found: C, 65.95; H, 4.52.

2-[2-(4-Bromo-phenyl)-vinyl]-5,7-dimethoxy-chromen-4-one (4e): Compound 4e was synthesized from the procedure described for compound 4a. M.p. 172–173 °C. 1H NMR (300 MHz, CDCl3)d 3.941 (s, 3H), 3.962 (s, 3H), 6.8963 (s, 1H), 6.924 (d, J = 2.3 Hz, 1H), 7.245 (d, J = 2.3 Hz, 1H), 7.275 (d, J = 16.0 Hz, 1H), 7.587 (d, J = 8.5 Hz, 2H), 7.595 (d, J = 16.0 Hz, 1H), 7.616 (d, J = 8.5 Hz, 2H) ppm. 13C NMR (75MHz,CDCl3) d56.5, 61.1, 110.5, 114.8, 115.6, 116.2, 119.8, 120.1, 122.5, 130.1, 136.1, 137.2, 145.1, 145.5, 147.5, 148.6, 155.8ppm, FTIR (3326.77, 3202.20, 2920.22, 1659.01, 1611.84, 1376.36, 1201.00, 1168.0,515.82,419.19,MASS(311.1550,415.2176,445.2636, 519.2795,HRMS(M+1)+calcd for C19H16BrO4 388.2314; found 388.0143. Anal. Calcd for C19H15BrO4: C, 58.93; H, 3.90. Found: C, 58.42; H, 3.92.

5,7-Dimethoxy-2-[2-(4-methoxy-phenyl)-vinyl]-chromen-4-one (4f): Compound 4f was synthesized from the procedure described for compound 4a. M.p. 175–176 °C. 1H NMR (300 MHz, CDCl3)d 6.8825 (s, 3H), 6.8995 (s, 3H), 6.9287 (s, 3H), 6.9462 (s, 1H), 7.4227 (d, J = 2.3 Hz, 1H), 7.4401 (d, J = 2.3 Hz, 1H), 7.6324 (d, J = 16.0 Hz, 1H), 7.6366 (d, J = 8.5 Hz, 2H), 7.6494 (d, J = 16.0 Hz, 1H), 7.6535 (d, J = 8.5 Hz, 2H) ppm.13C NMR (75MHz, CDCl3) d113.9, 114.4,115.0,115.1,115.2,115.5,120.0,122.8,132.8,136.9,145.0,145.8,147.3,149.6,172.4ppm,MASS(134.0,340.1,430.22, 473.27,945.5,1006.5,FTIR(2920.33,1737.61,1632.53,1441.47,1252.30,1161.2,830.01,644.29,960.35,527.88HRMS (M)+ calcd for C20H18O5 338.1154; found 338.1154. Anal. Calcd for C20H18O5: C, 70.99; H, 5.36. Found: C, 70.23; H, 5.29.

2-(2-Benzo[1,3]dioxol-5-yl-vinyl)-5,7-dimethoxy-chromen-4-one (4g): Compound 4g was synthesized from the procedure described for compound 4a. M.p. 217–218 °C. 1H NMR (300 MHz, CDCl3)d 5.1933 (s, 3H),5.2282 (s, 3H), 6.4828 (s, 2H), 6.5086 (s, 1H), 6.5355 (d, J = 3.8 Hz, 1H), 6.5613 (d, J = 15.9 Hz, 1H), 6.4828 (d, J = 2.2 Hz, 1H), 6.5086 (d, J = 7.9 Hz, 1H), 6.5355 (d, J = 7.9 Hz, 1H), 7.0939 (d, J = 3.8 Hz, 1H), 7.1006 (d, J = 15.9 Hz, 1H) ppm. 13C NMR (75 MHz, CDCl3)d 56.1,60.7, 71.0,71.5, 102.7, 113.4, 114.5, 115.7, 127.2, 127.4, 128.0, 128.6, 136.7, 136.8, 137.0,142.5,145.1,149.1,150.4,158.3,192.4ppm.MASS(84.9599,143.0017,201.0433,297.1389,375.0497,545.0056,FTIR(3455.25,2918.92,1735.09,1629.38,1436.10,1301.11,1198.26,1162.2,1017.85,836.30,746.78,549.5HRMS (M)+ calcd for C20H16O6 352.0947; found 352.0946. Anal. Calcd for C20H16O6: C, 68.18; H, 4.58. Found: C, 68.04; H, 4.44.

2-[2-(3,5-Dimethoxy-phenyl)-vinyl]-5,7-dimethoxy-chromen-4-one (4h): Compound 4h was synthesized from the procedure described for compound 4a. M.p. 188–189 °C. 1H NMR (300 MHz, CDCl3)d 3.9249, 3.9464 (s, 3H), (s, 3H), 5.1349

(s, 3H), 5.18 (s, 3H), 6.49 (s, 1H), 6.52 (d, J = 2.3 Hz, 1H), 6.86 (d, J = 2.3 Hz, 1H), 6.88 (s, 1H), 6.92 (d, J = 16.0 Hz, 1H), 6.95 (s, 2H), 7.03 (d, J = 16.0 Hz, 1H) ppm. 13C NMR (75MHz, CDCl3)d 55.9, 56.0, 70.7, 74.7, 104.3,109.1,111.1,115.7,121.6,122.5,124.9,125.7,127.2,128.1,128.2,128.6,129.1,136.2,137.6ppm.MASS(121.064,258.14,327.149,447.207,521.22,893.4077,FTIR(3326.77,3202.20,2920.22,1744.65,1611.84,1376.36,1246.61,1168.0,1082.22,831.46,726.58,619.08,515.82,419.19,HRMS (M)+ calcd for C21H20O6 368.1260; found 368.1263. Anal. Calcd for C21H20O6: C, 68.18; H, 4.58. Found: C, 68.04; H, 4.44.

5,7-Dimethoxy-2-[2-(4-trifluoromethyl-phenyl)-vinyl]-chromen-4-one (4i):

Compound 4i was synthesized from the procedure described for compound 4a. M.p. 201–202 °C. 1H NMR (300 MHz, CDCl3)d 3.91 (s, 3H),3.95 (s, 3H), 5.20 (s, 1H), 6.50 (d, J = 2.3 Hz, 1H), 6.53 (d, J = 2.3 Hz, 1H), 6.80 (d, J = 16.0 Hz, 1H), 6.84 (d, J = 16.0 Hz, 1H), 6.85 (m, 4H)ppm. 13CNMR (75MHz, CDCl3)d 56.1, 60.7,71.0, 71.5,102.7,113.4,114.5,115.7,127.2,127.4,128.0,128.6,136.7,137.8,138.0ppm,MASS(235.1226,331.0993,365.0610,491.2120,695.1361,FTIR(2930.05,2853.83,1686.22,1454.32,1359.94,1203.19,1035.31,1012.88,831.77,758.90,742.31,615.47,520.68,484.58,434.00 HRMS (M)+ calcd for C20H15F3O4 376.0922; found 376.0921. Anal. Calcd for C20H15F3O4: C, 63.83; H, 4.02. Found: C, 63.75; H, 4.13.

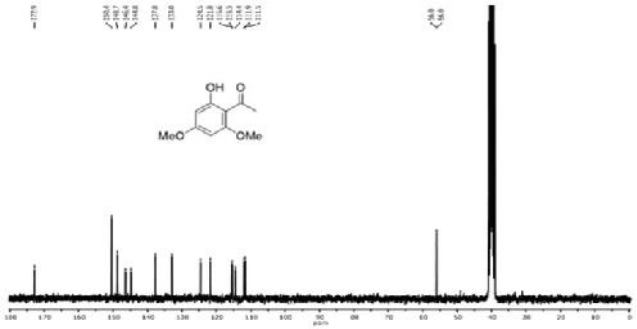

Fig 7: ^{13}C NMR spectrum of 2-sterylenechromonone compounds

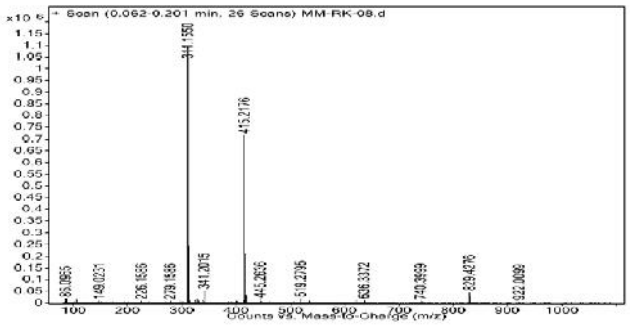

Fig 8: Mass spectrum of 2-sterylenechromonone compounds

Table 1: ADME studies of the designed molecules

Sr. No.	Dipole moment	Total SASA	Molecular volume	QP log HERG	Metabolite	QP log BB
1.	6.231	719.3	1286.732	-7.872	1	-0.272
2.	6.544	123.512	1368.285	-7.898	2	-0.349
3.	6.293	723.499	1304.264	-7.810	1	-0.166
4.	6.211	755.908	1348.396	-7.842	2	0.291
5.	4.618	746.716	1331.395	-7.830	1	-0.110
6.	6.270	743.684	1334.218	-7.765	1	-0.106
7.	5.966	710.525	1321.047	-7.253	1	-0.110
8.	6.212	744.783	1336.548	-7.747	1	0.091
9.	4.913	750.985	1340.940	-7.836	1	-0099
10.	7.268	757.529	1360.293	-7.789	2	-0.347
11.	6.628	546.522	916.798	-6.045	0	-0.189
12.	6.483	549.650	923.859	-6.015	1	-0.379

4. Conclusion

Chromone derivatives are abundant in nature and exhibit a wide range of pharmacological activity like anti-bacterial, anti-fungal, anti-cancer, anti-oxidant, anti-HIV, anti-ulcers, immunostimulators, biocidal, wound healing, anti-inflammatory, and immune-stimulatory. Hence we considered chromone as basic fundamental pharmacophore in order to show antioxidant properties. We have performed molecular docking studies of synthesized compounds to check the ligand interactions with target protein. In addition, ADMET studies and molecular simulations studies also performed to know the toxicity and other parameters of synthesized molecules. Finally, through molecular modelling studies it is concluded that the synthesized molecules follows Lipinski rule of five.

5. References

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