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Research Paper

In-Silico Design, Synthesis and Antiprolifertive Evaluation of Thiazolidino-Chromone Derivatives

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ABSTRACT

Chromones are a group of naturally occurring chemical compound that being existing everywhere in nature, predominantly in plants. The word chromone is derived from the Greak word Chroma,which means colour, which bringing up that most of chromone derivatives can exhibit distinctiveness, in colour.Chromones are the oxygen containing heterocyclic compounds with a benzoannelated γ-Pyrone ring (4H-Chromone-4-one,4H-benzopyran-4-one). Now a days chromone act as a valid scaffold in medicinal chemistry. Our aim was to develop novel thizolidino- chromone derivatives which inhibiting Human Topo (II)α ATPase and provide anti-proliferative activity. In-silico design of novel analogues were carried out using ACD labs ChemSketch 12.0. Molinspiration software was used to analyse 'Lipinski Rule of Five' and drug likeness properties. Biological activity was predicted by PASS software. Preliminary docking study was carried out using GLIDE software by SCHRODINGER. Five derivatives which obeyed rule of five and having predicted antitumor activity on Human Topo (II)α ATPase were synthesized by four step process. After the completion of reaction in each step, the compounds were isolated, recrystallised by using suitable solvents, purified by TLC and column chromatography. Analogues were characterized by FT-IR, H1NMR, C13NMR and Mass Spectroscopy. The Biological evaluation was done by MTT assay using HCT 116 cancer cell lines. The results were compared with standard anticancer drug 5-Flurouracil.

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The results were compared with standard anticancer drug 5-Flurouracil. The results of present research work showed that novel thizolidino- chromone derivatives have comparable antiproliferative effect with that of standard anticancer drug 5-Flurouracil. This will lead to the development of promising lead compounds for target specific anticancer therapy and encourage further optimization to develop potent antiproliferative agents.

INTRODUCTION

Cancer is emerging as a first major health problem in developing as well as developed countries. Surpassing cardiac diseases, it is taking number one killer worldwide due to various social, economic and lifestyle factors. There are many chemotherapeutic strategies for cancer treatment have been proposed, tested and in some cases implemented in the past two decades, these diseases still remain deadly. Therefore, there is a desperate need to develop treatments with new chemical entities with novel mechanism of action to combat this disease. One of the most important receptor which is overexpressed in majority of solid tumors is Human Topo (II) α ATPase.The potential inhibitor f this receptor will definitely prevent thisenzyme cascade mechanism and blocks cell division. The chromones are the interesting as structural scaffolds and have been assigned as privileged structures for drug development as probes to study lipid membranes and proteins [8-10]. The versatile biological applicability of chromone derivatives and their potential use in drug discovery implicates the importance of access to efficient synthetic routes to well-designed substituted chromones. 4-Thiazolidinones and their derivatives are an import class of compounds in organic and medicinal chemistry. The 4 thiazolidinone ring system is a core structure in various synthetic pharmaceutical agents, displaying a broad spectrum of biological activities such as, antitubercular, anti-bacterial, anti-HIV, anti-inflammatory, anti-mycobacterial, anti-convulsant, anti-histaminic, anti-cancer, anti-protocol and analgesic. 4- Thiazolidinones are derivatives of thiazolidine with carbonyl group at the 4th position and formed by the attack of sulphur nucleophile on imine carbon followed by intramolecular cyclization witheli mination of water. The rationale behind this research work is that on combining these two therapeutically significant heterocyclic moiety results into a new chemical nucleus which could specifically inhibit Human Topo (II)α receptor, which ultimately leads to the prevention of growth and proliferation of cancerous tissue. So, we aimed to *in-silico* design and development of Thiazolidino chromone derivatives as potential anticancer agents.

MATERIALS AND METHODS

Materials and instrumentation

All the chemicals and reagents used in this research work were of analytical or synthetic grade from Sigma Aldrich,E-Merck (Germany) and S D Fine Chemicals (India). All the chemicals were dried and purified according to standard methods before use, wherever necessary. Software used in this study include ACD Labs Chemsketch, Chemdraw Ultra 8.0, Molinspiration, PASS online,The synthetic procedures were carried out by using both conventional and microwave method . All the reaction courses and product mixtures were routinely monitored by TLC plates and visualized with UV light or iodine chamber. Melting point of synthetic compounds was determined on a Labindia MR-VIS visual melting point apparatus and is uncorrected. Absorbance values against wavelength were taken on a Systronic double beam UV-166 spectrophotometer. The FT-IR spectra were recorded using FT-IR (Agilent Cary 630 FT-IR spectrophotometer using KBr pellet). 1H NMR spectra were recorded using NMR spectrophotomer (Bruker 400 ultra schield DPX 400) and chemical shifts are expressed as δ (ppm) using TMS as an internal standard in DMSO*d6*. Mass spectra of the compounds were done with

mass spectrometer (micromass-O-TOF-MS ES+). Anticancer evaluation was done by MTT assay using the HCT 116 cell lines.

***In-silico* methods**

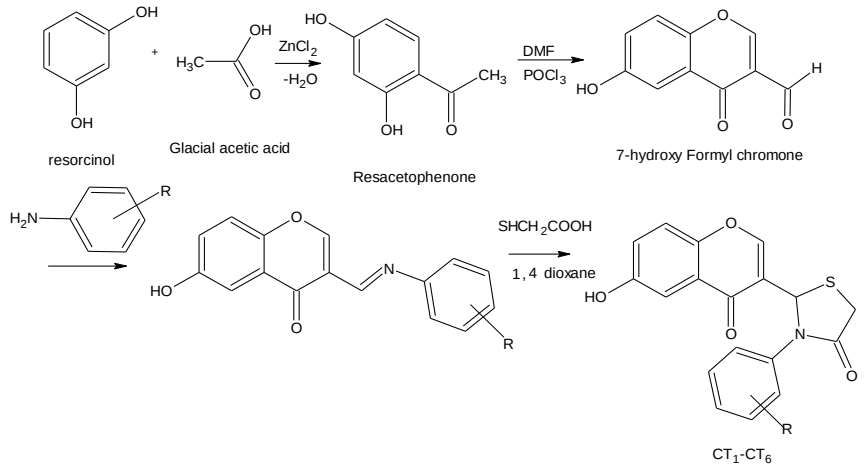
➢ ***In-silico* molecular modeling**

In silico methods in drug discovery can be used for the identification and quantification of the physico- chemical properties of the new drug candidate and also to analyse whether any of these properties of the new drug candidate and also to analyse whether any of these properties having significant effect on it's biological activity. In silico designing of drug candidate will helps to identifying the possible target of the drug candidate and predicts it's biological activity. The physic chemical properties of the drug candidate were discovered by using various computer software., in which the electronic,lipophylic and steraric parameters can be determined by using ACD Lab chemsketch.Molinspiration software will helps to determine the drug likeness by analyzing lipinsky rule of five. The approach used in PASS is based on the suggestion that the affinity = f (structure).

➢ **Docking studies**

Docking is the computational simulation of a ligand binding to a receptor, which helps to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and the activity of the small molecule. Docking is very important tool in the rational design of drugs. Schrodinger is a comprehensive software suite for analyzing and modeling molecular structures, biological macromolecules (proteins and nucleic acid). The selected analogues were docked onto the binding pocket Human Topo (II)α ATPase Receptor (PDB ID. 1ZXM). These docking studies gives best matching between two molecules: designed thiazolidino chromone and the binding pocket of target protein. Different steps involved in docking studies include; preparation of ligand and protein, docking methods, scoring of docking results and analysis, refinement and filtering tools.

Synthetic methodology



Scheme 1: Synthesis of Thiazolidino chromone (CT1-CT6)

Step 1 Synthesis of resacetophenone (2,4-dihydroxyacetophenone)

2,4-dihydroxyacetophenone was synthesized by reported method. Briefly, the synthesis was carried out by dissolving freshly fused and powdered zinc chloride (0.24 mole) in 32 ml of glacial acetic acid by heating in sand bath. Dry resorcinol (0.2 mole) was added with stirring at 140^0C. The solution was heated until it just begins to boil and kept for 20 minutes at 150^0C. Dilute HCl (1:1) was added to the mixture and the solution was cooled to 5˚C. The separated product was filtered and washed

with dilute HCl. The product was recrystallised from hot water.

Step 2 Synthesis of formyl chromone

$POCl_3$ (0,49 mol) was added drop wise to dimethylformamide (DMF) (121 ml) with stirring at 30-35˚ C, after the addition, the mixture was stirred at 50˚C for 1 h. Then the solution of acetophenone derivatives **(**0.12 mol) in least amount of DMF was added drop wise with stirring to the above mixture. After that the mixture was stirred at 45-55˚C for 2 hours, kept over the night at room temperature and slowly poured over mixture ice and water(200g). Product was stirred for 6 hours, then filtered off and recrystallized from ethanol.

Step 3 Synthesis of Schiff base

A 50 ml borosilicate glass beaker was charged with formyl chromone (188 mg, 0.001mol) and aromatic amine (93 mg, 0.001 mol) in methanol (5 mL). The reaction mixture was irradiated inside a microwave oven for 10 min at an output of 340 watts power. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into the ice water and the product obtained was separated by filtration. The product was purified by recrystallization from ethanol.

Step 4 Synthesis of thiazolidinone substituted chromone derivatives

To the mixture of schifff base (0.01 mol) and mercapto acetic acid (0.01) mol dissolved in dioxane (20 ml), anhydrous zinc chloride (0.0004 mol) was added and refluxed, for 8 hrs. The reaction mixture were poured into ice water, filtered, washed with 10% sodium carbonate solution and recrystalized using methanol.

Antiproliferative evaluation (MTT Assay)

Determination of cell growth rates is widely used in the testing of drug action, cytotoxic agents and screening other biologically active compounds. MTT assay is a colorimetric assay that measures the reduction of yellow3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The MTT enters the cells and passes into the mitochondria where it is reduced to an insoluble,colored (dark purple) formazan product. The cells are then solubilized with an organic solvent (e.g. Dimethylsulfoxide) and the released, solubilized formazan reagent is measured spectrophotometrically at 540 nm. Since reduction of MTT can only occur in metabolically active cells the level of activity is a measure of the viability of the cells. The cells were washed with 1x PBS and then added 30 µl of MTT solution to the culture (MTT- 5mg/mL dissolved in PBS). It was then incubated at 37°C for 3h. MTT was removed by washing with 1x PBS and 200µlof DMSO was added to the culture. Incubation was done at room temperature for 30 minutes until the cell got lysed and color was obtained. The solution was transferred to centrifuge tubes and centrifuged at top speed for 2minutes to precipitate cell debris. Optical density was read at 540 nm using DMSO as blank in a ELISA microplate reader.

% viability = (OD of Test/ OD of Control) X 100

Percentage mortality= 100 - %viability

RESULTS AND DISCUSSION

***In-silico* molecular modeling studies**

The *In-silico* molecular modeling studies of novel thiazolidino chromone derivatives were carried out successfully with the aid of different software for selection of suitable drug candidates prior to wet lab synthesis. *In-silico* studies were performed on designed 12 derivatives by means of ACD Lab ChemSketch 12.0, Chem Draw 8.0, Molinspiration, PASS, Schrodinger software. Among the 12 designed analogues, six analogues were found to obey Lipinski rule of five and their drug likeness were predicted by Molinspiration software. The analogues which are having desired physico-chemical properties were chosen for wet lab synthesis **(Table 1, Table 2, Table 3, Table 4).**

Table 1: Molecular descriptors for designed analogues generated by ACD Labs Chemsketch 12.0

Compound	Mol. wt	Molar volume cm^3	Parachor Cm^3	Surface tension Dyne/cm	Polarisability (10^{-24} cm^3)
CT1	339.336	227±3.0	663.5±6.0	72.8±30	35.60±0.5
CT2	384.364	238.9±3.0	720.6±6.0	82.7±30	38.20±0.5
CT3	384.364	238.9±3.0	720.6±6.0	82.7±30	38.20±0.5
CT4	373.811	239±3.0	700.7±6.0	73.8±30	37.55±0.5
CT5	355.336	225.5±3.0	678.7±6.0	82.0±30	36.35±0.5

Table 2: Analysis of Lipinski rule of five for selected thiazolidino-chromone derivatives analogues

Compound	Log P	Molecular Weight	No. of Hydrogen bond acceptors	No. of Hydrogen bond donors	No. of Rotatable Bonds	Violations
CT1	2.62	339.37	5	1	2	0
CT2	2.53	384.37	8	1	3	0
CT3	2.53	384.37	8	1	3	0
CT4	2.68	369.40	6	1	3	0
CT5	2.14	335.37	6	2	2	0
CT6	3.79	389.43	5	1	2	0

Table 3: Analysis of drug likeness score for selected derivatives

compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor Ligand
CT1	-0.39	-0.65	-0.85	-0.57
CT 2	-0.48	-0.62	-0.90	-0.59
CT3	-0.49	-0.66	-0.93	-0.77
CT4	-0.40	-0.82	-0.79	-0.70
CT5	-0.37	-0.63	-0.81	-0.54
CT6	-0.26	-0.63	-0.67	-0.60

Table 4: Prediction of Biological activity of proposed analogues using PASS software

Compounds	Effect	Pa	Pi
CT1	Anticancer	0.291	0.023
CT2	Anticancer	0.271	0.031
CT3	Anticancer	0.294	0.022
CT 4	Anticancer	0.299	0.020
CT5	Anticancer	0.283	0.026
CT6	Anticancer	0.284	0.025

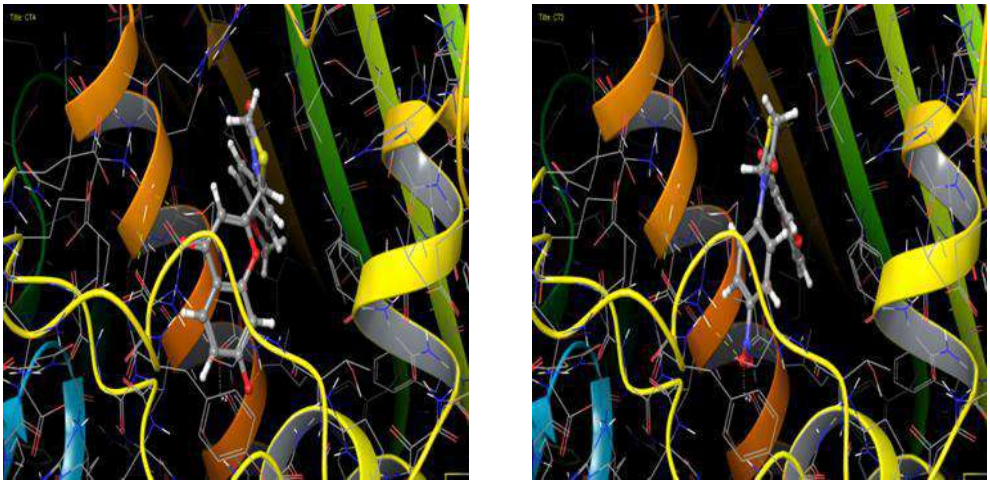


Figure 1: Docking images of Thiazolidino chromone derivatives (A. CT2 and B CT4)) on binding pocket of Human TOPO (ii) A

Table 5: Docking scores of selected derivatives with target protein

Target	PDB ID	Compound Name	GLIDE Score
Human TOPO(II) A	1ZXM	CT1	-5.7
		CT 2	-6.43
		CT3	-4.1
		CT4	-10.17
		CT5	-5.92
		CT6	-5.94

Molecular docking

All the proposed derivatives were subjected to flexible docking on to the binding pocket of Human TOPO(II) α (Pdb ID: 1ZXM) using GLIDE Programe of Schrodinger. The docking scores were calculated on the basis of Glide score **(Figure 1, Table 5).**

Synthetic methods

The analogues which were designed by *in-silico* studies were selected for wet lab synthesis based on Lipinski rule of five, PASS value and docking energy score. The synthetic scheme involved was a five-step reaction. After the isolation of product in each step the products were recrystallised and purified by TLC. The structure of proposed analogue is shown in **Figure 2.** Five new derivatives were synthesized by conventional both conventional and microwave maethod). The percentage yield of the reaction, melting point, and Rf value of each compounds were calculated and shown in **Table 6.**

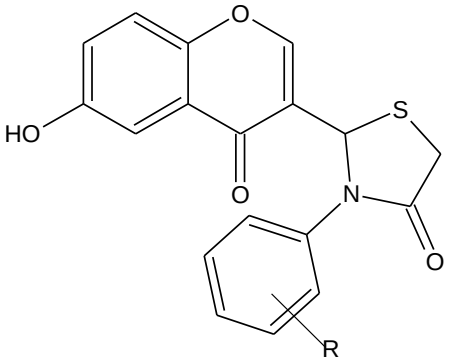


Figure 2: General structure of thiazlidino chromone derivatives.

Table 6: Characterization data of synthesized acetidino-quinazoline derivatives

Compound code	Molecular formula	Molecular Weight (g)	Melting point	% yield	Rf value
CT 2	$C_{18}H_{12}N_2O_6S$	384.364	240-242	70	6.9
CT 3	$C_{18}H_{12}N_2O_6S$	384.364	226-228	72	6.7

CT 4	$C_{18}H_{12}N_2O_6S$	373.811	221-223	68	6.5
CT 5	$C_{18}H_{13}NO_5S$	355.336	214-217	55	6.1
CT 6	$C_{22}H_{17}NO_4S$	391.441	291-293	77	7.1

Table 7: Characteristic FT-IR, 1HNMR and Mass spectral analysis of synthesized analogues

Compound	IR (KBr υ cm-1)
STEP 1	3648.098 OH stretch, 3047.792 aromatic CH,3002.975AliphaticCH,1516.987 Aromatic C=C, 1202.628 OH-bend.
STEP 2	3592 OH stretch, 3040.44aromatic CH, 1274.282 OH-bend,3592 OH stretch, 2918.855 aliphatic CH, 1740.571 C=0 stretch (aldehyde), 1692.347 C=O stretch, 1441.747 aromatic C=C,1274 and1142C-O-C
STEP 3	3600.217 OH stretching, 2999.543 aromatic CH, 1691.809 C=O, 1569.291 and1349 NO stretch, 1428.341 aromatic C=C, 1102.945 C-O, 800.00 C-N.
STEP 4(CT2)	3600.337 OH stretching, 3111.241 aromatic CH, 1645.809 C=O, 1560 and1349.907 NO stretch, 1428.341 aromatic C=C, 1102.945 C-O, 782.00 C-N,650.00 C-S-C,
1HNMR (CT2)	3.3112(S, CH_2),5.0210(S'AromaticC-OH),5.3160(S, CH),6.6208-7.9631(M,Aromatic proton)
Mass spectral Analysis (CT2)	384.3 (Molecular ion peak), 161.02 (Base peak)

Table 8: Comparative evaluation of Antiproliferative effect of CT2, CT4 and CT6 on HCT116 cells

Concentration	Percentage viability (%)			
	standard	CT4	CT6	CT2
10µg/ml	59.32	66.92	79.88	80.44
20µg/ml	55.86	59.45	78.10	78.32
30µg/ml	53.85	54.27	72.51	69.60
40µg/ml	44.58	51.92	65.69	66.92

Spectral characterization of Thiazolidino chromone derivatives

The newly synthesized novel Acetidino-quinazoline derivatives were further characterized by FT-IR, 1HNMR, and Mass spectral studies. The complete spectral

analysis of prototype lead molecule CT2 is shown in**Table 7.**

Evaluation of antiproliferative effect (MTT Assay)

After the preliminary in-silico molecular modeling studies followed by the docking studies on the binding pocket of Human TOPO (II)A receptor, thiazoliino chromne derivatives were selected for wet lab synthesis. The synthesized compounds were purified and characterized by FT-IR, 1HNMR and Mass spectral studies. Docking studies proved that the CT2, CT4 and CT6 were more effectively bind with the receptor based on glide score. Four concentrations of the test compounds were used for MTT assay. The results were compared with that of standard drug 5-flurouracil. The concentrations used were 10,20,30 and 40 µg/mL.The cell lines used was HCT 116 cell line. Test results showed that the anticancer activity of the proposed derivatives is less than that of the standard drug 5-flurouracil. The compound CT4 shows more activity than CT6 and Cl **(Table 8, Figure 3)**

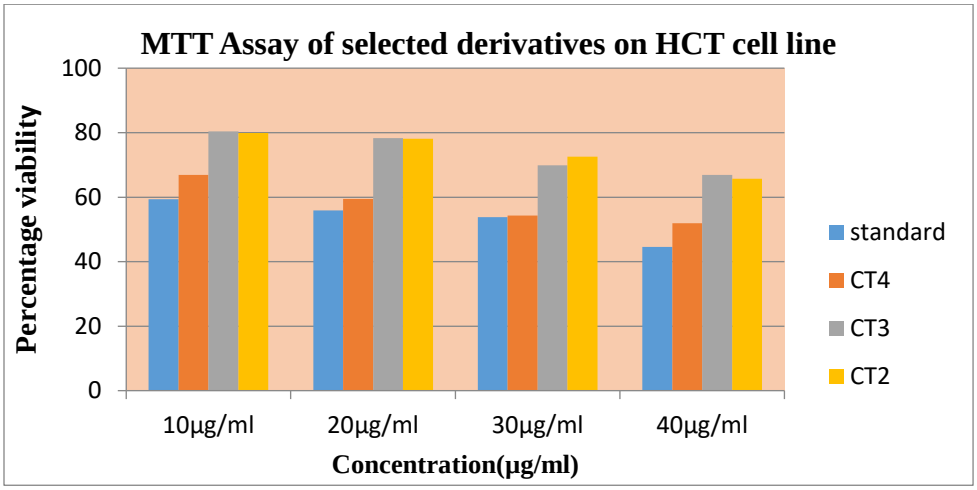


Figure 3: Comparative evaluation of antiproliferative effect of CT2, CT4 and CT6

CONCLUSION

The present work led to the development of novel antitumor molecules containing Thiazolidino chrmone pharmacophore. This research work was focused on the structure-based drug design and development of novel Thiazlidino chromne derivatives and their antiproliferative evaluation. We have designed 12 new analogues and after *in-silico* molecular modeling and docking studies, selected six analogues for wet lab synthesis. These derivatives were spectrally characterized by FT-IR,1HNMR, mass spectroscopy. The antiproliferative evaluation of three derivatives was done against HCT116 cell line.The compounds CT2 and CT4 have shown significant activity against HCT 116 cell line and compared with that of standard drug5- flurouracil. Thus this work presents a potentantiproliferative effect of synthesized analogues. The Activity prediction by *in-silico* methods are very well correlated with biological activity. From this study, this can be concluded that the synthesized Thiazolidino chromone derivatives can be lead candidate to be developed into useful antiproliferative agents that could lead further research work on this potent nucleus. An extensive study is also warranted to determine additional physiochemical and biological parameters to have deeper insight into SAR and optimize the effectiveness of these lead molecules.

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REFERENCES

1. W.L Jorgenson. The many Roles of computation in drug discovery. Oxford Univercity press. 2004; 303:1813-25
2. T. Nogrady, D F Weaver. Medicinal chemistry amolecular and biochemical approach. Oxford University press .2005;3: 9-13
3. G.L Patric . An introduction to medicinal chemistry. Oxford University press.2012;5:187-200
4. http://c2d2.org/Assets/Files/Medicinal_ chemst_ role_drug_discovery_pdf
5. http://www.pharma.org/sites/default/files/159/ rd brochure 022307.pdf
6. http.//enm.wikipedia.org/wik/docking_(molec ular)
7. Jounal of molecular biology. Oxford Univercity press.2006;357(1):275-291.
8. A.Tawfeek,E F Ewies, W.S El-houmouly.synthesis of chromones and their application during the last ten years,Intr nation.jounl.of resrch.2014;4(4):1046-1085.

9. R.S Keri, S. Budagump,R.K Pai, R.G Balakrshna.Chromones as a privileged scaffold in drug discovery:A review , Europ.joul. Med. Chem.2014; 78:340-374
10. D. P Mehtha, N.P.Sengar and A.K Pathak. 4-Thiazolidinone; A new profile of various pharmacological activities.Oriental. .2009;21:810-812.
11. A. Mantovani, M. A. Cassatella, C. Costantini, S. Jaillon. Neutrophils in the activationand regulationof innate and adaptive immunity. Nat. Rev. Immunol.2011;11: 519 –531.
12. Carlos F. M. Silva, Diana C. G. A. Pinto, and Artur M. S. Silva. Chromones: A Promising Ring System for New Antiinflammatory Drugs. Nat. Rev. Immunol.2011;11:519 –531.
13. J. Y. Fu, J. L. Masferrer, K. Seibert, A. Raz, P. Needleman, J.The induction and suppression of prostaglandin H2 synthase (Cycloxigenase) in Human monocytes. Biol. Chem.1990;265: 16737 –16740.
14. P. Singh, M. Kaur, P. Verma Flavones: An important scaffold for medicinal Chemistry Bioorg. Med. Chem. Lett. 2014; 19:3054 – 3058.
15. R. Gautam, S. M. Jachak, V. Kumar, C. G. Mohan.Synthesis, biological evaluation and molecular docking studies of of stellatin derivatives as cycloxigenase(COX1. COX2) inhibitors and anti-inflammatory agents Bioorg. Med. Chem. Lett.2011; 21(6): 1612 – 1616.
16. M. Peters-Golden, T. G. Brock.Lipoxigenase and FLAP.U S national library of medicine. 2003;69(2-3): 99–109.
17. A. Heller, T. Koch, J. Schmeck, K. van Ackern, Drugs 1998, 55, 487 –496.
18. W. W. Busse, Am. J. Respir.Efficiancy and safety of inhaled corticosteroids: new devolepments. ATS Jounl. 1998; 157: S210 – S213.
19. J. N. Sharma, L. A. Mohammed, Inflammopharmacology 2006; 14:10–16.
20. S. Khanapure, D. Garvey, D. Janero, L. Gordon.Ntric oxide releasing particles for nitric oxidetherapeutics and biomedical applications. Letts, Curr. Top. Med.Chem. 2007;7:311 – 340.
21. 21 D. Altavilla, F. Squadrito, A. Bitto, F. Polito, B. Burnett, V. Di Stefano, L. Minutoli, Br. J. Pharmacol. 2009, 157, 1410– 1418.
22. J. Augstein, J. B. Farmer, T. B. Lee, P. Sheard, M. L. Tattersall, Nat. New Biol. 1973, 245, 215 –217.
23. P.-R. Bernstein, Am. J. Respir.Chemistry and structure activity relationships of Leucotriene receptor antagonists.ATS Jounl 1998:157: S220 – S226.
24. Carlos F. M. Silva, Diana C. G. A. Pinto, and Artur M. S. Silva. Chromones: A Promising Ring System for New Antiinflammatory Drugs. Nat. Rev. Immunol.2011;11:519 –531.
25. R S sathoskar,S.D sBhandarkar,N.N Rege, .pharmacology and pharmaco therapeutics.2009;21:810-812
26. M. W Anderson, S .H Reinolds, R.M Maronpot. Role of Proto-oncogenes in carcinogenesis.Envirnment Health Prospectives.1992;98:1992.
27. G.Schwartsmann et al.,Anticancer drug discovery and development throughout the world .ATS Joun.2002;20(18):47S-59S.
28. Li J.-J.; Corey E. J. Name Reactions in Heterocyclic Chemistry, John Wiley & Sons, Inc., 2005;18: 495-543..
29. Reddy B. P.; Krupadanam G. L. D.; "The synthesis of 8-allyl-2-styrylchromones by the modified baker-venkataraman transformation". J. Heterocycl. Chem. 1996;33(6): 1561-1565.
30. .Nohara A.; Umetani T.; Sanno Y.; "Studies on antianaphylactic agents—I : A facile synthesis of 4-oxo-4H-1-benzopyran-3-

carboxaldehydes by Vilsmeier reagents". Tetrahedron 1974; 30(19): 3553-3561.
31. Ellis G. P. Chemistry of Heterocyclic Compounds, John Wiley & Sons, Inc., 1977; 495-555
32. Kumar P.; Bodas M. S.; "A Novel Synthesis of 4H-Chromen-4-ones via Intramolecular Wittig Reaction". Org. Lett. 2000;2(24): 3821-3823.
33. Foley P.; Gerlach M.; Youdim M. B.; Riederer P.; "MAO-B inhibitors: multiple roles in the therapy of neurodegenerative disorders?". Parkinsonism Relat. Disord. 2000; 6(1): 25-47.
34. Ismail KA, Abd El Aziem T. Synthesis and biological evaluation of some novel 4Hbenzopyran- 4-one derivatives as nonsteroidal antiestrogens. Eur J Med Chem. 2001;36(3): 243-253.
35. Fillion E.; Dumas A. M.; Kuropatwa B. A.;Malhotra N. R.;Sitler T. C.Yb(OTf)3-Catalyzed Reactions of 5-Alkylidene Meldrum's Acids with Phenols: One-Pot Assembly of 3,4-Dihydrocoumarins, 4-Chromanones, Coumarins, and Chromones". J. Org. Chem. 2005;71(1): 409-412.
36. Sabui SK, Venkateswaran RV. Synthesis of heliannuol D, an allelochemical from Helianthusannus. Tetrahedron Lett 2004; 45: 983-985.
37. Griffin RJ, Fontana G, Golding BT, Guiard S, Hardcastle IR, Leahy JJJ, Martin N, Richardson C, Rigoreau L, Stockley M, Smith GCM. Selective Benzopyranone and Pyrimido[2,1-a]isoquinolin-4-one Inhibitors of DNA-Dependent Protein Kinase: Synthesis, Structure−Activity Studies, and Radiosensitization of a Human Tumor Cell Line in Vitro. J Med Chem 2005; 48:569-585.
38. Malolanarasimhan K, Lai CC, Kelley JA, IaccarinoL, Reynolds D, Young HA, Marquez VE.Synthesis and biological study of a flavone acetic acid analogue containing an azido reporting group designed as a multifunctional binding site probe. Bioorg Med Chem 2005;13: 2717-2722.
39. Banavara M, Groton L. Eur pat 1 373 259 B1.WO 2002/079198 (10.10.2002 Gazette2002/41).
40. Rossollin, V.; Lokshin, V.; Samat, A.; Guglielmetti, R.Reinvestigation of prototropicphotochromism: 3-benzoyl-2-benzylchromones. Tetrahedron 2003; 59(39): 7725-7731.
41. Lee KS, Seo SH, Lee YH, Kim HD, Son MH, Chung BY, Lee JY, Jin C, LeeYS. Synthesisand biological evaluation of chromone carboxamides as calpain inhibitors. Bioorg Med ChemLett 2005; 15(11): 2857-2860.
42. I.Ionuţ et al., synthesis and in vitro anticancer activity of new thiadiazolines and thiazolinones containing a chromenyl scaffold. Digest Journal of Nanomaterials and Biostructures.2013;8: 1509 – 1523.
43. B.Sing et.al., Synthesis and In Vitro Cytotoxic Activity of Chromenopyridones. International Journal of Medicinal Chemistry.2013;1;17.
44. .D.H Nam,K.Y Lee,C.S Moon, Y.S Lee. Synthesis and anticancer activity of chromone-based analogs of lavendustin A. Eur J Med Chem.2010; 45:4288-42292.
45. E. venkadeswara Rao et al., Synthesis and SAR Studies of bis-chromenone derivatives for anti-proliferative activity against human cancer cells. Bioorg Med Chem.2014; 7:435-444.
46. J A Hutter et al., Cyclooxigenase inhibitory activity of Aloe species.south African Jounal of Botany,2002; 68(1):47-50.
47. K.M. Khan, N. Ambreen, U.R. Mughal, S. Jalil, S. Perveen, M.I. Choudhary, 3-Formylchromones: potential antiinflammatory agents, European Journal of Medicinal Chemistry (2010);45: 4058-4064.

48. C.A. Moldovan, O. Oniga, A. Parvu, B. Tiperciuc, P. Verite, A. Pirnau, O. Crisan, M. Bojita, R. Pop, Synthesis and anti-inflammatory evaluation of some new acyl-hydrazones bearing 2-aryl-thiazole, European Journal of Medicinal Chemistry (2010); 46:526-534.
49. S.M. Hasan, M.M. Alam, A. Husain, S. Khanna, M. Akhtar, M.S. Zaman, Synthesis of 6-aminomethyl derivatives of benzopyran-4-one with dual biological properties: anti-inflammatory-analgesic and antimicrobial, EuropeanJournal of Medicinal Chemistry.2009;44:4896-4903.
50. P. Thanigaimalai, T.A.L. Hoang, K. Lee, V.K. Sharma, S. Bang, J.H. Yun, E. Roh,Y. Kimb, S. Jung, Synthesis and evaluation of novel chromone analogs for their inhibitory activity against interleukin-5, European Journal of Medicinal Chemistry.2010;45: 2531-2536
51. Ottana, R R. Maccari, M L Barreca , G. Bruno.5-arelidene-2-imino-4-thizolidinones:Design and synthesis of novel anti-inflammatory agents. Bio. And Med chem.., 2005; 13: 4243-4252
52. Khaled R A et al. design, synthesis and biological screening of new 4-thiazolidinone derivatives with promising COX -2 selectivity, anti- inflammatory activity.Bio organic chemistry., 2016;64:1-12
53. Monther F. M, Ayad M. R.R, Farah A.H. Design, synthesis and acute anti-inflammatory evaluation of new non-steroidal anti-inflammatory agents having 4-thiazolidinone pharmacophore. Journal of Natural Sciences Research.,2015;5:21-29
54. V Ravichandran; BRP Kumar; S Sankar; RK Agrawal. 2,3 disubstituted 4-thiazolidinone derivatives for antiproliferative and tumor inhibitory activity Eur J Med Chem, 2009;44:1180-1187.
55. Havrylyuk D et al. The synthesis and anticancer activity evaluation of 4-thiazolidinones containing benzothiazole moiety.Eur Jenoul Med Chem.2010; 45(11):5012-21
56. Asish B et al., synthesis, characterization and evaluation of anticancer activity of some novel thiazolidinone derivatives. Bio organic chemistry.2014;6:4536-4574.
57. R.B Ptil,Snjay D, Savant, A Pankaj,Thrombare. Design, synthesis and pharmacological evaluation of chromones and related analogues. IJPRIF.2012;4(1):375-381.
58. Nencki M and Seiber N . Nncky reaction, J prakt.chem.1881;23:150-160.
59. Rerong Wang. Comprahensive name reaction and reagents.2009;3:2035-2037.
60. http: www.molinspiration.com/cgl-bin/properties.
61. http://www.pharmaexpert.ru/PASS online/predict php
62. S. Srestha, S Y Hwang, K H Lee and H Cho. Synthesis of formyl chromone derivatives inactivation of protein thyrosin phosphataseKorean Chem.sos.2005;26(7):1138-1141.
63. .M.Laacova, D. LOOS, M Fardik,Hafez M,El.Shaaer. Synthetic reaction and theoretical study of 3 formyl chromones.ECOSOC.1997; 1:3356-3381.
64. https://en.m.wikipedia.org.
65. .R C Rajanna, F Solomon, M.M Ali, P K Sai prakash. Kinetics and mechanism of Vilsmier Hack synthesis of 3-formylchroonederived from o-hydroxy aryl/alkyl ketone:structure reactivity study.Elsvier ssciences.1996;10:3669-3682.
66. J H Kini,V K Pai E.Y.OBodke.Physicochemical approach in design, synthesis antimicrobial study of some novel Schiff bases

ofchromones.INJAPBC.2016;5(3):2277-4688.

67. .G Mhaske,P Nikanth,A Auti,S Davange,. aqua medicated, microwave assisted, synthesis of schiff bases and their biological evaluation. INJIRIS.2014;3(1):2319-8753.
68. H Skolnik,J GMiller A L Day. The allylic character of 2-α- chloro alkyl benzimidazoleJACS.1943;65(10):1854-1858.
69. MMJ Vijayakumar,T S Nagaraja. N – substituted thiazolidinone synthesis characterizationof new novel anti-inflammatory agentsInt, j.pharma.sci.2009;1(1):42-45.
70. H Kitagawa,T Ozava, T S Lida .Phenyl imidazole derivativesas new inhibitors of bacterial enoyilACP reductase. agentsInt, j.pharma.sci.2007;17:4982-4986.
71. Deep A, Jain S, Sharma PC. Synthesis and anti-inflammatory activity of some novel biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amides. Acta Pol Pharm. 2010;67(1):63-7.
72. Gore RP.Synthesis, characterization and antimicrobial screening of 4-thiazolidinone derivatives of some N'-(substituted)benzylidene-2-(1H-azol-1-yl) acetohydrazides, Int. J.Chem.Tech Res. 2012.
73. Shah PM, Patel MP. Zinc (II) chloride catalysed one pot synthesis of some new 4-thiazolidinone derivatives as biologically potent agents. Indian Journal of Chemistry-Part B OrganicIncluding Medicinal. 2011;50(3):310.
74. Gadir SA. Assessment of bioactivity of some Sudanese medicinal plants using brine shrimp (Artemiasalina) lethality assay. J. Chem. Pharma. Res. 2012. 4(12): 236-238.
75. Riss TL, Moravec RA, Niles AL. Cell viability assays. NCBI books. 2013. 43(4): 22-30.
76. Kumar N S. Evaluation of RBC membrane stabilization and anti-oxidant activity of Bombaxceiba in an invitromethod.Int. J. of Pharma and Biosci. 2011. 2(1): 220-226.
77. Manivarnnana R, Sukumar D. The RBC membrane stabilization in an invitro method by the drug isolated from Leucasaspera. Int. J. Appli. Sci. 2007. 5(2): 133-138.

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