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RESEARCH ARTICLE

METHYLCHROMONYL LINKED BENZYLIDENES AS NOVEL PARTIAL PPARγ AGONISTS: SYNTHESIS, CHARACTERIZATION AND DOCKING STUDIES.

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Abstract

The synthetic and docking studies of 2-Methylchromonyl linked para/meta substituted phenyl containing thiazolidenedione (TZD), diethyl malonate (DEM), methyl acetoacetate (MAA), barbituric acid (BA) and thiobarbituric acid (TBA) analogues in an effort to develop novel peroxisome proliferator activated receptors ligands expected to exhibit PPARγ partial agonism in the management of hyperglycemia and hyperlipidemia for the treatment of type 2 diabetes is reported. Docking studies showed expected results.

Introduction:-

Chromone and its derivatives are pharmacologically active compounds, having immense medicinal significance and known to exhibit a broad spectrum of therapeutic activities including antidiabetic.[1] Peroxisome Proliferator Activated Receptors (PPARs), specially the 'α' and 'γ' subtypes are very important therapeutic targets for the treatment of type 2 diabetes mellitus.[2] Activation of PPARα reduces triglycerides and is involved in regulation of energy homeostasis, activation of PPARγ causes insulin sensitization and enhances glucose metabolism.[3] Thiazolidinediones (TZDs) have been shown to increase the insulin sensitivity of target tissues. TZDs, pioglitazone and rosiglitazone are PPARγ full agonists have many beneficial effects in Type 2 diabetes mellitus (T2DM). The full potential of these drugs has not been realized due to undesirable side effects including weight gain, peripheral edema, anemia, loss of bone mass following their prolonged usage.[4,5] Later on several dual PPARα/γ agonists have been developed to treat T2DM and have been shown to be beneficial in comparison to full PPARα or PPARγ agonists because they improve lipid and glucose homeostasis.[6] However, despite extensive efforts from industry and academia, no such agents have advanced to the clinic. Lately, several reports in literature have demonstrated that Selective PPARγ Modulators (SPPARγMs) could bind to the receptor in a distinct mode relative to full agonists, providing a physical basis for different biological effects.[7] As a result, such ligands act as partial agonists. The 2.4-thiazolidinediones (TZD) analogs, barbituric acid analogs and 1,3 diketones have been found to exhibits antidiabetic activities.[2] A series of potent benzylidene thiazolidenediones have been reported to possess euglycemic as well as hypolipidemic activities.[7] Keeping in view the importance of partial agonism, we, in this research paper have computationally docked and synthesized novel 2-methylchromonyl linked benzylidene with H-bonding groups (TZD, RH, DEM, MAA, BA and TBA) while introducing conformational and geometric constrains by introducing unsaturation to attach the hydrogen bonding parts with the phenyl moiety, as potential PPARγ partial agonist for the management of Type 2 Diabetes and Metabolic Syndrome.

Experimental:-

Material and methods:-

Chemicals and reagents:-

All the chemicals used in the present study were purchased from Sigma Aldrich and Sdfine chemicals. The melting/boiling points reported here were recorded using an open conc. sulphuric acid bath and are uncorrected.

Equipments and analytical instrument:-

The Infrared and ^{1}H NMR spectra of the reported compounds were recorded on Perkin-Elmer Spectrum RX FTIR Spectrophotometer and AC400F, 400MHz Bruker spectrometer respectively at RSIC, Panjab University, Chandigarh. LCMS of the compounds were recorded on LCMS LCQ Finnigan Matt (APCI +ve mode) at Central Instrumentation Lab, NIPER, SAS Nagar, Mohali, Punjab. GCMS and Elemental analysis of these compounds were carried out on Shimadzu GCMS-QP2010 Plus and Vario Micro CHN Elemental Analyzer respectively at Instrumental Laboratory, Department of Chemistry, Punjabi University, Patiala. Molecular docking studies were carried out following procedure as per Verma *et al.,* 2013.

Procedure for Synthesis intermediates 2, 3, 4, 5:-

2 :- A mixture of compound 1 and ethylacetate was taken in dry clean RBF, stirred for 10 min. at 20-25 ^{o}C. NaH was added in small portions for 4 min. with stirring. After complete addition, stir for 5 min. at the same temperature, then it was heated gently on water bath for 20 min. at 60-70 ^{o}C (yellow brown highly viscous mass). This was kept overnight at 30 ^{o}C. Water with ice poured to RBF, brown solution was formed. The solution once extracted with ether. The aqueous part acidifies with dilute acetic acid and ether, ether layer was extracted with cold water and dried on $MgSO_4$.

3:- To a solution of compound 2 (2.5 g, 0.014 mol) in ethanol (30 mL) was gradually added with stirring a solution of bromine (3.36 mL, 0.021 mol) in ethanol (8 mL) over a period of 15 min, and the mixture was allowed to stand for a further 2 h at room temperature. Concentrated hydrochloric acid (2 mL) was added, and the reaction mixture was refluxed for 2 h. After cooling and dilution with water (25 mL), the solid so obtained was collected and recrystallized from petroleum ether (60-80 °C) to give compound 3.

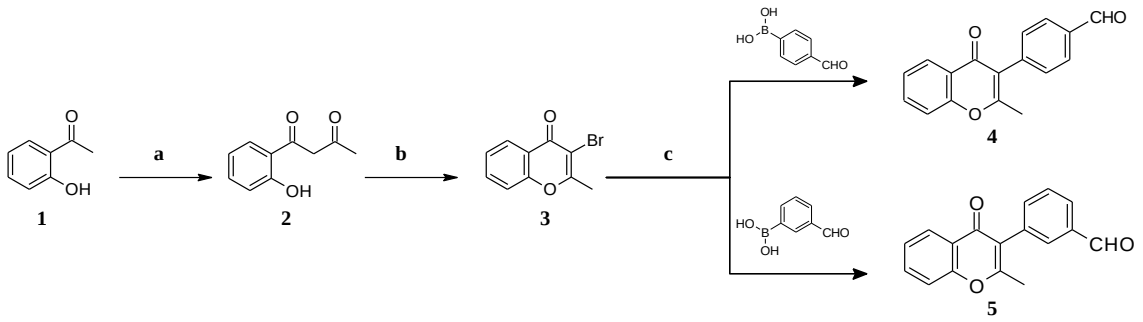
4 and 5:- To a solution of **3** (0.500 g**,** 0.00209 mol) and 4-boronobenzaldehyde/3-boronobenzaldehyde (0.209 g, 0.0014 mol) in a mixture of Dioxane and Water (4:1, 15 mL) was added K_2CO_3 (0.580 g, 0.0042 mol). The resulting mixture was degassed, stirred at ambient temperature for 20 minutes and catalytic amount (0.005mmol) of $Pd(PPh_3)_4$ were added. The mixture was degassed again and then refluxed under nitrogen gas for 8 hours. It was allowed to cool, filtered through celite, and extracted using EtOAc (3×20mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an oil which was subjected to column chromatography using a mixture of EtOAc/hexane to afford the title compound **4** and **5**.

General Procedure for Synthesis 6, 7, 8, 10, 11 and 12:-

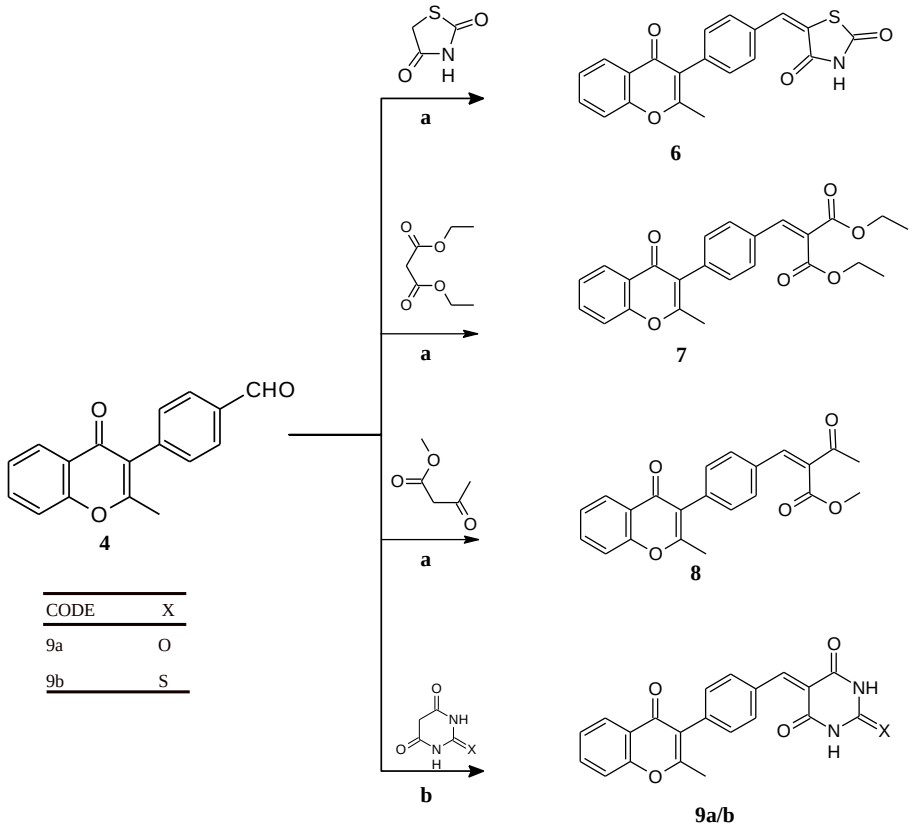
A mixture of (**4/5**) (1 mmol), thiazolidine-2,4-dione/diethylmalonate/methyl acetoacetate (1 mmol), and piperidinium acetate (catalytic amount) in toluene (25 ml) was refluxed for 7-14 h with continuous removal of water using a Dean–Stark trap. The reaction mixture was cooled to room temperature, refrigerated overnight, and concentrated. The precipitate was collected by filtration under vacuum, washed with cold hexane, and dried/purified by column chromatography using EtOAc/hexane as eluent to give the target compound (**6, 7, 8, 10, 11 and 12).**

General Procedure for Synthesis 9a/b and 13a/b:-

Compound **4/5** (0.0004 mol) and barbituric or thiobarbituric acids (0.00044 mol) were reflux in methanol for 4-6 hours., on completion of reaction (Monitor by TLC), the reaction mass was cooled to room temperature, filtered, and washed with methanol to afford pure solid product.

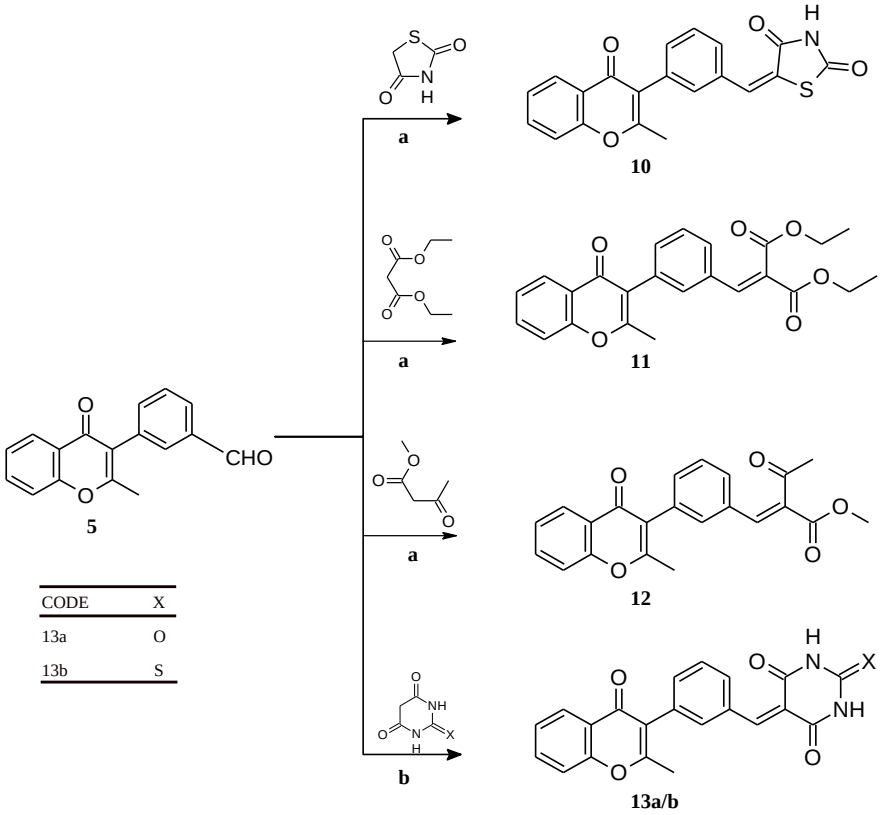


Scheme 1:- Reagents and conditions: (a) ethylacetate, NaH (b) Br_2, ethanol (c) $Pd(PPh_3)_4$, dioxane:water



CODE	X
9a	O
9b	S

Scheme 2:- Reagent and Conditions: (a) piperidinium acetate, toluene (b) methanol.



Scheme 3:- Reagent and Conditions: (a) piperidinium acetate, toluene (b) methanol.

Structural Characterization:-

Compound 2:- 1-(2-hydroxyphenyl)butane-1,3-dione, ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.64 (s, 3H, CH_3), 2.53 (d, 1H, *J* = 1.12 Hz), 2.71 (d, 1H, *J* = 0.76 Hz), 6.78(s, 1H, Ar), 6.98 (m, 2H, Ar), 7.73 (m, 1H, Ar); FTIR (KBr): 3233 and 3100, 1702, 1694, 1542, 1421, 1289 cm^{-1}; LC-MS (m/z): 179 (M+1); Anal. (%) for $C_{10}H_{10}O_3$ Calcd. C, 67.41; H, 5.66; Found C, 67.41; H, 5.66.

Compound 3:- 3-bromo-2-methyl-4*H*-chromen-4-one, ^{1}H NMR(500 MHz $CDCl_3$) δ = 2.65 (s, 3H, CH_3), 7.44 (m, 2H, Ar), 7.69 (m, 1H, Ar), 8.23 (dd, 1H, Ar, *J* = 1.44, 7.92 Hz); FTIR (KBr): 3233 and 3100, 1680,1542, 1421, 1289, 741 cm^{-1}; LC-MS (m/z): 240 (M+1), 241(M+2); Anal. (%) for $C_{10}H_7BrO_2$ Calcd. C, 50.24; H, 2.95; Found C, 50.24; H, 2.87.

Compound 4:- 4-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzaldehyde, ^{1}H NMR(500 MHz $CDCl_3$) δ = 2.31 (s, 3H, CH_3), 7.41 (m, 1H, Ar), 7.56 (d, 1H, Ar, *J* = 2.12 Hz), 7.67 (m, 2H, Ar), 7.73 (m, 1H, Ar), 7.83 (m, 1H, Ar), 7.95 (m, 1H, Ar), 8.33 (m,1H, Ar), 10.37 (s, 1H, CHO); FTIR (KBr): ,3258, 3217 and 3156, 1705, 1564, 1458, 1299cm^{-1}; LC-MS (m/z): 265 (M+1); Anal. (%) for $C_{17}H_{12}O_3$ Calcd. C, 77.26; H, 4.58; Found C, 77.47; H, 4.61.

Compound 5:- 3-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzaldehyde, , ^{1}H NMR(500 MHz $CDCl_3$) δ = 2.28 (s, 3H, CH_3), 7.33 (m, 1H, Ar), 7.42 (d, 1H, Ar, *Jm* = 1.04 Hz), 7.54 (m, 2H, Ar),7.64 (m, 1H, Ar), 7.65 (t, 1H, Ar), 7.85 (m, 1H, Ar), 8.18 (m,1H, Ar), 10.04 (s, 1H, CHO); FTIR (KBr): 3347, 3233 and 3100, 1740, 1542, 1421, 1289cm^{-1}; ; LC-MS (m/z): 265 (M+1); Anal. (%) for $C_{17}H_{12}O_3$ Calcd. C, 77.26; H, 4.58; Found C, 77.45; H, 4.51.

Compound 6:- 5-[4-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzylidene]-1,3-thiazolidine-2,4-dione, ^{1}H NMR(500 MHz $CDCl_3$) δ = 2.36 (s, 3H, CH_3), 7.11 (s, 1H, Ar), 7.54 (m, 1H, Ar), 7.87 (m, 2H, Ar), 7.90 (m, 1H, Ar), 7.95 (d, 1H, Ar, *J* = 2.44 Hz), 8.09 (dd, 1H, Ar, *J* = 1.48,7.88 Hz), 8.21 (m, 1H, Ar), 8.37 (s, 1H, benzylidenic); FTIR (KBr): 3224 and 3195, 1746, 1549, 1423, 1295cm^{-1}; LC-MS (m/z): 364 (M+1); Anal. (%) for $C_{20}H_{13}NO_4S$ Calcd. C, 66.10; H, 3.61; N, 3.85; Found C, 66.15; H, 3.71; N, 3.81.

Compound 7:- diethyl [4-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzylidene]malonate, ^{1}H NMR ($CDCl_3$), δ = 1.26 (s, 3H, CH_3),1.38 (overlapping triplet, 6H, O=COCH$_2$C**H**$_3$), 4.39 (overlapping quartet, 4H, O=C-OC**H**$_2$CH$_3$), 6.82 (s, 1H, Ar), 7.47 (m, 1H, Ar), 7.64 (m, 2H, Ar), 7.75 (m, 1H, Ar), 7.81 (s, 1H, Ar), 8.06 (s,1H, Ar), 8.25 (m, 1H, Ar), 8.47 (s, 1H, benzylidenic); FTIR (KBr): 2850 and 2962, 1746, 1680, 1549, 1423, 1295cm^{-1}; LC-MS (m/z): 407 (M+1); Anal. (%) for $C_{24}H_{22}O_6$ Calcd. C, 70.92; H, 5.46; Found C, 70.98; H, 5.40.

Compound 8:- methyl-2-[4-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzylidene]-3-oxobutanoate, ^{1}H NMR ($CDCl_3$) δ = 1.22 (s, 3H, CH_3), 1.95 (s, 3H, O=CC**H**$_3$), 3.85 (s, 3H, O=C-OC**H**$_3$), 6.90 (s,1H, Ar), 7.52 (m, 1H, Ar), 7.64 (d, 1H, Ar, *J* =8.08 Hz), 7.77 (m, 2H, Ar), 8.08 (dd,1H, Ar, Jmo = 1.08, 8.92 Hz), 8.19 (dd,1H, Ar, *J* = 1.08, 8.92 Hz), 8.27 (dd, 1H, Ar, *J* = 1.76, 7.84 Hz), 8.47 (s, 1H, benzylidenic); FTIR (KBr): 3280,3257, 3230 and 3056, 1751, 1628,1537, 1401, 1209 cm^{-1}; LC-MS (m/z): 363 (M+1); Anal. (%) for $C_{22}H_{18}O_5$ Calcd. C, 72.92; H, 5.01; Found C, 72.88; H, 5.08.

Compound 9a:- 5-[4-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzylidene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione, ^{1}H NMR(500 MHz $CDCl_3$) δ = 2.36 (s, 3H, CH_3), 7.42 (d, 2H, Ar, *J*= 8.24 Hz), 7.48 (d, 1H, Ar, *J* = 7.72 Hz), 7.60 (d, 2H, Ar, *J* = 8.32 Hz),7.78 (m, 1H, Ar), 8.09 (dd, 1H, Ar, *J*= 1.32, 7.92 Hz), 8.22 (d, 1H, Ar, *J* = 8.60 Hz), 8.36 (s, 1H, benzylidenic), 11.29 (s, 1H, N-H), 11.42 (s, 1H, N-H); FTIR (KBr): 3390,3347, 3233 and 3100, 1740, 1727,1542, 1421, 1289cm^{-1}; LC-MS (m/z): 375 (M+1); Anal. (%) for $C_{21}H_{14}N_2O_5$ Calcd. C, 67.38; H, 3.77; N, 7.48; Found C, 67.45; H, 3.85; N, 7.52.

Compound 9b:- 5-[4-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzylidene]-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione, ^{1}H NMR (500 MHz $CDCl_3$) δ = 2.30 (s, 3H, CH_3), 7.14 (d, 2H, Ar, *J*= 8.08 Hz), 7.19 (m, 1H, Ar), 7.42 (d, 2H, Ar, *J* = 7.80 Hz), 7.78 (d, 1H, Ar, *J* = 8.44 Hz), 8.08 (s, 1H, benzylidenic), 8.22 (m, 2H, Ar), 12.07 (s, 2H, N-H); FTIR (KBr): 3356, 3324, 3253 and 3123, 1741, 1728,1513, 1321, 1259cm^{-1}; LC-MS (m/z): 391 (M+1); Anal. (%) for $C_{21}H_{14}N_2O_4S$ Calcd. C, 64.60; H, 3.61; N, 7.18; Found C, 64.65; H, 3.53; N, 7.22.

Compound 10:- 5-[3-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzylidene]-1,3-thiazolidine-2,4-dione, ^{1}H NMR (500 MHz $CDCl_3$) δ = 2.42 (s, 3H, CH_3), 7.16 (s, 1H, Ar), 7.45 (m, 1H, Ar), 7.86 (m, 1H, Ar), 7.90 (m, 2H, Ar), 7.99 (d, 1H, Ar, *J* = 2.49 Hz), 8.15 (dd, 1H, Ar, *J* = 1.48, 7.88 Hz), 8.29 (m, 1H, Ar), 8.39 (s, 1H, benzylidenic), 11.84 (N-H of TZD); FTIR (KBr): 3204 and 3183, 1723, 1557, 1456, 1282cm^{-1}; LC-MS (m/z): 365 (M+1); Anal. (%) for $C_{20}H_{13}NO_4S$ Calcd. C, 66.10; H, 3.61; N, 3.85; Found C, 66.01; H, 3.76; N, 3.86.

Compound 11:- diethyl [3-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzylidene]malonate, 1.23 (s, 3H, CH_3), 1.31 (t, 6H, O=C-OCH$_2$C**H**$_3$), 4.13 (overlapping quartet, 4H, O=C-OC**H**$_2$CH$_3$), 6.94 (s, 1H, Ar), 7.56 (m, 1H, Ar), 7.77 (m, 3H, Ar), 7.85 (m, 1H, Ar), 7.98 (s, 1H, Ar), 8.45 (s,1H, Ar), 8.62 (m, 1H, Ar), 8.64 (s, 1H, benzylidenic); FTIR (KBr): 3224 and 3195, 1746, 1549, 1423, 1295cm^{-1}; LC-MS (m/z): 407 (M+1); Anal. (%) for $C_{24}H_{22}O_6$ Calcd. C, 70.92; H, 5.46; Found C, 70.88; H, 5.40.

Compound 12:- methyl-2-[3-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzylidene]-3-oxobutanoate, ^{1}H NMR ($CDCl_3$) δ = 1.26 (s, 3H, CH_3), 1.87 (s, 3H, O=CC**H**$_3$), 3.93 (s, 3H, O=C-OC**H**$_3$), 7.01 (s, 1H, Ar), 7.63 (m, 1H, Ar), 7.77 (d, 1H, Ar, *J* = 8.08 Hz), 7.96 (m, 2H, Ar), 8.23 (dd, 1H, Ar, *J* = 1.08, 8.92 Hz), 8.38 (dd, 1H, Ar, *J* = 1.08, 8.92 Hz), 8.43 (dd, 1H, Ar, *J* = 1.76, 7.84 Hz), 8.52 (s, 1H, benzylidenic); FTIR (KBr): 3389,3298, 3257 and 3102, 1692, 1613,1523, 1399, 1126 cm^{-1}; LC-MS (m/z): 363 (M+1); Anal. (%) for $C_{22}H_{18}O_5$ Calcd. C, 72.92; H, 5.01; Found C, 72.84; H, 5.11.

Compound 13a:- 5-[3-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzylidene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione, ^{1}H NMR (500 MHz $CDCl_3$) δ = 2.32 (s, 3H, CH_3), 7.38 (d, 2H, Ar, *J*= 8.24 Hz), 7.46 (d, 1H, Ar, *J* = 7.72 Hz), 7.56 (d, 1H, Ar, *J* = 8.12 Hz), 7.63 (m, 2H, Ar), 8.12 (dd, 1H, Ar, *J* = 1.28, 7.67 Hz), 8.23 (d, 1H, Ar, *J* = 8.52 Hz), 8.38 (s,1H, benzylidenic), 11.23 (s, 1H, N-H), 11.31 (s, 1H, N-H); FTIR (KBr): 3363, 3353, 3248 and 3200, 1756, 1723,1514, 1489, 1245cm^{-1}; LC-MS (m/z): 375 (M+1); Anal. (%) for $C_{21}H_{14}N_2O_5$ Calcd. C, 67.38; H, 3.77; N, 7.48; Found C, 67.35; H, 3.82; N, 7.47.

Compound 13b:- 5-[3-(2-methyl-4-oxo-4*H*-chromen-3-yl)benzylidene]-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione, ^{1}H NMR (500 MHz $CDCl_3$) δ = 2.33 (s, 3H, CH_3), 7.25 (d, 2H, Ar, *J*= 8.45 Hz), 7.45 (d, 2H, Ar, *J* = 7.21 Hz), 7.56 (m, 1H, Ar), 7.85 (d, 1H, Ar, *J* = 8.02 Hz), 8.08 (d, 1H, Ar, *J*= 7.96 Hz), 8.26 (m, 1H, Ar), 8.40 (s,1H, benzylidenic), 12.02 (s, 1H, N-H), 12.13 (s, 1H, N-H); FTIR (KBr): 3359, 3334, 3251 and 3203, 1769, 1738,1533,

1329, 1275cm^{-1}; LC-MS (m/z): 391 (M+1); Anal. (%) for $C_{21}H_{14}N_2O_4S$ Calcd. C, 64.60; H, 3.61; N, 7.18; Found C, 64.58; H, 3.64; N, 7.27.

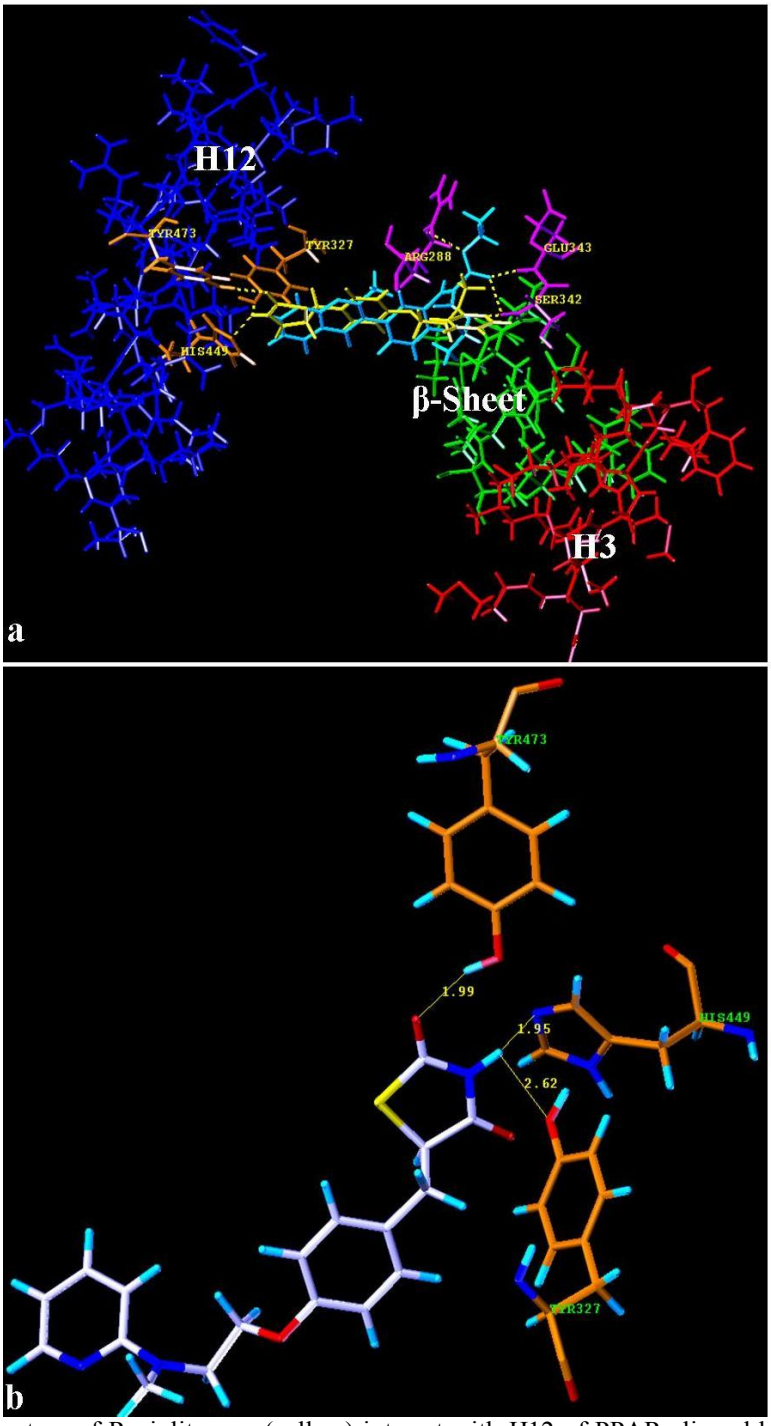


Fig 1:- (a) Crystal structure of Rosiglitazone (yellow) interact with H12 of PPARγ ligand binding domain (LBD) through H-bond with TYR327, HIS449, and TYR473 amino acid residues (orange). The hydrogen bonding part of compound **11** (cyan) interact with β-sheet (green) of PPARγ-LBD through H-bond with SER342 amino acid residue (magenta) and lie between H3 (red) and β-sheet region (green). (b) Crystal structure of rosiglitazone showing H-bond with TYR327, HIS449, and TYR473 amino acid residue (orange).

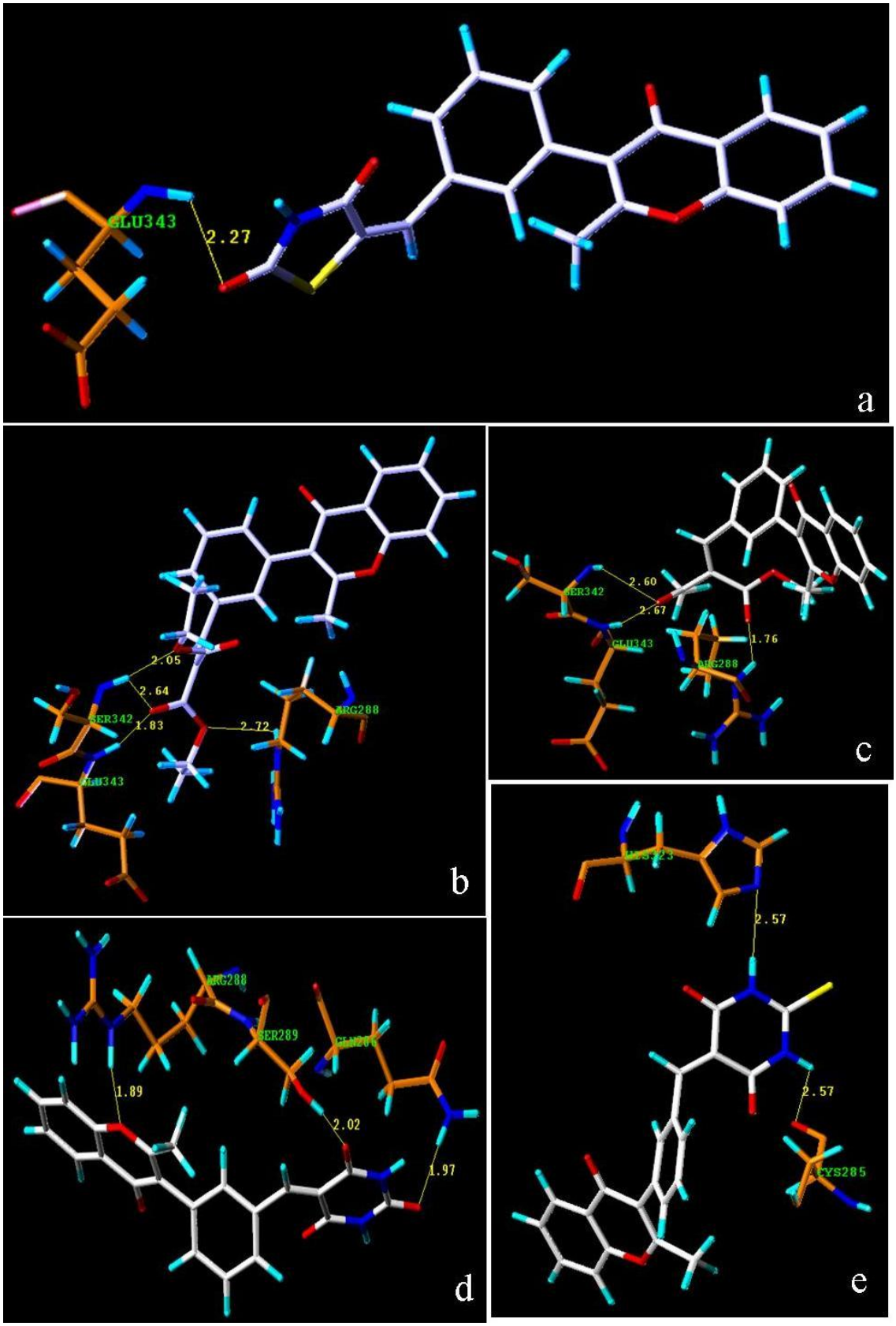


Fig 2. Crystal structure of synthesized compounds **6-13b** forming H-bond with SER342 amino acid residues (orange) **a-e** respectively.

Table 1:- Docking results of the synthesized compounds as compared to Rosiglitazone at the active site of $PPAR_{\gamma}$ (2prg)

Compound Code	G score	H-bonding interactions between the ligands and the active site amino acid (AA) residues			
		Atoms of ligands*	AA residues	Bond distance (Å)	No. of H-bonds
Rosiglitazone	-225.54	4 C=**O** of TZD N-**H** of TZD N-**H** of TZD	TYR473 HIS449 TYR327	1.99 2.62 1.95	3
6	-232.03	**O** of chromone 2 C=**O** of TZD 3 N-**H** of TZD 4 C=**O** of TZD	ARG288 TYR473 HIS3323 SER289	2.62 1.87 2.24 2.42	4
7	-263.92	-	-	-	-
8	-223.86	**O**=C-CH_3 **O**=C-OCH_3	GLU343 SER342	1.65 1.78	2
9a	-244.54	**O** of chromone 2 C=**O** of BA 3 N-**H** of BA 3 N-**H** of BA 4 C=**O** of BA	ARG288 TYR327 TYR473 HIS449 GLN286	2.35 2.20 2.64 1.86 1.93	5
9b	-249.99	N-**H** of TBA	HIS449	1.78	1
10	-233.96	2 C=**O** of TZD	GLU343	2.27	1
11	-247.22	**O**=C-OC_2H_5 **O**=C-OC_2H_5 O=C-**O**C_2H_5 O=C-**O**C_2H_5	SER342 GLU343 ARG288 SER342	2.64 1.83 2.72 2.05	4
12	-219.41	**O**=C-OCH_3 **O**=C-CH_3 **O**=C-CH_3	ARG288 GLU343 SER342	1.76 2.67 2.60	3
13a	-240.21	**O** of chromone 2 C=**O** of BA 4 C=**O** of BA	ARG288 SER289 GLN286	1.89 2.02 1.97	3
13b	-226.76	1 N-**H** of TBA 3 N-**H** of TBA	HIS323 CYS285	2.57 2.57	2

*The particular atom involved in hydrogen bond formation has been indicated by bold face.

Result and Discussion:-

Chromonyl linked benzaldehydes (**4, 5**), were prepared by Suzuki coupling of **3** with 4-formylphenylboronic acid and 3-formylphenylboronic acid respectively using K_2CO_3 as base and catalyst $Pd(PPh_3)_4$ (**Scheme 1**). **3** in turn was prepared by cyclisation of 2 using bromine and further **2** was prepared by reaction of commercially available ortho-hydroxylacetophenone with ethylacetate in presence of NaH (**Scheme 1**). The targeted compounds (**6-8 and 10-12**) were prepared in fairly good yields through 'Knoevenagel Condensation' of the 2,4-Thiazolidinediones (TZD), Rhodanine (Rh), Diethyl malonate (DEM) and Methyl acetoacetate (MAA) based hydrogen bonding parts with the chromonyl linked benzaldehyde **(4** and **5) (Schemes 2 and 3)** while using piperidinium acetate/toluene as base under reflux conditions. The targeted compounds **(9a-b and 13a-b)** were prepared in fairly good yields through refluxing compound **(4 and 5)** and barbituric/thiobarbituric acids in methanol for 4-6 hours. All the synthesized molecules possess almost all the structural features to be expected for achieving partial PPARγ modulating activity and were docked (with Surflex dock module of Sybyl 7.3, a Tripos Inc. software available at our *in silico* drug design laboratory) at the active site of the receptor proteins (PPARγ: 2prg) for the prediction of binding affinities (gold score energies, Table 1) in reference to standard molecule (Rosiglitazone). It was found from the analysis of the results of docking studies that all synthesized compounds 6, 7, 8, 9a, 9b, 10, 11, 12, 13a, and 13b having G score (-232.03, -263.92, -223.86, -244.54, 249.99, -233.96, -247.22, -219.41 and -240.21 respectively) exhibits comparable PPARγ affinities (Table 1) in comparison to the standard molecule rosiglitazone (-225.54) in the active site of the protein (PPARγ: 2prg). Rosiglitazone form the H-bonding with HIS449, TYR327 and TYR473 where TYR473 stabilize helix12 (H12) and is responsible for the full transactivation of PPARγ.[8] The synthesized compounds 8, 10, 11and 12 interacted with H3 and β-sheet through hydrogen bonding with ARG288, SER342 and GLU343 amino acid residues which are responsible for partial agonism.[9] However 9b, 13a and 13b interacted with the key residues HIS449, SER289, HIS323 but lack TYR473 interaction. TYR473 interaction is responsible for full agonism as in rosiglitazone.[10] Compounds 6 and 9a showed similar binding modes as rosiglitazone interacted with

TYR473 so they can be act as full agonists. Research work from our lab concerning design and computational validation studies of novel PPAR dual activators analyzing important structural features of PPAR ligands have also been reported previously.[11-13]

Conclusion:-

In the present work, we report the syntheses and characterization of biologically significant 2-methylchromone based novel partial PPAR agonists. The binding affinities in terms of G Score and results of comparison of the binding modes between all the synthesized molecules and the AA residues in the active sites of PPARγ proteins, to that of Rosiglitazone also support the design of the molecules with expected partial agonism.

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