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International Journal of Current Research
Vol. 8, Issue, 06, pp.32506-32511, June, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

SYNTHESIS, CHARACTERIZATION AND DOCKING STUDIES OF CHROMONYL LINKED *meta*-SUBSTITUTED BENZYLIDENES AS BIOLOGICALLY SIGNIFICANT PARTIAL PPARγ AGONISTS

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ARTICLE INFO

Article History:
Received 23rd March, 2016
Received in revised form
05th April, 2016
Accepted 18th May, 2016
Published online 15th June, 2016

Key words:

Chromone,
Benzylidene,
Docking,
PPAR, Partial agonism.

ABSTRACT

The synthetic and docking studies of Chromonyl linked thiazolidenedione (TZD), rhoadanine (RH), 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 PPAR*γ* partial agonism in the management of hyperglycemia and hyperlipidemia for the treatment of type 2 diabetes is reported. Docking studies showed expected results.

Citation: Gagandeep Singh, Amanjot Singh, Raman K Verma, and Rajiv Mall. 2016. "Synthesis, characterization and docking studies of chromonyl linked *meta*-substituted Benzylidenes as biologically significant partial PPARγ agonists", *International Journal of Current Research*, 8, (06), 32506-32511.

INTRODUCTION

The metabolic disorder, Type 2 Diabetes Mellitus (T2DM) is characterized by insulin resistance and hyperglycemia. During the past 20 years, the number of diabetic people worldwide has increased to almost double (Zimmet *et al.,* 2016). Peroxisome proliferator activator receptors (PPARs) belongs to the nuclear receptors super family, especially the α and γ subtypes, are very important therapeutic targets for treatment of type 2 diabetes mellitus (Verma *et al.,* 2013). PPARα activation reduces triglycerides and PPARγ activation causes insulin sensitization and enhances glucose metabolism. The full agonism of PPARγ drugs is associated with side effects including weight gain, edema, and congestive heart failure. Later on, PPARα/γ dual agonists combining the features of both glucose and lipid lowering have been identified as potential therapeutic agents for diabetic hyperglycemia and dyslipidemia (Verma *et al.,* 2013). 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 (Suh *et al*., 2008). As a result, such ligands act as partial agonists. The 2.4-thiazolidinediones (TZD) analogs, barbituric acid analogs and 1,3 diketones (Liu *et al*., 2005; Penthala *et al*., 2015; Shinkai *et al*., 1998 and Verma *et al*., 2015) have been found to exhibits antidiabetic activities. A series of potent benzylidene thiazolidenediones have been reported to possess euglycemic as well as hypolipidemic activities (Lohray *et al*., 1998). Chromone nucleus is an important heterocyclic pharmacophoric component having immense medicinal significance and known to exhibit a broad spectrum of pharmacological activities including antidiabetic (Nazreen *et al*., 2014). Keeping in view the importance of above cited facts, we, in this research paper have computationally docked and synthesized novel chromonyl linked meta-substituted phenyl containing active methylene 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.

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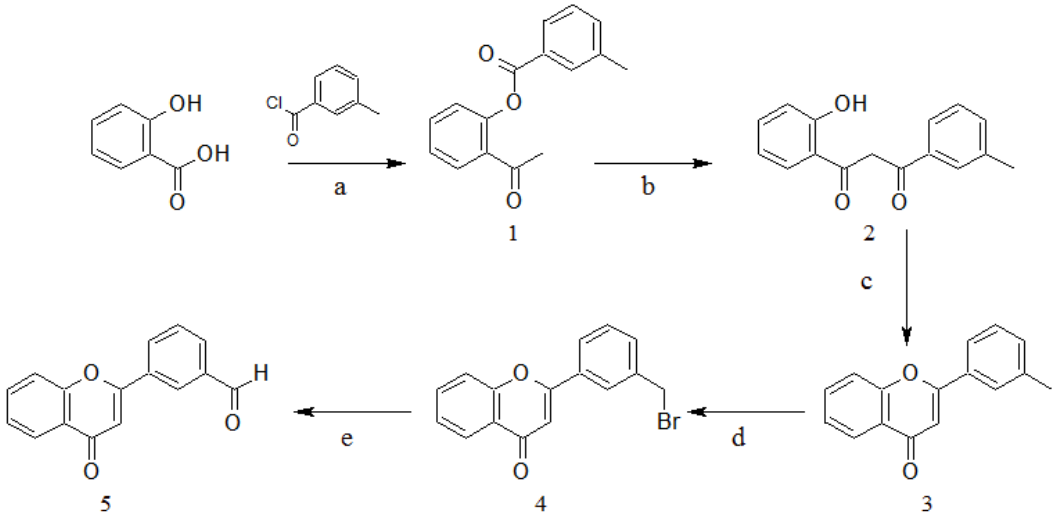
EXPERIMENTAL

MATERIAL AND METHODS

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. 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.



Scheme 1. Reagent and Conditions: (a) pyridine: (b) powder KOH/pyridine: (c) conc sulfuric acid: (d) N-bromosuccinimide: (e) hexamethylenetetramine

Synthesis of 1: 2-acetylphenyl 3-methylbenzoate

m-methylbenzoyl chloride (4.63g, 0.03mol), was added to a mixture of *o*-hydroxyacetophenone (4.08g, 0.03mol) in pyridine (10mL) and heated for 30min. at 80^{o}C. The mixture was cooled and poured into water, washed with dilute Na_2CO_3 solution and water, recystallisation from ethanol to gave 1 (6.70g, 88%). IR (KBr) cm^{-1}: 3059 (aromatic C-H), 2951, 2925 (aliphatic C-H symmetric and antisymmetric), 1698 (C=O), 1154 (C-O-C). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.95 (d, 2H, Ar, *Jo*= 7.48 Hz), 7.80 (dd, 1H, Ar, *Jmo*=1.6, 7.8 Hz), 7.53 (m, 1H, Ar), 7.40 (m, 3H, Ar), 7.18 (m, 1H, Ar), 2.47 (s, 3H, CH_3), 2.37 (s, 3H, CH_3). LCMS m/z (% intensity): 255 (100) [M+1].

1-(2-hydroxyphenyl)-3-(3-methylphenyl)propane-1,3-dione

Compound 1 (6.35g, .025mol) in 40mL pyridine and powdered KOH (3g) was stirred for 1h at 60^{o}C, the reaction mixture was cooled, water was added and the pH adjusted to 5 with HCl acid. The yellow precipitate formed was filtered, washed with water and recrystallized using acetone–methanol to obtained **2** (4.88g, 76.85%). mp 65-67^{o}C. IR (KBr) cm^{-1}: 3430 (O-H), 2956 (aromatic C-H), 2919, 2850 (aliphatic C-H symmetric and antisymmetric), 1593 (C=O), 1158 (C-O-C). ^{1}H NMR ($CDCl_3$), δ (ppm): 15.55 (s, 1H, O-H), 12.11 (s, 1H, O-H), 7.80 (m, 1H, Ar), 7.75 (m, 2H, Ar), 7.49 (m, 1H, Ar), 7.38 (m, 2H, Ar), 7.01 (dd, 1H, Ar, *Jmo*=1.0, 8.36 Hz), 6.95 (m, 1H, Ar), 6.83 (s, 1H, H-C=C), 2.44 (s, 3H, -CH_3). LCMS m/z (% intensity): 255 (100) [M+1].

2-(3-methylphenyl)-4*H*-chromen-4-one

A mixture of **2** (14.37g, 0.57mol) and conc H_2SO_4 (81mL) was stirred at room temperature for 1h. Water was added, precipitate formed was collected and recrystallized from ethanol to obtained **3** (12.1g, 90.6%) as white needles. mp 253^{o}C. IR (KBr) cm^{-1}: 3029 (aromatic C-H), 2851, 2734 (aliphatic C-H symmetric and antisymmetric), 1699 (C=O). ^{1}H NMR ($CDCl_3$), δ (ppm): 8.24 (dd, 1H, Ar, *Jmo*=1.56, 7.92 Hz), 7.72 (m, 3H, Ar), 7.58 (d, 1H, Ar, *Jo* = 7.96 Hz), 7.43 (m, 2H, Ar), 7.35 (d, 1H, Ar, *Jo* = 7.96 Hz), 6.81 (s, 1H, Ar), 2.45 (s, 3H, -CH_3). LCMS m/z (% intensity): 237 (100) [M+1].

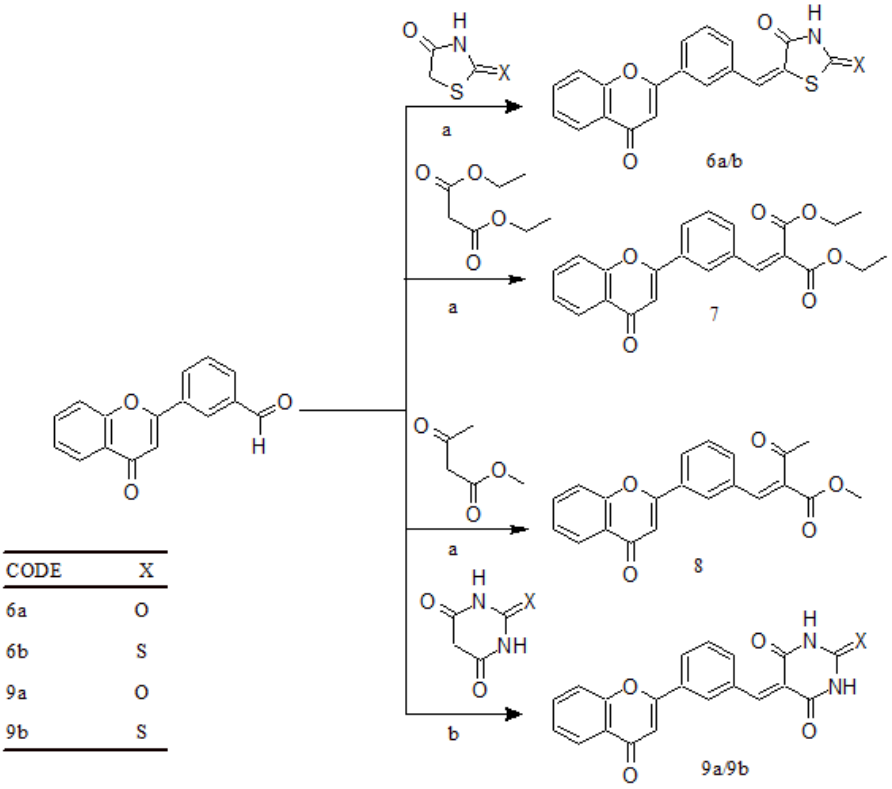
2-[3-(bromomethyl)phenyl]-4*H*-chromen-4-one

A mixture of **3** (0.8g, 4.6mmol) and N-bromosuccinimide (0.82g, 4.6mmol) in CCl_4 (20mL) was heated at reflux overnight. The mixture was filtered while it was hot and CCl_4 was evaporated. The solid residue was crystallized from EtOAc–n-hexane, mp115-121^{o}C, a second time crystallization from EtOAc to gave pure cubic crystal compound, yield (5.21g, 36.70%). mp 138–139^{o}C. IR (KBr) cm^{-1}: 3138 (aromatic C-H), 2926, 2851 (aliphatic C-H symmetric and antisymmetric), 1705 (C=O), 742 (C-Br). ^{1}H NMR (CDCl3), δ (ppm): 8.25 (dd, 1H, Ar, *Jmo* = 1.60, 7.96 Hz), 7.97 (s, 1H, Ar), 7.87 (m, 1H, Ar), 7.74 (m, 1H, Ar), 7.61 (m, 2H, Ar), 7.54 (m, 1H, Ar), 7.46 (m, 1H, Ar), 6.84 (s, 1H, Ar), 4.58 (s, 2H, -CH_2Br). LCMS m/z (% intensity): 315 (100) [M$^+$], 317 (96) [M+2].

3-(4-oxo-4*H*-chromen-2-yl)benzaldehyde

A mixture of **5** (1.00g, 0.00317mol) and hexamethylenetetramine (5.17g, 5.17mol) in 40mL of acetic

acid (50%) was reflux for 2h. HCl acid (12.88mL, 50%) was added and refluxed for 30min. The reaction mixture was diluted with water and saturated with NaCl, then extracted with EtOAc. The organic layer was evaporated and the residue was crystallized from ethanol–water, yield (0.58 g, 73.4%). mp 171–172°C. IR (KBr) cm^{-1}: 3051 (aromatic C-H), 2930, 2918 (C-H symmetric and antisymmetric), 2849, 2790 (aldehydic C-H), 1703 (C=O). ^{1}H NMR ($CDCl_3$), δ (ppm): 10.14 (s, 1H, CHO), 8.47 (d, 1H, Ar, *Jm* = 1.6 Hz), 8.26 (dd, 1H, Ar, *Jmo*= 1.64, 7.92 Hz), 8.17 (d, 1H, Ar, *Jm* = 2.92 Hz), 8.06 (d, 1H, Ar, *Jm* = 1.32 Hz), 7.75 (m, 2H, Ar), 7.64 (d, 1H, Ar, *Jo* = 7.88 Hz), 7.48 (d, 1H, Ar, *Jp*= 0.96 Hz), 6.90 (s, 1H, Ar). LCMS m/z (% intensity): 251 (100) [M+1].



CODE	X
6a	O
6b	S
9a	O
9b	S

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

General procedure for synthesis of Targeted NCEs (6a/6b, 7 and 8)

A mixture **5** (0.00192mol), TZD/RH/DEM/MAA (0.00192mol), and piperidinium acetate (0.15mL) in toluene (25mL) was refluxed for 10h with continuous removal of water using a Dean-Stark trap. The reaction mixture was cooled to room temperature and kept in refrigerator overnight. The precipitate was collected by filtration under vacuum, washed with cold hexane and dried to give the title compound 6a/b (as yellow solid), 7 and 8 (as viscous mass).

5-[3-(4-oxo-4H-chromen-2-yl)benzylidene]-1,3-thiazolidine-2,4-dione

IR (KBr) cm^{-1}: 3463 (N-H), 3192 (aromatic C-H), 2957 (C-H), 1741 and 1699 (C=O). ^{1}H NMR (DMSO), δ (ppm): 8.37 (s, 1H, benzylidenic), 8.21 (m, 1H, Ar), 8.09(dd, 1H, Ar, *Jmo* = 1.48,7.88 Hz), 7.90 (d, 1H, Ar, *Jm* = 2.44 Hz), 7.88 (m, 1H, Ar), 7.86 (m, 3H, Ar), 7.55 (m, 1H, Ar), 7.13 (s, 1H, Ar). LCMS m/z (% intensity): 350 (100) [M+1].

5-[3-(4-oxo-4*H*-chromen-2-yl)benzylidene]-2-thioxo-1,3-thiazolidin-4-one

IR (KBr) cm^{-1}: 3422 (N-H), 3068 (aromatic C-H), 3028, 2908 (C-H symmetric and antisymmetric), 1740 (C=O) 1701 (C=S). ^{1}H NMR (DMSO-d_6), δ (ppm): 8.38 (s, 1H, benzylidenic), 8.18 (d, 1H, Ar, *Jo*= 7.96 Hz), 8.09 (dd, 1H, Ar, *Jmo* = 1.48,7.92 Hz), 7.88 (m, 3H, Ar), 7.78 (s, 1H, Ar), 7.76 (m, 1H, Ar), 7.55 (m, 1H, Ar), 7.14 (s, 1H, Ar). LCMS m/z (% intensity): 366 (100) [M+1].

diethyl [3-(4-oxo-4*H*-chromen-2-yl)benzylidene] malonate

IR (KBr) cm^{-1}: 3063 (aromatic C-H), 2983, 2959 (C-H symmetric and antisymmetric),1711 (C=O), 1262 and 1178 (C-O-C symmetric and antisymmetric of ester).^{1}H NMR ($CDCl_3$), δ (ppm): 8.47 (s, 1H, benzylidenic), 8.25 (m, 1H, Ar), 8.06 (s,1H, Ar), 7.81 (s, 1H, Ar), 7.75 (m, 1H, Ar), 7.64 (m, 3H, Ar), 7.47 (m, 1H, Ar), 6.82 (s, 1H, Ar), 4.39 (overlapping quartet, 4H, O=C-OC**H**$_2$CH$_3$), 1.38 (overlapping triplet, 6H, O=C-OCH$_2$C**H**$_3$). LCMS m/z (% intensity): 393 (100) [M+1].

methyl-3-oxo-2-[3-(4-oxo-4*H*-chromen-2-yl)benzylidene] butanoate

IR (KBr) cm^{-1}: 2954 (aromatic C-H), 2921, 2852 (C-H symmetric and antisymmetric), 1703 (C=O), 1246 and 1221 (C-O-C symmetric and antisymmetric of ester). ^{1}H NMR ($CDCl_3$), δ (ppm): 8.47 (s, 1H, benzylidenic), 8.27 (dd, 1H, Ar,

Jmo = 1.76, 7.84 Hz), 8.19 (dd,1H, Ar, Jmo = 1.08, 8.92 Hz), 8.08 (dd,1H, Ar, Jmo = 1.08, 8.92 Hz), 7.77 (m, 3H, Ar), 7.64 (d, 1H, Ar, Jo=8.08 Hz), 7.52 (m, 1H, Ar), 6.90 (s,1H, Ar), 3.85 (s, 3H, O=C-OC**H**$_3$), 1.95 (s, 3H, O=CC**H**$_3$). LCMS m/z (% intensity): 349 (100) [M+1].

General procedure for the synthesis of barbituric and thiobarbituric based NCE (9a/b)

Compound **5** (0.0004mol) and BA/TBA (0.00044mol) were reflux in methanol for 4-6 hours, on completion of reaction

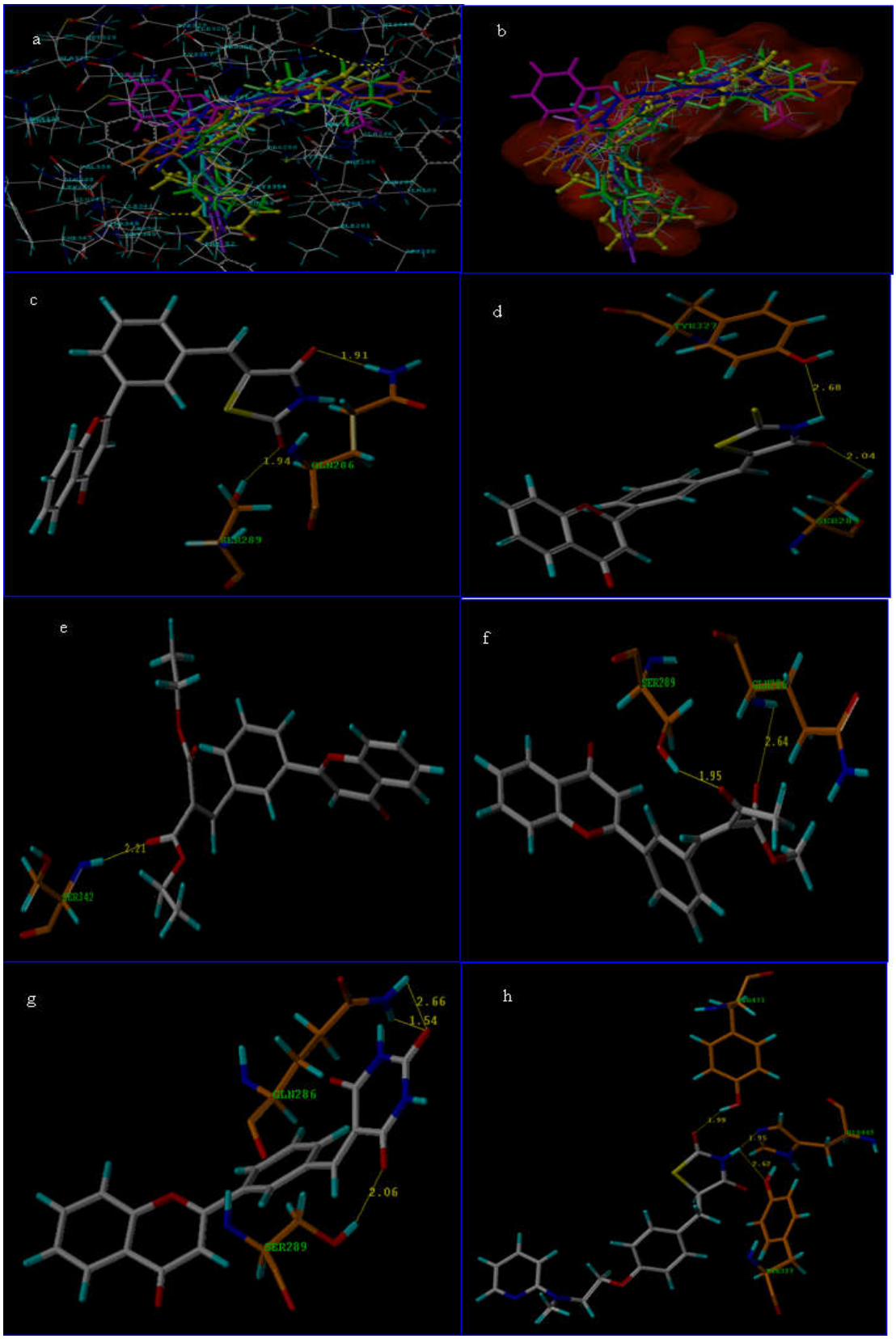


Fig. 1. (a) Docked confirmations of synthesized molecules (sticks; 6a: blue, 6b: cyan, 7:green, 8: magenta, 9a: orange, 9b: purple) compared to Rosiglitazone (ball and stick in yellow) at PPARγ (PDB Code: 2prg) active site (hydrogen bonds between Rosiglitazone and the interacting amino acid residues are shown in yellow). (b) Binding dispositions of synthesized molecules (sticks) compared to Rosiglitazone (ball and stick) at the binding cavity of PPARγ. (c-h) Crystal structure of synthesized compounds 6a-b, 7, 8, 9a and Rosiglitazone forming H-bond with amino acid residues (orange) c-h respectively

(monitor by TLC), the reaction mass was cooled to room temperature, filtered, and washed with methanol to afford pure solid product.

5-[3-(4-oxo-4*H*-chromen-2-yl)benzylidene]pyrimidine-2,4,6 (1*H*,3*H*,5*H*)-trione

IR (KBr) cm^{-1}: 3403 (N-H), 3026 (aromatic C-H), 2957, 2927 (C-H symmetric and antisymmetric), 1737, 1696 (C=O). ^1H NMR (DMSO), δ (ppm): 11.51 (s, 1H, N-H), 11.38 (s, 1H, N-H), 8.79 (s, 1H, benzylidenic), 8.46 (s, 1H, Ar), 8.22 (d, 1H, Ar, *Jo* = 7.8 Hz), 8.18 (d, 1H, Ar, *Jo* = 8.04 Hz), 8.11 (d, 1H, Ar, *Jo* = 9.88 Hz), 7.82 (d, 1H, Ar, *Jo* = 7.8 Hz), 7.80 (d, 1H, Ar, *Jo* = 7.12 Hz), 7.72 (m, 1H, Ar), 7.49 (t, 1H, Ar), 6.97 (s, 1H, Ar). LCMS m/z (% intensity): 361 (100) [M+1].

5-[3-(4-oxo-4*H*-chromen-2-yl)benzylidene]-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione

IR (KBr) cm^{-1}: 3459 (N-H), 3181 (aromatic C-H), 3027, 2983 (C-H symmetric and antisymmetric), 1742 (C=O), 1701 (C=S). ^1H NMR (DMSO), δ (ppm): 12.17 (s, 2H, N-H), 8.09 (s, 1H, benzylidenic), 8.08 (m, 2H, Ar), 7.64 (d, 1H, Ar, *Jo* = 8.32 Hz), 7.47 (d, 1H, Ar, *Jo* = 7.96 Hz), 7.43 (d, 1H, Ar, *Jo* = 7.84 Hz), 7.37 (d, 1H, Ar, *Jo* = 7.48 Hz), 6.81 (s, 1H, Ar), 5.99 (s, 1H, Ar). LCMS m/z (% intensity): 377 (100) [M+1].

RESULTS AND DISCUSSION

For the synthesis of 2-(3-methylphenyl)-4*H*-chromen-4-one (3), the Baker–Venkataraman rearrangement, a general procedure for the preparation of flavones, was chosen (Scheme 1). 2-hydroxy-acetophenone was first converted into a 2-acetylphenyl 3-methylbenzoate (1), which further upon treatment with KOH/pyridine gave 1,3-diketone (2). The 1,3-diketone (2) produced was cyclised to 2-(3-methylphenyl)-4*H*-chromen-4-one (3) using conc. H_2SO_4 and its subsequent benzylic bromination using N-bromosuccinimide in the presence of benzoyl peroxide gave 2-[3-(bromomethyl)phenyl]-4*H*-chromen-4-one (4).

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 (5) as per Synthetic Schemes 2 while using piperidinium acetate/toluene as base under reflux conditions and the targeted compounds (9a-b) were prepared in fairly good yields through refluxing compound (5) and barbituric/thiobarbituric acids in methanol for 4-6 hours respectively. NCEs 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 benzylidenes (synthesized compounds) exhibits lesser or comparable PPARγ affinities (Table 1 compounds 6a, 6b, 7, 8, 9a and 9b). The benzylidene compounds 6a, 6b, 8 and 9a have lesser values of G score (-211.30, -210.96, -206.59, -214.48 respectively) than as observed for standard Rosiglitazone (-225.54) in the active site of the protein (PPARγ: 2prg). Compounds 7 and 9b have comparable G score (-234.72 and -243.21) to Rosiglitazone (-225.54) in the active site of the protein (PPARγ: 2prg). The hydrogen bond interactions between the synthesized ligands and the AA residues in the active site of PPARγ were explored and compared with those of Rosiglitazone to explain the binding modes and binding affinities of the ligands. The hydrogen bonds for each of the novel ligands are less in number as compared to Rosiglitazone (3 hydrogen bonds) at the PPARγ active site. All the synthesized molecules except 7, 9a and 9b showed 2 H-bonds each, whereas 7 showed only one, 9a showed three and 11c no interaction (Table 1). The synthesized compounds showed similar binding modes but with different amino acid interactions as compared to Rosiglitazone. The H-bond distances (Å) between the ligands and the interacting AA residues were in range and most of the cases shorter as found in case of Rosiglitazone. Rosiglitazone form the H-bonding with HIS449, TYR327 and TYR473. TYR473 is most potent AA residue for full agonism. All synthesized compounds lack this TYR473 interaction rather

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	TYR473	1.99	3
		N-H of TZD	HIS449	2.62	
		N-H of TZD	TYR327	1.95	
6a	-211.30	4 C=O of TZD	GLN286	1.91	2
		2 C=O of TZD	SER289	1.94	
6b	-210.96	C=O of RH	SER289	2.04	2
		N-H of RH	TYR327	2.68	
7	-234.72	O=C-OC_2H_5	SER342	2.21	1
8	-206.59	O=C-CH_3	SER289	1.95	2
		O=C-OCH_3	GLN286	2.64	
9a	-214.48	4 C=O of BA	GLN286	1.54	3
		4 C=O of BA	GLN286	2.66	
		2 C=O of BA	SER289	2.66	
9b	-243.21	-	-	-	-

Compound (4) was treated with hexamethylenetetramine in glacial acetic acid to gave 3-(4-oxo-4*H*-chromen-2-yl)benzaldehyde (5). The targeted compounds (6a-b,7-8) were prepared in fairly good yields through 'Knoevenagel

they interact with SER289, SER342, GLN286 and TYR327 which is responsible for partial agonism (Liu *et al.,* 2011; Bruning *et al.,* 2007 and Einstein *et al.,* 2008). Research work from our lab concerning design and computational validation

studies of novel PPAR activators analyzing important structural features of PPAR ligands have also been reported previously (Verma *et al.,* 2012, Verma *et al.,* 2013 and Verma *et al.,* 2015).

Conclusion

The present work deals with the syntheses and characterization of Chromone linked benzylidene based partial PPAR agonists as anti type 2 diabetic compounds. The results of comparison of the binding modes and also the hydrogen bond interactions, between all the synthesized molecules and the AA residues in the active sites of PPARγ proteins, to that of Rosiglitazone and subsequent support from the comparison of predicted binding affinities in terms of G Score values lead to the classification of these novel ligands as partial PPARγ agonists.

Acknowledgements

We are thankful to the Punjabi University, Patiala authorities for providing the necessary research facilities. We are also grateful to the Director and Mr. Avtar Singh of Regional sophisticated Instrumentation Centre (RSIC), Panjab University, Chandigarh and Director National Institute of Pharmaceutical Sciences and Research (NIPER), SAS Nagar, Mohali, Punjab respectively for extending the facilities for spectral analysis of the compounds reported in this paper.

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