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MICROWAVE ASSISTED SYNTHESIS, QSAR AND MOLECULAR DOCKING STUDIES OF 2,4-THIAZOLIDINEDIONE DERIVATIVES

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ABSTRACT

Synthetic organic chemistry involves selection and optimization of lead, synthesis and characterization of work for practical purposes. A series of new thiazolidinedione derivatives have been designed and synthesized through microwave-assisted technique. The synthesized compounds were screened by Insilco methods like molecular docking, QSAR studies in order to explore the anti-diabetic activity, synthetic assessability of compounds against the peroxisome proliferator-activated the receptor (PPARγ). Compounds which showed higher glide score than standard (Pioglitazone) were synthesized using the microwave. Compounds were characterized with the help of FT-Infrared spectroscopy, Proton NMR, C-13 NMR spectroscopic studies and Lc-Ms.

Keywords: Anti-diabetic activity, Peroxisome proliferator-activated receptor (PPARγ), 2, 4-thiazolidinedione derivatives, pioglitazone, Molecular Docking.

INTRODUCTION

Thiazolidinediones (TZDs) are known to minimize insulin levels, lipid and plasma glucose and also used in the treatment of hyperglycemia[1,2] . Peroxisome proliferator-activated receptor gama (PPARγ) has been recognized as a target of the TZDs because of PPARγ agonistic activity, which is related to glucose-lowering activity[3-5]. PPARγ is evidenced predominantly in adipocytes, it is involved in the retinoid X receptor (RXR) within the nucleus. The thiazolidinedione side chain with the lipophilic nature passes into the cells and binds to PPARγ with more affinity by causing a conformational change in the PPARγ-RXR complex which causes transcription of insulin-sensitive genes taking part in glucose uptake and lipoprotein lipase (LPL), lipogenesis[6]. These observations have been promoted to synthesize the title compounds with more efficacy and minimize the toxicity of a diabetic drug by directing the drug to its target and sustaining its concentration at the site for an adequate time for curative action to take place.

According to a survey on Thiazolidinediones (TZDs) class of PPARγ agonists, quantitative structure-activity-relationship (QSAR) studies reveal that the molecule consists of three regions: (1) Effector site, (2) Binding site and (3) Linker[7,8]. TZD ring makes more specific bonding interactions with different amino acids(Fig.-1)[9]. Docking study also reveals that the presence of the thiazolidinedione ring shows good antidiabetic activity[10].

Based on the results of QSAR and docking studies, various new thiazolidinediones are aimed to synthesize. Molecules are synthesized based on the synthetic accessibility and good glide scores in order to reduce the wastage of chemicals and environment pollution. A series of 23 antidiabetic agents were designed moreover by altering electron donating/withdrawing groups on sterically hindered aromatic ring

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system or linker region, which consist of 2,4-thiazolidinedione ring (binding site), sterically hindered aromatic group (Effector site) and Linker. Total 12 compounds were prepared which are found to be high anti-diabetic activity and confirmed with physical and spectral characterization.

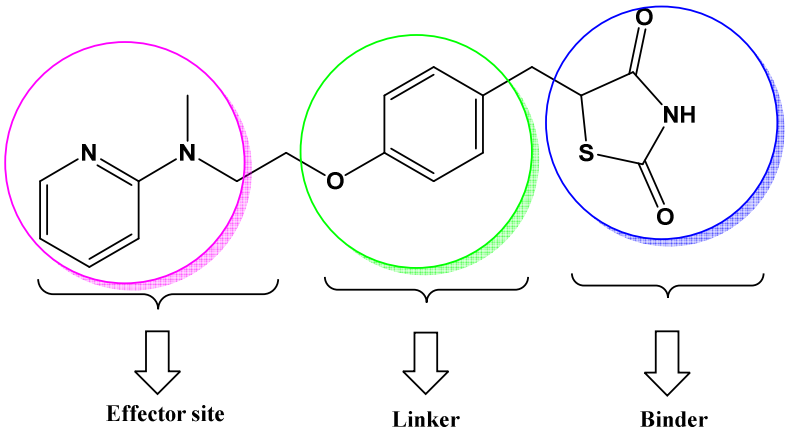


Fig.-1: Three Regions of Thiazolidinediones based upon QSAR Study of Various Anti-diabetic Compounds.

EXPERIMENTAL

Molecular Docking Studies

Preparation of Ligand

The structures of thiazolidinediones IIA1-IIA12, IIP1-IIP6 and IIM1-IIM4 were designed using ChemDraw professional 16.0 and converted to 3D model by using Chem 3D 16.0 (Cambridge software)[11].

Selection of Protein

Protein is selected based on various factors i.e. resolution should be between 2.0-2.5A^0, it should contain a co-crystallized Ligand and structure should be evaluated by X-ray diffraction. Selected protein should not contain breaks in their 3D structure[12-14].

Preparation of protein

Peroxisome proliferator-activated receptor (PPARγ) protein structure (PDB ID:1ZGY) was selected from the protein data bank (http://www.rcsb.org/pdb).[15,16]

Docking Studies

Docking software Autodock 4.2 version was used to dock the protein with the drug molecule. Autodock provides interfaces between the binding site of the target protein and the screening compounds. Docking program was executed to forecast the binding pocket of 1ZGY. All the designed Ligands were docked using the standard accuracy. The analysis of molecular docking of synthetic compounds and Pioglitazone were executed using Autodock software 4.2 version.[17,18]

General

All reactions were regulated under microwave criteria and conducted by utilizing sterilized glassware. All the synthesized compounds melting points were evaluated by Guna Digital Melting Point apparatus and also in open capillaries. Thin Layer Chromatography (TLC) was conducted by using Pre-coated silica gel 60 F254 TLC Aluminium sheet (20X20cm) (Merk). Visualization of spots was done with the help of Ultra-Violet cabinet and by exposing the TLC to Iodine vapor (Table 1). Characterization of compounds was done by using FT-IR BRUKER spectrophotometer, Proton NMR and C-13 NMR spectra were acquired using BRUKER 400MHZ instrument and Dimethyl sulfoxide (DMSO) as a solvent. Mass of

compounds was obtained by LCMS 2010 EV Mass spectrometer. All designed compounds were docked against PPARγ as a target in order to know the higher activity compounds (Fig.-2).

Table-1: Physical and Chemical Properties of Synthesized Compounds

Comp. Codes	R	Mol. Formula	Mol. Wt. (gm)	Melting Point (^{0}C)	Rf Value	% Yield
IIA2	2,4-dimethyl aniline	$C_{18}H_{16}N_2O_2S$	324	215-217	0.59	73
IIA5	4-nitro aniline	$C_{16}H_{11}N_3O_4S$	341	201-203	0.63	68
IIA6	4-bromo aniline	$C_{16}H_{11}BrN_2O_2S$	375	168-170	0.61	72
IIA7	4-methyl aniline	$C_{17}H_{14}N_2O_2S$	310	189-191	0.68	67
IIA8	4-phenylazo aniline	$C_{22}H_{16}N_4O_2S$	400	204-206	0.71	60
IIA9	2-chloro aniline	$C_{16}H_{11}ClN_2O_2S$	330.5	222-224	0.73	87
IIA12	3-(trifluoromethyl) aniline	$C_{17}H_{11}F_3N_2O_2S$	364	206-208	0.73	66
IIP2	1-phenyl piperazine	$C_{20}H_{19}N_3O_2S$	365	198-200	0.70	68
IIP3	1-methyl-3-phenyl piperazine	$C_{21}H_{21}N_3O_2S$	379.5	218-220	0.65	73
IIP4	1-(4-fluorophenyl) piperazine	$C_{20}H_{18}FN_3O_2S$	383	199-201	0.67	64
IIP5	1-(2,4-difluorophenyl) piperazine	$C_{20}H_{17}F_2N_3O_2S$	401	241-243	0.72	67
IIP6	1-benzyl piperazine	$C_{21}H_{21}N_3O_2S$	379.5	234-236	0.64	72

Synthesis of 2,4-thiazolidinedione (3)

Chloroacetic acid (1) (0.6 mol) in 60ml of water and solution containing thiourea (2) (0.6 mol) in 60ml of water were placed in a 250ml round-bottomed flask. While cooling, the mixture was stirred for 15min to obtain a white precipitate. To the round bottom flask 60ml of the con. HCl was added slowly from dropping funnel. By using the microwave, the mixture was refluxed for 6min at 250Watts. On cooling, the content in the flask solidified into a cluster of white needles. Formed product was filtered and washed with water to remove the trace of HCl and kept for drying. Recrystallization was done using ethanol[19]. Yield 89%; Mass m/z 118 $[M+H]^+$; Melting Point 124-126^{o}C; IR (cm^{-1}) 3125(NH), 1745(C=O), 1605, 1558 and 1456 (C=C Ar).

Synthesis of 5- (4-chlorobenzylidine)-2,4- thiazolidinedione (5)

2,4-thiazolidinedione (3) (0.25 mol) in hot glacial acetic acid (50ml), fused sodium acetate (1.8 gm) was added to a solution of 4-chlorobenzaldehyde (4) (0.25 mol) and refluxed for 5 min. in the microwave at 200 watts. A precipitate was formed by adding 300ml of water to the reaction mixture. The obtained product was filtered and washed with water. Glacial acetic acid is used for recrystallization[20,21]. Yield 87%; Mass m/z 240.2 $[M+H]^+$; Melting Point 182-184^{o}C; IR (cm^{-1}) 3145(NH), 1752(C=O), 1605(C=C Ar) and 845(Ar C-Cl).

Synthesis of 5- [4-(substituted) benzylidene] 2,4- thiazolidinedione (7)

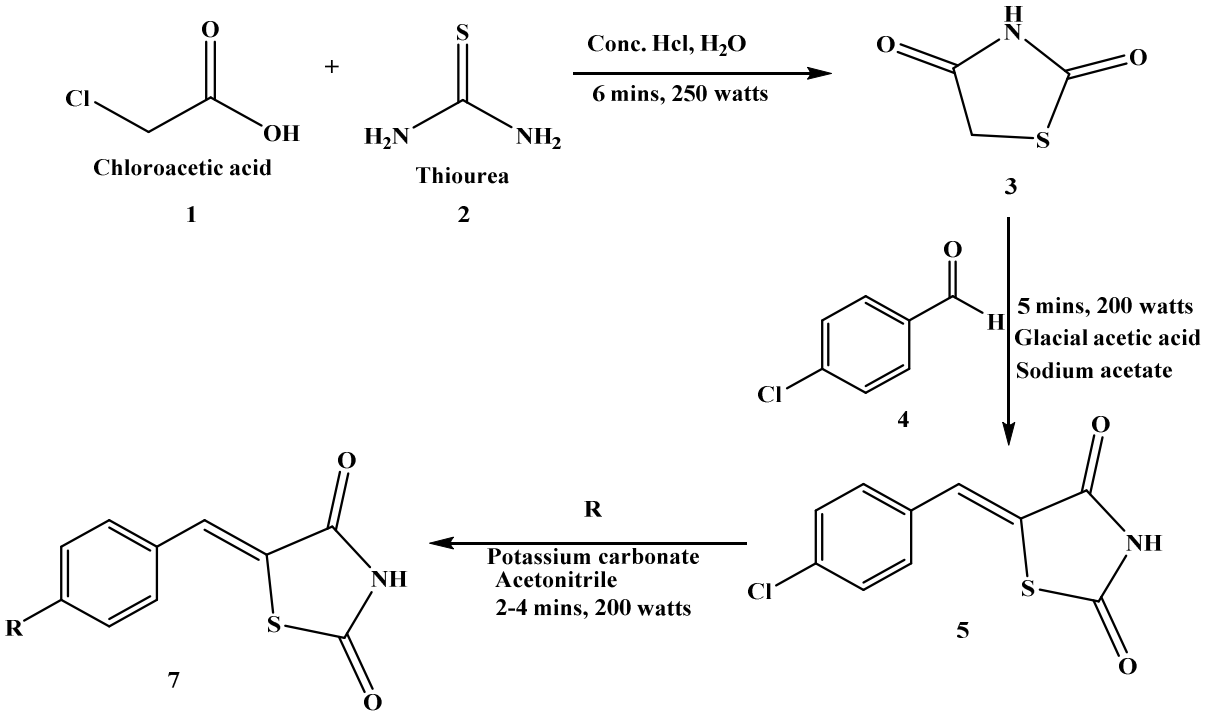
5-(4-chlorobenzylidene)-2,4-thiazolidinedione (5) (0.01 mol), applicable substituent (6) (0.01 mol) [i.e. aniline, piperazine derivatives], acetonitrile (7 ml) and Potassium carbonate (0.012 mol) were refluxed in microwave at 200 watts for 2-4 min. Then 30ml of ice-cold water was added to the reaction mixture. The obtained product was filtered and recrystallized from ethyl alcohol.

Characterization of 5- [4-(substituted) benzylidene] 2,4- thiazolidinediones

(Z)-5-(4-((2,4-dimethylphenyl)amino)benzylidene)thiazolidine-2,4-dione (IIA2)

Yield 73%; light brown; R_f 0.59; Melting point 215-217^{0}C; Mass m/z 325.2 $[M+H]^+$; FT-IR (cm^{-1})(KBR) 3207(N-H), 2914(C-H), 1668(C=O), 1566(C=C), 1085(C-N), 975(C-S); ^{1}H NMR (ppm) δ: 2.28(s, 6H, Ar-CH_3), 6.98-7.06(m, 3H, Ar-H), 7.53-7.59(m, 2H, Ar-H), 7.94-7.96(d, 2H, Ar-H), 8.31(s, 1H, Ar-CH-), 10.2(s, 1H, Ar-NH-Ar), 12.31(s, 1H, -C=O-NH-C=O); ^{13}C NMR (ppm) δ: 17.91, 20.99, 115.2, 116.0, 117.9, 124.7, 127.7, 129.6, 131.24, 131.34, 132.10, 136.23, 143.3, 147.8, 166.3, 167.1.

(Z)-5-(4-((4-nitrophenyl)amino)benzylidene)thiazolidine-2,4-dione (IIA5)
Yield 68%; Dark yellow; R_f 0.63; Melting Point 201-203^{0}C; Mass m/z 342.2 $[M+H]^+$; FT-IR (cm^{-1})(KBR) 3358(N-H), 3213(C-H), 1670(C=O), 1469(N=O), 1087(C-N), 837(C-S); ^{1}H NMR (ppm) δ: 6.59-6.62(d, 2H, Ar-H), 6.71-6.74(d, 2H, Ar-H), 7.58-7.60(d, 2H, Ar-H), 7.93-7.95(d, 2H, Ar-H), 8.2(s, 1H, Ar-CH-), 8.9(s, 1H, Ar-NH-Ar), 12.31(s, 1H, -C=O-NH-C=O); ^{13}C NMR (ppm) δ: 112.8, 116.0, 124.7, 126.42, 128.4, 129.8, 136.1, 142.0, 143.3, 148.5, 166.3, 167.1.



Where R= Aniline, Piperazine, Morpholine Derivatives

Fig.-2: Scheme of Synthesis

(Z)-5-(4-((4-bromophenyl)amino)benzylidene)thiazolidine-2,4-dione (IIA6)
Yield 72%; Dark brown; R_f 0.61; Melting Point 168-170^{0}C; Mass m/z 377.2 $[M+H]^+$; FT-IR (cm^{-1})(KBR) 3197(N-H), 2941(C-H), 1670(C=O), 1562(C=C), 1083(C-N), 1004(C-S); ^{1}H NMR (ppm) δ: 7.23-7.25(d, 2H, Ar-H), 7.58-7.61(m, 5H, Ar-H), 7.94-7.96(d, 2H, Ar-H), 8.64(s, 1H, Ar-NH-Ar), 12.31(s, 1H, -C=O-NH-C=O); ^{13}C NMR (ppm) δ: 114.2, 116.2, 119.2, 123.7, 127.9, 129.6, 131.4, 141.4, 141.6, 143.3, 166.3, 167.1.

(Z)-5-(4-(p-tolylamino)benzylidene)thiazolidine-2,4-dione (IIA7)
Yield 67%; Cream; R_f 0.68; Melting Point 189-191^{0}C; Mass m/z 311 $[M+H]^+$; FT-IR (cm^{-1}) (KBR) 3186(N-H), 2912(C-H), 1676(C=O), 1585(C=C), 1008(C-N), 819(C-S); ^{1}H NMR (ppm) δ: 2.32(s, 3H, Ar-CH_3), 7.18-7.24(m, 4H, Ar-H), 7.56-7.58(d, 2H, Ar-H), 7.93-7.95(d, 2H, Ar-H), 8.3(s, 1H, Ar-CH-), 8.63(s, 1H, Ar-NH-Ar), 12.31(s, 1H, -C=O-NH-C=O); ^{13}C NMR (ppm) δ: 21.06, 114.52, 116.0, 121.5, 124.7, 128.1, 129.8, 130.7, 139.4, 141.6, 143.3, 166.3, 167.1.

5-((Z)-4-((4-((E)-phenyldiazenyl)phenyl)amino)benzylidene)thiazolidine-2,4-dione (IIA8)
Yield 60%; Orange; R_f 0.71; Melting Point 204-206^{0}C; Mass m/z 401 $[M+H]^+$; FT-IR (cm^{-1})(KBR) 3477(N-H), 2976(C-H), 1685(C=O), 1500(C=C), 1122(C-N), 914(C-S); ^{1}H NMR (ppm) δ: 6.67-6.69(d, 2H, Ar-H), , 7.39-7.43(m, 2H, Ar-H), 7.49-7.55(m, 4H, Ar-H0, 7.65-7.68(d, 2H, Ar-H), 7.73-7.75(d, 2H, Ar-H), 7.9(s, 1H, Ar-NH-Ar), 7.97-8.01(t, 1H, Ar-H), 8.3(s, 1H, Ar-CH-), 12.31(s, 1H, -C=O-NH-

C=O); ^{13}C NMR (ppm) δ: 113.8, 116.0, 122.1, 122.9, 124.3, 125.6, 129.5, 12.9, 131.04, 141.6, 143.28, 144.28, 144.64, 152.92, 166.3, 167.1.

(Z)-5-(4-((2-chlorophenyl)amino)benzylidene)thiazolidine-2,4-dione (IIA9)
Yield 87%; Dark yellow; R_f 0.73; Melting Point 222-224^{0}C; Mass m/z 332.7 $[M+H]^+$; FT-IR (cm^{-1})(KBR) 3203(N-H), 2926(C-H), 1668(C=O), 1506(C=C), 1138(C-N), 752 (C-S); ^{1}H NMR (ppm) δ: 7.21-7.23(t, 1H, Ar-H), 7.58-7.68(m, 3H, Ar-H), 7.92-7.99(m, 4H, Ar-H), 8.34(s, 1H, Ar-CH-), 10.0(s, 1H, Ar-NH-Ar), 12.31(s, 1H, -C=O-NH-C=O); ^{13}C NMR (ppm) δ: 112.5, 116.0, 123.1, 124.9, 125.8, 126.3, 128.07, 129.6, 130.2, 133.5, 141.6, 143.3, 166.3, 167.1.

(Z)-5-(4-((3-(trifluoromethyl)phenyl)amino)benzylidene)thiazolidine-2,4-dione (IIA12)
Yield 66%; Dark Cream; R_f 0.73; Melting Point 206-208^{0}C; Mass m/z 365 $[M+H]^+$; FT-IR (cm^{-1})(KBR) 3196(N-H), 2953(C-H), 1668(C=O), 1508(C=C), 1271(C-F), 1138(C-N), 1002(C-S); ^{1}H NMR (ppm) δ: 7.21-7.60(m, 6h, Ar-H), 7.73-7.75(d, 2H, Ar-H), 8.1(s, 1H, Ar-CH-), 8.63(s, 1H, Ar-NH-Ar), 12.31(s, 1H, -C=O-NH-C=O); ^{13}C NMR (ppm) δ: 114.0, 114.8, 116.0, 118.1, 122.9, 124.1, 124.7, 129.4, 129.7, 130.8, 141.6, 142.2, 143.3, 166.3, 167.1.

(Z)-5-(4-(4-phenylpiperazin-1-yl)benzylidene)thiazolidine-2,4-dione (IIP2)
Yield 68%; Yellow; R_f 0.70; Melting Point 198-200^{0}C; Mass m/z 366.2 $[M+H]^+$; FT-IR (cm^{-1})(KBR) 3253(N-H), 2970(C-H), 1676(C=O), 1595(C=C), 1118(C-N), 914(C-S); ^{1}H NMR (ppm) δ: 3.42(s, 8H, Piperazine), 6.75-6.84(t, 1H, Ar-H), 6.88-7.0(m, 2H, Ar-H), 7.13-7.26(m, 2H, Ar-H), 7.58-7.62(m, 2H, Ar-H), 7.68-7.70(d, 2H, Ar-H), 7.95(s, 1H, Ar-CH-), 12.31(s, 1H, -C=O-NH-C=O); ^{13}C NMR (ppm) δ: 48.6, 115.8, 116.0, 119.2, 121.9, 124.7, 129.7, 129.8, 130.5, 143.3, 151.6, 166.3, 167.1.

(Z)-5-(4-(4-methyl-2-phenylpiperazin-1-yl)benzylidene)thiazolidine-2,4-dione (IIP3)
Yield 73%; dark Cream; R_f 0.65; Melting Point 218-220^{0}C; Mass m/z 380 $[M+H]^+$; FT-IR (cm^{-1})(KBR) 3460(N-H), 2864(C-H), 1741(C=O), 1552(C=C), 1029(C-N), 1002(C-S); ^{1}H NMR (ppm) δ: 2.18(s, 3H, Ar-CH_3), 2.65-2.91(m, 3H, Piperazine), 3.0-3.18(m, 3H, Piperazine), 3.81-3.86(t, 1H, Piperazine), 6.52-6.55(m, 2H, Ar-H), 7.3-7.35(m, 5H, Ar-H), 7.43-7.45(d, 2H, Ar-H), 7.97(s, 1H, Ar-CH-), 12.31(s, 1H, -C=O-NH-C=O); ^{13}C NMR (ppm) δ: 43.5, 44.9, 55.4, 60.8, 64.1, 111.7, 116.0, 124.7, 127.0, 127.9, 128.5, 129.7, 134.8, 143.3, 148.8, 166.3, 167.1.

(Z)-5-(4-(4-(4-fluorophenyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione (IIP4)
Yield 64%; Brown; R_f 0.67; Melting Point 199-201^{0}C; Mass m/z 384 $[M+H]^+$; FT-IR (cm^{-1})(KBR) 3184(N-H), 2897(C-H), 1672(C=O), 1517 (C=C), 1089(C-N), 912 (C-S); ^{1}H NMR (ppm) δ: 3.42(s, 8H, Piperazine), 6.52-6.55(d, 2H, Ar-H), 6.69-6.71(d, 2H, Ar-H), 6.98-7.02(d, 2H, Ar-H), 7.43-7.45(d, 2H, Ar-H),7.97(s, 1H, Ar-CH-), 12.31(s, 1H, -C=O-NH-C=O); ^{13}C NMR (ppm) δ: 48.6, 111.7, 115.8, 116.0, 116.4, 124.7, 129.7, 130.5, 143.3, 145.2, 151.6, 166.3, 167.1.

(Z)-5-(4-(4-(2,4-difluorophenyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione (IIP5)
Yield 67%; light brown; R_f 0.72; Melting Point 241-243^{0}C; Mass m/z 402 $[M+H]^+$; FT-IR (cm^{-1})(KBR) 3421(N-H), 3005(C-H), 1735 (C=O), 1602(C=C), 1155(C-N), 927 (C-S); ^{1}H NMR (ppm) δ: 3.42(s, 8H, Piperazine), 6.52-6.55(d, 2H, Ar-H), 6.61-6.63(t, 1H, Ar-H), 6.69-6.72(m, 2H, Ar-H), 7.43-7.45(d, 2H, Ar-H),7.97(s, 1H, Ar-CH-), 12.31(s, 1H, -C=O-NH-C=O); ^{13}C NMR (ppm) δ: 48.6, 105.6, 111.7, 112.4, 115.2, 116.0, 124.7, 129.7, 130.5, 132.9, 143.3, 151.6, 157.1, 166.3, 167.1.

(Z)-5-(4-(4-benzylpiperazin-1-yl)benzylidene)thiazolidine-2,4-dione (IIP6)
Yield 72%; Orange; R_f 0.64; Melting Point 234-236^{0}C; Mass m/z 380 $[M+H]^+$; FT-IR (cm^{-1})(KBR) 3194(N-H), 2954(C-H), 1670(C=O), 1585(C=C), 1066(C-N), 883(C-S); ^{1}H NMR (ppm) δ: 2.23-2.28(m, 4H, Piperazine), 2.72-2.81(m, 4H, piperazine), 3.59s, 1H, Ar-CH-), 6.52-6.55(d, 2H, Ar-H), 7.21-7.27(m, 5H, Ar-H), 7.43-7.45(d, 2H, Ar-H),7.97(s, 1H, Ar-CH-), 12.31(s, 1H, -C=O-NH-C=O); ^{13}C NMR (ppm) δ: 48.6, 51.51, 63.2, 111.7, 116.0, 124.7, 127.2, 128.2, 128.6, 129.7, 130.5, 138.6, 143.3, 166.3, 167.1.

RESULTS AND DISCUSSION

Molecular docking and QSAR studies of 23 compounds were executed by using PPARγ (1ZGY) as a target. Autodock was engaged for docking studies. The activity of prepared compounds depends on docking score and hydrogen bonds interaction. The elevated binding affinity of the compound with the receptor indicates the higher negative value of docking score. Docking studies (Table-2) reveals that compound IIA8 is the most effective binding compound with glide score -10.5 Kcal/mol, which involved in bonding with amino acid residues Ser 342, His 266, Asp 260, Leu 330, Ile 341, Cys 285, His 449, Phe 282, met 364 and Arg 288 (Fig.-3)[22-24]. Similarly, IIP3 has also shown higher binding affinity towards the target with glide score -9.6 Kcal/mol and involved in binding with amino acid residues Tyr 473, His 323, Leu 340, Arg 288, Met 364, Cys 285, Ile 341, Phe 363, His 449 residues(Fig.-4). Almost 12 compounds were showing higher binding affinity towards target PPARγ (1ZGY).

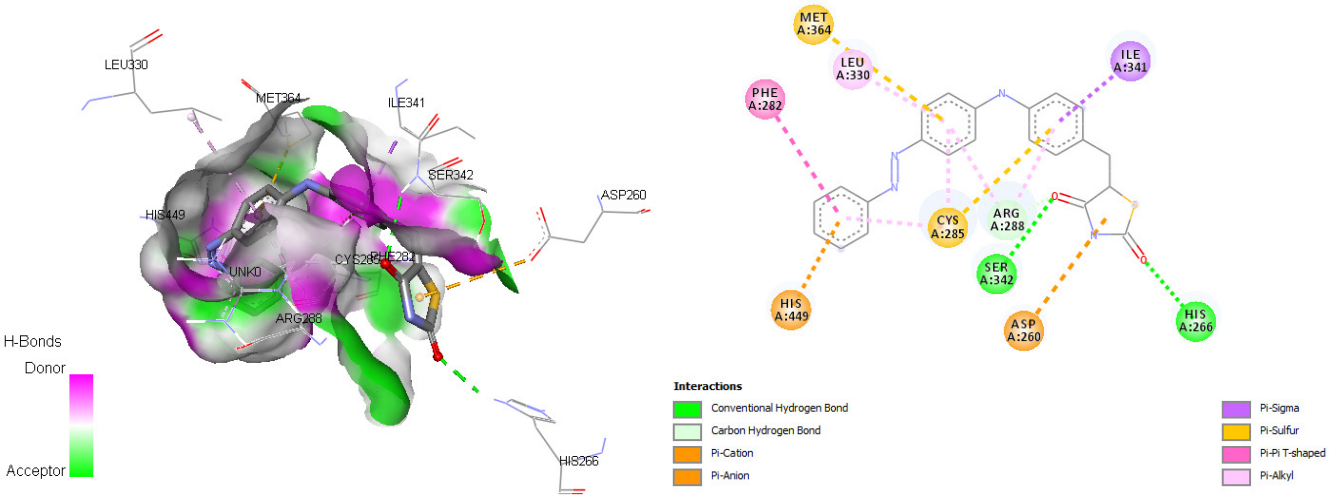


Fig.-3: Molecular Docking 3D- and 2D- pose of IIA8 with 1ZGY

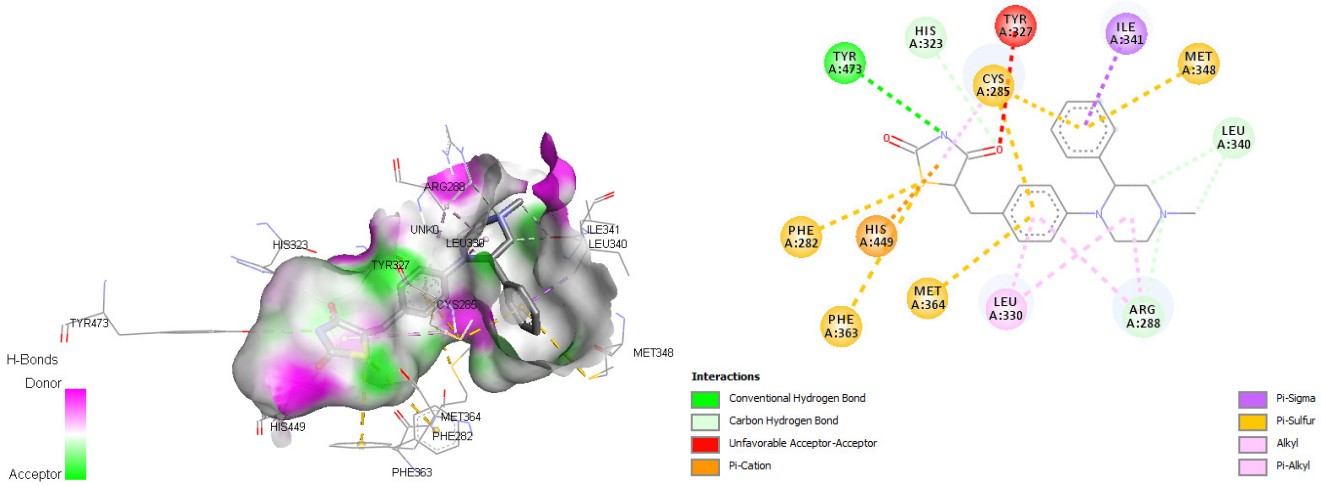


Fig.-4: Molecular Docking 3D- and 2D- pose of IIP3 with 1ZGY

Table-2: Molecular docking studies of compounds IIA1-IIA12, IIP1-IIP6, IIM1-IIM4 with PPAR-γ using Autodock (PDB ID: 1ZGY)

S. No.	Compound Code	Binding Energy(Kcal/mol)
1	Pioglitazone	-8.7
2	IIA1	-8.7
3	IIA2	-9.2

4	IIA3	-8.7
5	IIA4	-8.6
6	IIA5	-9.0
7	IIA6	-8.8
8	IIA7	-8.9
9	IIA8	-10.5
10	IIA9	-8.8
11	IIA10	-8.7
12	IIA11	-8.7
13	IIA12	-9.2
14	IIP1	-7.4
15	IIP2	-9.2
16	IIP3	-9.6
17	IIP4	-9.3
18	IIP5	-9.3
19	IIP6	-8.9
20	IIM1	-8.1
21	IIM2	-8.0
22	IIM3	-8.5
23	IIM4	-8.0

QSAR studies and druglikeness are also predicted in order to know the Log Po/w, TPSA, Hydrogen bond donor, Hydrogen bond Acceptor, Lipinski rule and synthetic accessibility (Table-3).

Table-3: Predicted QSAR parameters and druglikeness of the compounds IIA1-IIA12; IIP1-IIP6; IIM1-IIM4

S. No.	Comp. Code	Mol. Wt.	HBD	HBA	[a]Log $P_{o/w}$	[b]TPSA	[c]Lipinski Rule	Synthetic accessibility
1	Pioglitazone	356.44	1	5	3.07	93.59	Yes	3.46
2	IIA1	330.79	2	2	4.15	83.50	Yes	3.11
3	IIA2	324.40	2	2	4.30	83.50	Yes	3.36
4	IIA3	312.34	3	3	3.00	103.73	Yes	3.11
5	IIA4	326.37	2	3	3.48	92.73	Yes	3.19
6	IIA5	341.34	2	4	3.43	129.32	Yes	3.24
7	IIA6	375.24	2	2	4.28	83.50	Yes	3.18
8	IIA7	310.37	2	2	3.92	83.50	Yes	3.26
9	IIA8	400.45	2	4	5.67	108.22	Yes	3.75
10	IIA9	330.79	2	2	4.10	83.50	Yes	3.12
11	IIA10	330.79	2	2	4.13	83.50	Yes	3.11
12	IIA11	326.37	2	3	3.53	92.73	Yes	3.15

13	IIA12	364.34	2	5	4.35	83.50	Yes	3.29
14	IIP1	303.38	1	3	1.48	77.95	Yes	3.18
15	IIP2	365.45	1	2	3.17	77.95	Yes	3.43
16	IIP3	379.48	1	3	3.06	77.95	Yes	3.79
17	IIP4	383.44	1	3	3.34	77.95	Yes	3.39
18	IIP5	401.43	1	4	3.43	77.95	Yes	3.42
19	IIP6	379.48	1	3	2.88	77.95	Yes	3.44
20	IIM1	304.36	1	4	1.13	83.94	Yes	3.14
21	IIM2	334.39	1	5	1.42	93.17	Yes	3.29
22	IIM3	332.37	1	4	0.86	101.01	Yes	3.20
23	IIM4	318.39	1	4	1.54	83.94	Yes	3.21

a - Predicted octanol/water partition coefficient (< 5);
b-Van der Waals surface area of polar nitrogen and oxygen atoms and carbonyl carbon atoms (Range 7 to 200);
c- Lipinski's violations (≤ 1)

Based on the results from Insilico methods, 12 compounds having better anti-diabetic activity were synthesized out of 23 compounds in order to reduce the wastage of chemicals, time and environmental pollution. Characterization of synthesized compounds was done by using FT-IR, NMR and LC-MS spectroscopic studies. In the series of synthesized compounds, the compound IIA8, IIP3, IIP4, IIP5 are showing potent anti-diabetic activity in docking due to the electron releasing groups $–NH_2$, -F, -CN, $-CH_3$ respectively, on the aromatic ring. The compounds IIP2, IIA2 IIA5 and IIA12 are showing moderate anti-diabetic activity because of $-CH_3$, -F, $–CF_3$, -CN groups respecticvely. The Compounds IIA6, IIA7, IIA9 and IIP6 are showing better activity due to the presence of –Br, $-NO_2$, -CN groups respecticely. The remaining compounds are showing less activity when compared to pioglitazone due to the presence of 4-Chloro, 4-hydroxy, 2-Methoxy, 3-Chloro, 4-Methoxy, 4-Ethyl respectively.

CONCLUSION

The present work was about focusing on finding novel drug like molecules as anti-diabetic compounds using Insilico methods. This work concludes that compounds containing thiazolidinedione ring with amine groups in it will have better anti diabetic activity. Thiazolidine-2,4-dione compounds with more lipophilic groups elevate the anti-diabetic activity. Compounds are showing potent antidiabetic activity because of thiazolidine-2,4-dione ring which strongly interacts with the target binding site and shows effective binding. If the compounds are with electron releasing groups at the 2^{nd} and 4^{th} position of the aromatic ring in the lipophilic region are more like to synthesize in future and they may exhibit potent antidiabetic activity. In the future, compounds with potent antidiabetic activity are to be selected from the insilico methods and going to perform In-vivo studies using Oral Glucose Tolerance Test (OGTT).

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