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DESIGN, SYNTHESIS AND VIRTUAL SCREENING OF CERTAIN 2-PYRAZOLIN-5-ONE AND PYRAZOLIDINE-3, 5-DIONE DERIVATIVES AS POTENTIAL PPARγ AGONISTS

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Design

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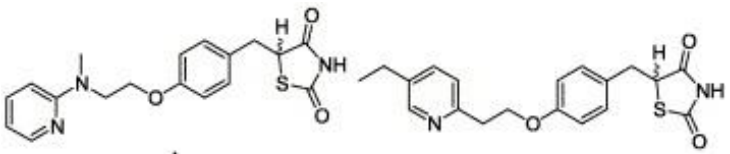
ABSTRACT

In the quest for novel PPARγ agonists as putative drugs for the treatment of type 2 diabetes, a new series of 2-pyrazolin-5-one and pyrazolidine-3, 5-dione derivatives, were designed and synthesized, as analogues to the anti-diabetic thiazolidinedione agents (TZDs). Extensive molecular modeling studies for the designed molecules were performed; including their compare-fit studies on the generated and validated PPARγ agonist's hypothesis and their molecular docking on the binding sites of the 3D structure of the PPARγ receptors.

INTRODUCTION: Diabetes is the fourth leading killer disease in the developed world. There are more than 200 million diabetics worldwide, accounting for a huge economic and social burden [1, 2]. Thus, the development of new effective therapeutic agents is the major thrust for research and is germane to both the national and international scenario. Type 2 diabetes mellitus (T2DM) is the most important type of diabetes, as more than 80% of diabetics are of this class.

The peroxisome proliferator-activated receptors (PPARs) are legitimate molecular targets for the development of the antidiabetic agents. The reported synthetic ligands such as rosiglitazone (**I**) and pioglitazone (**II**) [3, 4] had high affinity for PPAR-γ receptor, belong to the thiazolidinediones (TZDs) class of antidiabetic agents (**Fig. 1**) and have significantly improved the clinical situation of Type 2 diabetics.

Unfortunately, theses agents have serious side effects of hepatotoxicity, weight gain, and edema. This situation emphasized the need to identify strategies to develop new antihyperglycemic agents that could retain the insulin sensitizing properties of TZDs through PPARγ agonistic activities with minimum or no adverse side effects. This necessitated a search for highly effective and safe antihyperglycemic agents, particularly those that normalize both insulin and glucose levels.



I II

FIGURE 1: ROSIGLITAZONE (I) AND; PIOGLITAZONE (II)

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A survey of various classes of PPARγ agonists, 3D-QSAR studies and crystal structure information reveals that the pharmacophoric features of these agents essentially consists of three parts:

(i) an acidic head group,
(ii) central aromatic region and
(iii) terminal lipophillic side chain and a linker (**Fig. 2**) [5a]. These features are clearly represented in the highly potent lead molecule (cpd 154329) [5a].

The TZD ring of rosiglitazone is reported to make three important H-bonds with His323, Tyr473 and His449 that are important for the activation of the receptor [5b]. This observation was instrumental in the design of a variety of non-TZD PPAR agonists based on free carboxyl group, oxazolidinedione, tetrazoles, etc [6]. However, such reports are limited and most of the reported PPARγ agonists still belong to either 'glitazone' class (possessing TZD ring) or 'glitazar' class (possessing free carboxylic acid). Thus, we set our objective to explore newer head groups for designing novel series of PPARγ ligands.

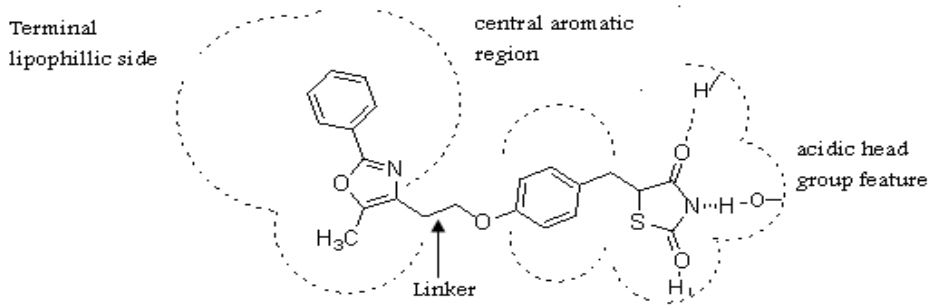


FIGURE 2 [5]: PROPOSED LEAD FEATURES OF PPARγ AGONIST AGENTS REPRESENTED ON CPD (154329)

The design of new molecules (**4a-c, 5-8, 9a-c, 10a, b, 11a, b and 12a, b**) in this investigation was based on, firstly, the ligand receptor binding knowledge and bioisoteric replacement of TZD head group by **2-pyrazolin-5-one and pyrazolidinedione** ring systems, or the potentially active malonate precursors, as it was reported earlier that malonate derivatives provide potent PPAR γ agonists, as well as, isosteric replacements in both the central aromatic (flat hydrophobic region) and the terminal hydrophobic side chain (Fig. 2).

Secondly, the perfect selection of the final PPARγ agonist active hits was peformed by virtual screening through molecular modeling simulation studies. Such studies involved two important techniques:

A. Generation and validation of novel PPARγ agonist hiphop hypothesis, derived from frozen bioactive conformations of reported PPARγ agonists, using cerius2 and catalyst software modules, followed by utilizing the compare-Fit studies between the hypothesis and the proposed test set targeted molecules. The molecules having high fit values with low conformation energies are considered active hits.

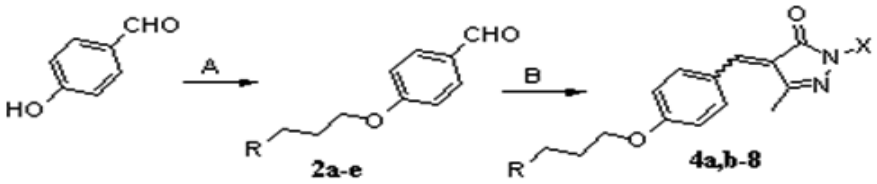
B. The promising test set compounds which showed high fit values to the generated hypothesis were subjected to further molecular modeling studies employing the docking program Molsoft (ICM 3.4-8c) in order to investigate the binding mode of the designed compounds and evaluate their binding affinities through the calculation of their docking scores.

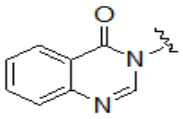
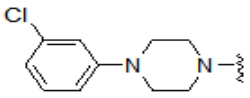
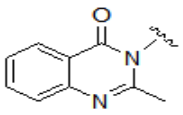
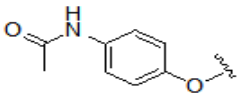
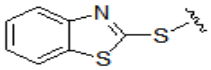
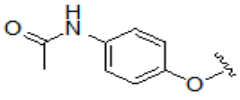
The above two virtual screening studies indicated that the molecules (**4a-c, 5-8, 9a-c, 10a,b, 11a, b and 12a, b**) have high potential PPARγ agonist activities. Thus, these molecules are synthesized adopting Schemes 1 and 2; in order to be available for further in-vivo testing for their effect on T2DMs.

RESULTS:

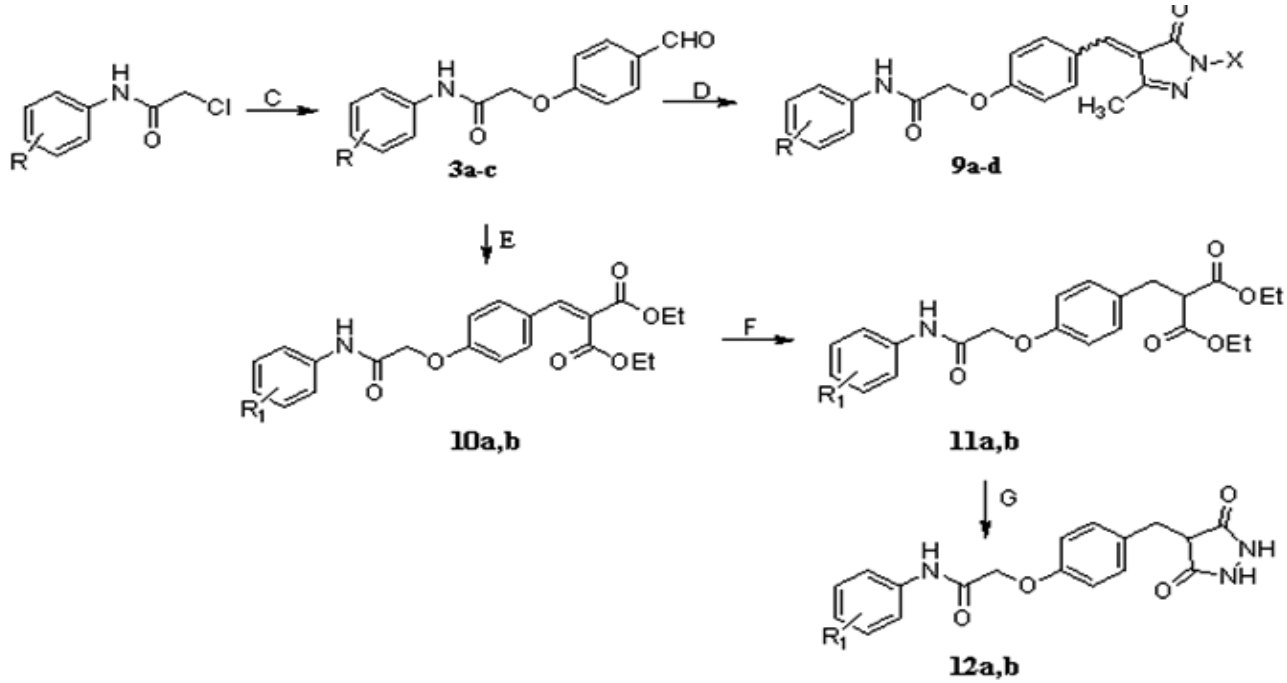
1. **Synthesis of 2-pyrazolin-5-one, pyrazolidine-3,5-diones:** In **scheme 1**, the synthesis of the designed 2-pyrazoline-5-one derivatives (**4a, b-8**) was carried out through uncatalysed Knoevenagel condensation of the substituted aldehydes (**2a-e**) with 3-methylpyrazolin-5(4H)-one and 3-methyl-1-phenyl-2-pyrazolin-5(4H)-one molecules to produce **4a, b-8** following the procedure described by Mohit [6].

In scheme 2, condensation of aldehydes (**3a-c**) with 3-methylpyrazolin-5(4H)-one and 3-methyl-1-phenyl-2-pyrazolin-5(5H)-one molecules yielded the pyrazoline derivative (**9a-c**). Pyrazolidine-3,5-diones, (**12a, b**), were synthesized starting from the aldehyde derivatives (**2a, b**) through knoevenagel condensation with diethyl malonate to produce the arylidene derivatives [7] (**10a, b**) followed by catalytic reduction of the benzylidene double bond to produce the aryl methyl derivatives (**11a, b**). The latter intermediates were reacted with hydrazine hydrate in presence of sodium ethoxide to produce (**12a, b**).



Cpd;	R ,	X ,	R ,	X
4a;		, Ph	**6** 	, H
4b		, Ph	**7** 	,Ph
5		, Ph	**8** 	, H

SCHEME 1: Compounds: 2a, R= 4(3H)-Quinazolonyl; 2b, R= 2-Methyl-4(3H)-quinazolonyl; 2c, R= 4-(N-acetamido)phenyl; 2d, Benzo[*d*]thiazole-2-thiolyl; 2e, R=4-(3-Chlorophenyl)piperazin-1-yl. Reagents: A= 3-substituted-propyl chloride, acetone or DMF, K_2CO3; B= 3-methylpyrazolin-5(4H)-one or 3-methyl-1-phenyl-2-pyrazolin-5(4H)-one, H_2O/ Ethanol, pipredine



SCHEME 2: Compounds: 3a, R= 4-Cl; 3b, R= 4-CH_3; 3c, R= 3,5-CH_3; 9a, R= 4-Cl, X= H; 9b R= 4-Cl, X= Ph; 9c, R= 4-CH_3, X=Ph; 9d, R= 3,5$(CH_3)_2$, X= Ph; 10a, R= 4-CH_3; 10b, R= 3,5$(CH_3)_2$. Reagents: C= p-hydroxybenzaldehyde, acetone, K_2CO_3; D= 3-methylpyrazolin-5(4H)-one or 3-methyl-1-phenyl-2-pyrazolin-5(4H)-one, H_2O/ Ethanol, pipredine; E= Diethyl malonate, benzene, acetic acid, pipredine; F= abs. Ethanol, H_2/pd; G= abs. ethanol, hydrazine hydrate, sodium ethoxide.

2. **Generation of PPARγ Hiphop Hypothesis:** The docked leads, Rosiglitazone (**I**), [3] AZ242 (**III**), [8] YPA101(**IV**), [9] 570200(**V**), [10] 54441(**VI**),[11] DRF 101(**VII**) [12] (**Figure 3**), at the PARγ binding site , were selected from their binding sites and used without any conformational changes to generate the common feature hypotheses of the PPARγ agonists. Using the protein tool deck in Cerius 2 software, such frozen bioactive conformers of the mentioned lead compounds, were used to generate the common feature hypotheses (by default), where 10 hypotheses were generated.

   The assessment of the ideal hypothesis among the generated ones indicated that hypothesis no. 7 was the ideal one, as it encompasses the crucial constraint features for selective PPARγ agonists; where the orientation of the two ring aromatic features were perpendicular to each other, which coincide with the gauche conformation adopted by the ligands in the PPARγ binding site as demonstrated in **Fig. 4a, 4b, 5**. In addition, hypothsis no. 7 had more consistent simulation fitting values to the respective ligands and the test set compounds than other hypotheses.

   Such an ideal hypothesis, that is reported here as the first time by our research team, encompassed four features namely; two hydrogen bond acceptor (HBA1 and HBA2), two ring aromatic features (RA1 and RA2) (figures 4a, b). Herein, we report the range of constraint angles and distances between all features; (**Table 1**) and Figures (4a, 4b, 5).

TABLE 1: CONSTRAINT DISTANCES AND ANGLES BETWEEN FEATURES OF THE GENERATED PPARγ AGONIST HYPOTHESIS

Dimensions	Our Catalyst ACEI Hypothesis (values are recorded in ranges)
Constraint distances (Å) between different features	RA2-HBA1,10.159-12.159; RA2-HBA2,10.625-12.625; RA1-RA2, 6.144-8.144; RA1-HBA1, 5.808-7.808; RA1-HBA2, 4.951-6.951; HBA1-HBA2, 3.433-5.433
Constraint angles (°) between different features	HBA1-RA2-RA1,41.2988-51.2998; RA2-RA1-HBA2, 119.897-129.898; RA2-RA1-HBA1, 101.199-111.2; RA1-HBA2-HBA1, 36.8986-86.8993.

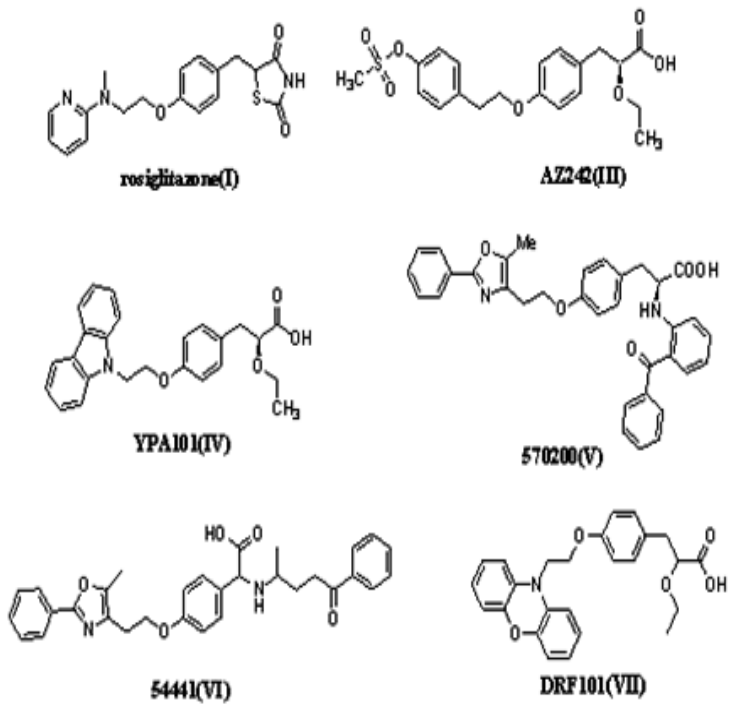


FIGURE 3: STRUCTURES OF PPARγ AGONIST LEAD COMPOUNDS USED FOR THE GENERATION OF PPARγ AGONIST HYPOTHESIS.

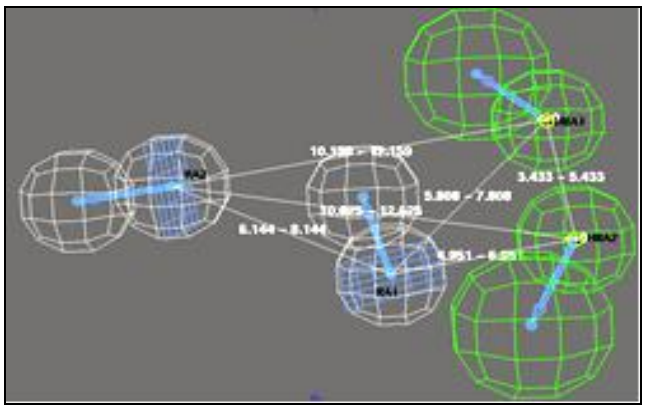


FIGURE 4A: CONSTRAINT DISTANCES OF PPARγ AGONIST HYPOTHESIS

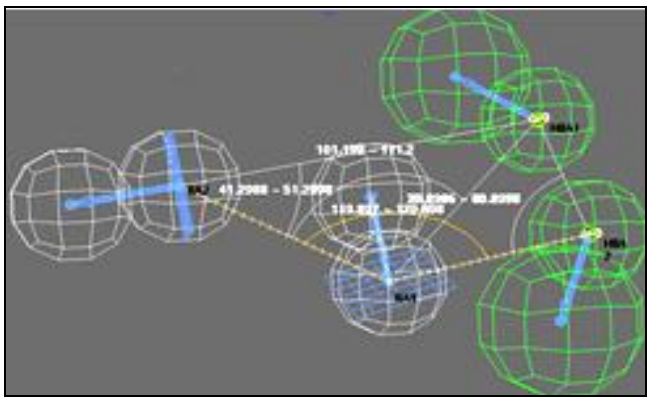


FIGURE 4B: CONSTRAINT ANGLES OF PPARγ AGONIST HYPOTHESIS

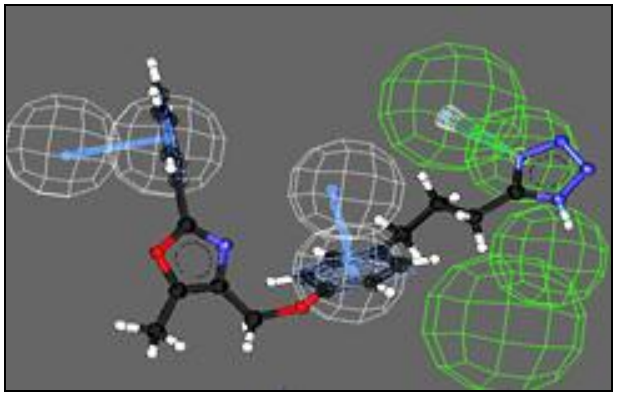


FIGURE 5: MAPPING OF PPARγ AND TetVIII

Further validation of the PPARγ agonist hypothesis was assessed through the following:

a. The database search study for examining the mapping of such PPARγ agonist hypothesis with the molecular structures of the provided databases with Catalyst 4.8, namely NCI 2000, Maybridge 2001, and MiniMaybridge, which contain 296092 compounds, revealed that only 467 molecules (~0.002% of the total), have been retrieved from the databases (**table 2**), including several anti-T2DMs agents. Such a low percentage of the recognized database molecules by our hypothesis, may indicate a reasonable selectivity for this hypothesis.

TABLE 2: MAPPING OF CATALYST DATABASE MOLECULES WITH PPARγ AGONIST HYPOTHESIS

Database	Total numbers of molecules	Number of retrieved (mapped) hits.	% of retrieved (mapped) hits
NCI2000	238819	250	0.001
Maybridge2001	55273	193	0.003
MiniMaybridge	2000	24	0.012
Total	296092	467	0.002

b. Further validation and evaluation of the predictive power of the hypothesis was performed through mapping of compounds having potent PPARγ agonistic activity; obtained from literature, viz; Tet (**VIII**) [13], DRH (**IX**) [14], CO1(**X**) [15], 3EA(**XI**) [16], PLB(**XII**) [17] (**Figure 6**). The mapping results indicated high fit values with these compounds (**table 3**).

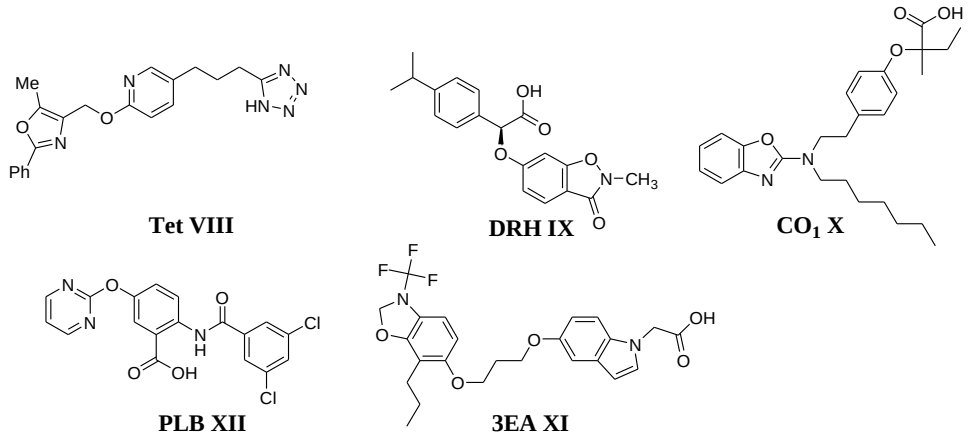


FIGURE 6: KNOWN PPARγ , EVALUATION SET COMPOUNDS, WHICH WERE MAPPED BY OUR PPARγ AGONIST HYPOTHESIS

TABLE 3: COMPARE/FIT AND CONFORMATIONAL ENERGY VALUES OF THE BEST FITTED CONFORMERS OF THE EVALUATION SET COMPOUNDS (VIII-XII) AND PPARγ AGONIST HYPOTHESIS

Cpd.	No. of conformers	Conf. energy	Fit Value/4
Tet VIII[13]	151	10.10	3.45
DRH IX[14]	205	14.64	2.93
COI X[15]	81	12.99	2.5
3EA XI[16]	229	4.75	2. 79
PLB XII[17]	72	8.6	2.95

Results of The Compare/Fit studies of compounds (4a-c, 5-8, 9a-c, 10a,b, 11a,b, and 12a,b): The compare/fit score values mentioned in **table 4**, revealed that most of the designed molecules showed high fitting affinities to the generated ideal new PPARγ receptor agonist hypothesis, indicated that all of these molecules have promising activity as PPARγ agonists and compounds **7**, **8**, **11a** & **12a** are the most promising hits. Accordingly, further molecular docking studies of **7**, **8**, **11a** & **12a** with the 3D PPARγ receptor binding sites would be performed.

TABLE 4: COMPARE/FIT AND CONFORMATIONAL ENERGY VALUES OF THE BEST FITTED CONFORMERS OF 2-PYRAZOLIN-5-ONE AND 3,5-PYRAZOLIDINEDIONES AND THE PPARγ AGONIST HYPOTHESIS

Compounds	Number of conformers	Conf. energy at the agonist hyothesis (Kcal mol^{-1})	Fitting values with PPARγ agonist hypothesis
Rosiglitazone (I)	1	-	3.99
9b	78	9.02	2.49
9c	81	16.13	2.36
9d	118	5.95	2.88
9a	77	16	2.87
4a	116	2.3	2.86
4b	130	9.47	2.84
5	122	12.92	2.94
6	124	12.14	2.43
7	160	5.5	2.89
8	178	6.355	2.98
11a	204	7.21	3.54
11b	211	6.165	3.45
12a	137	12.7	3.22
12b	191	15.46	3.28

3. **Docking results:** Molecular modeling docking studies using Molsoft software between the 3D PPARγ receptor binding sites and small molecules were performed. The docking scores (displayed in (ΔG) energy terms) of binding of a ligand to a receptor, is based upon the virtual calculation of various interaction of various small molecular ligand with protein. The present study adopted rigid receptor/flexible ligand approach between the 3D PPARγ receptor binding sites and small molecules of a lead drug and the designed molecules. Five potential energy maps combining hydrophobicity, electrostatics, hydrogen bond formation, and two van der Waal parameters were selected by default, to get the docking score [18]. The Molsoft could be used to deduce the binding affinity (ΔG values) of the lead molecule; Rosiglitazone (1) and the binding affinities of the promising test set molecules (**7**, **8**, **11a** & **12a**) with the targeted PPARγ receptor. The study indicated that these test set molecules have potential agonist activity similar or higher than Rosiglitazone. **Table 5** shows the recorded docking score of Rosiglitazone in comparizone to the active hit molecules (**7**, **8**, **11a** & **12a**).

TABLE 5: FITTING VALUES WITH PPARγ AGONIST HYPOTHESIS AND DOCKING SCORE ENERGIES AT THE PPARγ BINDING SITE OF COMPOUNDS (I, 7, 8, 11a, 12a)

Compounds	Fitting values with PPARγ agonist hypothesis	Docking score/△G(Kcal/mol)	Amino acid residues and corresponding hydrogen bond s length in Å
Rosiglitazone (I)	3.99	-96.35	S289 : 1.90 A H323: 1.75 A H449: 1.87 A Y473 : 2.27 A
7	2.89	-95.22	R288 : 2.68 A S342 : 1.70 A R288: 1.71 A S289: 1.93 A
8	2.98	-89.41	H323: 1.68 A H449: 2.45 A Y473: 2.24 A
11a	3.54	-114.46	R288: 1.48 A R288: 1.86 A S342: 2.35 A S342 :2.66 A
12a	3.22	-95.9	S289: 2.53 A H323: 2.24 A Q286 : 2.62 A Y473: 2.41 A

All selected compounds (7, 8, 11a, 12a) showed similar or relatively high docking scores in the PPARγ binding pocket compared to rosiglitazone (I). Compound **12a,** form hydrogen bonding interaction to the same aminoacid residues as those that interact with Rosiglitazone (**I**) in the PPARγ binding pocket; [18] (**Fig. 6a**).

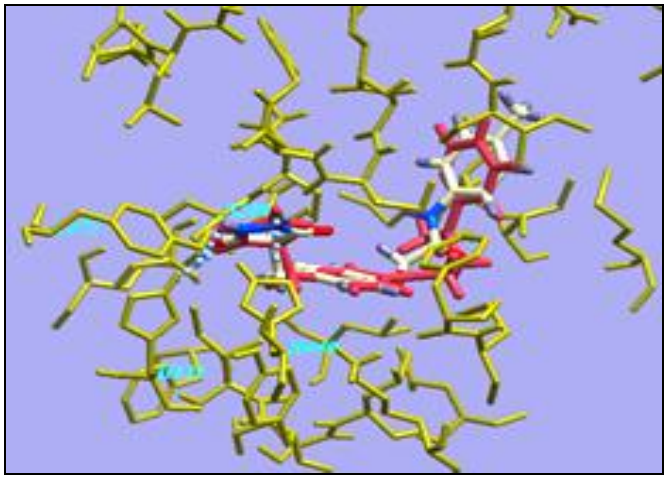


FIGURE 6A: SHOWS SIGNIFICANT ALIGNMENT INDICATED BY SUPERIMPOSITION OF THE MIDDLE PHENOXY RING AND SIMILARITIES IN THE HEAD GROUP PYRAZOLIDINE-3, 5-DIONE IN 12A (PINK) AND THIAZOLIDINEDIONE RING OF ROSIGLITAZONE (WHITE). The carbonyl oxygen of rosiglitazone (**I)** is considered as the most essential pharmacophore for the binding with PPARγ. Projection of pyrazolidine-3, 5-dione ring in 12a, toward thiazolidinedione region of **I** as illustrated, prompted to visualize its importance to act as a head group.

However, compound 11a that showed the highest docking score, makes hydrogen bonding interactions with amino acid residue no. S342 and R288 indicating a different binding mode than that of Rosiglitazone (**Fig. 6b**).

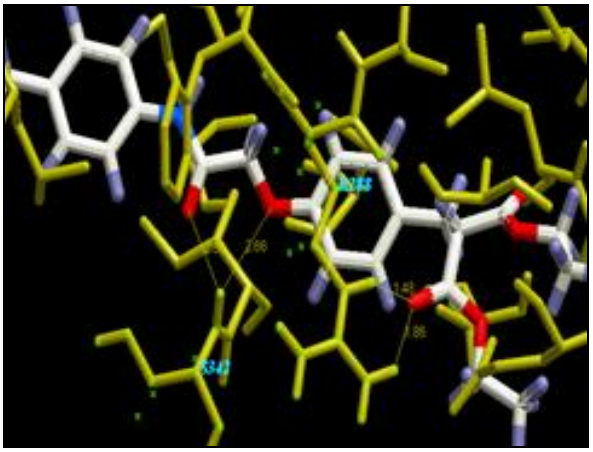


FIGURE 6B: COMPOUND 11A DOCKED AT PPARγ BINDING POCKET WITH HYDROGEN BOND FORMATION TO RESIDUES S342, R288

Conclusion of Molecular Modeling Studies: Comparing the Fit values of the virtual screening of the generated and validated PPARγ agonist hypothesis obtained by using Catalyst HipHop modules, together with the docking score of ICM-Pro (as illustrated in table (5) indicated that the fit values for the selected compounds (**7, 8, 11a, 12a**) with the ideal valid hypothesis were coincide with their docking scores. The binding of the compound (**11a**) exhibit a different hydrogen bond interaction when compared to Rosiglitazone, through forming hydrogen bond interaction with amino acid residues; R288 and S342. Such binding showed high affinity to the receptor than that of Rosiglitazone. This may indicate that such new binding mode may increase the PPARγ agonistic activity.

Accordingly, these active hit molecules were synthesized to be available for future *in vitro* and *in vivo* evaluation as anti-type 2 diabetes mellitus (anti-T2DM).

Experimental: Melting points were determined with a Stuart Scientific apparatus and are uncorrected. FT-IR spectra were recorded on a Perkin-Elmer spectrophotometer and measured by m0 cm^{-1} scale using KBr cell. 1H NMR spectra were measured in d scale on a JEOL 270 MHz spectrometer. Unless otherwise stated, the spectra were obtained on solutions in DMSO and referred to TMS. The electron impact (EI) mass spectra were recorded on Finnigan Mat SSQ 7000 (70 ev) mass spectrometer. The peak intensities, in parentheses, are expressed as percentage abundance.

Analytical thin layer chromatography (TLC) was performed on Merk Kieselgel 60PF254 silica on Aluminum backed sheets. All Rf values were recorded from the center of the spots. All TLC solvent proportions were measured volume by volume. Column chromatography was performed using Merk Silica gel (mesh size = 0.032–0.064 mm). All reagents and solvents were purified and dried by standard techniques. Solvents were removed under reduced pressure in a rotary evaporator. Elemental microanalysis was performed at the Microanalytical Center, Ain-Shams University. Catalytic hydrogenation was performed under atomospheric pressure at the National Research Centre, Dr. Nabil Aboul-enin

laboratory. The preparation of 3-Methyl-1-phenyl-1H-pyrazolin-5(4H)-one, [19] 3-Methylpyrazol-5-one, [20] N-[4-(3-chloropropoxy) phenyl] acetamide, [21] Benzo[*d*] thiazole-2-thiol, [22] 3-(3-Chloropropyl)-2- substituted quinazoline-4(3H)-on [23] was performed according to the reported procedures.

1. **Preparationof4-[3-(2-substituted-3,4-dihydro-4-oxoquinazolin-3-yl)-propoxy]benzald-ehyde (2a, b)**:

   General Procedure: A mixture of the 3-(3-Chloropropyl)-2- substituted quinazoline-4(3H)-one (15 mmol of each), few specks of KI, 4-hydroxybenzaldehyde (1.83 g, 15 mmol) and anhydrous K_2CO_3 (2.75 g, 20 mmol) in dry acetone (30 ml) was refluxed for 8 hrs, cooled and filtered. The filtrate was distilled under vacuum till dryness, the residue was washed with 10% NaOH solution, extracted with ethylacetate. The organic layer was dried over anhydrous Na_2SO_4, then concentrated in vacuo. The resulting solid was separated, crystallized from acetone.

a. **For compound (2a):** It was separated as white crystals (66% yield), m.p. 110°C. (Found: C, 70.35; H, 5.12; N, 8.98, $C_{18}H_{16}N_2O_3$ requires C, 70.12; H, 5.23; N, 9.09) MS (EI): m/z 308 (M+, 40%); IR(FT): 1684 (CO aldehydic). 1H NMR; 2.18 (m, 2H, J=7 Hz, -N-CH_2-$\underline{CH_2}$-CH_2-O-), 3.56 (t, 2H, J= 7Hz,-N-$\underline{CH_2}$-CH_2-CH_2-O-), 4.15 (t, 2H, J=7 Hz , -N-CH_2-CH_2-$\underline{CH_2}$-O-), 6.78-6.90 (m, 3H, Ar-H), 7.51-7.82 (m, 3H, Ar-H), 8.13-8.15 (d, 2H, Ar-H), 8.35 (S, 1H, quinazolyl-2H-), 9.94 (S, 1H, -CHO).

b. **For compound (2b):** It was separated as faint yellowish white crystals. (53% yield), m.p. 107°C. (Found: C, 71.1; H, 5.43; N, 9.47, $C_{19}H_{18}N_2O_3$ requires C, 70.79; H: 5.63; N, 8.69) MS (EI): m/z 322 (M+, 4.5%); IR (FT): 1695(CO aldehydic). 1H NMR; 2.17(m, 2H, J=7 Hz , -N-CH_2-$\underline{CH_2}$-CH_2-O-, 3H, CH_3), 3.58 (t, 2H, J= 7Hz,-N-$\underline{CH_2}$-CH_2-CH_2-O-), 4.20 (t, 2H, J=7 Hz , -N-CH_2-CH_2-$\underline{CH_2}$-O-), 6.92-7.07 (d, 2H, Ar-H), 7.43-7.64 (m, 3H, Ar-H), 7.74-7.84 (m, 3H, Ar-H), 9.94 (S, 1H, -CHO).

2. **Preparation of N-[4-[3-(4-Formylphenoxy) propoxy] phenyl]acetamide (2c)**: To a mixture of N-[4-(3-chloropropoxy)phenyl]acetamide (3.41 g, 15 mmol), anhydrous K_2CO_3 (20 mmol) in DMF (20 mL) and few specks of KI, 4-hydroxybenzaldehyde (15 mmol) was added. The reaction mixture was stirred in a water bath at 70°C for 36 h, cooled then evaporated till near dryness under vaccum, ice cold water and brine were added where white solid was precipitated. The precipitate was filtered, washed with water and 10% NaOH solution, dried, then crystallized from acetone-ether mixture to produce the title compound (9).

a. **For compound (2c)**: It was separated as faint yellowish white crystals. (90% yield), m.p. 120°C. (Found: C, 65.12; H, 5.67; N, 11.21, $C_{18}H_{19}NO_4$ requires C, 65.38; H: 5.76; N, 11.44) MS (EI): m/z 313 (M+, 4.5%); IR (FT): 3249 (NH Stretching). 1H NMR; 1.97 (s, 3H, NH-CO-CH_3), 2.15 (m, 2H, J=6Hz, O-CH_2-$\underline{CH_2}$-CH_2-O), 4.06 (t, 2H, J=6Hz, O-$\underline{CH_2}$-CH_2-CH_2-O), 4.22 (t, 2H, J=6Hz, O-CH_2-CH_2-$\underline{CH_2}$-O), 6.85-7.12 (m, 4H, Ar-H), 7.43-7.82 (m, 4H, Ar-H), 9.74 (s, 1H, NH)(D_2O exchangeable), 10.01 (s, 1H, CHO)

3. **Preparation of 4-[3- (Benzo[d]thiazol-2-ylthio) propoxy]benzaldehyde (2d):** The title compound was prepared from 4-(3-chloropropoxy) benzaldehyde (15 mmol) and 2-mercapto-benzothiazole (15 mmol) following the same general procedure of **3a, b**, the reaction was stirred at 70°C for 72 h. The resulting yellow solid was crystallized from dry acetone. It was separated as faint yellow crystals. (40% yield), m.p. 112°C. (Found: C, 62.02; H, 4.49; N, 5.12, $C_{17}H_{15}NO_2S_3$ requires C, 61.98; H: 4.58; N, 4.25) MS (EI): m/z 329 (M+, 45%); IR (FT): 1695 (CO aldehydic). 1H NMR; 2.28 (m, 2H, J=9Hz, S-CH_2-$\underline{CH_2}$-CH_2-O), 3.22 (t, 2H, J=9Hz, S-$\underline{CH_2}$-CH_2-CH_2-O) 4.22 (t, 2H, J=9Hz, S-CH_2-CH_2-$\underline{CH_2}$-O), 7.03-7.24 (m, 3H, Ar-H), 7.37-7.47 (m, 2H, Ar-H), 7.69-7.86 (m, 3H, Ar-H), 9.89 (s, 1H, CHO).

4. **Preparation of 4-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propoxy]benzaldehyde(2e):** The title compound was prepared from 1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine.HCl (4.63 g, 15 mmol) and 4-hydroxybenzaldehyde (15 mmol) using the same general procedure described for the preparation of **5a, b** The resulting solid was crystallized from dry acetone and separated as white solid. (80% yield), m.p. 116°C. (Found: C, 67.01; H, 6.51; N, 7.92, $C_{20}H_{23}ClN_2O_2$ requires C,

66.94; H: 6.46; N, 7.81) MS (EI): m/z 358 (M+, 45%); IR (FT): 1695 (CO aldehydic). 1H NMR; 1.94 (m, 2H, J=6Hz, N-CH_2-$\underline{CH_2}$-CH_2-O),3.13-3.18 (m, 8H, 4$\underline{CH_2}$ piperazine), 3.45 ((t, 2H, J=6Hz, N-$\underline{CH_2}$-CH_2-CH_2-O), 4.13 (t, 2H, J=6Hz, N-CH_2-CH_2-$\underline{CH_2}$-O), 6.74-6.85 (m, 3H, Ar-H), 7.09-7.21 (m, 3H, Ar-H), 7.83 (d, 2H, Ar-H), 9.85 (s, 1H, CHO).

5. **Preparation of 4-[4-[4-{2-(Arylamino)oxoethoxy} phenyl]methylene]-3-methyl-1-phenyl-1H-pyrazol -5(4H)-one (9b-d): General procedure**: To a stirring solution of 2a-c (0.35 g, 2 mmol) in ethanol 95% (8 mL), the corresponding (2 mmol each) were added. After complete addition, the mixture was stirred for 24 hours at room temp. The reaction mixture was filtered, dried, washed with ether, then crystallized from acetone-ether mixture.

a. **For compound (9b):** It was separated as white crystals. (70% yield), m.p. 165°C. (Found: C, 68.95; H, 4.96; N, 9.97, $C_{25}H_{22}ClN_3O_2$ requires C, 69.52; H: 5.13; N, 9.97) MS (EI): m/z 445 (M+, 75%); IR (FT): 1665 (CO amidic). 1H NMR; 2.11 (s, 3H, CH_3), 4.79 (s, 2H, CO-$\underline{CH_2}$-O), 7.12-7.35 (m, 6H, Ar-H), 7.45 (s, 1H, $\underline{CH}$=C), 7.64-7.71 (m, 5H, Ar-H), 7.72-7.85 (m, 3H, Ar-H), 9.5 (s, 1H, NH) D_2O exchangeable

b. **For compound (9c):** It was separated as faint yellowish white crystals. (85% yield), m.p. 143°C. (Found: C, 75.7; H, 6.23; N, 10.32, $C_{26}H_{25}N_3O_2$ requires C, 75.89; H: 6.12; N, 10.21) MS (EI): m/z 425 (M+, 75%); IR (FT): 1665 (CO amidic). 1H NMR; 2.11 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.70 (s, 2H, CO-$\underline{CH_2}$-O), 7.11-7.21 (m, 6H, Ar-H), 7.38-7.51 (m, 4H, Ar-H, $\underline{CH}$=C), 7.71-7.90 (m, 4H, Ar-H), 9.5 (s, 1H, NH) D_2O exchangeable.

c. **For compound (9d):** It was separated as faint white crystals. (65% yield), m.p. 137°C. (Found: C, 76.36; H, 6. 3; N, 10.01, $C_{27}H_{27}N_3O_2$ requires C, 76.21; H: 6.4; N, 9.87) MS (EI): m/z 439 (M+, 75%); IR (FT): 1660 (CO amidic). 1H NMR; 2.11 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.65 (s, 2H, CO-$\underline{CH_2}$-O), 6.94 (d, 2H, Ar-H), 7.05-7.17 (m, 3H Ar-H), 7.38-7.68 (m, 5H, Ar-H, $\underline{CH}$=C), 7.72-7.82 (m, 3H, Ar-H), 9.5 (s, 1H, NH) D_2O exchangeable.

6. **Preparation of 2-Substituted-3-[3-[4-{(3-methyl-4,5-dihydro-5-oxo-1-phenyl-1H-pyrazol-4-ylidene)methylene}phenoxy]propyl]quinazolin-4(3H)-one(4a,b),4-[3-4-{(3-Methyl-5-oxo-1-phenyl -1H-pyrazolin-4(5H) ylidene) methyl} phenoxy] propoxy] acetanilide (7), 4-[[4-{3-(Benzo[d] thiazol-2-ylthio)propoxy} phenyl] methylene]-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (5):** The title compounds were prepared from 3-methyl-1-phenyl(5H)pyrazolin-5-one (2 mmol) and the corresponding aldehydes (2a-d) (2 mmol) using the same general procedure described for the preparation of 9b-d to give crude products which were further recrystallized from acetone-ether mixture.

a. **For compound (4a)**: (66% yield), m.p. 190°C. (Found: C, 72.37; H, 4.96; N, 11.87, $C_{28}H_{24}N_4O_3$ requires C, 72.4; H: 5.21; N, 12.06) MS (EI): m/z 464 (M+, 20%); IR (FT): 1665 (CO amidic). 1H NMR; 2.11 (s, 3H, CH_3), 2.21 (m, 2H, J=7 Hz, N-CH_2-$\underline{CH_2}$-CH_2-O-), 4.18 (t, 2H, J=7 Hz, -N-CH_2-CH_2-$\underline{CH_2}$-O-), 7.18-7.23 (m, 4H , Ar-H), 7.41 (m, 3H, Ar-H, ($\underline{CH}$=C-), 7.52-7.63 (m,3H, Ar-H), 7.65-7.71 (d, 2H, Ar-H), 7.81 (d, 2H, Ar-H), 8.36 (S, 1H, quinazolyl-2H-).

b. **For compound (4b):** (53% yield), m.p. 196°C. (Found: C, 72.54; H, 5.39; N, 11.82, $C_{29}H_{26}N_4O_3$ requires C, 72.79; H: 5.48; N, 11.71) MS (EI): m/z 478 (M+, 5%); IR (FT): 1665 (CO amidic). 1H NMR; 2.08 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.21 (m, 2H, J=7 Hz, N-CH_2-$\underline{CH_2}$-CH_2-O-), 4.18 (t, 2H, J=7 Hz, -N-CH_2-CH_2-$\underline{CH_2}$-O-), 7.18-7.23 (m, 4H , Ar-H), 7.41 (m, 3H, Ar-H, $\underline{CH}$=C-)), 7.52-7.63 (m,3H, Ar-H), 7.65-7.71 (d, 2H, Ar-H), 7.81 (d, 2H, Ar-H).

c. **For compound (7):)**.(0.71g, 76%yield, m.p. 170°C(Found: C, 71.45; H, 5.6; N, 9.04, $C_{28}H_{27}N_3O_4$ requires C, 71.62; H: 5.8; N, 8.94) MS (EI): m/z 469 (M+, 75%); IR (FT): 1665 (CO amidic). 1H NMR; 1.98 (s, 3H, NH-CO-CH_3), 2.11 (s, 3H, CH_3), 2.23 (m, 2H, J=6Hz, O-CH_2-$\underline{CH_2}$-CH_2-O), 4.05 (t, 2H, J=6Hz, O-$\underline{CH_2}$-CH_2-CH_2-O), 4.22 (t, 2H, J=6Hz, O-CH_2-CH_2-$\underline{CH_2}$-O), 6.84-7.16 (m, 6H, Ar-H), 7.39-7.67 (m, 3H, Ar-H, $\underline{CH}$=C), 7.71-7.88 (m, 5H, Ar-H), 9.74 (s, 1H, NH) D_2O exchangeable, 10.01 (s, 1H, CHO).

d. **For compound (5):** (0.68g, 60% yield), m.p. 185°C (Found: C, 66.92; H, 4.65; N, 8.57, $C_{27}H_{23}N_3O_2S_2$ requires C, 66.87; H: 4.77; N, 8.65)

MS (EI): m/z 485 (M+, 25%); IR (FT): 1660 (CO amidic). 1H NMR; 2.01 (s, 3H, CH_3), 2.25 (m, 2H, J=9Hz, S-CH_2-$\underline{CH_2}$-CH_2-O), 3.45 (t, 2H, J=9Hz, S-$\underline{CH_2}$-CH_2-CH_2-O), 4.19 (t, 2H, J=9Hz, S-CH_2-CH_2-$\underline{CH_2}$-O), 7.01-7.32 (m, 4H, Ar-H), 7.34-7.73 (m, 5H, Ar-H, $\underline{CH}$=C), 7.82-7.99 (m, 5H, Ar-H).

7. **Preparation of 4-[4-[2-N-(4-Chlorophenyl) acetamido)phenoxy]methylene]-3-methyl -1H-pyrazo-5(4H)-one (9a), [4-[2-N-(4-Chlorophenyl) acetamido)phenoxy]methylene]-3-methyl -1H-pyrazo-5(4H)-one(4a),4-[3-[4-{(3-Methyl-4,5-dihydro-5-oxo-1H-pyrazol-4-ylidene)methyl} phenoxy]propoxy]acetanilide(8), 4-[4-[3-{4-(3-Chlorophenyl)piperazin-1-yl}propoxy]benzyli dene]-3-methyl-1H-Pyrazol-5(4H)-one (6):** General procedure: A stirred mixture of 3-methylpyrazolin-5-(4H)-one (10 mmol) and 3a, 2c, 2e (10 mmol) in absolute ethanol (20 mL) containing 5-6 drops of piperidine was refluxed for 7 hrs. After cooling, the solution was evaporated in vacuo, the residue was recrystallized from CHCl3/hexane.

a. **For compound (9a)**: It was separated as white solid, (54% yield), m.p. 189°C(Found: C, 61.84; H, 4.43; N, 11.28, $C_{19}H_{16}ClN_3O_3$ requires C, 61.71; H: 4.36; N, 11.36) MS (EI): m/z 369 (M+, 25%); IR (FT): 1680 (CO amidic). 1H NMR; 1.47 (s, 3H, CH_3), 4.55 (s, 2H, CH_2), 6.88 (d, 2H, Ar-H), 7.03 (d, 2H, Ar-H), 7.24-7.33 (m, 4H, Ar-H), 7.42 (s, 1H, $\underline{CH}$=C), 8.73 (s, 1H, pyrazol NH) D_2O exchangeable.

b. **For compound (8):** It was separated as white solid, (46% yield), m.p. 170°C(Found: C, 66.98; H, 5.7; N, 10.54, $C_{19}H_{16}ClN_3O_3$ requires C, 67.16; H: 5.89; N, 10.68) MS (EI): m/z 393 (M+, 40%); IR (FT): 1675 (CO amidic). 1H NMR; 1.47(s, 3H, CH_3), 1.99 (s, 3H, NH-CO-$\underline{CH_3}$), 2.18 (m, 2H, J=6Hz, O-CH_2-$\underline{CH_2}$-CH_2-O), 3.95 (t, 2H, J=6Hz, O-CH_2-CH_2-$\underline{CH_2}$-O), 4.07 (t, 2H, J=6Hz, O-$\underline{CH_2}$-CH_2-CH_2-O), 6.75-6.98 (m, 4H, Ar-H), 7.45-7.65 (m, 5H, Ar-H, $\underline{CH}$=C), 8.75 (s, 1H, pyrazol NH) D_2O exchangeable, 9.73(s, 1H, $\underline{NH}COCH_3$) D_2O exchangeable. 4.07 (t, 2H, J=6Hz, O-CH2-CH2-CH2-O), 6.75-6.98 (m, 4H, Ar-H), 7.45-7.65 (m, 5H, Ar-H, CH=C), 8.75 (s, 1H, pyrazol NH) D2O exchangeable, 9.73(s, 1H, NHCOCH3) D2O exchangeable.

c. **For compound (6):** It was separated as white solid, (65% yield), m.p.150°C (Found: C, 65.96; H: 6.15; N, 12.58, $C_{24}H_{27}ClN_4O_2$ requires C, 65.67; H: 6.2; N, 12.76) MS (EI): m/z 439 (M+, 40%); IR (FT): 1680 (CO amidic). 1H NMR; 1.49(s, 3H, CH_3), 1.94 (p, 2H, J=6Hz, O-CH_2-$\underline{CH_2}$-CH_2-O), 3.15 (m, 4H, 2$\underline{CH_2}$ piperazine, 2H, N-$\underline{CH_2}$-CH_2-CH_2-O), 4.16 (t, 2H, J=6Hz, N-CH_2-CH_2-$\underline{CH_2}$-O), 6.75-6.98 (m, 4H, Ar-H), 7.45-7.65 (m, 3H, Ar-H, $\underline{CH}$=C), 8.67 (s, 1H, pyrazol NH) D_2O exchangeable

8. **Preparation of Diethyl 2-[4-(2-arylamino-2-oxoethoxy)benzylidene]malonate (10a,b):** General procedure: A mixture of (2b,c) (32.75 mmol) alternatively and diethyl malonate (5.35 mL, 39.3 mmol) in benzene (50 mL) containing piperidinium acetate (1.41 g, 9.82 mmol) was refluxed in Dean-Stark trap for 5 h. The solution was concentrated in vacuo, cooled in a refrigerator and filtered. The residue was crystallized from ether.

a. **For compound (10a):** It was separated as faint yellowish white crystals. (75% yield), m.p. 85□ C (Found: C, 66.59; H, 5.84; N, 4.51, C23H25NO6 requires C, 67.14; H: 6.12; N, 3.4) MS (EI): m/z 411 (M+, 30%); IR (FT): 1770 (CO of ester). 1H NMR; 1.18-1.24 (m,6H,, 2(COOCH2CH3)), 2.22 (s, 3H, CH3), 4.16-4.30 (m, 4H, 2(COOCH2CH3)), 4.73(s, 2H, CO-CH2-O-), 7.03-7.11 (m, 4H, Ar-H), 7.45-7.49 (m, 4H, Ar-H), 7.65 (s, 1H, CH=C-), 9.33 (s,1H, NH) D_2O exchangeable.

b. **For compound (10b):** It was separated as faint yellowish white crystals. (86% yield), m.p. 115°C (Found: C, 67.84; H, 6.3; N, 3.1, $C_{23}H_{25}NO_6$ requires C, 67.75; H: 6.40; N, 3.29) MS (EI): m/z 425 (M+, 60%); IR (FT): 1770 (CO of ester). 1H NMR; 1.15-1.26 (m, 6H, 2($COOCH_2\underline{CH_3}$)), 2.10 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 4.09-4.30 (m, 4H, 2($COO\underline{CH_2}CH_3$)), 4.78 (s, 2H, CO-$\underline{CH_2}$-O-), 6.98 (d, 2H, J=6Hz, Ar-H), 7.09 (d, 2H, Ar-H), 7.21 (s, 1H, Ar-H) 7.49 (d, 2H, J=6Hz, Ar-H), 7.65 (s, 1H, $\underline{CH}$=C-), 9.33 (s,1H, NH) D_2O exchangeable.

9. **Preparation of diethyl2-[4-(2-arylamino-2-oxoethoxy)benzyl]malonate (11a,b):** Suspension of compounds (10a,b) (4.23 mol each) in absolute ethanol was stirred in the presence of 10%

palladium on charcoal (0.6g) under atmosphere of hydrogen at room temperature for 24 hrs. The solution was filtered through Celite, and the filtrate was evaporated under vacuum to produce a light yellow solid. The product was crystallized with ether.

a. **For compound (11a):** It was separated as white crystals. (80% yield), m.p. 70°C (Found: C, 66.93; H, 6.43; N, 3.27, $C_{23}H_{27}NO_6$ requires C, 66.81; H: 6.58; N, 3.39) MS (EI): m/z 413 (M+, 70%); IR (FT): 1770 (CO of ester). 1H NMR; 1.09(t, 6H, J=9Hz, 2($COOCH_2\underline{CH_3}$)) 2.24 (s, 3H, CH_3), 3.02 (d, 2H, J=6Hz, $\underline{CH_2}$-CH-$(COO)_2$-), 3.77 (t, 1H, J=6Hz, CH_2-$\underline{CH}$-$(COO)_2$-), 4.08 (q, 4H, J=9Hz, 2($COO\underline{CH_2}CH_3$)), 4.66 (s, 2H, CO-$\underline{CH_2}$-O-), 6.90 (d, 2H, Ar-H), 7.14 (d, 2H, Ar-H), 7.17-7.22 (m, 4H, Ar-H), 9.33 (s,1H, NH)D_2O exchangeable.

b. **Compound (11b):** It was separated as white crystals. (86% yield), m.p. 105°C (Found: C, 68.13; H, 5.96; N, 3.78, $C_{24}H_{29}NO_6$ requires C, 67.43; H: 5.96; N, 3.28) MS (EI): m/z 427 (M+, 30%); IR (FT): 1770 (CO of ester). 1H NMR; 1.11 (t, 6H, J=9Hz, 2($COOCH_2\underline{CH_3}$)) 2.09 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.02 (d, 2H, J=6Hz, $\underline{CH_2}$-CH-$(COO)_2$-), 3.85 (t, 1H, J=6Hz, CH_2-$\underline{CH}$-$(COO)_2$-), 4.10 (q, 4H, J=9Hz, 2($COO\underline{CH_2}CH_3$)), 4.66 (s, 2H, CO-$\underline{CH_2}$-O-) 6.90-7.14 (m, 4H, Ar-H), 7.17 (d, 2H, Ar-H), 7.22 (s, 1H, Ar-H), 9.33 (s,1H, NH) D_2O exchangeable.

10. **Preparation of N-aryl-2-[4-[(3,5-dioxopyrazolidin-4-yl)methyl]phenoxy]acetanilide (12a, b):**

General procedure: To stirring solution of (11a,b) (20 mmol each), add hydrazine hydrate 99% (2.5g, 50 mmol), then reflux for 30 minutes, a precipitate is formed. After cooling, a solution of sodium ethoxide (0.02 atom/ g) in a absolute ethanol (20 ml) was added, then the reaction mixture was refluxed once more for 1 h. After cooling, the solution was evaporated under vacuum, the residue was dissolved in 20% HCl solution. A solid was precipitated. The precipitate was filtered, dried and crystallized from THF.

a. **For compound (12a):** It was separated as white crystals. (64% yield), m.p. 219°C (Found: C, 64.67; H, 5.35; N, 11.72, $C_{19}H_{19}N_3O_4$ requires C, 64.58; H: 5.42; N, 11.89) MS (EI): m/z 353 (M+, 50%); IR (FT): 1670 (CO amidic). 1H NMR; l2.23, (s, 3H, CH_3), 2.98 (d, 2H, J=6Hz, $\underline{CH_2}$-CH-CO), 3.25 (t, 1H, J=6Hz, CH_2-$\underline{CH}$-CO), 4.64 (s, 2H, CO-$\underline{CH_2}$-O), 6.78-7.07(m, 4H, Ar-H), 7.17-7.27 (m, 4H, Ar-H).

b. **For compound (12b):** It was separated as white crystals. (54% yield), m.p. 220°C (Found: C, 65.27; H, 5.82; N, 11.37, $C_{20}H_{21}N_3O_4$ requires C, 65.38; H: 5.76; N, 11.44) MS (EI): m/z 367(M+, 30%); IR (FT): 1675 (CO amidic). 1H NMR; 1.11 (t, 6H, J=9Hz, 2($COOCH_2\underline{CH_3}$)), 2.09 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.02 (d, 2H, J=6Hz, $\underline{CH_2}$-CH-$(COO)_2$-), 3.85 (t, 1H, J=6Hz, CH_2-$\underline{CH}$-$(COO)_2$-), 4.10 (q, 4H, J=9Hz, 2($COO\underline{CH_2}CH_3$)), 4.66 (s, 2H, CO-$\underline{CH_2}$-O-), 6.90-7.14 (m, 4H, Ar-H), 7.17 (d, 2H, Ar-H), 7.22 (s, 1H, Ar-H), 9.33 (s,1H, NH) D_2O exchangeable.

Hypothesis Generation Experiments: Molecular modeling work was performed on Silicon Graphic (SGI), Fuel workstation (500 MHz, R 14000 ATM processor, 512 MB memory) using the Catalyst package of Molecular Simulation (version 4.8), under an IRIX 6.8 operating system, at Faculty of Pharmacy, Ain Shams University. A generalized visualizer, confirm, info, HipHop, Compare/fit, force field was used throughout.

The frozen bioactive conformation of the training set molecules were isolated from their respective PDB files using the protein tools deck in Cerius2 module. Using Cerius2 3D-Sketcher, the 3D structures of corrected bioactive conformations of the training set were saved and transformed to Tripos. Mol2 format.

The training molecules with their associated conformational models were submitted to catalysis by using default common features hypothesis generation by using HipHop commands. The chemical function groups (features) used in this generation step included H-bond acceptor, ring aromatic groups, and hydrogen bond donor groups.

The training set molecules: Molecules were built within the catalyst and conformational models for each compound were generated automatically using the poling algorithm. This emphasizes representative coverage over a 20 kcal mol^{-1} energy range above the estimated global energy minimum and the best searching procedure was chosen.

Molsoft Molecular Modeling Experiments: The docking algorithm implemented in ICM optimizes the entire ligand in the receptor field, applying a multistart Monte Carlo minimization procedure in internal coordinate space. The number of Monte Carlo steps and iterations of the local energy minimization was determined automatically by an adaptive algorithm depending on the size and number of flexible torsions in the ligand [18].

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