IJPT
International Journal of Pharmacy & Technology

**ISSN: 0975-766X**

**Available Online through** ***Research Article***

**www.ijptonline.com**

# COMPUTER-AIDED DESIGN AND SCREENING OF CHALCONES AS NOVEL PPAR GAMMA AGONISTS

**Archana Kumari. D. N. S. S.*[1], Manga Ratnam. B[1], Arun Kumar Kuna[2], Srinivasulu. D[3]**

[1]Avanthi Institute of Pharmaceutical Sciences, Cherukupally (V), Bhogapauram (M), Near Tagarapuvalasa Bridge, Vizianagaram - 531162, India.

[2]Vels College Of Pharmacy, Velan Nagar, P.V.Vaithiyalingam Road, Pallavaram, Chennai – 600117, India.

[3]University College Of Pharmaceutical Sciences - Andhra University, Visakhapatnam-530003, India.

**E-mail:** *archana19d@yahoo.co.in,*

***Received on 25-12-2009*** ***Accepted on 15-01-2010***

**Abstract**

Type II diabetes mellitus is a chronic metabolic disorder and PPARs were found to be better targets in lowering glucose levels. Here, we report a computer-aided drug design approach to screen various chalcones, designed using substituted benzaldehydes and acetophenones from e-molecule library, as possible PPAR gamma agonists using Molegro Virtual Docker software. Based on the dock scores and molecular weight comparisons of top 50 compounds from a designed data set of 2500 chalcones, compound 17_37 displayed a dock score of -230.10 kcal/mol with a maximum of 11 H-bond interactions.

**Keywords:** chalcone, diabetes, PPARgamma, docking

## 1. Introduction

Chalcone is an aromatic ketone that forms the central core for a variety of important biological compounds. Chalcones are prepared by aldol condensation reaction between a benzaldehyde and an acetophenone in the presence of sodium hydroxide as a catalyst. Compounds with chalcone as backbone have been reported to exhibit a wide variety of pharmacological effects and the presence of a reactive α,β-unsaturated keto function in chalcones is found to be responsible for their activity, which may be altered depending on the type and position of the substituent on the aromatic rings.[1]

Chalcones can also be prepared by claisen schimdt reaction and Allan Robinson's reaction. They are known to possess a wide variety of therapeutic uses where the (E)-4-aminoalkylthiochalcones and (E)-4-amino alkoxychalcones exhibited good antibacterial property against *Staphylococcus aureus*, *Enterococcus faecalis* and *Bacillus subtilis*.[2,3] Chalcones belong to the flavonoid family and it was reported that 2′-methoxy-3,4-dichlorochalcone, 2′-hydroxy-6′-methoxy chalcone, 2′-hydroxy-3-bromo-6′-methoxy chalcone and 2′-hydroxy-4′,6′-dimethoxy chalcone potently inhibit iNOS-catalyzed NO production by different cellular mechanisms and found to possess anti-inflammatory activities.[4,5] Moreover, chalcones possess anti-fungal activity where some of them were found to exhibit specificity with some proteins of *Saccharomyces cerevisiae*, *Hansenula polymorpha* and *Kluyveromyces lactis*, respectively.[6,7] Compounds like 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (DMC), isolated from the buds of *Cleistocalyx operculatus* possess anti-tumour activity when tested on human cancer cells[5,8] while some chalcones demonstrated the ability to block voltage-dependent potassium channels.[9] They are also intermediates in the biosynthesis of flavonoids, which are substances widespread in plants and with

an array of biological activities. Chalcone based aryloxypropanol amines were evaluated for their anti-hyperglycemic activity in rat models[10] and 3-nitro-2′-benzyloxychalcone has stimulated glucose uptake when tested on adipocytes.[11]

Type II diabetes mellitus is a chronic metabolic disorder, characterized by dysfunctioning of pancreatic beta cells associated with insulin resistance, if not controlled leads to macro and microvascular disorders.[12,13] Dipeptidyl peptidase IV,[14-16] GLP-1,[17] Glucokinase[18] and PPARs (Peroxisome Proliferator Activated Receptors)[19-21] have been identified as potential targets of type II diabetes. Among these, PPARs which are a group of nuclear receptors were found to be better targets in lowering glucose levels along with lipids. They activate transcription factors of many genes and exist in three isoforms α (alpha), β (beta) and γ (gamma), of which, PPAR gamma agonists are known to improve insulin sensitivity. Several such agonists have so far been described in literature. They include benzimidazole derivatives,[22] docosahexaenoic acid derivatives,[23] *N*-(2-Benzoylphenyl)-L-tyrosine,[24] aryl-tetrahydropyridines,[25] carbamate-tethered aryl propanoic acids,[26] thiazolidinediones[27] and others.[28] However, certain side effects have been identified with these agents like congestive heart failure, edema, fluid retention and weight gain.[29] Thus, there is still a need to develop novel, selective PPAR gamma agonists with reduced side effects. Therefore, in this paper, a computer-aided drug design approach was employed to screen various chalcones as possible PPAR gamma agonists.

Synthesizing new compounds utilizing high-throughput screening are carried out at high cost and are also time consuming. However, an alternative process represents screening small molecule databases for novel compounds and docking them into the protein of interest followed by scoring the poses. This has become increasingly important in the context of drug discovery. Hence, we report designing and screening of novel chalcones as possible PPAR gamma agonists by extracting various

substituted benzaldehydes and acetophenones from e-molecule library followed by docking with PPAR gamma (PDB id: 2Q6S).

## 2. Methods

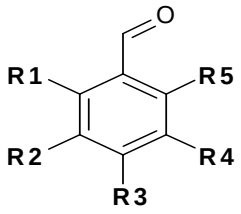
### Receptor X-ray structure

The X-ray crystal structure of PPAR gamma having PDB (Protein Data Bank) code 2Q6S[30] was selected as receptor model in this study. We used eMolecules[31] chemical library to design various chalcones and Molegro Virtual Docker to perform docking analysis.

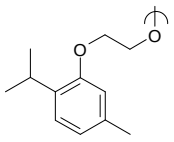
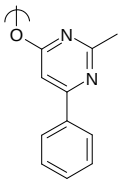
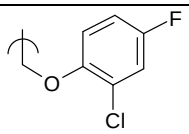
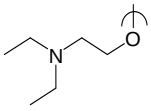
### eMolecules Database

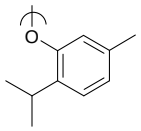
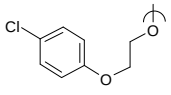
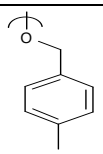
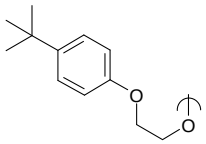
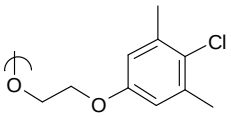
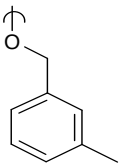
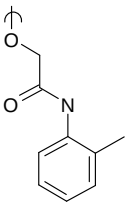
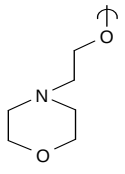
The database contains nearly 8 million unique chemical structures from 22 million sources. Searching can be done either by using text or by structure. Structure based searching involves sub-structure search or exact structure search and searching by text can be initiated by valid data formats or wild cards. A structure based search was employed to extract 50 different benzaldehydes and acetophenones, given in Tables 1 and Table 2.

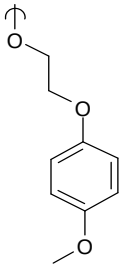
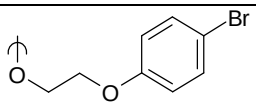
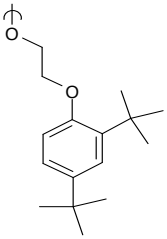
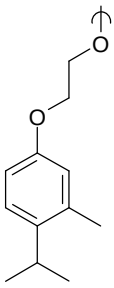
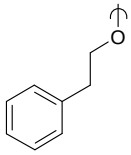
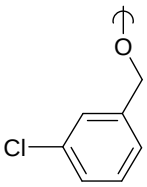
**Table 1:** Various substituted benzaldehydes extracted from e-molecules database.

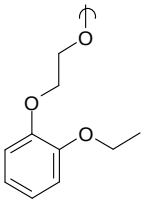
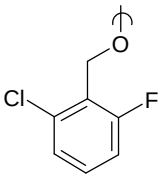
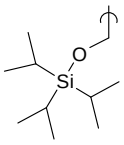
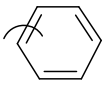
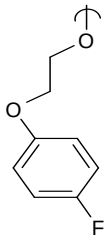
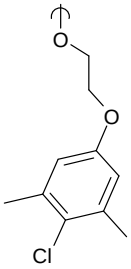
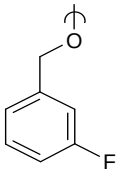


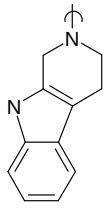
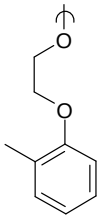
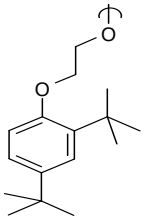
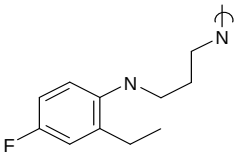
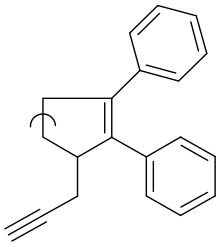
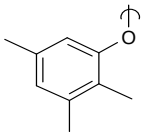

| S.NO | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|
| 1 | F | F | F | F | F |
| 2 | H | H | H | $CH_2Br$ | H |
| 3 | $CH_3$ | $CH_3$ | H | H | $CH_3$ |

| | | | | | |
|---|---|---|---|---|---|
| **4** | $OCH_3$ | H | $OCH_3$ | H | H |
| **5** | OH | Cl | Cl | H | Cl |
| **6** | H | Br | H | Br | NH2 |
| **7** | H | H | $OCH_3$ | Cl | H |
| **8** | $CH_3$ | H | H | H | $CH_3$ |
| **9** | H | Br | $O(CH_2)_4\ CH_3$ | $OCH_3$ | H |
| **10** | H | H | H | H | $OCHF_2$ |
| **11** | H | H |  | Br | H |
| **12** | H | H | $OCHF_2$ | $OCH_2CH_3$ | H |
| **13** |  | H | H | Br | H |
| **14** | H | H | $O(CH_2)_5CH_3$ | $OCH_2CH_3$ | H |
| **15** | H |  | $OCH_3$ | H | H |
| **16** |  | $OCH_3$ | H | H | H |

| | | | | | |
|---|---|---|---|---|---|
| **17** | H | H |  | H | H |
| **18** |  | Br | H | Cl | H |
| **19** | H | Br | H | H |  |
| **20** | H | $OCH_3$ |  | H | H |
| **21** | H | H |  | H | H |
| **22** | H | Br |  | Br | H |
| **23** | H | Cl | H | H |  |
| **24** | H | H |  | H | H |

| | | | | | |
|---|---|---|---|---|---|
| **25** | H | Br |  | Br | H |
| **26** | H | Cl |  | $OCH_3$ | H |
| **27** | H |  | $OCH_3$ | H | H |
| **28** |  | H | H | Br | H |
| **29** | H | H | H |  | H |
| **30** | H | $OCH_2CH_3$ |  | Br | H |

| | | | | | |
|---|---|---|---|---|---|
| **31** |  | H | H | Cl | H |
| **32** | H | H | $OCH_2OCH_3$ | H | $OCH_2OCH_3$ |
| **33** | H | H |  | Br | H |
| **34** | Cl | H | H |  | Cl |
| **35** |  | H | H |  | |
| **36** | H | H |  | $OCH_2CH_3$ | H |
| **37** | H | $OCH_2CH_3$ |  | Cl | H |

| | | | | | |
|---|---|---|---|---|---|
| **38** | H | H | H | H |  |
| **39** | H | H | H |  | H |
| **40** | H | H |  | $OCH_2CH_3$ | H |
| **41** |  | H | H | F | H |
| **42** | $OCH_2CHCH_2$ | $OCH_2CH_2$<br>$OCH_2CH_2OH$ | H | H | H |
| **43** |  | $OCH_3$ | H | $OCH_3$ | |
| **44** | H |  | $O(CH_2)_5CH_3$ | $OCH_3$ | H |

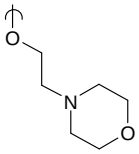
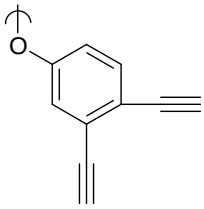
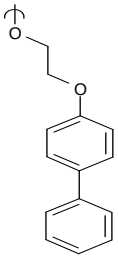
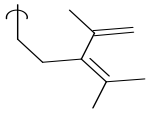
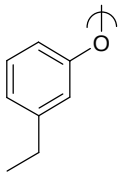
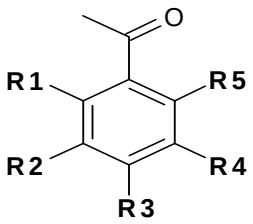
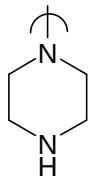
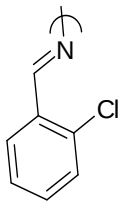
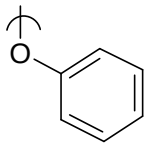
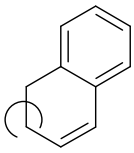
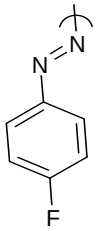
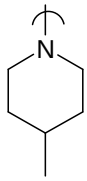
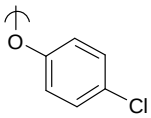
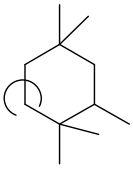
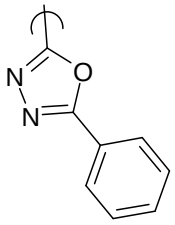
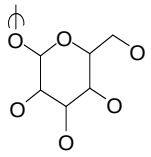
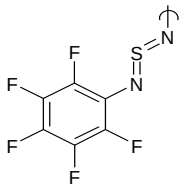
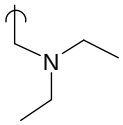
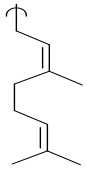
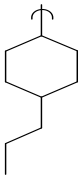
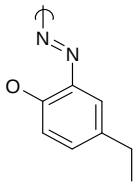
| | | | | | |
|---|---|---|---|---|---|
| **45** |  | Br | H | Cl | H |
| **46** | H | H |  | H | H |
| **47** | H |  | $OCH_3$ | H | H |
| **48** | H | H | H | H | H |
| **49** |  | H | H | H | $OCH_3$ |
| **50** | H |  | $O(CH_2)_5CH_3$ | $OCH_3$ | H |

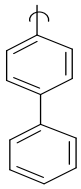
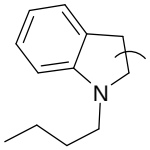
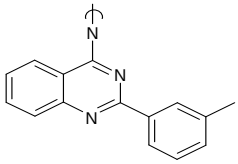
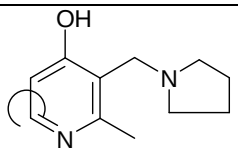
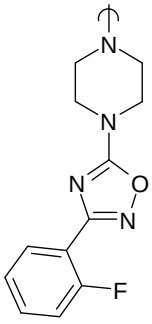
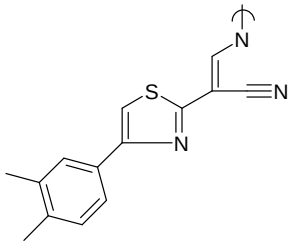
**Table 2:** Various substituted acetophenones downloaded from e-molecules database.

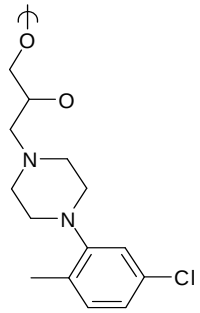
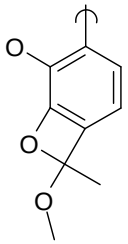
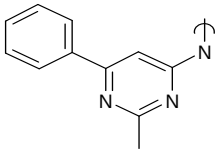
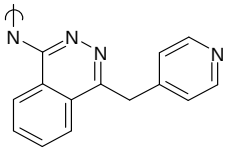
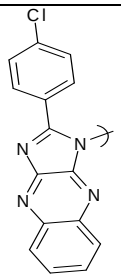
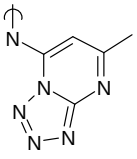


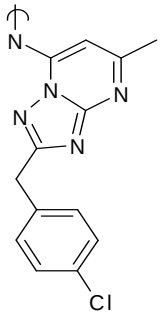
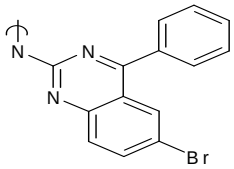
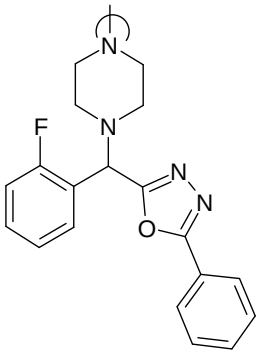
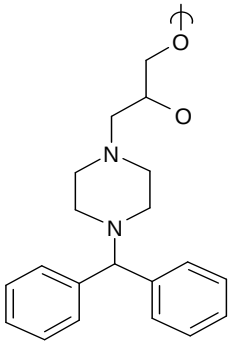

| S.NO | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|
| 1 | H | F | F | F | F |
| 2 | H | H | F | H | OH |
| 3 | Cl | Cl | F | H | H |
| 4 | H | $CH_3$ | $CH_3$ | $CH_3$ | H |
| 5 | H | H | NH-Si-$(CH_3)_3$ | H | H |
| 6 | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| 7 | H | $C(CH_3)_3$ | H | $C(CH_3)_3$ | OH |
| 8 | $C_6H_5$ | H | $C_6H_5$ | | |
| 9 | H | H | $(CH)_2(CH_2)_3$ $CH_3$ | H | H |
| 10 | H | H |  | F | H |
| 11 | H | H |  | H | H |

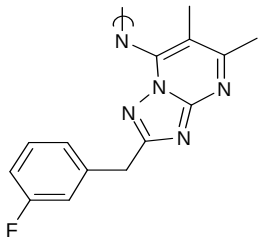
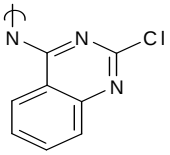
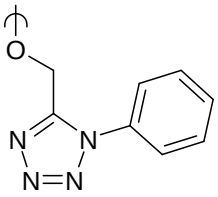
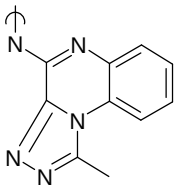
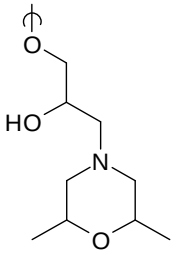
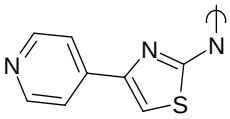
| | | | | | |
|---|---|---|---|---|---|
| **12** | H | H | H |  | H |
| **13** |  | H | H | H | |
| **14** | H | H | H |  | H |
| **15** | H | H |  | F | H |
| **16** | H | $CH_3$ | $CH_3$ | H | OH |
| **17** |  | H | H | H | H |
| **18** | $CH_3$ | H |  | H | |

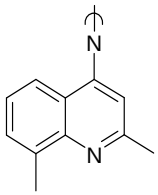
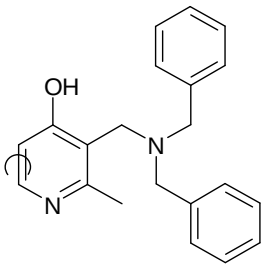
| | | | | | |
|---|---|---|---|---|---|
| **19** | H | H |  | H | H |
| **20** | OH | H | H | H |  |
| **21** | H | H |  | H | H |
| **22** | H | H | $OCH_2CH_3$ |  | H |
| **23** | OH |  | OH | H | H |
| **24** | H | H |  | H | H |
| **25** | H | H |  | H | H |

| | | | | | |
|---|---|---|---|---|---|
| **26** | H | H |  | H | H |
| **27** | H |  | H | H | |
| **28** | H | H | H |  | H |
| **29** | H | H |  | H | |
| **30** | H | H |  | H | H |
| **31** | H | H |  | H | H |

| | | | | | |
|---|---|---|---|---|---|
| **32** | H | H |  | H | H |
| **33** | H | H | OH |  | OH |
| **34** | H | H |  | H | H |
| **35** | H |  | H | H | H |
| **36** | H | H |  | H | H |
| **37** | H | H | H |  | H |

| | | | | | |
|---|---|---|---|---|---|
| **38** | H | H |  | H | H |
| **39** | H |  | H | H | H |
| **40** | H | H |  | H | H |
| **41** | H | H |  | H | H |

| | | | | | |
|---|---|---|---|---|---|
| **42** | H | H |  | H | H |
| **43** | H | H |  | H | H |
| **44** | H | H |  | H | H |
| **45** | H | H |  | H | H |
| **46** | H | H |  | H | H |
| **47** | H |  | H | H | H |
| **48** | H | H | H | H | H |

| | | | | | |
|---|---|---|---|---|---|
| **49** | H | H | H |  | H |
| **50** | H | H |  | | H |

**Molegro Virtual Docker**

Molegro Virtual Docker is a docking analysis tool used to predict the protein-ligand interactions. It determines the potential binding site of the target protein and lead candidates are identified by a molecular docking algorithm called MolDock, which is based on a new search algorithm that combines differential evolution with a cavity prediction algorithm.[32] The scoring scheme was derived from PLP (Piecewise Linear Potential) scoring functions originally proposed by Gehlhaar et al[33] and later extended by Yang et al.[34] The scoring function was further improved to include new hydrogen bonding term and charge schemes.

**Data Set**

The combinations of various substituted benzaldehydes and acetophenones were transformed into 2500 chalcones using ISIS draw software. Before docking, an energy minimization routine was performed to generate three dimensional structures of all the molecules using corina make 3D option, derived charges and the geometries were optimized using cosmic module of Tsar software and exported them as sybyl mol2 files. Water molecules were discarded from the PDB file,

hydrogens were added and docking was performed using MolDock docking engine of Molegro software. The binding site was defined as a spherical region which encompasses all protein atoms within 15.0 Å of bound crystallographic ligand atom (dimensions X (38.52 A°), Y (31.61 A°), Z (42.08 A°) axes, respectively). Default settings were used for all the calculations. Docking was performed using a grid resolution of 0.3 Å and for each of the 10 independent runs; a maximum number of 1000 iterations were executed on a single population of 50 individuals.

**3. Results and Discussion**

Before screening e-molecule library, the docking protocol was validated. 2Q6S protein bound ligand was docked into the binding pocket to obtain the docked pose and the RMSD of all the atoms between these two conformations is 0.71 A° (dock score of -159.57 kcal/mol), indicating that the parameters for docking simulation are good in reproducing the X-ray crystal structure and can be extended to search the new ligand binding conformations.

Various combinations of benzaldehyde and acetophenone moieties resulted in nearly 2500 chalcones with varied structural complexity that eventually reflected in their respective dock scores, varying from -27.06 to -230.10 kcal/mol, respectively. Hence, keeping in view, the original ligand dock score (-159.57 kcal/mol), the compounds were segregated based on their molecular weights. The main emphasis is to extract chalcones with reasonable molecular weights, which have the ability to pass through cell membranes[35] as well as to identify best combinations that represent PPAR gamma agonists. Therefore, given in Table-3 are dock scores and molecular weight comparisons of top 50 compounds from a designed data set of 2500 chalcones, and the 2D structures are given in Table-4. From Table-3 it is evident that the molecular weight Vs dock score comparisons resulted in gradual increase of dock scores from 189.27 kcal/mol (400-450 KDa) to a peak value of -230.10

kcal/mol (500-550 KDa) and there after a gradual decrease in dock scores were observed with simultaneous increase in molecular weights of chalcones. This suggests the fact that the chalcones with molecular weights more than 500 KDa are detrimental and hence these represent novel scaffolds for ligand design and development.

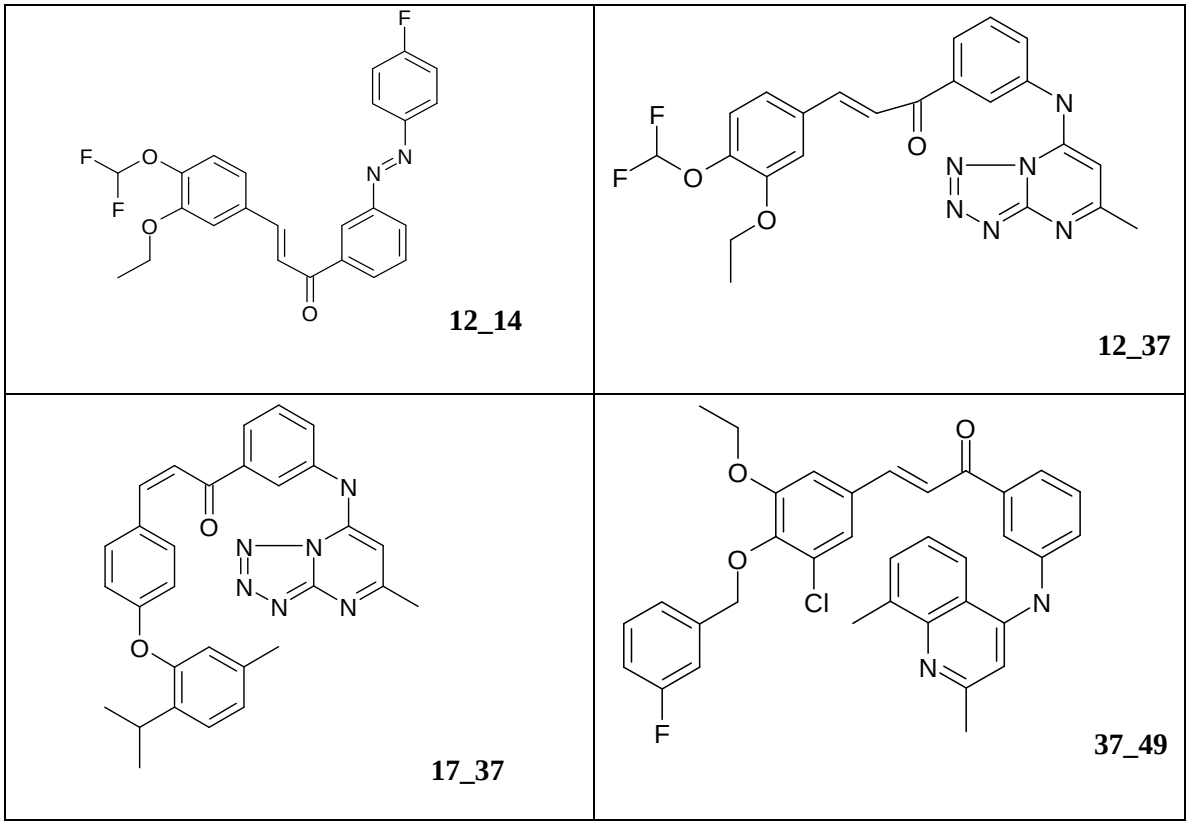
**Table 3:** Molecular weight based comparison of designed chalcones with dock scores in kcal/mol against PPAR gamma enzyme 2Q6S

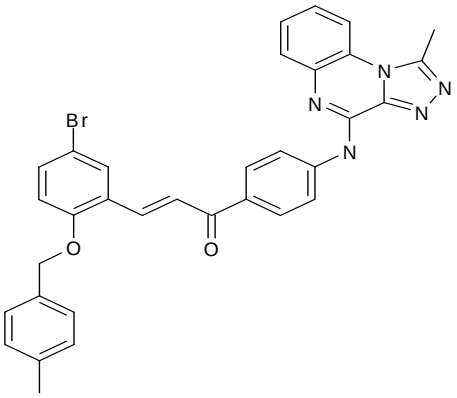
| **MW 400-450** | **MW 450-500** | **MW 500-550** | **MW 550-600** | **MW 600-650** | **MW 650-700** | **MW >700** |
|---|---|---|---|---|---|---|
| **12_14 (-189.27)** | 12_23 (-159.42) | 14_23 (-165.29) | 23_37 (-195.96) | 13_19 (-215.72) | 13_45 (-199.90) | **13_36 (-195.59)** |
| 12_15 (-180.06) | 12_29 (-197.97) | 14_29 (-176.04) | 23_49 (-183.95) | 13_27 (-206.28) | **19_36 (-202.98)** | 13_42 (-182.04) |
| 12_17 (-171.72) | **12_37 (-204.08)** | 14_37 (-194.69) | **37_49 (-226.36)** | 13_43 (-192.52) | 19_42 (-195.69) | 36_42 (-165.28) |
| | 12_49 (-178.01) | 14_49 (-175.31) | 19_27 (-194.99) | **19_45 (-225.38)** | 27_43 (-189.31) | |
| | 14_15 (-173.40) | 15_17 (-170.50) | 19_43 (-204.15) | 36_43 (-166.88) | 27_45(-180.16) | |
| | 14_17(-158.05) | 15_37 (-198.58) | 42_45 (-212.72) | 36_45 (-166.56) | | |
| | 29_23(-162.41) | 17_29 (-187.59) | | 43_49 (-168.05) | | |
| | 29_37(-190.73) | **17_37 (-230.10)** | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 29_49(-173.98) | 17_49 (-177.33) | | | | |
| | | 42_43 (-183.07) | | | | |

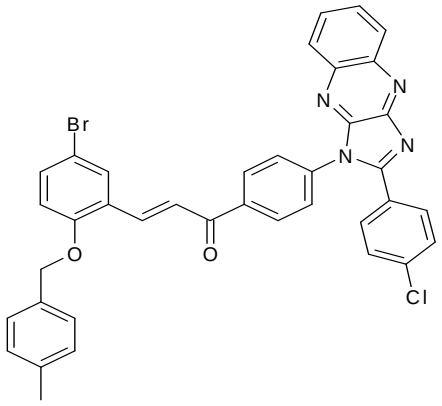
MW represents Molecular Weight and values in parentheses indicate molecular dock scores (kcal/mol) of compounds against PPAR gamma. Benzaldehyde and acetophenone ids are separated by underscore '_'.

**Table 4:** Top seven best chalcone 2D structures obtained from 2500 total data set.

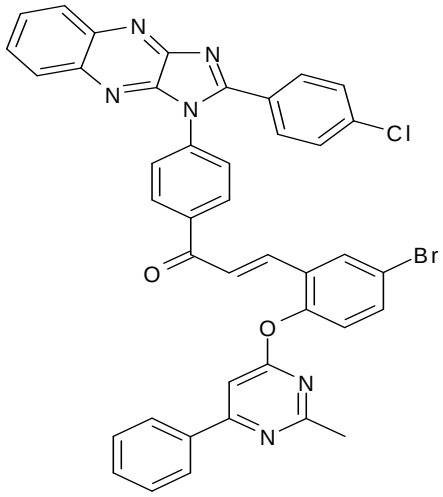




**19_45**



**19_36**



**13_36**

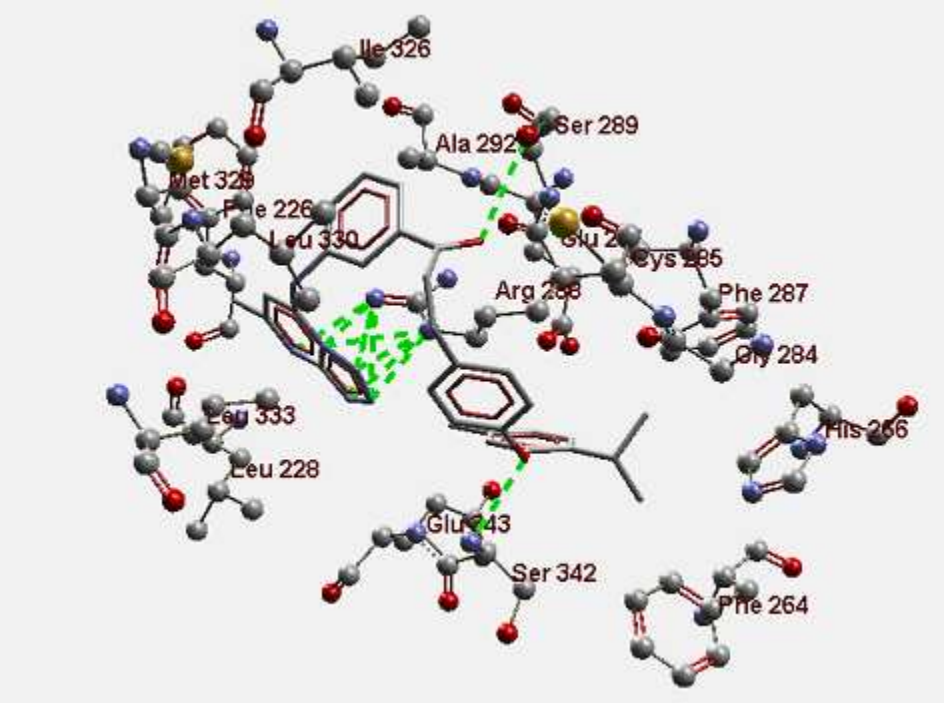



**Figure 1:** Best chalcone id 17_37 displaying 11 H-bond interactions with active site residues of PPAR gamma 2Q6S.

In the next step, H-bond interactions of best dock scores in each molecular weight category are tabulated and the geometric orientations within the active site region of PPAR gamma are compared. Interestingly, 17_37 chalcone showed maximum number of interactions (11 H-bonds) with Arg288, Ser342 and Ser289 of PPAR gamma. Other chalcones, given in Table 5, displayed only a minimum of one to five H-bond interactions. Moreover, 2Q6S bound ligand glitazone formed two H-bonds with His266 and Ser342 but reported a low affinity than 17_37 chalcone (-159.57 Vs -230.10 kcal/mol). It has also been observed from Table 5 that most of the chalcones displayed H-bonds with Arg288 residue. This is in agreement with other reports which have indicated that a high affinity towards partial agonism was observed with various ligands.[36,38] Literature search on similar aspects revealed H-bond interactions with Cys285, Arg288 and Ser342 in 5(2-pyrimidinyloxy) 2-

benzoylaminobenzoic acids[36,37], whereas interactions with Arg288 has been observed in 1-*O*-octadecenyl-2-hydroxy-*sn*-glycero-3-phosphate, which is a high affinity partial agonist.[38]

**Table 5:** H-bond interacting residues and dock scores of best chalcones from each molecular weight category.

| S. No. | Ligand | No. of interactions | Residues | Atom | MolDock Score (kcal/mol) |
|---|---|---|---|---|---|
| **1.** | 2Q6S bound ligand | 2 | His266<br>Ser342 | $NE_2$<br>N | -159.57 |
| **2.** | 12_14 | 1 | Cys285 | SG | -189.27 |
| **3.** | 12_37 | 5 | His266<br>Ser342<br>Arg288 | $NE_2$<br>N<br>NE | -204.08 |
| **4.** | 17_37 | 11 | Arg288<br>Ser342<br>Ser289 | $NH_2$, NE<br>N<br>OG | -230.10 |
| **5.** | 37_49 | 4 | Ser342<br>His266<br>Cys285<br>Ser289 | N<br>$NE_2$<br>SG<br>OG | -226.36 |
| **6.** | 19_45 | 4 | Cys285<br>Arg288 | SG<br>$NH_2$ | -225.38 |
| **7.** | 19_36 | 2 | Arg288 | $NH_2$ | -202.98 |
| **8.** | 13_36 | 5 | Arg288<br>Glu343<br>Ser342 | $NH_2$, NE<br>N<br>N | -195.59 |

**4. Conclusion:** Screening of 2500 chalcones as possible PPAR gamma agonists resulted in seven best compounds with dock scores far better than the original 2Q6S ligand. Molecular weight based comparison of chalcones resulted in compound 17_37 with dock score -230.10 kcal/mol and a maximum of 11 H-bond interactions suggest that accurate predictions can be achieved with few computational efforts in a relatively short time and experimental evaluation of their biological activities would help in designing compounds based on computer-aided techniques.

**5. References**

1. Y. Rajendra Prasad, P. Ravi Kumar, D. Jesse Smiles, P. Ajay Babu, *Arkivoc.* 2008, *xi*, 266-276.
2. Z. Nowakowska, B. Kedzia, G. Schroeder, *Eur. J. Med. Chem.* 2008, *43*, 707-713.
3. S. F. Nielsen, M. Larsen, T. Boesen, K. Schønning, H. Kromann, *J Med Chem.* 2005, *48*, 2667-2677.
4. Y. H. Kim, J. Kim, H. Park, H. P. Kim, *Biol & Pharm Bull.* 2007, *30*, 1450-1455.
5. S. J. Won, C. T. Liu, L. T. Tsao, J. R. Weng, H. H. Ko, J. P. Wang, C. N. Lin, *Eur. J. Med. Chem.* 2005, *40*, 103-112
6. K. L. Lahtchev, D. I. Batovska, St. P. Parushev, V. M. Ubiyvovk, A. A. Sibirny, *Eur. J. Med. Chem.* 2008, *43*, 2220-2228
7. L. Jayasinghe, B. A. Balasooriya, W. C. Padmini, N. Hara, Y. Fujimoto, *J. Phyto Chem.* 2004, *65*, 1287-1290
8. C. L. Ye, J. W. Liu, D. Z. Wei, Y. H. Lu, F. Qian, *Pharmacol Res.* 2004, *50*, 505-510.

9. J. Cianci, J. B. Baell, B. L. Flynn, R. W. Gable, J. A. Mould, D. Paul, A. J. Harvey, *Bioorg Med Chem Lett*. 2008, *18*, 2055-2061.
10. P. Shukla, A. B. Singh, A. K. Srivastava, R. Pratap, *Bioorg Med Chem Lett*. 2007, *17*, 799-802.
11. R. Kamei, M. Kadokura, Y. Kitagawa, O. Hazeki, S. Oikawa, *Life Sci*. 2003, *73*, 2091-2099.
12. A. R. Saltiel, *Cell*. 2001, *104*, 517-529.
13. D. E. Moller, *Nature*. 2001, *414*, 821-827.
14. D. Kim, L. Wang, M. Beconi, G. J. Eiermann, M. H. Fisher, H. He, G. J. Hickey, J. E. Kowalchick, B. Leiting, K. Lyons, F. Marsilio, M. E. McCann, R. A. Patel, A. Petrov, G. Scapin, S. B. Patel, R. S. Roy, J. K .Wu, M. J. Wyvratt, B. B. Zhang, L. Zhu, N. A. Thornberry, A. E. Weber, *J. Med. Chem*. 2005, *48*, 141-151.
15. E. B. Villhauer, J. A. Brinkman, G. B. Naderi, B. F. Burkey, B. E. Dunning, K. Prasad, B. L. Mangold, M. E. Russell, T. E. Hughes, *J. Med. Chem*. 2003, *46*, 2774-2789.
16. I. Gill, R. Patel, *Bioorg. Med. Chem. Lett*. 2006, *16*, 705-709.
17. S. V. Joy, P. T. Rodgers, A. C. Scates, *Ann. Pharmacother*. 2005, *39*, 110-118.
18. F. M. Matschinsky, *Diabetes.* 2002, *51*, S394-S404.
19. R. S. Savkur, A. R. Miller, *Expert Opin. Invest. Drugs*. 2006, *15*, 763-778.
20. B. R. Henke, *J. Med. Chem*. 2004, 47, 4118-4127.
21. B. Staels, J. Fruchart, *Diabetes.* 2005, *54*, 2460-2470.
22. G. Matthias, S. Bart, U. Thomas, K. Ulrich, G. Ronald, *Chem. Med. Chem.* 2009, *4*, 1136-1142.

23. T. Itoh, I. Murota, K. Yoshikai, S. Yamada, K. Yamamoto, *Bioorg. Med. Chem.* 2006, *14*, 98-108.

24. B. R. Henke, S. G. Blanchard, M. F. Brackeen, K. K. Brown, J. E. Cobb, J. L. Collins, W. W. Harrington Jr, M. A. Hashim, E. A. Hull-Ryde, I. Kaldor, S. A. Kliewer, D. H. Lake, L. M. Leesnitzer, J. M. Lehmann, J. M. Lenhard, L. A. Orband-Miller, J. F. Miller, R. A. Mook Jr, S. A. Noble, W. Oliver Jr, D. J. Parks, K. D. Plunket, J. R. Szewczyk, T. M. Willson, *J. Med. Chem.* 1998, *41*, 5020-5036.

25. E. Kim, C. S. Park, T. Han, M. H. Bae, W. Chong, C. H. Lee, Y. A. Shin, B. N. Ahn, M. K. Kim, C. Y .Shin, M. H. Son, J. K. Kim, H. S. Moon, H. J. Shim, E. J. Kim, S. H. Kim, J. I. Lim, C. H. Lee, *Bioorg. Med. Chem. Lett.* 2008, *18*, 4993-4996.

26. N. J. Kim, K. O. Lee, B. W. Koo, F. Li, J. K. Yoo, H. J. Park, K. H. Min, J. I. Lim, M. K. Kim, J. K. Kim, Y. G. Suh, *Bioorg. Med. Chem. Lett.* 2007, *17*, 3595-3598.

27. C. R. Kahn, L. Chen, S. E. Cohen, *J. Clin. Invest.* 2000, *106*, 1305-1307.

28. H. Oon Han, S. H. Kim, K. H. Kim, G. C. Hur, H. Joo Yim, H. K. Chung, S. Ho Woo, K. Dong Koo, C. S. Lee, J. Sung Koh, G. T. Kim, *Bioorg. Med. Chem. Lett.* 2007, *17*, 937-941.

29. Z. T. Bloomgarden, *Diabetes care*. 2005, *28*, 488-493.

30. J. B. Bruning, M. J. Chalmers, S. Prasad, S. A. Busby, T. M. Kamenecka, Y. He, K. W. Nettles, P. R. Griffin, *Structure*. 2007, *15(10)*, 1258-1271.

31. *Chemical Structure Drawing Search*, www.emolecules.com (accessed: 11th Feb. 2009).

32. R. Thomsen, M. H. Christensen, *J. Med. Chem.* 2006, *49*, 3315–3321.

33. D. K. Gehlhaar, G. Verkhivker, P. A. Rejto, D. B. Fogel, L. J. Fogel, S. T. Freer, *Docking Conformationally Flexible Small Molecules into a Protein Binding Site through Evolutionary Programming*, in: J. R. McDonnell, R. G. Reynolds, D. B. Fogel (Eds.) Proceedings of the Fourth Annual Conference on Evolutionary Programming, MIT Press, Cambridge, Massachusetts. 1995, 615-627.
34. J. M. Yang, C. C. Chen, *Proteins.* 2004, *55*, 288-304.
35. C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Deliv. Rev.* 1997, *23*, 3-25.
36. T. Ostberg, S. Svensson, G. Selén, J. Uppenberg, M. Thor, M. Sundbom, M. Sydow-Bäckman, A. L. Gustavsson, L. Jendeberg, J. Biol. Chem. 2004, 279, 41124-41130.
37. A. L. Ambrosio, S. M. Dias, I. Polikarpov, R. B. Zurier, S. H. Burstein, R. C. Garratt, J. Biol. Chem. 2007, 282, 18625-18633.
38. T. Tsukahara, R. Tsukahara, S. Yasuda, N. Makarova, W. J. Valentine, P. Allison, H. Yuan, D. L. Baker, Z. Li, R. Bittman, A. Parrill, G. Tigyi, J. Biol. Chem. 2006, 281, 3398-3407.

## Current Author Address:

**Archana Kumari. D. N. S. S***
**Avanthi Institute of Pharmaceutical Sciences,**
**Cherukupally (V), Bhogapauram (M),**
**Near Tagarapuvalasa Bridge,**
**Vizianagaram - 531162, India.**
**Tel: +91-9394509950.**