Three-dimensional quantitative structure-activity relationships and docking studies of some structurally diverse flavonoids and design of new aldose reductase inhibitors

Abstract

Aldose reductase (AR) plays an important role in the development of several long-term diabetic complications. Inhibition of AR activities is a strategy for controlling complications arising from chronic diabetes. Several AR inhibitors have been reported in the literature. Flavonoid type compounds are shown to have significant AR inhibition. The objective of this study was to perform a computational work to get an idea about structural insight of flavonoid type compounds for developing as well as for searching new flavonoid based AR inhibitors. The data-set comprising 68 flavones along with their pIC50 values ranging from 0.44 to 4.59 have been collected from literature. Structure of all the flavonoids were drawn in Chembiodraw Ultra 11.0, converted into corresponding three-dimensional structure, saved as mole file and then imported to maestro project table. Imported ligands were prepared using LigPrep option of maestro 9.6 version. Three-dimensional quantitative structure-activity relationships and docking studies were performed with appropriate options of maestro 9.6 version installed in HP Z820 workstation with CentOS 6.3 (Linux). A model with partial least squares factor 5, standard deviation 0.2482, \( R^2 = 0.9502 \) and variance ratio of regression 122 has been found as the best statistical model.

Key words: Aldose reductase, flavonoids, three-dimensional quantitative structure-activity relationships, extra precision glide docking, designed inhibitor

INTRODUCTION

Diabetes mellitus has become a common disease in many countries around the world, currently 387 million people worldwide suffering from this disease and expected to affect about 592 million peoples by 2035 (Figure 1).[1,2]

Under normal glycemic conditions, the majority of glucose is metabolized through glycolysis and only a small fraction of glucose is metabolized through the polyol pathway[3,4]. However, in diabetic condition glucose concentrations are elevated in tissues leading to increased flux of glucose through the polyol pathway where aldose reductase (AR) plays an important role as a key enzyme. AR being present in the lens, retina, Schwann cells of peripheral nerves may lead to blindness associated with increased risk for painful neuropathy, heart disease and kidney failure due to increased sorbitol flux and NADH/NAD\(^+\) ratio associated with decreased NADPH/NADP\(^+\) ratio [Figure 1], which plays an important role on other enzymes. Thus, AR is primarily important in the development of degenerative long-term diabetic complications such as cataract, neuropathy, retinopathy, and nephropathy.[5-9] Inhibition of AR activities is, therefore, a useful strategy for prevention and treatment of complications arising from chronic diabetes. Several classes of compounds have been reported in the literature[10-16] as AR inhibitors such as flavonoids, isoflavonoids, coumarins, stilbenes, rosmarinic acid derivatives, thiazolidinediones.[17]
etc., Among these, flavonoids and 2, 4-thiazolidinedione derivatives have been found to be more potent. These facts prompted us to perform a computational work with a view to get an idea regarding the structural insight of flavonoids to develop and searching for new selective and effective flavonoid based AR inhibitors.

MATERIALS AND METHODS

Data-set
The data-set is comprising 68 flavones along with their pIC₅₀ values ranging from 0.44 to 4.59 have been collected from literature.[18] It is hypothesized that active compounds share all or most of the required features for binding with the active site of the target molecule while the inactive compounds experience steric hindrance and other disfavored interactions. In view of these, the whole data-set of 68 molecules were clustered, and 54 flavonoid molecules were selected for the computational study. The selected subset randomly divided into a training set of 38 compounds (~70%) and a test set of 16 compounds [Table 1].

Ligand preparation
Structure of all the flavonoids were drawn in Chembiodraw Ultra 11.0 (Cambridge Soft), converted into corresponding three-dimensional structure, saved as mole file and then imported to maestro project table. Imported ligands were prepared using LigPrep option of Schrodinger maestro 9.6 version[19] where ligand minimization was done applying orthogonal partial least squares_2005 force field. Maximum of 100 conformers was generated by 100 steps preprocess and 50 steps postprocess minimization. Conformers were filtered for 11.4 kcal/mol energy and 2Å atom deviation with chiralities form three-dimensional structure and retaining original states of ionization.

Building three-dimensional-quantitative structure-activity relationships model
Ligand data-set was aligned [Figure 2] by atom type macro model option under shape screen. In Build quantitative structure-activity relationships (QSAR) option randomly selected 70% molecules were kept as training set and model was generated with 1Å grid spacing and partial least squares (PLS) factor 7. A model with PLS factor 5, 0.2482 as a standard deviation, 0.9502 as R² and 122 as F (variance ratio for the regression) has been found as the best statistical model.

Docking study
The docking studies were carried out with human AR (PDB ID: 3M01, resolution 1.07 Å7 retrieved from RCSB protein data bank. The root mean square deviation (0.20 Å) of superimposition between docking and co-crystalline pose of co-ligand was calculated. This AR was mutated with Val-113, refined by protein preparation wizard of Schrodinger Maestro version 9.6. A grid box with maximum 12Å edge lengths was generated centering the co-ligand and retaining other default settings. We have virtually replaced Val-113 (mutated residue) of 3M01 by Thr-113 (normal residue) and compared the ligand interactions with the receptor. Extra precision (XP) glide docking[19-21] was performed with both AR separately for the entire data-set [Table 1] enabling the XP descriptor option and other default values in glide module[22] of maestro 9.6 were retained. The co-crystal ligand structure of 3M01 was superimposed [Figure 3] on the docking poses of the same with mutated (Val-113) and nonmutated AR.

RESULTS AND DISCUSSION
Atom-based three-dimensional QSAR models were generated for a series of 54 structurally diverse flavonoid
derivatives with pIC₅₀ ranging from 3.96 to 6.59 [Table 1].

A statistically significant three-dimensional -QSAR model was generated, and over-fitting was avoided with the results of different PLS factor and relevant statistical parameters are summarized in Table 2.

**Three-dimensional quantitative structure-activity relationships analysis**

In this study, AR inhibitory activity of the selected ligands were tried to visualize by a developed QSAR model. Different statistical parameters of QSAR models so far generated are presented in Table 2. Results of different structural features viz. hydrogen bonding, hydrophobic interaction and electron withdrawing effect were applied to the most active compound 1 and the least active compound 54 and are shown [Figures 4-6]. Inspection of three-dimensional QSAR visualization [Figure 4] generated by PHASE [23] revealed that 5, 7, 3, 4 positions as indicated by blue cubes are favorable for hydrogen bond donor groups in flavonoid skeleton and the orange cubes in the vicinity of 6, 3 and 2' positions are unfavorable. These observations are corroborated by the activity of compound 1 (highest active) in which the hydrogen bond donor groups are available at position 5, 7, 3', 4' while in least active compound 54, the 7-OH and 3'-OH groups are replaced by O-CH₃.

Similarly presence of hydrophobic groups at 3, 6 and 8 positions as indicated by green color [Figure 5] are favorable for better activity while presence of similar group at 7, 3' and 4' indicated by purple color are detrimental for activity. It is seen that in compound 1, O-CH₃ group occupied 3 and 6 positions and had favorable contribution to its enhanced

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**Table 1: List of the flavonoid derivatives with their observed and predicted biological activities**

| Comp. number | Substituent | Exp. pIC₅₀ | Pred. pIC₅₀ | Comp. No. | Substituent | Exp. pIC₅₀ | Pred. pIC₅₀ |
|-------------|-------------|-----------|-------------|-----------|-------------|-----------|-------------|
| 1           | 5,7,3',4'-OH; 3,6-OCH₃ | 7.59 | 7.58 | 28 | 5,3',4'-OH; 3,6,7-OCH₃ | 6.46 | 6.60 |
| 2*          | 3',4'-OH; 5,6,7,8-OCH₃ | 7.49 | 7.21 | 29 | 5,7,4'-OH; 6,8-OCH₃ | 6.39 | 6.29 |
| 3*          | 6,3',4'-OH; 5,7,8-OCH₃ | 7.44 | 6.92 | 30* | 5, 4'-OH; 6,7,8-OCH₃ | 6.27 | 6.00 |
| 4           | 5,7,3',4'-OH; 6-OCH₃,8-OCH₃,Ph | 7.47 | 7.53 | 31 | 5,6,3',4'-OH; 3, 7-OCH₃ | 6.09 | 6.25 |
| 5           | 5,3',4'-OH; 6,7,8-OCH₃ | 7.41 | 7.31 | 32 | 3,5,7,3',4'-OH | 6.02 | 5.84 |
| 6           | 3',4'-OH; 5,7,8-OCH₃ | 7.35 | 7.14 | 33 | 5,6,4'-OH; 7,8-OCH₃ | 6.07 | 5.94 |
| 7           | 5,6,7,3',4'-OH; 3-OCH₃ | 7.24 | 6.92 | 34 | 5,6,7,4'-OH; 8-OCH₃ | 5.92 | 6.05 |
| 8*          | 5,6,3',4'-OH; 7,8-OCH₃ | 7.19 | 6.37 | 35 | 5,6,7,4'-OH; 8,3'-OCH₃ | 5.92 | 5.34 |
| 9           | 7,3',4'-OH; 5,8-OCH₃ | 7.13 | 7.01 | 36* | 5,4'-OH; 6,7-OCH₃ | 5.85 | 6.51 |
| 10          | 5,3',4'-OH; 7,8-OCH₃ | 7.11 | 7.20 | 37* | 5,7,3',4'-OH; 3-O-Ph | 6.54 | 6.35 |
| 11          | 3',4'-OH; 5,6,7-OCH₃ | 7.04 | 7.14 | 38* | 5,7,4'-OH; 6,8,3'-OCH₃ | 5.35 | 5.20 |
| 12          | 5,6,7,3',4'-OH; 8-OCH₃ | 6.92 | 6.86 | 39 | 6,4'-OH; 5,7,8,3'-OCH₃ | 5.20 | 5.36 |
| 13          | 6,3',4'-OH; 5,7-OCH₃ | 6.85 | 6.86 | 40 | 5,4'-OH; 6,7,3'-OCH₃ | 5.17 | 4.41 |
| 14          | 4'-OH; 5,6,7,8-OCH₃ | 6.79 | 6.62 | 41 | 5,7-OH; 6,8,4'-OCH₃ | 5.14 | 5.16 |
| 15*         | 8,3',4'-OH; 5,7-OCH₃ | 6.79 | 7.09 | 42* | 5,6,7-OH; 8-OCH₃ | 5.09 | 5.11 |
| 16          | 3',4'-OH; 3,5,7,8-OCH₃ | 6.77 | 6.87 | 43 | 5,6-OH; 7,8-OCH₃ | 5.08 | 4.11 |
| 17          | 5,6,7,3',4'-OH | 6.69 | 7.05 | 44 | 3',4'-OH; 5,6,7,8-OCH₃; 3-COCH₃ | 5.05 | 6.1 |
| 18*         | 5,3',4'-OH; 6,7-OCH₃ | 6.92 | 6.77 | 45 | 5,3',4'-OH; 6,7-OCH₃; 4'-O-Glc | 5.09 | 4.88 |
| 19*         | 5,8,3',4'-OH; 7-OCH₃ | 6.64 | 6.97 | 46* | 5-OH; 6,7,3'-OCH₃; 4'-O-Glc | 4.81 | 4.69 |
| 20          | 5,7,3',4'-OH; 3,8-OCH₃ | 6.62 | 6.52 | 47 | 5-OH; 6,7,3'-OCH₃; 4'-O-Glc | 4.60 | 5.44 |
| 21          | 6,4'-OH; 5,7-OCH₃ | 6.60 | 6.03 | 48* | 5,7-OH; 6,8,3'-OCH₃; 4'-O-Glc | 4.33 | 5.38 |
| 22          | 3',4'-OH; 5,6,7-OCH₃ | 6.57 | 6.55 | 49 | 4'-OH; 5,6,7,3'-OCH₃ | 4.74 | 4.7 |
| 23          | 5,7,3',4'-OH; 8-OCH₃ | 6.55 | 6.85 | 50 | 5,4'-OH; 6,8,3'-OCH₃; 7-O-Glc | 4.15 | 4.05 |
| 24*         | 7,3',4'-OH; 3,5,8-OCH₃ | 6.55 | 7.04 | 51* | 5,7-OH; 6,8,3',4'-OCH₃ | 4.67 | 4.98 |
| 25          | 8-OCH₃, 5,6,7,3',4'-OOCCH₃ | 6.52 | 6.66 | 52 | 5,4'-OH; 6,7,8,3'-OCH₃ | 4.42 | 4.5 |
| 26*         | 5,6,3',4'-OH; 7-OCH₃ | 6.52 | 0.41 | 53 | 6-OH; 5,7,8-OCH₃ | 4.44 | 4.14 |
| 27          | 6,3',4'-OH; 3,5,7-OCH₃ | 6.52 | 6.94 | 54 | 5,6,4'-OH; 7,8,3'-OCH₃ | 3.96 | 4.01 |

*Test set molecules

Figure 4: Hydrogen bonding interactions: Blue implies positive and orange implies negative effect; 1: Highest active, 54: Lowest active
activity. In compound 54 presence of –OH group at position 6, -OCH₃ group at 7 and absence of the hydrophobic group at 3 positions greatly reduced the activity.

Three-dimensional quantitative structure-activity relationships visualization [Figure 6] indicates that electron withdrawing group at 3, 3 and 4n positions that is, in the vicinity of green region are favorable but position 8 should be devoid of such groups for better activity. This is further corroborated by the activity of compound I in which electron withdrawing oxygen atom is present at position 3’, 4’ (as –OH), and 3 (as -OCH₃). On the other hand in compound 54 one of the favorable positions (3’) is occupied by weak electron withdrawing -OCH₃ group (-OH>–OCH₃ due to +I effect of -CH₃) and least favorable ‘8’ position is occupied by –OCH₃ group represented by orange color in Figure 6.

The experimental and predicted pIC₅₀ values of the training and test sets are given in Table 1 while regression graph of experimental versus predicted pIC₅₀ values of the training and test sets are illustrated [Figure 7].

Docking analysis
The docking results (XP Glide docking parameters) of the selected flavonoids with mutated, as well as normal AR, are summarized in Table 3.

Ligand-receptor interactions in mutated as well as in normal AR are found similar. This may be due to because mutation of the AR (Thr-113 ↔X) is not in the active site. The highest active compound 1 and the co-ligand show similar interactions with residues viz. Leu-300 [Figure 8a]. This result also corroborated with the three-dimensional-QSAR model that developed in Phase module. The docking study also indicates that the 5-OH act as favorable hydrogen bond acceptor in flavones. This feature is supported by the activity (within parenthesis) of 1 (7.59), 7 (7.24), 17 (6.69), 26 (6.52), 32 (6.02) that interacts with Leu-300 of protein (AR) that is, interaction of 5-OH with Leu-300 is crucial for potential activity. Hydrogen bond donor interaction with Val-47 and 5-OH of flavones were found in 31 (6.09), 33 (6.07), 34 (5.92), 35 (5.92), 37 (6.54), 42 (5.09), 43 (5.08) and attributed the observed activity of these compounds. The πhe staking interaction between Trp-111 and R1 of flavones in compound 1 (7.59), 7 (7.24), 17 (6.69), 32 (6.02) are also plays an important role to have good activity. The interaction of Trp-111, an amino acid residues in the active site of AR with Ri [Figure 9] of flavones are also found in maximum number (41) of compounds such as 2 (7.49), 3 (7.44), 4 (7.47), 5 (7.41), 6 (7.35), 8 (7.19), 9 (7.13), 10 (7.11), 11 (7.04), 12 (6.92), 13 (6.85), 14 (6.79), 16 (6.77), 18 (6.92), 19 (6.64), 20 (6.62), 22 (6.57), 23 (6.55), 24 (6.55), 26 (6.52), 27 (6.52), 28 (6.46), 29 (6.39), 30 (6.27), 31 (6.09), 32 (6.02), 34 (6.02), 35 (6.02), 36 (6.85), 37 (6.54), 38 (5.35), 39 (5.20), 40 (5.17), 41 (5.14), 42 (5.09), 43 (5.08), 44 (5.05), 49 (4.74),
Table 2: Summary of statistical parameters of the more significant models with different PLS factors

| Factors | SD  | R²   | R² scramble | Stability | F    | P    | RMSE | Q² | Pearson (r) |
|---------|-----|------|-------------|-----------|------|------|------|----|-------------|
| 1       | 0.603 | 0.669 | 0.3711      | 0.446     | 72.8 | 3.63E-10 | 0.68 | 0.5254 | 0.7259 |
| 2       | 0.483 | 0.7935 | 0.5548     | 0.473     | 57.3 | 1.02E-12 | 0.54 | 0.694 | 0.8362 |
| 3       | 0.3612 | 0.8878 | 0.6884     | 0.546     | 94.7 | 3.17E-16 | 0.47 | 0.7693 | 0.8801 |
| 4       | 0.2871 | 0.9312 | 0.8068     | 0.455     | 111.7| 1.08E-18 | 0.43 | 0.8116 | 0.904 |
| 5       | 0.2482 | 0.9502 | 0.8641     | 0.45      | 122  | 7.28E-20 | 0.42 | 0.8204 | 0.9078 |
| 6       | 0.2207 | 0.9618 | 0.8999     | 0.465     | 130.1| 1.41E-20 | 0.45 | 0.7908 | 0.8946 |
| 7       | 0.198 | 0.9703 | 0.9333     | 0.481     | 139.8| 4.04E-21 | 0.45 | 0.7892 | 0.901 |

SD: Standard deviation, PLS: Partial least square, RMSE: Root mean square error

Table 3: XP glide docking parameters of some selected (pIC₅₀>7) flavonoids of the dataset

| Comp. number | Major interactions, residues, bond length with mutated AR (Val-113) | XPGS | Major interactions, residues, bond length with mutated AR (Thr-113) | XPGS |
|--------------|----------------------------------------------------------------------------|------|----------------------------------------------------------------------------|------|
| 1            | HBA: Leu-300 (5-OH), 2.07Å; π-π staking: Trp-20 (R'), Trp-111 (R1), Phe-122 (R') | −12.16 | HBA: Leu-300 (4-CO), 2.18Å; π-π staking: Trp-20 (R'), Trp-111 (R1), Phe-122 (R'), Trp-79 (R') | −12.963 |
| 2            | π-π staking: Trp-111 (R') | −9.36 | HBA: Trp-20 (5-OCH₃), 2.01Å; π-π staking: Trp-111 (R') | −9.12 |
| 3            | HBA: Leu-300 (4'-OH), 1.98Å; π-π staking: Trp-111 (R') | −9.46 | HBA: Trp-20 (6-OH), 2.18Å; Leu-300 (3'-OH), 1.94Å; π-π staking: Trp-111 (R'), Trp-219 (R1) | −10.66 |
| 4            | HBA: Trp-20 (6-OCH₃), 2.13Å; π-π staking: Trp-20 (8-CH₂CH₂OH), Trp-111 (R') | −11.43 | π-π staking: Phe-122 (8-CH₂Ph), Trp-122 (R') | −10.29 |
| 5            | π-π staking: Trp-111 (R') | −10.17 | π-π staking: Trp-111 (R') | −9.79 |
| 6            | π-π staking: Trp-111 (R') | −9.36 | π-π staking: Trp-111 (R') | −9.16 |
| 7            | HBA: Leu-300 (5-OH), 2.20Å; π-π staking: Trp-20 (R'), Trp-111 (R1), Phe-122 (R') | −11.64 | HBA: Trp-20 (4'-OH), 2.25Å, Leu-300 (4-CO), 1.82Å; π-π staking: Trp-111 (R1) | −13.30 |
| 8            | π-π staking: Trp-111 (R') | −10.86 | π-π staking: Trp-111 (R') | −10.23 |
| 9            | π-π staking: Trp-111 (R') | −9.46 | HBA: Trp-111 (8-OCH₃), 2.00Å; π-π staking: Trp-20 (R1), Trp-111 (R') | −10.91 |
| 10           | π-π staking: Trp-111 (R') | −10.13 | HBD: Val-47 (5-OH), 2.31Å; staking: Trp-111 (R') | −9.93 |
| 11           | HBA: Leu (3'-OH), 2.30Å; π-π staking: Trp-111 (R') | −9.73 | HBA: Leu-300 (4-CO), 2.20Å; π-π staking: Trp-20 (R'), Trp-111 (R1), Phe-122 (R') | −10.74 |

HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor, XPGS: XP glide score, XP: Extra precision, AR: Aldose reductase

Figure 9: Skeletal structure of flavone

51 (4.67), 52 (4.42), 54 (3.96). Out of these 41 interacting flavones twenty-seven have activity > 6, ten have activity in the range of 5–6 and only four have activity < 5. Therefore, interaction between Trp-111 and R2 of flavones play an important role in the activity against AR. Another two-staking interaction with Trp-20 and Rn of flavones play a significant role in ligand interaction and are also observed in 1 (7.59), 7 (7.24), 15 (6.79), 17 (6.69), 21 (6.60), 25 (6.52), 28 (6.46), 32 (6.02), 53 (4.44). Considering altogether the favorable and unfavorable features we have designed a large number of AR inhibitors and performed similar docking studies. Two-dimensional views of ligand-receptor interaction diagram of co-ligand, highest active ligand and two best designed new molecules [Figure 8a and b]. Since we are practically not in a position to study the AR inhibition and hence we did not attempt to synthesize the highly active designed molecule. However, it can be tried in the future.

CONCLUSION

This atom based three-dimensional-QSAR model and docking studies could help in understanding the relationship between structure and activity of flavonoid type compounds as AR inhibitors and gives us various options to design a novel and potent inhibitors for AR. However, other conditions like transport properties and steric factors are also needed to be considered while further new molecules are designed.

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