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# PREDICTING MOLECULAR INTERACTIONS IN SILICO: HHEX - DRUG DOCKING APPROACHES IN D2M

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**ABSTRACT:**

D2M is a metabolic syndrome, which is highly associated with human life and may possess like with other metabolic and aging diseases. HHEX is a gene significantly involved in developing D2M. .The metabolic pathway provides the information regarding the molecules responsibe for the cause of D2M. The molecular docking predicts the lowest binding energy using Emin values. All the drugs has shown negative energies, predicted that all the ligands act on hhex. Based on R-value and energy value in Hex,, Glimepride, Vitamin E and Acarbose showed better results. Based on GEMDOCK energy values, Glibenclamide and Mazindol predicted better results.

**Keywords**: Docking, Hex, GEMDOCK, D2M, hhex gene

## [I] INTRODUCTION

Diabetes mellitus is recognized as being a metabolic syndrome [1] and the most prevalent chronic disease [2] with a collection of disorders that have hyperglycemia and glucose intolerance [3] as their trait. Type 2 diabetes (D2M) is due to a combination of lifestyle [4] and genetic factors with long-term complications from high blood sugar, can include increased risk of heart attacks, strokes, amputation, and kidney failure [5].

Environmental toxins and environmental changes may also contribute to recent increases in the rate of type 2 diabetes [6]. In addition, there is also a mutation to the Islet Amyloid Polypeptide gene that results in an earlier onset, more severe, form of diabetes [7].

Genes significantly associated with developing type 2 diabetes, include *TCF7L2*, *PPARG*, *FTO*, *KCNJ11*, *NOTCH2*, *WFS1*, *CDKAL1*, *IGF2BP2*, *SLC30A8*, *JAZF1*, and *HHEX*. *KCNJ11* (potassium inwardly rectifying channel, subfamily J, member 11), encodes the islet ATP-sensitive potassium channel Kir6.2, and *TCF7L2* (transcription factor 7–like 2) regulates proglucagon gene expression and thus the production of glucagon-like peptide-1 [8, 9].

The PRH (proline-rich homeodomain) protein, also known as the Hex (haematopoietically expressed homeobox) protein (also termed Hhex or HHEX) [10] is a transcription factor and a critical regulator of vertebrate development.

PRH is able to regulate cell proliferation and differentiation and is required for the formation of the vertebrate body axis, the vascular systems and haematopoietic and the formation of many vital organs. PRH can also stimulate the expression of proteins that block the action of signalling pathways in the posterior mesoderm including the expression of Cerberus, aNodal and Wnt antagonist.

The role of PRH in pancreatic development has been eminent and allows the possibility that PRH could be involved in the development of diabetes [11].

## [II] MATERIALS AND METHODS

### 2.1. System requirements

Analysis of drug targeting on diseased molecule using *in silico* methods has been conducted with the following infrastructure.

1. **SYSTEM USED** – Intel Pentium 4, 3,4 GHz, 2GB RAM
2. **OPERATING PLATFORM** Microsoft Windows XP pro 2002 service pack
3. **SOFTWARE PACKAGES** – HEX 6.3, GEMDOCK v2.1

### 2.2. PDB

The Protein Data Bank (PDB) is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. The data, typically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists from around the world. The PDB is a key resource in areas of structural biology, such as structural genomics.

### 2.3. DRUG BANK

The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information.

### 2.4. KEGG

Metabolic pathway database such as KEGG provides the biological information for the cause of diseases. Molecular changes in the system may form a new pathway, cause useful or harmful effects inside the biological systems.

### 2.5. Docking studies

Various ligands are selected from DrugBank. and are docked against selected PDB diseased molecules using Hex and GEMDOCK. The relative stabilities were evaluated using free energy simulations.

Hex is an interactive molecular graphics program for calculating and displaying feasible docking modes of molecular pairs. Hex can also calculate protein-ligand docking, assuming the ligand is rigid.

GEMDOCK - a Generic Evolutionary Method for molecular DOCKing GEMDOCK is a program for computing a ligand conformation and orientation relative to the active site of target protein.

## [III] RESULTS

### 3.1. Diseased protein identification

KEGG provides a base for identification of diseased molecule in the system. Figure.1 provided the information and pathway for the cause of D2M

### 3.2. Docking with Hex

Docking of various 3D molecules of D2M proteins against ligands has been conducted. The minimum energy (Emin) value for the protein-ligand complex was calculated and is presented in Tables 1. Glimepride, Vitamin E and Acarbose showed better results, based on R-value and Emin. Hence the above drugs may be helpful in the treatment of D2M.

### \3.3. Docking with GEMDOCK

(Table 2) Glibenclamide, and Mazindol predicted better results with GEMDOCK. Hence the above drugs may be highly applicable in the treatment of D2M.

## [IV] DISCUSSION

A number of explanations were postulated for association of Alzheimer's disease in the development of impaired fasting glucose and type 2 diabetes mellitus. Pancreatic islets in diabetes contain neurofibrillary tangles may cause cytotoxic effect by interacting with cell membranes, may therefore be mediated by common regulatory elements [12].

Diabetes Mellitus is the most prevalent chronic disease in the world [13], engaged with physical,

psychological, and social changes and is related to an aging factor.

Docking approach establishes distinct roles for the “lock-and-key” (recognition) and the “handshake” (binding) paradigms for drug design strategies [14].

Pharmacophore-based and docking techniques are the two important aspects involved in predicting molecular-interactions in computer-aided drug design (CADD). Computational methods for the detection and characterisation of protein ligand-binding sites have increasingly become an area of interest as an important tool for small-molecule lead discovery [15].

In the past decade, studies using traditional linkage analysis and candidate-gene association approach have found that large number of genes harboring common variants that were related to the common-form type 2 diabetes. Since 2007, genome-wide association (GWA) studies emerged to generate a list of new diabetes genes such as hhex [16]. Acarbose seems to be of moderate efficacy for type II diabetes and vitamin E-like structure and may have antioxidant properties [17].

Differing mechanisms of action, combination therapy is evolving as a means of optimizing glycemic control in patients in D2M [18].

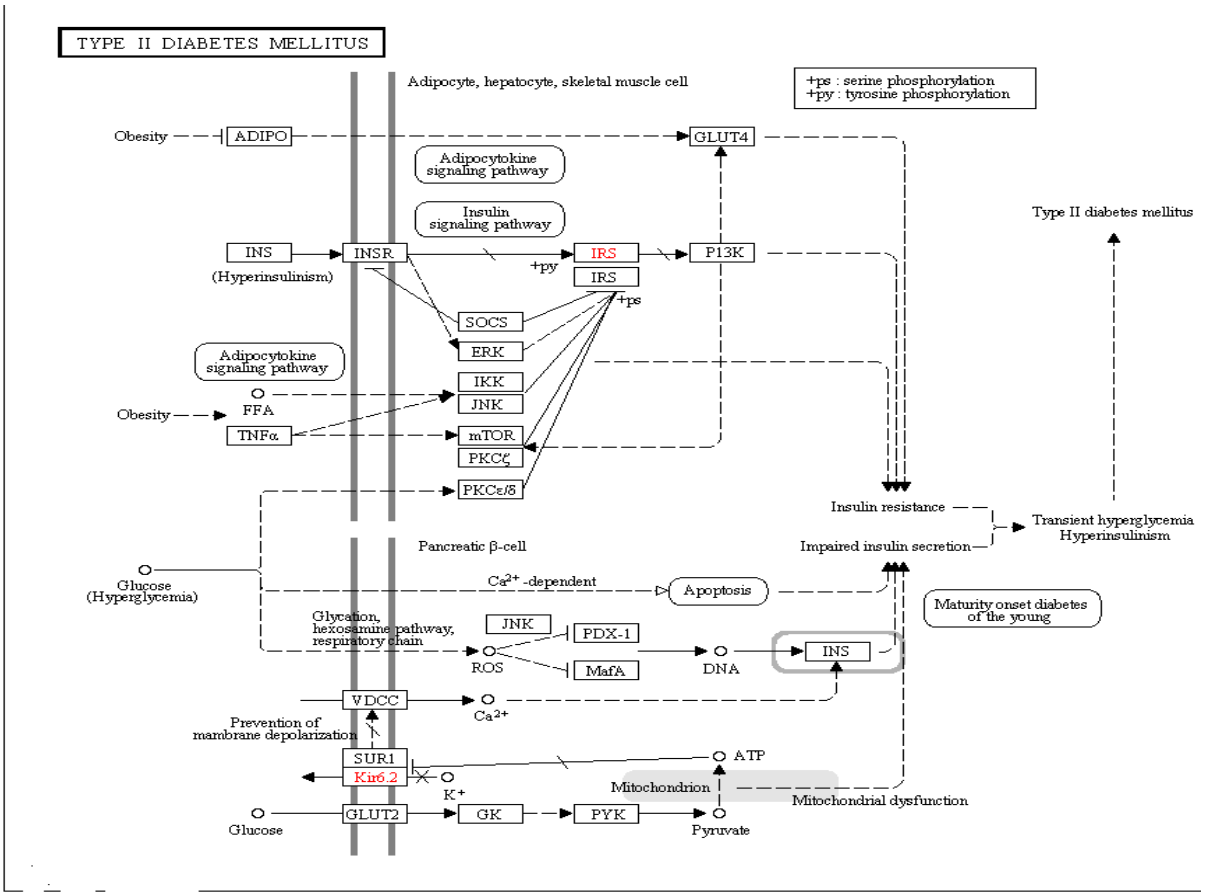


Figure: 1. Metabolic cause of Diabetes 2 mellitus from KEGG

## [V] CONCLUSION

The increasing availability of protein three-dimensional structures coupled with continuing advances in docking and scoring methods through binding energies/ Emin. Predicting protein interactions is one of the most important challenging problems in functional proteomics. The present Docking methods provided virtual screening from a database of compounds to predict the

strongest binders based on various scoring functions.

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| S.NO | LIGAND | 2E1O (Homeobox protein PRH) | | | |
|---|---|---|---|---|---|
| | | Emin | Emax | Etot | R-value |
| 1. | **VITAMIN E** | -229.33 | -179.35 | -262.87 | 7.2 |
| 2. | **LIPOIC ACID** | -143.03 | -118.48 | -156.94 | 8.8 |
| 3. | **RAMILPRIL** | -201.18 | -163.47 | -225.92 | 8.8 |
| 4. | **TROGLITAZONE** | -210.69 | -177.79 | -231.03 | 9.6 |
| 5. | **GLIMEPRIDE** | -222.09 | -186.93 | -249.43 | 6.4 |
| 6. | **ACARBOSE** | -237.04 | -190.41 | -273.62 | 7.2 |
| 7. | **ROSIGLITAZONE** | -289.83 | -220.25 | -289.83 | 11.2 |
| 8. | **ACETOHAEXAMIDE** | -185.94 | -149.46 | -193.80 | 9.6 |
| 9. | **STREPTOZOCIN** | -161.74 | -131.24 | -169.22 | 8.8 |
| 10. | **DULOXETINE** | -199.67 | -164.56 | -199.67 | 13.6 |
| 11. | **MIGLITOL** | -227.15 | -180.20 | -234.71 | 16.0 |
| 12. | **FOSINOPRIL** | -178.77 | -134.78 | -178.77 | 7.7 |
| 13. | **TRANDOLAPRIL** | -215.46 | -167.12 | -225.07 | 9.4 |
| 14. | **MAZINDOL** | -174.94 | -135.5 | -176.70 | 8.0 |
| 15. | **DEMECLOCYCLINE** | -244.63 | -201.31 | -244.63 | 8.9 |
| 16. | **LISINOPRIL** | -272.89 | -190.01 | -272.89 | 9.3 |
| 17. | **NATEGLINIDE** | -209.71 | -189.32 | -209.71 | 8.1 |
| 18. | **PENTAMIDINE** | -199.01 | 153.21 | -199.01 | 7.3 |
| 19. | **TOLAZAMIDE** | -176.78 | -123.67 | -176.78 | 8.0 |
| 20. | **PREDNISOLONE** | -184.77 | -151.7 | -184.77 | 7.8 |
| 21. | **TACROLIMUS** | -199.01 | 153.21 | -199.01 | 9.2 |
| 22. | **QUINAPPRIL** | -201.18 | -163.47 | -225.92 | 8.8 |
| 23. | **REPAGLINIDE** | -178.14 | -129.94 | -178.14 | 9.3 |
| 24. | **PHENOFORMIN** | -191.21 | -168.90 | -191.21 | 9.1 |
| 25. | **TELMISARTAN** | -289.83 | -220.25 | -289.83 | 11.2 |
| 26. | **HYDROCHLOROTHIAZIDE** | -143.03 | -118.48 | -156.94 | 8.8 |
| 27. | **GLIBENCLAMIDE** | -209.71 | -189.32 | -209.71 | 8.1 |
| 28. | **IRBESARATAN** | -174.94 | -135.5 | -176.70 | 8.0 |
| 29. | **GLIPIZIDE** | -289.83 | -220.25 | -289.83 | 7.8 |
| 30. | **GLICLAZIDE** | -172.50 | -133.76 | -172.50 | 7.0 |
| 31. | **TOLBUTAMIDE** | -191.21 | -168.90 | -191.21 | 9.1 |
| 32. | **PIOGLITAZONE** | -227.15 | -180.20 | -234.71 | 16.0 |
| 33. | **DEXFENFLURAMINE** | -178.77 | -134.78 | -178.77 | 7.7 |
| 34. | **DEXAMETHASON** | -174.94 | -135.5 | -176.70 | 8.0 |
| 35. | **GLIQUIDONE** | -200.18 | -165.23 | -200.18 | 8.9 |
| 36. | **SITAGLIPTIN** | -199.01 | 153.21 | -199.01 | 7.3 |
| 37. | **GLYCODIAZINE** | -192.11 | -163.27 | -192.11 | 8.8 |
| 38. | **SODIUM BICARBONATE** | -112.31 | -94.5 | -112.31 | 9.2 |
| 39. | **BEZAFIBRATE** | -184.77 | -151.7 | -184.77 | 7.8 |
| 40. | **VILDAGLIPTIN** | -161.74 | -131.24 | -169.22 | 8.8 |
| 41. | **VOGLIOBOSE** | -229.33 | -179.35 | -262.87 | 7.2 |
| 42. | **RIMONABANT** | -201.18 | -163.47 | -225.92 | 8.8 |
| 43. | **SAXAGLIPTIN** | -157.53 | -113.20 | -157.53 | 21.6 |

**Table: 1. Docking of 2E10 with various ligands using Hex software**

| S.NO | LIGAND | 2E1O (Homeobox protein PRH) | | | |
|---|---|---|---|---|---|
| | | ENERGY | VDW | HBOND | ELEC |
| 1. | VITAMIN E | -89.12 | -81.78 | -12.3 | 0 |
| 2. | LIPOIC ACID | -92.3 | -87.6 | -11.2 | -0.95 |
| 3. | RAMILPRIL | -77.45 | -70.89 | -6.7 | 0 |
| 4. | TROGLITAZONE | -92.01 | -87.11 | -11.2 | -0.1 |
| 5. | GLIMEPRIDE | -65.77 | -62.33 | -2.9 | 0 |
| 6. | ACARBOSE | -88.91 | -88.91 | 0 | 0 |
| 7. | ROSIGLITAZONE | -91.77 | -87.98 | -17.7 | 0 |
| 8. | ACETOHAEXAMIDE | -92.76 | -87.88 | -9.8 | 0 |
| 9. | STREPTOZOCIN | -76.77 | -73.4 | -7.7 | 0 |
| 10. | DULOXETINE | -81.11 | -78.2 | -7.3 | 0 |
| 11. | MIGLITOL | -65.77 | -62.33 | -2.9 | 0 |
| 12. | FOSINOPRIL | -88.91 | -88.91 | 0 | 0 |
| 13. | TRANDOLAPRIL | -91.77 | -87.98 | -17.7 | 0 |
| 14. | MAZINDOL | -98.66 | -90.01 | -18.9 | 0 |
| 15. | DEMECLOCYCLINE | -92.11 | -88.12 | -14.5 | 0 |
| 16. | LISINOPRIL | -91.10 | -86.21 | -11.2 | 0 |
| 17. | NATEGLINIDE | -87.65 | -82.62 | -9.8 | 0 |
| 18. | PENTAMIDINE | -77.45 | -71.7 | -8.1 | 0 |
| 19. | TOLAZAMIDE | -87.65 | -82.62 | -9.8 | 0 |
| 20. | PREDNISOLONE | -77.45 | -71.7 | -8.1 | 0 |
| 21. | TACROLIMUS | -65.77 | -62.33 | -2.9 | 0 |
| 22. | QUINAPPRIL | -88.91 | -88.91 | 0 | 0 |
| 23. | REPAGLINIDE | -91.77 | -87.98 | -17.7 | 0 |
| 24. | PHENOFORMIN | -98.66 | -90.01 | -18.9 | 0 |
| 25. | TELMISARTAN | -92.11 | -88.12 | -14.5 | 0 |
| 26. | HYDROCHLOROTHIAZIDE | -91.10 | -86.21 | -11.2 | 0 |
| 27. | GLIBENCLAMIDE | -98.02 | -93.1 | -14.6 | 0 |
| 28. | IRBESARATAN | -89.1 | -89.1 | 0 | 0 |
| 29. | GLIPIZIDE | -77.7 | 72.1 | -12.1 | 0 |
| 30. | GLICLAZIDE | -63.2 | -61.2 | -4.5 | 0 |
| 31. | TOLBUTAMIDE | -92.11 | -88.7 | -12.5 | 0 |
| 32. | PIOGLITAZONE | -83.66 | -81.33 | -1.83 | 0 |
| 33. | DEXFENFLURAMINE | -87.49 | -72.09 | -15.4 | 0 |
| 34. | DEXAMETHASON | -85.51 | -65.75 | -19.76 | 0 |
| 35. | GLIQUIDONE | -78.89 | -67.72 | -9.54 | -1.62 |
| 36. | SITAGLIPTIN | -66.31 | -62.61 | -2.80 | -0.84 |
| 37. | GLYCODIAZINE | -77.4 | -59.56 | -8.19 | 0 |
| 38. | SODIUM BICARBONATE | -87.91 | -78.99 | -8.92 | 0 |
| 39. | BEZAFIBRATE | -81.99 | -68.03 | -13.96 | 0 |
| 40. | VILDAGLIPTIN | -89.12 | -81.78 | -12.3 | 0 |
| 41. | VOGLIOBOSE | -92.3 | -87.6 | -11.2 | -0.95 |
| 42. | RIMONABANT | -77.45 | -70.89 | -6.7 | 0 |
| 43. | SAXAGLIPTIN | -89.1 | -89.1 | 0 | 0 |

**Table: 2. Docking of 2E10 with various ligands using ZEMDOCK software**

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