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**Research Paper**

# Computer-aided drug repurposing for identification of potential therapeutic candidate for diabetes retinopathy

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***Abstract***
*Diabetic Retinopathy (DR) is the leading cause of blindness in industrialized countries. Blood retinal barrier, polyol pathway, and protein kinase C activation pathway are the major pathways involved in DR. In this study, drug repurposing strategy using virtual screening to identify therapeutic candidates for treating DR was used. We selected six major proteins involved in three pathways in DR as potential targets through literature study: Vascular endothelial growth factor (VEGFR), Angiotensin-converting enzyme, TNF-α, Interleukin-1-β, Aldose reductase and Protein kinase C β. The pathogenesis study, connectivity map analysis, docking and interaction studies were conducted to elucidate the best-repurposed drugs for DR. Initial pathogenesis study of the six targets expounds inhibitory action of the proteins in the treatment of DR. Next, Connectivity Map analyses of these targets and the drugs explicate 66 drugs to be repurposed. Based on the docking and interaction studies, the best 19 drugs are proposed as the repurposing candidates for DR. After scrutiny, five drugs - Dovitinib, linifanib, regorafenib, sorafenib and brivanib-alaninate, which target VEGFR – a major target in blood retinal barrier pathway that is not involved in the treatment of diabetes and its related diseases – is proposed to be repurposed for the treatment of DR. To conclude, the study articulates that the Dovitinib, linifanib, regorafenib, sorafenib, and brivanib-alaninate drugs are appropriate to be repurposed for the treatment of DR. These drugs target the VEGFR pathway, which is one of the major pathways to be targeted for the early cure* of DR.

***Keywords:*** *Drug repurposing, diabetes retinopathy, BRB, docking and interaction study.*

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## I. Introduction

Diabetic retinopathy (DR) is still a prominent consequence of diabetes and the primary cause of blindness in adults around the world. Diabetes is a progressive disease that affects both Type I and Type II diabetics at any stage of the disease. Drug safety in diabetic retinopathy is a significant problem throughout the development of new medications. Thiazolidinediones, such as Rosiglitazone and Pioglitazone, are clinically available in India until 2010 [1]; hypoglycemic effects of Rosiglitazone were a success but had adverse effects like heart attack, sometimes leading to death, which led to the withdrawal of the drug [2]. Pioglitazone produced severe DME after two weeks of usage, with 10% of patients experiencing fluid retention, and the condition was shown to resolve following discontinuation [3]. Ten medications have been attempted for diabetic retinopathy in top pharmaceutical companies' current therapeutic research pipelines; just six medications survived the early stages of drug development (Phase I and II clinical trials), Phase III clinical trials, or post-market surveillance [4].

Laser has been used to treat DME for almost 30 years, however new research have called into consideration its significance in current pharmaceutical era. Most patients' eyesight improves with aggressive treatment, although many still do not reach reading and driving vision. New medications are required to supplement the achievements made by existing therapy. As a result, fresh methodologies are required for more rapidly producing newer diabetes medications with lesser safety hazards.

Several drugs have been approved to treat diabetic retinopathy. Currently, these drugs are injected into the eye through intravitreal injection [5,6]. Intravitreal aflibercept (Eylea) and ranibizumab are two more drugs utilised in clinical practise and clinical research (Lucentis). Eylea has a significantly longer lifespan. Bevacizumab (Avastin) is the least expensive and almost definitely as effective as the widely used Lucentis [7].

The existing treatments for DR/DME – laser photocoagulation and vitrectomy – only address the disease's advanced stages. Several biochemical mechanisms, including protein kinase C–β activation, increased vascular endothelial growth factor production, oxidative stress, and accumulation of intracellular sorbitol and advanced glycosylation end products, may contribute to the vascular disruptions that characterize DR/DME[8].

Inhibiting these pathways provides the prospect of DR intervention at earlier, non–sight-threatening phases. Increased polyol pathway flux, increased advanced glycation end-products (AGE) formation, abnormal activation of signaling cascades such as activation of the protein kinase C (PKC) pathway, increased oxidative stress, increased hexosamine pathway flux, and peripheral nerve injury are some of the most researched mechanisms in diabetic retinopathy. Increased oxidative stress, inflammation, and vascular blockage are the end results of all of these processes [9, 10]. The collapse of the blood-retinal barrier (BRB) is a common early symptom of DR, and it can progress to macular edoema in later stages. VEGF, or vascular endothelial growth factor, is thought to play a role in the breakdown of BRB.

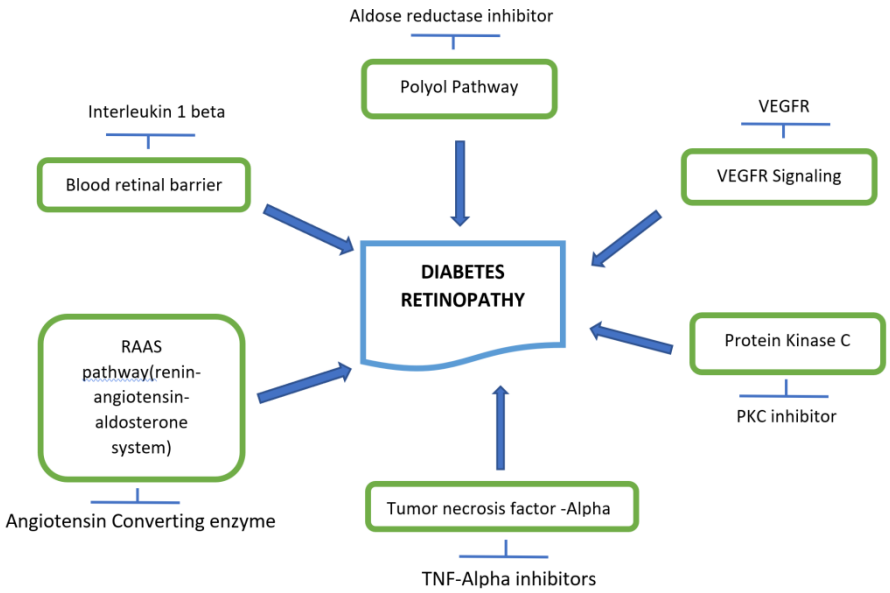



Fig 1: Processes and molecule involved in the pathogenesis of DR as potential drug targets.

The term "drug repurposing" refers to the discovery of new uses/targets for an approved or investigational medicine outside of its original medical indication [11]. The disease-centric approach, target-centric approach, and drug-centric approach are the three systematic approaches to medication repositioning. Disease-centric techniques uncover connections between old and emerging indications. A target-centric approach connects an unknown disease to a known target and its established treatment. Finally, a drug-centric approach links a well-known medication to a novel target and indication. A target centric approach is used to propose a new drug for the treatment of DR in this study, focusing on the targets in the BRB; Polyol pathway, Protein kinase C pathway, VEGFR Signaling, and the Blood-retinal barrier are the four major pathways selected. Aldose reductase (ALR2), vascular endothelial growth factor (VEGF), angiotensin-converting enzyme, protein kinase C (PKC), interleukin beta, and tumor necrosis factor-alpha (TNF-Alpha) are the six candidate proteins that are directly or indirectly involved in the four major pathways in diabetic retinopathy, and are elaborated in this study. The target centric approach explored here includes pathogenesis study, the connectivity map analysis, binding site analysis and docking, and interaction studies to acquire the drugs to be repurposed for the treatment of DR.

## II. Materials and Methods

### 2.1. Mechanisms involved in DR and identification of targets

The Blood Retinal Barrier is a physiologic barrier that regulates ion, protein, and water transit into and out of the retina and is extremely tight and restrictive. Diabetic retinopathy and age-related macular degeneration (AMD), the two most common and important retinal disorders, are linked to changes in the BRB [12]. The other pathways considered are the polyol pathway, protein kinase c pathway, and VEGFR signaling. Aldose reductase (ALR2), vascular endothelial growth factor (VEGF), angiotensin-converting enzyme, protein

kinase C (PKC), interleukin beta, and tumor necrosis factor (TNF) are the six major proteins in the primary pathways in the pathogenesis of DR are considered in this study.

Pathogenicity analysis of the targets elucidates the activity of the six targets. Connectivity Map analysis was conducted to obtain the FDA approved drugs for the selected targets and their present disease indication. The obtained significantly viable drugs were analyzed for binding site, docking, and interaction studies of the targets to elucidate the drugs to be repurposed for the treatment of DR. The overall workflow of the study is illustrated in Figure 2.

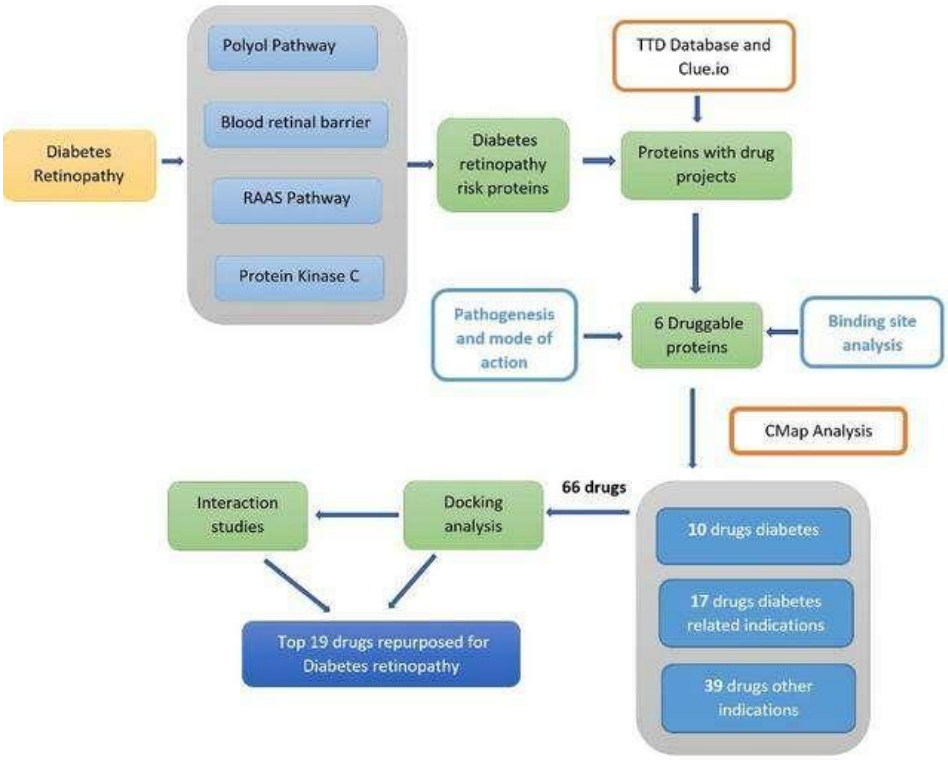



Fig 2: Workflow of the current study elucidating step-by-step process in drug repositioning.

**2.2. Pathogenesis study:**

To gather acquaintance on the pathogenesis of the six diabetic retinopathy targets OMIM (http://www.omim.org) and a literature search (PubMed) was used. Pathogenesis study of each target protein was performed for predicting the impact of the drug on the course of the disease phenotype. Function, chromosomal location and its phenotypic relation of each target protein and their diseases were studied.

**2.3. Connectivity Map analysis:**

The Therapeutic Target Database (TTD version 4.3.02) and Clue.io (https://clue.io/) were used for the connectivity analyses. The Connectivity map elucidates the connection of the targets and the drugs projects. The clue repurposing tool elaborates the clinical phase of the drugs for each target and the current disease indication of the drug. The Connectivity Map dataset comprises 1.3M L1000 profiles and the tools for analyses. A total of 27,927 perturbagens have been profiled to produce 476,251 expression signatures. Target proteins are analyzed for their respective drugs that can be repurposed. The Therapeutic Target Database contains information on 236 targets of 20667 drugs at approved, under clinical trial, and in experimental stages; TTD can be used to assess the feasibility of drug projects with diabetes retinopathy risk proteins [13]. In this study, drug projects with Diabetic Retinopathy risk proteins are studied based on the following information – target, current disease indication, drug name, drug progress stage, and drug action mode. The drugs at the stages of approved or under clinical trials were included in the subsequent studies. To emphasize the most promising drugs to be repurposed in diabetes retinopathy therapy, targets/drugs in Phases I and II were excluded.

**2.4. Binding site analysis of the target proteins:**

Binding site analysis was accomplished using the 3DLigandSite [14] and cofactor tools [15]. 3DLigandSite tool localizes the ligand binding in the protein. *Cofactor tool* is a structure, sequence, and protein-

protein interaction (PPI) based method for biological function annotation of protein molecules. Key binding site amino acids were identified for all the six targets; the binding pocket with all the binding amino acids was targeted in the docking scrutiny.

**2.5. Docking and Interaction analysis**:

Docking was done using AutoDock Vina in PyRx software [16], an online software for molecular graphics, modeling and simulation. Molecular docking is a structure-based drug design approach to identify the essential amino acid interactions between the selected protein and generated ligands with low energy conformation. Target proteins and the FDA-approved drugs were obtained from the Protein data bank (PDB) (https://www.rcsb.org/) and PubChem. Interaction analysis was done using PyMol [17]. Vascular endothelial growth factor (VEGF) -1vpf, Angiotensin-converting enzyme (ACE) – 2xy9, Tumor necrosis factor-alpha (TNF-a) – 1tnf, Interleukin-1 beta (il-1b) – 1t4q, Aldose reductase -3v36 and Protein kinase c beta -3pfq were obtained from PDB for further study. Interactions were calculated based on binding energy and number of polar bonds.

## III. Results and Discussion:

**3.1. Literature search and retrieval of DR related protein targets:**

Our literature search revealed six target proteins involved in three major pathways that are considered as the potential targets for DR in this study. The selected target proteins, their corresponding pathways, and functions are elucidated in Table 1.

**Table 1. DR targets, its pathways, and function**

| S. No | Target | Pathway | Function |
|---|---|---|---|
| **1** | Vascular endothelial growth factor receptor (VEGFR) | Blood retinal barrier | Pathological angiogenesis [18] |
| **2** | Angiotensin-converting enzyme | The renin-angiotensin system (RAS) | Help relax your veins and arteries to lower your blood pressure [19] |
| **3** | Tumor necrosis factor α | Blood retinal barrier | Promotes apoptosis and the loss of retinal microvascular cells.[20] |
| **4** | Interleukin-1-β (il-1β) | Blood retinal barrier | IL-1β accelerates apoptosis of retinal capillary cells [21] |
| **5** | Aldose reductase | Polyol pathway | Contribute to the BRB breakdown in diabetes [22] |
| **6** | Protein kinase C β | Protein Kinase C (PKC) Pathway | *PKC* - β inhibition could prevent BRB breakdown in *diabetic retinopathy [23]* |

**3.2. Pathogenesis study:**

Each of the above selected targets was studied for its pathogenesis against DR using OMIM and literature. Pathogenesis study confers the therapeutic potential of all the six targets against DR. The mode of action of each target was retrieved from OMIM and literature, and is shown in Table 2.

**Table 2: The protein targets and their biological mode of action**

| S. NO | Target | Mode of Action |
|---|---|---|
| **1** | Vascular endothelial growth factor receptor(VEGFR) | Inhibition of VEGF suppresses retinal neovascularization and increased retinal vascular permeability [24] |
| **2** | Angiotensin-converting enzyme | Angiotensin-converting enzyme inhibitor (ACE-I) can prevent the destruction of blood-retina barrier (BRB) and retard progression of the disease to PDR.1[25,26,27,28] |
| **3** | Tumor necrosis factor α | TNF α is involved in the breakdown of the blood retinal barrier in later stages of DR.[29] |
| **4** | Interleukin-1 β (il-1b) | IL-1β has an important role in retinal microglia activation and proliferation under diabetes, limiting IL-1β-triggered inflammatory processes may provide a new therapeutic strategy to prevent the progression of diabetic retinopathy.[30] |
| **5** | Aldose reductase | Increased aldose reductase activity contributes to retinal oxidative stress and retinal damage, inhibiting which will help in avoiding retinal damage. [31] |
| **6** | Protein kinase c β | PKC activation induces VEGF expression causing retinal neovascularization and vascular permeability [32,33] |

**3.3. Binding site analysis of the target proteins:**

The binding site analysis elucidates the particular sites for drugs to bind, thereby either inhibiting or activating the process or the protein itself. Pathogenesis studies suggest that inhibition of the target proteins was deemed to support diabetes retinopathy therapy. Literature study also elucidated that the binding sites are the inhibitory sites of the targets. Active sites of the respective targets are shown in below Table 3.

**Table 3: The protein targets and their binding site amino acids**

| SNo | Target | Binding SITES |
|---|---|---|
| **1** | Vascular endothelial growth factor (VEGF) | PRO21 MET48 PRO63 GLU66 LEU66 HIS92 PRO21 GLU65 ASN93 LYS94 CYS57 GLU30 PRO46 GLU66 SER50 ASN68 |
| **2** | Angiotensin-converting enzyme | HIS353 GLU345 HIS353 GLU384 GLN69 ASN374 ILE73 ASN33 THR302 GLU37 THR38 ASP307 ARG309 ASP13 ARG14 GLN281 ASP357 LEU358 PRO359, SER517 |
| **3** | Tumor necrosis factor α | THR77, GLU35, GLU116, LEU29, PHE144, ALA145, GLU146, ASP45, ASP140, TYR141, VAL17, HIS73, VAL74, GLN102 |
| **4** | Interleukin-1 β (il-1b) | VAL19, MET20, SER21, LEU31, ASP35, GLU37, GLN38, GLN39, THR137, GLY140, GLN141, ASP142, SER13, LYS109, SER70, VAL72, GLN81, GLU64, ARG98 |
| **5** | Aldose reductase | GLY39 THR40 TRP41 LYS42 ASP64 TYR69 LYS98 HIS131 TRP111 SER180 ASN181 GLN204 TYR230 SER231 PRO232 LEU233 GLY234 SER235 PRO236 ASP237 LEU249 ALA266 ILE281 PRO236 ASP237 LEU249 ALA266 ILE281 PRO282 LYS283 SER284 VAL285 THR286 ARG289 GLU292 ASN293 CYS319, SER302 |
| **6** | Protein kinase c β | ALA370, LYS372, THR405, MET421, GLU477, TYR123, VAL424, ASP471, ASN424, MET474, ALA484, ASP485 |

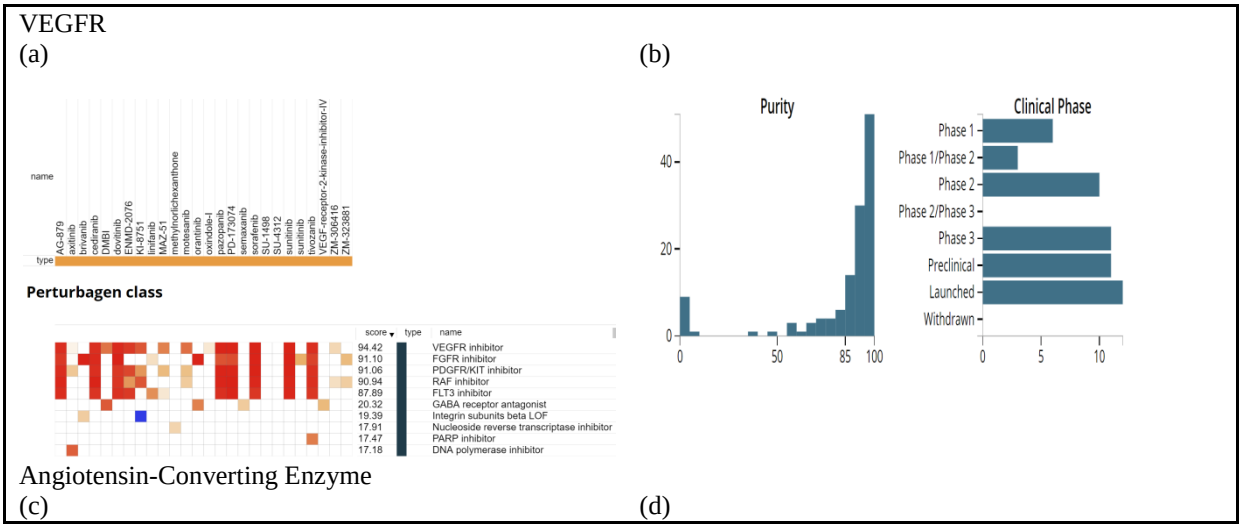
### 3.4. The Connectivity Map analysis:

Initial CMap analysis results for the selected six targets elucidate 66 drugs that can be repurposed for the treatment of DR. The number of active drugs for each target are as follows: Vascular endothelial growth factor (VEGF) – 26 drugs, Angiotensin-converting enzyme (ACE) – 20 drugs, Tumor necrosis factor α (TNF-a) – 2 drugs, Interleukin-1-β (il-1b) – 2 drugs, Aldose reductase – 6 drugs, and Protein kinase C β – 10 drugs (Table 4).

**Table 4: The targets and their respective drugs obtained for repurposing in the treatment of the DR**

| S.No | Protein | No. of Drugs | Drugs |
|---|---|---|---|
| **1** | VEGFR | 26 | Dovitinib, Sorafenib, Linifanib, Regorafenib, Brivanib-alaninate, KI-8751, MGCD-265, Nintedanib, Lenvatinib, Cabozantinib, DMH4, Pazopanib, Motesanib, ZM323881, Anlotinib, Axitinib, Fruquintinib, Semaxanib, KRN 633, Orantinib, PD-173074, Brivanib, Sunitinib, SU4312, SKLB1002 and SAR131675 (CID_71295845) |
| **2** | TNF-α | 2 | Thalidomide and Ligustilide |
| **3** | Interleukin-1-β | 2 | Diacerein and Bergenin |
| **4** | Angiotensin-converting enzyme | 20 | Deserpidine, Cilazapril, Delapril, Quinaprilat, Ramipril, Imidapril, Benazepril, Fosinoprilat, Benazepril, Enalapril, Quinapril, Temocapril, Fosinopril(monopril), Lisinopril, Moexipril, Enalaprilat, Nicainoprol, Captopril, Captopril and Deserpidine |
| **5** | Aldose reductase | 6 | Imirestat, Hyperin, Alrestatin, EBPC, Ranirestat, Cinnamaldehyde, Fidarestat, Epalrestat, Sorbinil and Ponalrestat (statil). |
| **6** | PKC-β | 10 | Enzastaurin, Bisindolylmaleimide-IX, Myricitrin, CGP-53353, Dequalinium, Ingenol, GF109203X, Ingenol-mebutate, Aurothioglucose and Ethylenediaminetetraacetic-acid. |

Further, repurposing analysis using Clue repurposing tool indicated that among the 66 drugs, 10 drugs have anti-diabetic information and 17 drugs show diabetes-related disease information. 39 of the total drugs did show any anti-diabetic information in CMap. Among the 66 drugs based on the best docking score and number of polar interactions, 19 drugs are proposed for repurposing in the treatment of DR. (Supplementary Table 1).

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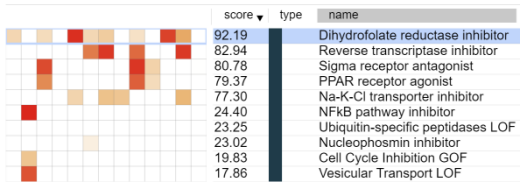


TNF-α

(e)


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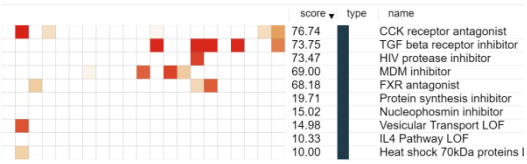
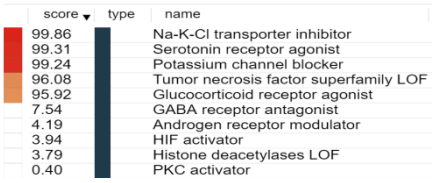



Interleukin-1-β

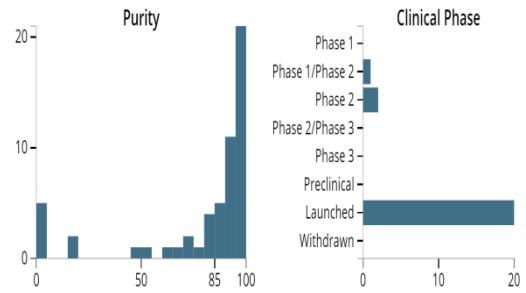
(g)


**Perturbagen class**

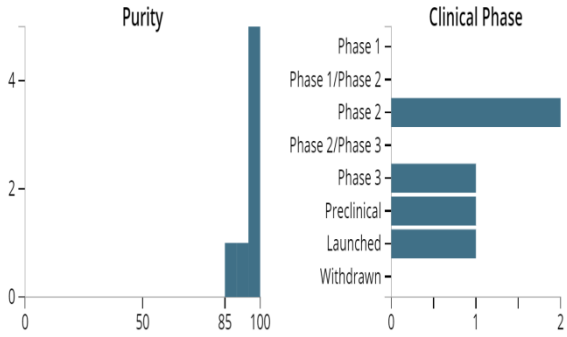



Aldose reductase

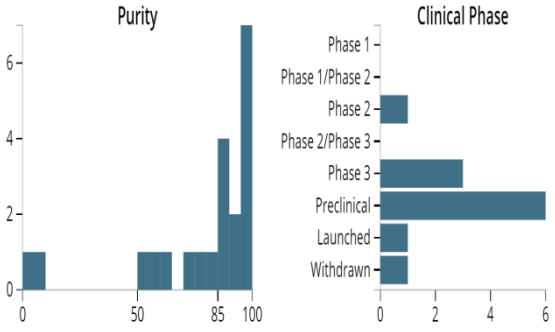
(i)



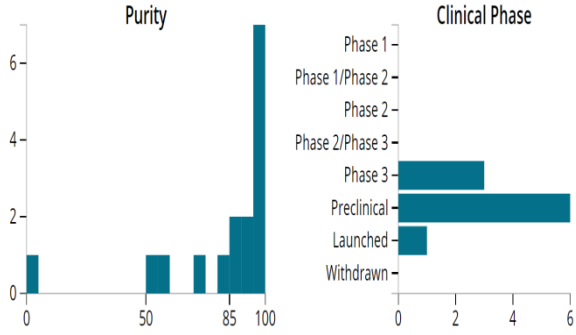

(f)




(h)




(j)



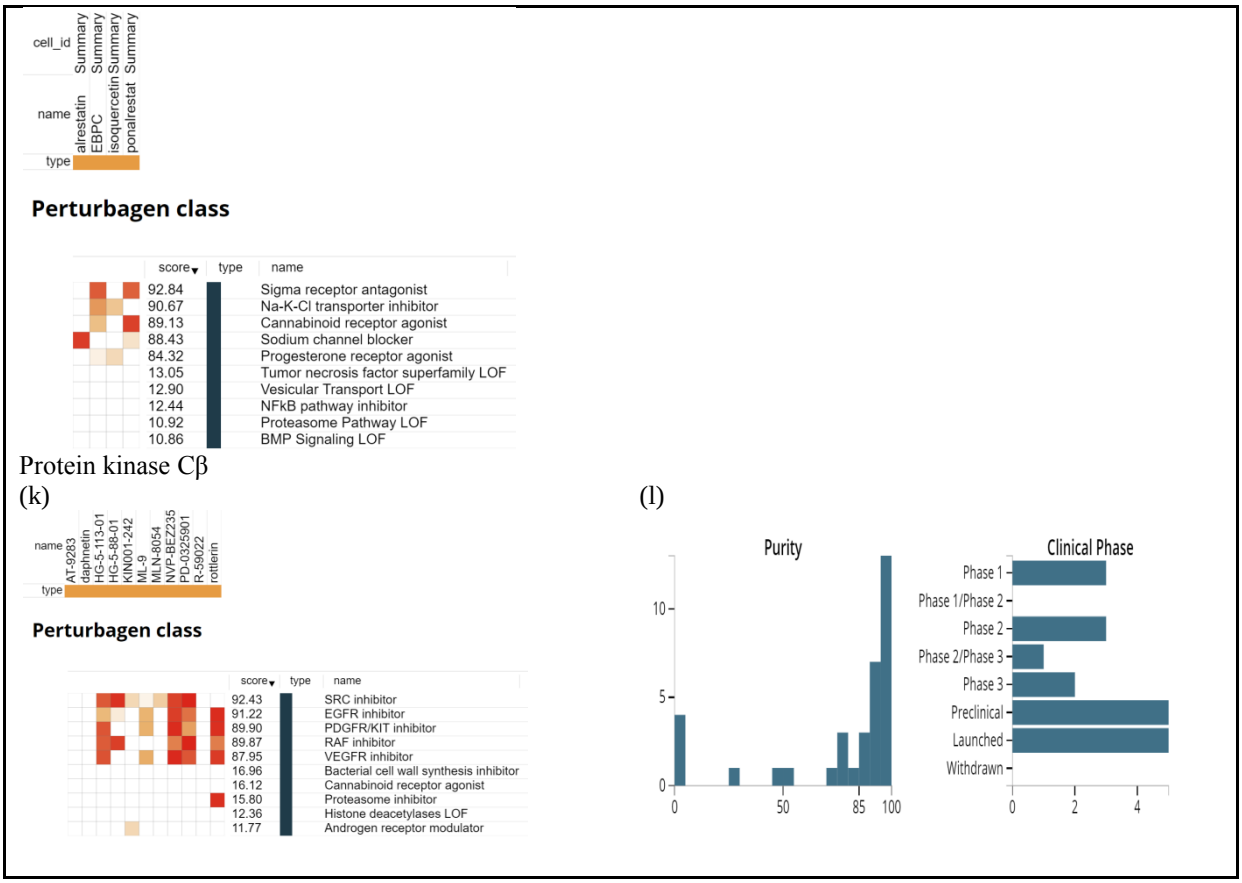



**Fig 3: The above figure (a, c, e, g, i, and k) explains the biological process and mode of action of all the targets. The box plots in the figure (b, d, f, h, j, and l) shows the clinical phase and purity of the drugs obtained for each target.**

**3.5. Interaction and Docking Analysis:**

Docking and interaction studies of the six targets and 66 drugs were performed. Based on the RMSD, and Binding affinity of the drug with the targets, the final top 19 drugs were considered for further analyses (Table 5). Each of the targets for their interaction with the drugs is discussed in detail below:

**i) Vascular endothelial growth factor receptor (VEGFR):** VEGFR is studied for its interaction with 26 drugs, and the best five drugs were considered for further analyses. The drugs Dovitinib, sorafenib, linifanib, regorafenib and Brivanib - alaninate with binding affinities of -9.3, -9.1, -8.7, -8.6 and -8.3 kcal/mol were studied for the interaction. Dovitinib interacts with LEU32(2 bonds) and GLU30 with a polar bond length of 2.2 and 2.3 Å (Fig 4(a)), Sorafenib interacts with ASP63, CYS61(2 bonds), SER50, and GLY59 with a polar bond length of 2.2, 2.5, 2.1, 2.8, and 2.6 Å respectively (Fig 4(b)), while Linifanib interacts with LEU66(2 bonds), LEU32, ASP63 and GLY59(2 bonds) with a polar bond length of 2.5, 2.6, 2.7, 2.0, 2.3 and 2.9 Å (Fig 4(c)). Regorafenib interacts with GLY59, ASP63(2 bonds), and CYS61with a polar bond length of 2.8, 2.6, 2.7, 2.0 2.3 and 2.9 Å (Fig 4(d)), whereas Brivanib-alaninate interacts with LEU66, CYS612(2 bonds), CYS68, and GLU30(2 bonds) with a polar bond length of 2.3, 2.0, 2.3, 2.5, 2.4, and 2.7 Å (Fig 4(e)) (Supplementary Table 2).

**ii) TNF-α:** The TNF-α is studied for two drugs – Thalidomide and Ligustilide, with a binding affinity of -8.4 and -5.9 kcal/mol. Thalidomide is studied based on binding affinity and polar interactions. Thalidomide interacts with GLN102(2 bonds), ARG103, and GLN102(2 bonds) with a polar bond length of 2.2, 2.3, 2.6, 3.5 and 2.2 Å respectively (Fig 4(f)) (Supplementary Table 2).

**iii) Interleukin-1-β:** Interleukin-1-β is studied for the interaction with two drugs, both were considered for further analyses. The drugs Diacerein and Bergenin with binding affinities of -6.3 and -6.2 kcal/mol were studied for the interaction. Diacerein interacts with LYS109, ASP145, SER13, THR144, ASP142, GLN126, and GLY140 with a polar bond length of 2.1, 3.0, 2.6, 1.9, 2.7, 2.8 and 2.3 Å respectively (Fig 4(g)) while Bergenin interacts with ASN7, SER43, TYR68, LYS65, and GLU64 with a polar bond length of 2.2, 2.4, 2.5, 2.3 and 2.6 Å (Fig 4(h)) (Supplementary Table 2).

**iv) Angiotensin-converting enzyme:** The Angiotensin-converting enzyme is studied for the interaction with 20 drugs and the best five drugs are considered for further analysis. The Drugs Deserpidine, Cilazapril, Delapril,

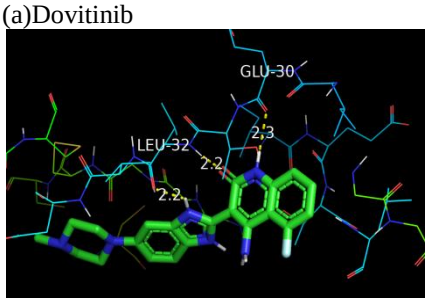
Quinaprilat, and Ramipril are studied for the interaction with binding affinities of -9.6, -8.7, -8.7, -8.6, and -8.3 kcal/mol respectively. Deserpidine interacts with TYR135, SER517, and TRP220 with a polar bond length of 2.4, 2.3, and 2.6 Aᵒ respectively (Fig 4(i)). The Cilazapril interacts with HIS513, LYS511, GLN281, and HIS353(2 bonds) with a polar bond length of 2.1, 2.1, 2.5, 2.6, and 2.6 Aᵒ respectively (Fig 4(j)). Delapril interacts with THR302 and ASN374 with a polar bond length of 2.7 and 2.9 Aᵒ respectively (Fig 4(k)). The Quinaprilat interacts with THR282(2 bonds) and LYS454(2 bonds) with a polar bond length of 2.7, 2.6, 2.3, and 2.2 Aᵒ respectively (Fig 4(l)), while Ramipril interacts with THR282 and ASN277 with a polar bond length of 2.6 and 2.4 Aᵒ (Fig 4(m)) (Supplementary Table 2).

**v) Aldose reductase:** Aldose reductase is studied for the interaction with six drugs, and the best three drugs are considered for further analysis. The Drugs imirestat, Hyperin, and Alrestatin are studied for the interaction with the binding affinities of -9.1, -8.3, and -7.8 kcal/mol respectively. Imirestat interacts with SER302(2 bonds) with a polar bond length of 2.4 and 2.3 Aᵒ (Fig 4(n)). The Hyperin interacts with TRP20(2), HIS110, TRP111, LEU301, and GLN49 with polar bond lengths of 1.8, 2.6, 2.2, 1.9, 2.3 and 2.2 Aᵒ respectively (Fig 4(o)) (Supplementary Table 2).

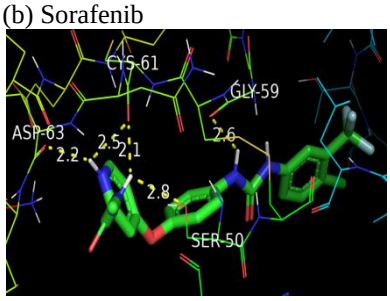
**vi) Protein kinase C β:** Protein kinase C is studied for the interaction with 10 drugs, and the best five drugs were considered for further analyses. The Drugs Enzastaurin, Bisindolylmaleimide-IX, Myricitrin, CGP-53353, and Dequalinium were studied for their interactions, with the binding affinities of -10.5, -9.7, -9.7, -9.5, and -9 kcal/mol respectively. Enzastaurin interacts with GLU477, SER477, SER476, ASN424, TYR123, and GLN128 with a polar bond length of 2.1, 2.1, 2.2, 3.3, 2.4 and 2.4 Aᵒ respectively (Fig 4(p)). Bisindolylmaleimide-IX was observed to interact with SER476, ASN424, TYR123, TYR422(2 bonds), and GLN128 with a polar bond length of 2.1, 2.2, 3.5, 2.5, 2.3 and 2.5 Aᵒ respectively (Fig 4(q)). Myricitrin interacts with TYR123, SER476, TYR422, LEU367, LYS141, and ARG142 with a polar bond length of 2.4, 2.5, 2.2, 2.6, 2.2, 2.7 and 2.2 Aᵒ respectively (Fig 4(r)). CGP-53353 interacts with GLU477, SER476, ASP475, TYR422, and GLU421 with a polar bond length of 2.5, 2.5, 2.6, 2.4 and 3.3 Aᵒ respectively (Fig 4(s)) (Supplementary Table 2).

**VEGFR**

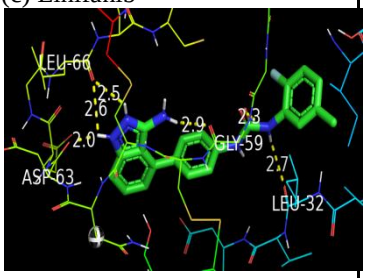
(a)Dovitinib



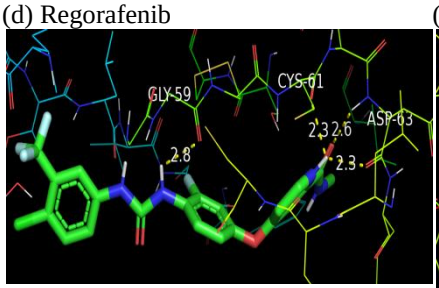

(b) Sorafenib



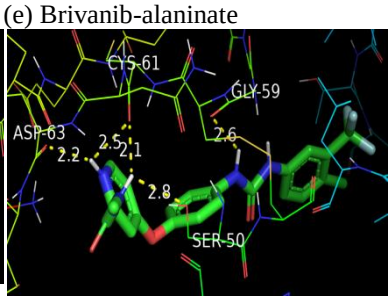

(c) Linifanib




(d) Regorafenib

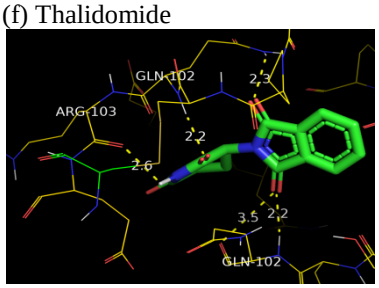



(e) Brivanib-alaninate




**TNF-α**

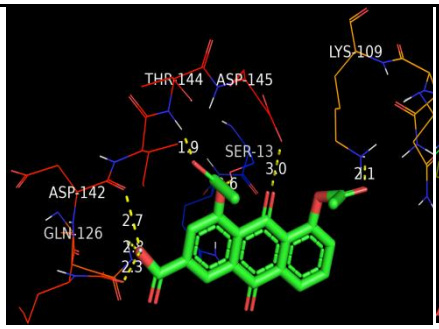
(f) Thalidomide

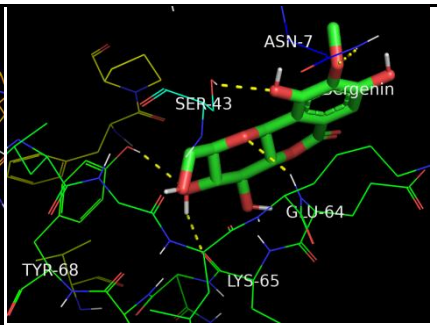



**Interleukin-1-β**

(g) Diacerein

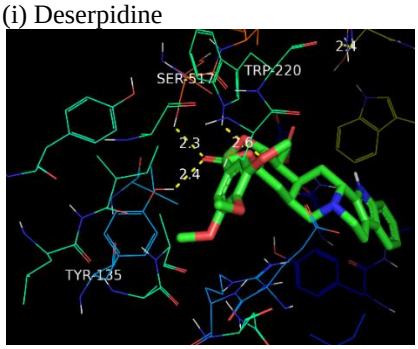
(h) Bergenin

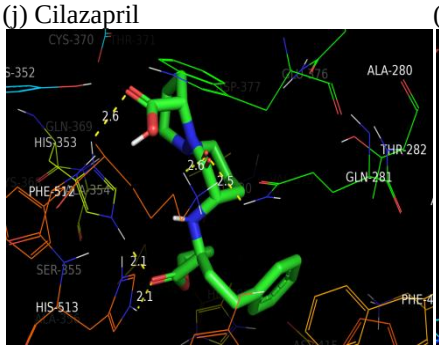


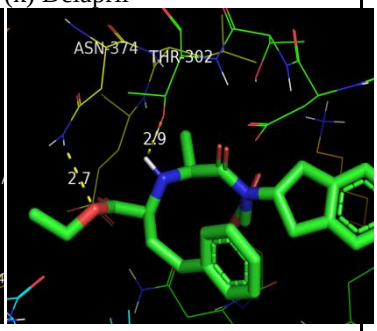




**Angiotensin-converting enzyme**

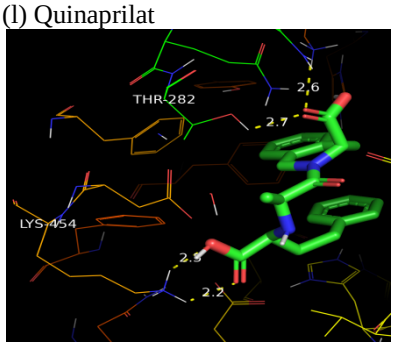
(i) Deserpidine (j) Cilazapril (k) Delapril

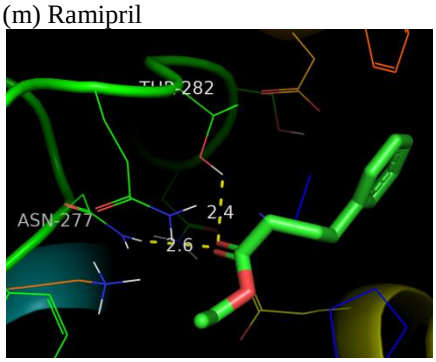


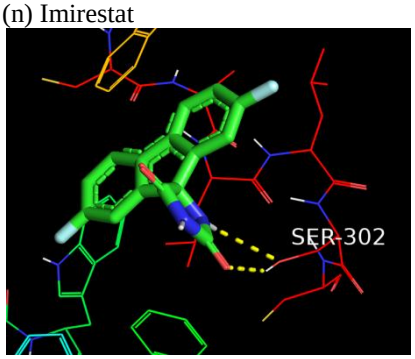

(l) Quinaprilat (m) Ramipril

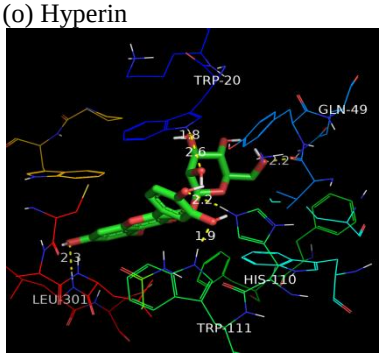



**Aldose reductase**

(n) Imirestat (o) Hyperin




**PKC-β**

(p) Enzastaurin (q) Bisindolylmaleimide-IX (r) Myricitrin

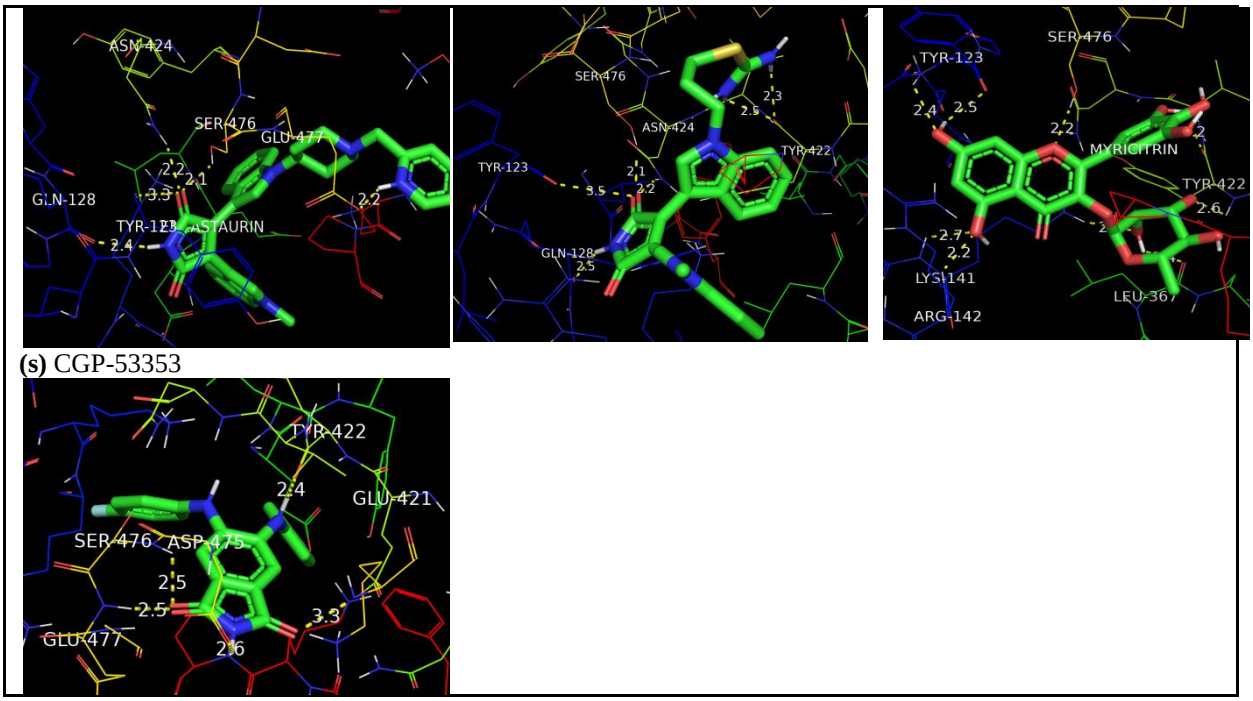



**Fig 4: The top 19 drugs to be repurposed and their docked poses showing the polar interaction of the drug and protein.**

**Table 5: The interaction studies of the six targets and their respective drugs.**

| SNo | Protein | Drug | RMSD(Å) | Binding energy(kcal/mol) | No. of H bonds | Amino acids involved |
|---|---|---|---|---|---|---|
| **1** | VEGFR | Dovitinib | 0.96 | -9.3 | 3 | LEU32(2 bonds), GLU30 |
| | | Sorafenib | 0.50 | -9.1 | 5 | ASP63, CYS61(2 bonds), SER50, GLY59 |
| | | Linifanib | 0.67 | -8.7 | 6 | LEU66(2 bonds), LEU32, ASP63, GLY59(2 bonds) |
| | | Regorafenib | 0.89 | -8.6 | 4 | GLY59, ASP63(2 bonds), CYS61 |
| | | Brivanib-alaninate | 0.54 | -8.3 | 6 | LEU66, CYS612(2 bonds), CYS68, GLU30(2 bonds) |
| **2** | TNF-α | Thalidomide | 1.87 | -8.4 | 5 | GLN102(2 bonds), ARG103, GLN102(2 bonds) |
| **3** | Interleukin-1-β | Diacerein | 1.45 | -6.3 | 7 | LYS109, ASP145, SER13, THR144, ASP142, GLN126, GLY140 |
| | | Bergenin | 0.56 | -6.2 | 5 | ASN7, SER43, TYR68, LYS65, GLU64 |
| **4** | Angiotensin-converting enzyme | Deserpidine | 0.87 | -9.6 | 3 | TYR135 SER517 TRP220 |
| | | Cilazapril | 1.28 | -8.7 | 5 | HIS513 LYS511 GLN281 HIS353(2 bonds) |
| | | Delapril | 1.85 | -8.7 | 2 | THR302 ASN374 |
| | | Quinaprilat | 0.67 | -8.6 | 4 | THR282(2 bonds), LYS454(2 bonds) |
| | | Ramipril | 0.45 | -8.3 | 2 | THR282 ASN277 |
| **5** | Aldose reductase | Imirestat | 0.67 | -9.1 | 2 | SER302(2 bonds) |
| | | Hyperin | 0.65 | -8.3 | 6 | TRP20(2 bonds), HIS110, TRP111, LEU301, GLN49 |
| **6** | PKC β | Enzastaurin | 1.54 | -10.5 | 6 | GLU477, SER477, SER476, ASN424, TYR123, GLN128 |
| | | Bisindolylmaleimide-IX | 1.21 | -9.7 | 6 | SER476 ASN424 TYR123 TYR422(2 bonds) GLN128 |
| | | Myricitrin | 0.98 | -9.7 | 6 | TYR123, SER476, TYR422, LEU367, LYS141, ARG142 |
| | | CGP-53353 | 0.78 | -9.5 | 5 | GLU477, SER476, ASP475, TYR422, GLU421 |
| | | Dequalinium | 0.65 | -9 | 2 | GLU477, GLU421 |

## IV. Discussion:

Diabetes retinopathy is a major complication in diabetes. The treatment being mostly only in the later stages, we have identified, in this study, six targets and possible 66 drugs to be repurposed for early treatment of DR. The drugs in Phase I and II are excluded from the study to avoid unwanted biological misperception.

Breakdown of the Blood Retinal Barrier (BRB) is an early event in DR, leading to macular edema in more advanced stages of the pathology. Vascular endothelial growth factor (VEGF) is considered a major factor in the breakdown of BRB. This study includes VEGFR, interleukin-1-β and TNF-α of the blood retinal barrier cascade among the six targets identified, and concentrates on the targets in the BRB – Polyol pathway and protein kinase C activation. The BRB breakdown being the early event in DR, focusing on three targets simultaneously in this cascade would perhaps help in the early treatment of the disease. The possible impact of 66 drugs with diabetes and the related diseases was studied. Clue repurposing analysis further showed 10 drugs to have anti-diabetic information. 17 drugs were shown to demonstrate diabetes-related disease information in Cmap scrutiny. A total of 39 drugs did not show any anti-diabetic information in CMap. Based on the drug target interactions, which complement the role of crucial binding residues (that were earlier defined), thereby inhibiting the targets and used in the DR therapy. The targets and the best drugs are given below: **VEGFR** – Dovitinib, sorafenib, linifanib, regorafenib, and Brivanib – alaninate, **TNF-α** – thalidomide, **Interleukin-1-β** – Diacerein and Bergenin, **Angiotensin-converting enzyme** – Deserpidine, Cilazapril, Delapril, Quinaprilat and Ramipril, **Aldose reductase** – imirestat and Hyperin and **Protein kinase C β** – Enzastaurin, Bisindolylmaleimide-IX, Myricitrin, CGP-53353, and Dequalinium. As given in 3.3 and 3.4, all the 6 targets are conferred with connectivity repurposing analysis, docking, and interaction study results.

**VEGFR:** The connectivity repurposing analyses show 70% of the VEGFR inhibitor drugs with 85–100% purity. Purity is defined as the compatibility of the drug in the treatment of specific diseases. The graph (Fig 3(a)) shows the percent of drugs in the different clinical phases. It was crucial to consider the drugs in Phase III, preclinical, and launched categories, hence, for fruitful results, drugs in Phases I and II are ignored. A list of 26 drugs was obtained, among which 14 drugs showed a score >95 (Fig. 3(b)) and is shown effective in the VEGFR inhibition. The score shows enrichment in the process, the VEGFR inhibitor. Dovitinib, Linifanib, and Sorafenib show lower binding energy values for VEGFR compared to regorafenib and Brivanib-Alaninate, as presented in Table 5. The RMSD value of Dovitinib, Linifanib, Sorafenib, regorafenib and Brivanib-Alaninate of 0.96, 0.05, 0.67, 0.89 and 0.54 Å (Table 5). The reference RMSD value (<1) shows all five drugs to be finest bound to the protein (Table 5).

**TNF-α:** The connectivity map analysis elucidates score in the range of 76.10–89.19 (Fig 3(c)) as CCK receptor antagonist, TGF β receptor inhibitor, which is a major progression in diabetic patients. 100% of angiotensin-converting enzyme inhibitor drugs fall into 85–100% purity Approximately 90% of the drugs are launched in the market; 10% of the drugs in Phases I and II are ignored in this study. (Fig 3(d)). Reference RMSD of Thalidomide are 1.87 Å, which fall into the reference range, indicating that thalidomide inhibits the TNF-α protein more than 50%.

**Interleukin-1-β:** The drugs show an enrichment score between 76.10–89.19 as Na-K-Cl transporter inhibitor, which is a major process in inflammatory diseases. (Fig 3(e)). The purity of the ace inhibitor drugs obtained is around 80–100%. The connectivity repurposing analysis illustrates that 90% of the drugs are at preclinical phase, and only 10% of the drugs are launched in the market, whereas 10% of the drugs are withdrawn. (Fig 3(f)). The RMSD of Diacerein and Bergenin are 1.45 and 0.56 Å, respectively. The values show that both the drugs have good binding ability and show more than 50% interleukin-1-β inhibition.

**Angiotensin-converting enzyme**: The drugs show a score in the range of 99.10–92.19 (Fig 3(g)) as a dihydrofolate inhibitor, a major process in vitamin absorption that is impaired in diabetic patients. 70% of angiotensin-converting enzyme inhibitor drugs fall into 85–100% purity. The 90% of the drugs are launched in the market, 10% of the drugs in Phase I and II are ignored in this study (Fig 3(h)). The RMSD of Deserpidine, Cilazapril, Delapril, Quinaprilat, and Ramipril are 0.87, 1.28, 1.85, 0.67 and 0.45 Å respectively (Table 5). Based on the RMSD and the binding energy values, Cilazapril and Quinaprilat were observed to show better binding and inhibition compared to other drugs obtained. Overall, all the best five drugs fall into the reference value and so they can be proposed for the best leads.

**Aldose reductase:** The drugs show a score between 92.84–98.30 as a sigma receptor antagonist, Na-K-Cl transporter inhibitor, which is a responsible for major microvascular inflammation process. (Fig 3(i)). 90% of aldose reductase inhibitor drugs fall into 85–100% purity. 80% of the drugs are in the preclinical and Phase III stage. Approximately 20% of the drugs are already launched in the market. (Fig 3(j)). The drugs Imirestat and Hyperin show reference RMSD values (<1) of 0.67 and 0.65 Å, which indicate that the binding is appropriate.

**Protein kinase C β:** The drugs show a score between 92.43–97.31 as SRC inhibitor and EGFR inhibitor, which is a major TNF-α inhibition process. (Fig 3(k)). 90% of aldose reductase inhibitor drugs fall into 85–100% purity. Around 20% of the drugs are launched in the market, 30% of the drugs in Phases II and III are ignored in this study (Fig 3(l)). The RMSD are 1.54, 1.21, 0.98, 0.78, and 0.65 Å for Enzastaurin, Bisindolylmaleimide-IX, Myricitrin, CGP-53353 and Dequalinium, respectively (Table 5). Inclusively, all the best five drugs fall into the reference value, hence can be proposed for the best leads.

In summary, drug repositioning provides a powerful tool to find novel indications for marketed drugs and clinical candidates of complex human diseases, such as diabetic retinopathy. By analyzing connectivity of the drug to the target, mapping diabetes retinopathy related proteins to drug projects (TTD and Clue.io), and

inputting pathogenesis knowledge, **19 drugs** are proposed to be repurposed with a potential indication for diabetic retinopathy treatment.

Diabetes retinopathy is an inflammatory disease. Bergenin (Interleukin-1-beta) and Hyperin (aldose reductase inhibitor) are currently being used in the treatment of inflammatory diseases. Two of the major drugs Imirestat (aldose reductase inhibitor) and Thalidomide (TNF-Alpha) are revealed to be used in diabetes. Aldose reductase inhibitor is involved in the polyol pathway, which is one of the major pathways in DR. Cilazapril, Delapril, Deserpidine, Quinaprilat, and Ramipril are used in the treatment of hypertension, targeting ACE protein. Among the six targets, the targets in the BRB are more significant since they target early cure of DR. BRB disruption being the major milestone in the development of DR, the VEGFR (Dovitinib, Linifanib, Regorafenib, Sorafenib, and Brivanib-Alaninate), TNF-alpha (Thalidomide) and Interleukin-1-beta (Bergenin and Diacerein) are the targets, and their respective drugs to be considered for treatment of DR. Therefore, concentrating on VEGFR, TNF-α, and Interleukin-1-β and their eight respective drugs will create a potential possibility of early treatment of DR. Dovitinib, linifanib, regorafenib, sorafenib, and brivanib-alaninate are the drugs that are not involved in the treatment of diabetes and diabetes related diseases. The drugs which do not have any information related to diabetes but target the major target sites in DR can be proposed to be repurposed for the treatment of DR. All **the five drugs** target VEGFR, which is a major target in the BRB. Preclinical or clinical trials may be initiated to establish the efficacy of these repositioned drugs for diabetic retinopathy treatment.

## V. Conclusion:

Drug repurposing is an effective strategy to treat new diseases caused by infectious agents that spread rapidly. In this paper, the drug repurposing strategy was applied using virtual screening to identify better and early therapeutic options for Diabetes retinopathy. By analyzing connectivity of the drug and the target, mapping diabetes retinopathy related proteins to drug projects, and inputting pathogenesis knowledge, **19 drugs** are proposed to be repurposed with a potential for diabetic retinopathy treatment. Preclinical or clinical trials might be initiated to establish the efficacy of these repositioned drugs for diabetic retinopathy treatment. From the analysis, we can suggest that early detection and treatment is a better way to treat DR. Targets in the BRB can be considered for the treatment of DR. The total of **8 drugs**; VEGFR-Dovitinib, sorafenib, linifanib, regorafenib, Brivanib-alaninate, TNF-α–thalidomide, Interleukin-1-β-Diacerein, and Bergenin can be considered for further study to treat DR. Among the eight drugs, Dovitinib, Linifanib, Regorafenib, Sorafenib, and Brivanib-Alaninate are not involved in the treatment of diabetes and diabetes related diseases, but target the major target sites in the BRB. To conclude, the above **five drugs** are appropriate to be repurposed for the treatment of DR. Summarizing, by creating an approach that reasonably selects drugs based on their described mode of action and repurposing already available drugs, the coming years would see increasing prospects in rapid increase in the repertoire of drugs available to treat Diabetic Retinopathy in its early stages.

**Supporting Information:**

**Supplementary table 1: The CMap analysis of the 6 targets and 66 drugs, their mode of action and current indication for treating Diabetic retinopathy are shown in this table.**

**Supplementary table 2: The table shows the interaction of the targets with the drugs and the polar bonds are also explicated. The lower the binding affinity and higher the polar bonds, it is a virtuous drug for the disease.**

**Declarations:**

**Conflict of Interest:**

Authors declare that there is no conflict of interests.

**Ethical Approval:**

This article does not contain any studies with human participants.

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**Computer-aided drug repurposing for identification of potential therapeutic candidate for diabetes retinopathy**

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**Supplementary table 1: The CMap analysis of the 6 targets and 66 drugs, their mode of action and current indication for treating Diabetic retinopathy are shown in this table.**

| Drug name | Current drug indication | Stage | Target | Action mode |
|---|---|---|---|---|
| Anlotinib | Thyroid cancer | Launched | VEGFR | Inhibitor |
| Axitinib | Renal cell carcinoma (RCC) | Launched | VEGFR | Inhibitor |
| Brivanib | Metastatic colorectal cancer | Phase 3 | VEGFR | Inhibitor |
| Brivanib-alaninate | Coronavirus Disease 2019(Phase 3) | Phase 3 | VEGFR | Inhibitor |
| Cabozantinib | Medullary thyroid cancer (MTC) | Launched | VEGFR | Inhibitor |
| Cediranib | Breast cancer | Phase 3 | VEGFR | Inhibitor |
| DMH4 | Lymphoma | Preclinical | VEGFR | Inhibitor |
| Dovitinib | Non-small-cell lung cancer | Phase 3 | VEGFR | Inhibitor |
| Elemene | Breast cancer | Phase 3 | VEGFR | Inhibitor |
| Fruquintinib | Colorectal cancer | Launched | VEGFR | Inhibitor |
| KI-8751 | Cancer | Preclinical | VEGFR | Inhibitor |
| KRN-633 | Cancer | Preclinical | VEGFR | Inhibitor |
| Lenvatinib | Thyroid cancer | Launched | VEGFR | Inhibitor |
| Linifanib | Mammary cancer | Phase 3 | VEGFR | Inhibitor |
| MGCD-265 | Colorectal cancer | Preclinical | VEGFR | Inhibitor |
| Motesanib | Thyroid cancer | Phase 3 | VEGFR | Inhibitor |
| Nintedanib | Idiopathic pulmonary fibrosis (IPF) | Launched | VEGFR | Inhibitor |
| Orantinib | Diabetes complications | Phase 3 | VEGFR | Inhibitor |
| Pazopanib | Renal cell carcinoma (RCC), soft tissue sarcoma (STS) | Launched | VEGFR | Inhibitor |
| PD-173074 | Cancer | Preclinical | VEGFR | Inhibitor |
| Regorafenib | Colorectal cancer, gastrointestinal stromal tumors (GIST) | Launched | VEGFR | Inhibitor |
| SAR131675 | Breast cancer | Preclinical | VEGFR | Inhibitor |
| Semaxanib | Renal cell carcinoma | Phase 3 | VEGFR | Inhibitor |
| SKLB1002 | Cancer | Preclinical | VEGFR | Inhibitor |
| Sorafenib | Renal cell carcinoma (RCC), thyroid cancer, hepatocellular carcinoma (HCC) | Launched | VEGFR | Inhibitor |
| Sunitinib | gastrointestinal stromal tumors (GIST), renal cell carcinoma (RCC), neuroendocrine tumors of pancreatic origin (PNET) | Launched | VEGFR | Inhibitor |
| SU4312 | Cancer | Preclinical | VEGFR | Inhibitor |
| TG-100572 | Age-related macular degeneration | Preclinical | VEGFR | Inhibitor |
| Tivozanib | Renal cell carcinoma (RCC) | Launched | VEGFR | Inhibitor |
| Vandetanib | Medullary thyroid cancer (MTC) | Launched | VEGFR | Inhibitor |
| Vatalanib | Cancer | Phase 3 | VEGFR | Inhibitor |
| XL647 | Cancer | Phase 3 | VEGFR | Inhibitor |
| ZM-306416 | Myocardial infarction | Preclinical | VEGFR | Inhibitor |
| ZM-323881 | Gastrointestinal stromal tumors | Preclinical | VEGFR | Inhibitor |
| Alacepril | Hypertension | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Benazepril | Hypertension | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Captopril | Hypertension, congestive heart failure, myocardial infarction, diabetes mellitus, diabetic nephropathy | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Cilazapril | Hypertension, congestive heart failure | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Delapril | Hypertension | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Deserpidine | Hypertension | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Enalapril | Hypertension, congestive heart failure, left ventricular systolic dysfunction (LVSD) | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Enalaprilat | Hypertension | Launched | angiotensin converting enzyme inhibitor | Inhibitor |

| | | | | |
|---|---|---|---|---|
| Fosinopril | Hypertension, congestive heart failure | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Fosinoprilat | Hypertension | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Imidapril | Hypertension, congestive heart failure | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Lisinopril | Hypertension, congestive heart failure, diabetes mellitus | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Moexipril | Hypertension | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Nicainoprol | Antiarrhythmic drug | Preclinical | angiotensin converting enzyme inhibitor | Inhibitor |
| Perindopril | Hypertension, myocardial infarction, coronary artery disease (CAD) | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Quinapril | Hypertension, congestive heart failure, angioedema | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Quinaprilat | Hypertension, angioedema | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Ramipril | Hypertension | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Temocapril | Hypertension, congestive heart failure, diabetic nephropathy, coronary artery disease (CAD) | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Trandolapril | Hypertension, myocardial infarction | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| Val-tyr | Metabolic diseases | Preclinical | angiotensin converting enzyme inhibitor | Inhibitor |
| Zofenopril-calcium | Hypertension | Launched | angiotensin converting enzyme inhibitor | Inhibitor |
| AurothioglucoSe | Rheumatoid arthritis | Launched | PKC inhibitor | Inhibitor |
| Bisindolylmaleimide-IX | Thrombocytopenia | Preclinical | PKC inhibitor | Inhibitor |
| CGP-53353 | Hereditary hemorrhagic telangiectasia | Preclinical | EGFR inhibitor, PKC inhibitor | Inhibitor |
| Dequalinium | Solid tumour/cancer | Launched | PKC inhibitor | Inhibitor |
| Enzastaurin | Metastatic colorectal cancer | Phase 3 | PKC inhibitor | Inhibitor |
| Ethylenediaminetetraacetic-acid | Coronavirus Disease 2019(Phase 3) | Launched | PKC inhibitor | Inhibitor |
| GF109203X | Idiopathic pulmonary fibrosis | Preclinical | PKC inhibitor | Inhibitor |
| Ingenol | Non-small-cell lung cancer | Launched | PKC activator | Inhibitor |
| Ingenol-mebutate | Psoriasis vulgaris; Diabetic macular edema; | Launched | PKC activator | Inhibitor |
| Midostaurin | Solid tumour/cancer (phase2) | Launched | FLT3 inhibitor, KIT inhibitor, PKC inhibitor | Inhibitor |
| Myricitrin | Solid tumour/cancer (phase3) | Preclinical | PKC inhibitor | Inhibitor |
| PD-407824 | Cancer | Preclinical | PKC inhibitor | Inhibitor |
| Ruboxistaurin | Metabolic Disease | Phase 3 | PKC inhibitor | Inhibitor |
| Vitamin-E | Inflammatory disseases | Launched | LDL oxidation inhibitor, PKC inhibitor | Inhibitor |
| 5-octanoylsalicylic-acid | Facial inflamation | Preclinical | protein kinase activator | Inhibitor |
| Alrestatin | diabetic | Preclinical | aldose reductase inhibitor | Inhibitor |
| Cinnamaldehyde | - | Preclinical | aldose reductase inhibitor, TRPV agonist | Inhibitor |
| EBPC | - | Preclinical | aldose reductase inhibitor | Inhibitor |
| Epalrestat | nephrology | Launched | aldose reductase inhibitor | Inhibitor |
| Fidarestat | Diabetes complication | Phase 3 | aldose reductase inhibitor | Inhibitor |
| Hyperin | Vascular inflammatory diseases | Preclinical | aldose reductase inhibitor | Inhibitor |
| Imirestat | Diabetes | Preclinical | aldose reductase inhibitor | Inhibitor |
| Ranirestat | Diabetic neuropathy | Phase 3 | aldose reductase inhibitor | Inhibitor |
| Sorbinil | Diabetic cataract | Phase 3 | aldose reductase inhibitor | Inhibitor |
| Statil | Diabetes complication | Preclinical | aldose reductase inhibitor | Inhibitor |
| Bergenin | Inflammatory diseases | Preclinical | Interleukin1beta | Inhibitor |
| Diacerein | osteoarthritis | Launched | Interleukin1beta | Inhibitor |
| Ligustilide | - | Preclinical | TNF-Aplha | Inhibitor |
| Thalidomide | Type 2 diabetes and cancer | Launched | TNF-Aplha | Inhibitor |

**Computer-aided drug repurposing for identification of potential therapeutic candidate for diabetes retinopathy**

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**Supplementary table 2 : The table shows the interaction of the targets with the drugs and the polar bonds are also explicated. The lower the binding affinity and higher the polar bonds, it is a virtuous drug for the disease.**

| SNo | Target | Drug | Binding Affinity | Polar bonds with bond length below 1 A | Interacting amino acid residues |
|---|---|---|---|---|---|
| 1 | VEGFR(26) | Dovitinib | -9.3 | 3 | LEU32(2), GLU30 |
| | | Sorafenib | -9.1 | 5 | ASP63, CYS61(2), SER50, GLY59 |
| | | Linifanib | -8.7 | 6 | LEU66(2), LEU32, ASP63, GLY59(2) |
| | | Regorafenib | -8.6 | 4 | GLY59, ASP63(2), CYS61 |
| | | Brivanib-alaninate | -8.3 | 6 | LEU66, CYS612(2), CYS68, GLU30(2) |
| | | KI-8751 | -8.3 | 3 | LYS107, GLY59, ASP63 |
| | | MGCD-265 | -8.3 | 3 | LEU66, GLY59, LEU32 |
| | | Nintedanib | -8.2 | 4 | GLY59, GLU30, LEU32(2) |
| | | Lenvatinib | -8 | 3 | LEU32(2), LEU66 |
| | | Cabozantinib | -7.9 | 3 | SER50, GLY59, THR31 |
| | | DMH4 | -7.8 | 2 | ASP63, CYS61 |
| | | Pazopanib | -7.8 | 4 | ASP34(2), CYS61(2) |
| | | Motesanib | -7.7 | 3 | SER50, LEU66, ASP63 |
| | | ZM323881 | -7.5 | 4 | GLU30(2), LEU32, GLY59 |
| | | Anlotinib | -7.4 | 4 | LEU32,THR31, CYS57,CYS61 |
| | | Axitinib | -7.4 | 3 | ASN62, CYS61, ASP63 |
| | | Fruquintinib | -7.3 | 4 | LEU32, GLU30, CYS57, GLY59 |
| | | Semaxanib | -7.2 | 3 | ASN62(2), PHE47 |
| | | KRN-633 | -7.1 | 3 | CYS68, CYS61, LEU32 |
| | | Orantinib | -7.1 | 4 | CYS61(2), ASP34, CYS68 |
| | | PD-173074 | -7.1 | 3 | LEU32, ASP34, CYS57 |
| | | Brivanib | -7 | 5 | Thr31,Glu30(2),Leu32,CYS57 |
| | | Sunitinib | -6.9 | 5 | ASP34, CYS57, GLY59, CYS61(2) |
| | | SU4312 | -6.9 | 2 | CYS61(2) |
| | | SKLB1002 | -6.6 | 3 | GLU30(2), CYS57 |
| | | SAR131675 (CID_71295845) | -6.4 | 7 | ASP34, SER50(3), CYS61, LEU66,LEU32 |
| 2 | TNF-α | Thalidomide | -8.4 | 5 | GLN102(2), ARG103, GLN102(2) |
| | | Ligustilide | -5.9 | 3 | GLN102(2), PRO100 |
| 3 | Interleukin -β | Diacerein | -6.3 | 7 | LYS109, ASP145, SER13, THR144, ASP142, GLN126, GLY140 |
| | | Bergenin | -6.2 | 5 | ASN7, SER43, TYR68, LYS65, GLU64 |
| 4 | Angiotensin converting enzyme(20) | Deserpidine | -9.6 | 3 | TYR135 SER517 TRP220 |
| | | Cilazapril | -8.7 | 5 | HIS513 LYS511 GLN281 HIS353(2) |
| | | Delapril | -8.7 | 2 | THR302 ASN374 |
| | | Quinaprilat | -8.6 | 4 | THR282(2), LYS454(2) |
| | | Ramipril | -8.3 | 2 | THR282 ASN277 |
| | | Imidapril | -8.2 | 6 | ASN277(2), THR282(2), LYS454, GLU376 |
| | | Benazepril | -8.1 | 3 | GLU384 HIS383 HIS353 |
| | | Fosinoprilat | -8.1 | | |
| | | Benazepril | -8.1 | 3 | GLU384 HIS383 HIS353 |
| | | Enalapril | -8 | 1 | THR302 |
| | | Quinapril | -8 | 4 | ASN66, ASP358, TYR394, HIS410 |
| | | Temocapril | -8 | 3 | ASN70, SER355, ASP358 |
| | | Fosinopril(monopril) | -7.9 | 3 | ASN277 HIS353 ALA354 |
| | | Lisinopril | -7.9 | 5 | ASP288, ASN285(2), GLU376, LEU375 |
| | | Moexipril | -7.8 | 4 | ALA356 HIS387 TYR360 ASN66 |
| | | Enalaprilat | -7.4 | 4 | LYS454 THR282 ASN277(2) |
| | | Nicainoprol | -6.8 | 3 | ASP453 SER284 MET299 |
| | | Captopril | -5.8 | 4 | HIS513 LYS511 GLN281 HIS353 |
| | | Captopril | -5.8 | 4 | HIS513 LYS511 GLN281 HIS353 |
| | | Deserpidine | -9.6 | 3 | TYR135 SER517 TRP220 |
| 5 | Aldose reductase(6) | Imirestat | -9.1 | 2 | SER302(2) |
| | | Hyperin | -8.3 | 6 | TRP20(2), HIS110 TRP111 LEU301 GLN49 |

| | | | | | |
|---|---|---|---|---|---|
| | | Alrestatin | -7.8 | 2 | HIS110 TRP111 |
| | | EBPC | -7.2 | 3 | TRP20 TRP111 HIS110 |
| | | Ranirestat | -7 | 4 | GLU314, ARG296(3) |
| | | Ponalrestat(statil) | -6.9 | 2 | ARG40 LEU15 |
| | | Cinnamaldehyde | -6.8 | 2 | ASN160, HIS110 |
| | | Fidarestat | -6.8 | 4 | SER2 LEU15 ARG40 GLY38 |
| | | Epalrestat | -6.6 | 5 | GLN49 TYR48 LYS21 SER22 TRP20 |
| | | Sorbinil | -6.3 | 4 | GLU314, LYS194, GLU193, ASN292 |
| 6 | PKC-β(10) | Enzastaurin | -10.5 | 6 | GLU477, SER477, SER476, ASN424, TYR123, GLN128 |
| | | Bisindolylmaleimide-IX | -9.7 | 6 | SER476 ASN424 TYR123 TYR422(2) GLN128 |
| | | Myricitrin | -9.7 | 6 | TYR123, SER476, TYR422, LEU367, LYS141, ARG142 |
| | | CGP-53353 | -9.5 | 5 | GLU477, SER476, ASP475, TYR422, GLU421 |
| | | Dequalinium | -9 | | GLU477, GLU421 |
| | | Ingenol | -8.6 | 3 | ASP470 ASP427, GLY426 |
| | | GF109203X | -7.5 | 3 | ASN471, ASP470, ASP427 |
| | | Ingenol-mebutate | -7 | 2 | LYS371 |
| | | Aurothioglucose | -6.1 | 5 | ARG415, LYS375, ASP414(2), ASP376 |
| | | Ethylenediaminetetraacetic-acid | -5.5 | 7 | GLU421, GLN405(2), LYS481, ASN481, ASN424, SER476 |