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Current Status of Computer-Aided Drug Design for Type 2 Diabetes

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Abstract: Background: Diabetes is a metabolic disorder that requires multiple therapeutic approaches. The pancreas loses its functionality to properly produce the insulin hormone in patients with diabetes mellitus. In 2012, more than one million people worldwide died as a result of diabetes, which was the eighth leading cause of death.

Objective: Most drugs currently available and approved by the U.S. Food and Drug Administration cannot reach an adequate level of glycemic control in diabetic patients, and have many side effects; thus, new classes of compounds are required. Efforts based on computer-aided drug design (CADD) can mine a large number of databases to produce new and potent hits and minimize the requirement of time and dollars for new discoveries.

Methods: Pharmaceutical sciences have made progress with advances in drug design concepts. Virtual screening of large databases is most compatible with different computational methods such as molecular docking, pharmacophore, quantitative structure-activity relationship, and molecular dynamic simulation. Contribution of these methods in selection of antidiabetic compounds has been discussed.

Results: The Computer-Aided Drug Design (CADD) approach has contributed to successful discovery of novel anti-diabetic agents. This mini-review focuses on CADD approach on currently approved drugs and new therapeutic agents-in-development that may achieve suitable glucose levels and decrease the risk of hypoglycemia, which is a major obstacle to glucose control and a special concern for therapies that increase insulin levels.

Conclusion: Drug design and development for type 2 diabetes have been actively studied. However, a large number of antidiabetic drugs are still in early stages of development. The conventional target- and structure-based approaches can be regarded as part of the efforts toward therapeutic mechanism-based drug design for treatment of type 2 diabetes. It is expected that further improvement in CADD approach will enhance the new discoveries.

Keywords: Computer-aided drug design, diabetes mellitus, FDA-approved therapeutic options, glucose level, hypoglycemia, therapeutic mechanism-based drug design.

Received: February 12, 2016

Revised: March 17, 2016

Accepted: April 19, 2016

1. INTRODUCTION

Diabetes is a group of diseases that result from high levels of blood glucose and that depend on insulin production and/or action. It involves multiple disorders of abnormal carbohydrates, lipids and protein metabolism [1]. People with diabetes may develop serious complications such as heart disease, stroke, kidney failure, blindness and premature death. Diabetes mellitus is a diverse and complicated disorder that is characterized by persistent hyperglycemia. It has been called a “third killer” of human health [2]. Hypoglycemic medication is used to lower the blood sugar level in the body or to treat other severe symptoms of diabetes mellitus. These medications can be categorized into insulin and insulin preparations, which are used only parenterally, and hypoglycemic medicine, which can be administered orally [3]. The 2014 National Diabetes

Statistics Report revealed that from 2010 to 2012, the number of American diabetic patients increased from 25.8 million to 29.1 million, and that the diabetes mellitus prevalence rate for adults aged 20 years and older increased from 11.3% to 12.3% [4].

The International Diabetes Federation recently reported that the number of people with diabetes is expected to rise from 382 million to 592 million by 2035. Most people with diabetes live in low- and middle-income countries [5].

By 2014, an estimated 90% of patients with diabetes had been diagnosed with type 2 diabetes. Although there are anti-diabetic medications currently approved by the U.S. FDA to treat patients with type 2 diabetes, most do not achieve appropriate glycemic control, and some have severe side effects. Successful treatment of type 2 diabetes, therefore, requires new drugs with improved mechanisms of action. In this review, we describe the use of computational tools for the discovery and design of new anti-diabetic drugs that are not currently approved, but that may lower glucose levels and decrease the risk of hypoglycemia, which is a major

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obstacle to glucose control and a special concern for therapies that increase insulin levels.

2. STATUS OF COMPUTER-AIDED DRUG DESIGN FOR FATAL DISEASES

The average cost of launching a new drug onto the market is estimated to 1.8 billion dollars [6], and few drugs make it to the market. From 1999 to 2008, only 50 compounds were approved by the FDA in the U.S., out of which 17 were identified as arising from target-based drug design methods [7]. This suggests that experimental libraries made by conventional high-throughput screening take more time, and that the results are not always efficient for developing novel drugs.

Computer-aided drug design provides advantages for experimental findings, mechanisms of action and new suggestions for molecular structures for new synthesis, and it can help in making cost-effective decisions before the costly process of drug synthesis begins. Numerous compounds were discovered and/or optimized using computational methods and they have reached the clinical stage of drug development or have even gained U.S. Food and Drug Administration (FDA) approval [8, 9]. Computer-aided drug design can increase the hit rate of novel anti-diabetic drug-like compounds because it better uses a large chemical search space to find a suitable target compared with traditional high-throughput screening and combinatorial chemistry. Several studies have compared conventional high-throughput screening and virtual screening, and virtual screens had hit rates of tenfold to 1700-fold those of conventional screening [10-14].

Computational methods are required because the amount of biological data has increased and manual screening against such data requires much time and human resources. Computer-aided drug design methods have been used in the development of therapeutic molecules for over three decades. The increasing use of this method is reflected in the number of publications about computer-aided drug design in fatal diseases. Publications on computer-aided drug design for the top 3 most fatal diseases [15] are shown in Fig. 1. Diabetes has the third most papers published on computer-aided drug design, but the number of published papers for diabetes was half of what it was for cancer or HIV. Thus, there is still room for improvement in antidiabetic drug design with the help of computational techniques.

3. CURRENT COMPUTATIONAL TECHNIQUES

Drug development requires extensive clinical testing and is a costly process. There are two main phases involved in creating a new drug: the discovery phase and the clinical testing phase. *In silico* approaches, including virtual high throughput screening, and *de novo* structure-based rational drug design, have been established as tools in the discovery phase. Virtual screening emerged for finding novel drug-like compounds. *In silico* virtual screening has become a reliable, cost effective and time-saving technique that is complementary to *in vitro* screening for the discovery and optimization of potent lead and hit compounds. There are two broad categories of screening techniques, the ligand-

Fig. (1). The number of publications related to computer-aided drug design and diseases. Key words used in the Google Scholar search [16] were as follows: computer-aided drug design and disease; e.g. diabetes.

based virtual screening and receptor-based virtual screening, to select candidate compounds that are likely to interact favorably with the target binding sites from a chemical database. The three-dimensional structure of protein or protein-ligand complex is helpful in lead identification using molecular modeling. Quantitative structure-activity relationship (QSAR), pharmacophore and biological assays can be helpful to optimize and design new leads. Structure-based drug design helps to provide potent and significant compounds more productively in the drug discovery process. Structure-based virtual screening is used more frequently than the ligand-based virtual screening (322 to 107 studies) [17].

Virtual screening uses high-performance computing to screen large chemical databases and prioritize compounds for synthesis. Current databases allow rapid virtual screening of up to 100,000 molecules per day using parallel computing techniques [18]. The databases of three-dimensional structures directly available for virtual screening are: Advanced Chemistry Development [19], InfoChem GmbH database [20], MDL Drug Data Report [21], MDPI database [22], National Cancer Institute Open Database Compound [23], Thomson Index Chemicus database [24], Tripos Discovery Research Screening Libraries [25] and ZINC [26]. They contain libraries that have been experimentally determined.

Several computer programs have been developed and used in research leading to drug discoveries for various diseases. They are based on computational techniques of drug design, using different algorithms and scoring functions. Some of the programs for virtual screening and docking studies are: AutoDock [27], CLC drug discovery work bench [28], DOCK [29], FlexX [30], FRED [31], Glide [32], GOLD [33] and MOE [34]. Several remarkable drug design applications using docking tools have been mentioned in this mini-review.

Pharmacophore modeling, or ligand-based virtual screening, is an efficient method to increase hit rates in drug discovery research. Catalyst [35], LigandScout [36, 37],

MOE [34] (its pharmacophore module) and PHASE [38] are widely used computer programs for pharmacophore elucidation and virtual screening. The effective pharmacophore models depend on two factors: the definite understanding and placement of pharmacophoric features, and the alignment method used for overlaying the three-dimensional pharmacophore model with a set of ligand compounds of screened data [39].

QSAR methods can be used to optimize lead compounds. Modern three-dimensional QSAR methods involve the interaction fields around a molecule by calculating the interaction energy in a grid. The well-known three-dimensional QSAR techniques are comparative molecular field analysis [40] and comparative molecular similarity index analysis [41]. These approaches calculate molecular properties including steric, electronic, hydrogen bonding, and hydrophobic fields. Some of the programs used in research and that are available for two-dimensional and three-dimensional QSAR analyses are CODESSA [42], Dragon [43], QSARpro-VLifesciences [44] and SYBYL-XSuite [45].

Another type of program is the versatile and advanced software for molecular modeling and simulation, which has broad applications to many-particle systems, and include Amber [46], CHARMM [47] and GROMACS [48].

4. CASE STUDIES OF COMPUTER-AIDED DRUG DESIGN FOR DIABETES

A diverse array of approaches using the computational method has been used for bioactive molecule discovery. Recent cases involving various computational strategies have been used together to discover anti-diabetic compounds.

4.1. Ligand-based Virtual Screening Followed by *in vitro* Bioassay Discovered Glucokinase Activator

Glucokinase activator (GKA) has been recently shown to be a valid anti-diabetic target. GKA serves as a glucose sensor in the insulin-producing pancreatic beta-cells, and determines the rate of glucose metabolism by regulating the amount of insulin produced and released from pancreatic beta-cells in response to the amount of glucose in the blood. Elevated levels of glucose will increase GKA levels in the pancreas, thereby increasing the release of insulin. In addition, GKA influences hepatic lipid metabolism and gluconeogenesis in the liver [49]. Target protein structure having PDB id: 3VF6 use in this study for new GKAs identification with good bioactivity is shown in Fig. 6 (A). Taha *et al.* identified a series of novel GKAs using virtual screening. They used a multistage approach, integrating pharmacophore modeling and QSAR analysis followed by virtual screening of the NCI library of 238,819 compounds. Pharmacophore exploration of GKA was performed using Catalyst software. QSAR-based pharmacophore analysis was conducted to select the best combination of molecular descriptors and pharmacophore models that are capable of explaining bioactivity variation across a list of training dataset. The authors concluded that a novel GKA activation pharmacophore model appeared in the optimal QSAR equation. The resulting pharmacophore model yielded a good receiver operating characteristic on validation, and

Fig. (2). The structure of the potent hit (NSC32458) identified by using the QSAR-based pharmacophore modeling and virtual screening approaches shows highest GK activation of ≈ 6 folds at $10\mu\text{M}$.

therefore this information was used as three-dimensional search query to screen the NCI database for new GKA activators. Virtual screening identified 10 promising bio-activators from the NCI library of compounds. The most potent NCI hit illustrated 6.3-fold GKA activation at $10\mu\text{M}$ shown in Fig. 2. These results illustrated that the ligand-based virtual screening protocol was helpful to identify novel GKA leads for subsequent development into potential anti-diabetic agents [50].

4.2. Combined Ligand- and Structure-Based Virtual Screening Techniques Discovered 11 β -HSD1 Inhibitor

The 11 β -HSD1 is an enzyme that regulates glucocorticoid metabolism at the tissue level by converting the inert hormone cortisone to its active form, cortisol, in target tissues. Active cortisol production can cause insulin resistance by inhibiting pancreatic beta-cell insulin secretion and peripheral glucose uptake, and encourages gluconeogenesis [51]. Lagos *et al.* discovered novel 11 β -HSD1 inhibitors by applying a combination of ligand and structure-based filtering methods. The NCI library of 260,071 structures was retrieved from the OpenNCI database [52] for the virtual screening and then filtered against ADMET constraints, and multiple conformations for each compound in the database were generated. Crystal structures of human 11 β -HSD (PDB id: 1Y5R) in complex with inhibitors were used as the source of structural information shown in Fig. 6 (B). Virtual screening of the generated NCI conformer database was performed using the FRED version 2.2.5 program [31]. The top-scoring binding mode of 1,000 compounds on each protein binding site was considered, and the scoring scheme was based on three scoring functions: ChemGauss3, OE-Chem and Piecewise Linear Potential [53]. The 100 top-scoring compounds on each docking run were visually inspected, and overlap analysis of obtained solutions using the Tanimoto similarity metric was performed with InstantJChem v5.9 to select 40 compounds that were requested along with the ball grid array obtained from the Developmental Therapeutic Program [54] at NCI-NIH. The selected compounds were identified using *in silico* methods and further tested in cell-based assays to check cytotoxicity and 11 β -HSD1-mediated cortisol production inhibitory

efficiency. Biological testing was used in the identification of four compounds in adipocytes and steroid quantification by HPLC-MS/MS mediated cortisol production inhibitory activity, with potencies in the μM range. Two compounds proved to be potent and selective for 11β -HSD1 reductase activity and over the 11β -HSD2 isoform. This study leads to development of more active derivatives with higher efficacies to target intracellular cortisol levels in type 2 diabetes and other metabolic syndromes [55]. 11β -HSD1 inhibitor discovered by ligand- and structure-based virtual screening techniques with the best score and activity is shown in Fig. 3.

4.3. Structure-Based Virtual Screening Identified the DPP-IV Inhibitor

Inhibition of dipeptidyl peptidase-IV (DPP-IV) does not cause weight gain, hypoglycemia and exhaustion of beta cells, and it has emerged as a promising approach for the treatment of patients with type 2 diabetes [56]. DPP-IV stimulates glucose dependent insulin release and suppression of elevated glucagon levels by prolonging the half-life of endogenous GLP-1. Recently, several DPP-IV inhibitors have been approved in the U.S. and Europe (Table 1). The withdrawal of glitazones from the market as well as concerns related to usage of sitagliptin raised a concern about long-term use of new anti-diabetic drugs. Previous knowledge has been used as a requirement to develop novel and safe clinical candidates for the treatment of type 2 diabetes using a structure-based virtual screening technique. Screening of the MDPI database was performed using structure-based virtual screening tools to identify DPP-IV inhibitors. The crystal structure of DPP-IV (PDB id: 1RWQ) was available in a protein drug bank [57] shown in Fig. 6 (C). After filtration of compounds from the MDPI database, docking operations were performed by Glide [32, 58], using three consecutive protocols: virtual high throughput screening, standard precision and extra precision docking. Docking results were further validated by redocking on DPP-IV enzyme using GOLD [33] software and select best hits for biological evaluation. Three of them were active at low μM concentrations. The 3-(1-hydrazinyl-1-(phenylamino) ethyl)-4-hydroxy-1-methylquinolin-2(1H)-one was most potent hit with an IC_{50} of $0.73 \mu\text{M}$ shown in Fig. 4. These compounds were then evaluated for their glucose-lowering effects in

Fig. (3). The structure and activity of the potent hit (NSC83182) identified by testing compounds for inhibition of 11β -HSD1 mediated cortisol production in LS14 cell lysates with ChemGauss3 score = 84.17, % inhibition = 57.2, IC_{50} = $5.85 \mu\text{M}$.

glucose-fed hyperglycemic female Wistar rats and confirmed to be potential anti-diabetic agents [59].

4.4. Structure-Based Virtual Screening and Three-dimensional QSAR-based Pharmacophore Modeling Discovered the PTP1B Inhibitor

In the insulin cascade, a cytosolic protein tyrosine phosphatase negatively controls insulin release by the dephosphorylation of several insulin receptor kinase substrates [60]. PTP1B inhibitors play a role in downregulation of leptin signaling also by dephosphorylating Janus kinase 2 found downstream of the leptin receptor [61]. Recently, several synthetic PTP1B inhibitors with sub-micromolar or nanomolar activities have been discovered through high-throughput screening and structure-based design [62, 63]. Novel PTP1B inhibitors for diabetes have been discovered by pharmacophore modeling, docking and scaffold hopping techniques. The three-dimensional QSAR based pharmacophore model generation protocol using 30 training-set molecules resulted in the development of 10 pharmacophore models using the Catalyst program. Target protein structure (PDB id: 1AAX) shown in Fig. 6 (D) was used for the docking experiments considering the binding site region around Arg-221, using the default protocols from two docking software packages from Molegro virtual docker, whose updated versions are available as the CLC drug discovery work bench [64] and GOLD [33]. Ten compounds were synthesized, which were retrieved from library of 86 compounds using *in silico* methods and positive results were found in the μM range for PTP1B *in vitro* inhibitory assays compared with Suramin (IC_{50} 9.5 mM). Five active compounds were tested using the streptozotocin-induced diabetic rat model, and the most active compound in this test was further tested in C57BL/KsJ-db/db mice, where the active compound significantly improved oral glucose tolerance test results along with the fasting and random blood glucose levels. Treatment with one selected compound significantly improved insulin resistance and insulin signaling by restoring the insulin level and normalizing the serum lipid profile shown in Fig. 5. This demonstrates the insulin action by modulating the expression of genes involved in the insulin signaling cascade, such as IRS 1e2, Akt2, PTPN1, PI3K, AMPK and PPAR- α with oral bioavailability of approximately 10.29% after an oral dose of 30 mg/kg in the rat [65].

4.5. Docking, QM and QM/MM Discovered the Glycogen Phosphorylase Inhibitor

Glycogen phosphorylase catalyzes the phosphorolytic cleavage of glycogen to produce glucose-1-phosphate, which is isomerized by phosphoglucomutase to glucose-6-phosphate, and it then enters the glycolytic pathway to produce glucose [66]. Crystallographic structure of glycogen phosphorylase complex with inhibitor is shown in Fig. 6 (E). Poly'ak *et al.* used GP inhibitors and conducted molecular modeling experiments in the form of docking, QM and QM/MM studies, and N-(b-D-glucopyranosyl)-1,2,4-triazolecarboxamides were suggested for evaluation as GP inhibitors. Analogues of N-(b-D-glucopyranosyl)-1,2,4-triazolecarboxamides generated with different aryl substituents showed more favorable binding to the GP site *via* docking

Table 1. Approved drugs for type 2 diabetes.

Therapeutic Class of Compound	Mechanism of Action	Approved Drugs	Potency (μM)	Pubchem CID	Date of First Compound Approved	Adverse Effects and/or Comments
Biguanide	Increases insulin sensitivity, suppresses glucose production in the liver.	Phenformin, Metformin	45.4 29	8249 4091	1957 (EMA), 1995 (FDA)	Nausea, vomiting, diarrhea and flatulence; If taken with meals, avoid use in patients with renal or hepatic impairment or with CHF, because of increased risk for lactic acidosis.
Second generation sulfonylureas	Stimulate insulin secretion from the pancreas.	Glimepiride, Glipizide, Gliclazide, Glibenclamide (Glyburide), Gliquidone	0.1 0.398 0.64033 0.0631 0.2512	3476 3478 3475 3488 91610	Glibenclamide (Glyburide): 1969 (EMA), 1984 (FDA)	Hypoglycemia and weight gain.
Insulin: regular human insulin, NPH insulin, insulin aspart, insulin lispro, insulin glargine, insulin detemir, insulin levemir	Helpful in lowering blood glucose.	Regular insulin, Bovine insulin	0.00193 1*	625273 16131099	Regular insulin: 1982 (FDA), 1984 (EMA), Bovine insulin: 1922	Severe hypoglycemia and weight gain. A new administration form of inhaled insulin has been recently approved (2014) (Afrezza) for type 1 and type 2 diabetes.
Alpha-glucosidase inhibitor	Delay complex carbohydrate absorption.	Acarbose, Miglitol, Voglibose	4.4668 3.5481 0.07	41774 441314 444020	Acarbose: 1991 (EMA), 1995 (FDA)	Flatulence, diarrhea, abdominal pain. Less effective than other agents, it is considered in all elderly patients with mild diabetes.
Glinides	Stimulate insulin secretion from the pancreas.	Repaglinide, Nateglinide	0.05 1.667	65981 5311309	Repaglinide: 1998 (EMA), 1997 (FDA)	Hypoglycemia and weight gain; the precaution is to take with meals to control rapid onset. Some partial agonists are in clinical trials. An example is INT131 (previously known as AMG-131), which progressed through the phase 2 clinical trials. C333H is a novel partial agonist in preclinical development.
Thiazolidinediones	Increase peripheral tissue insulin sensitivity.	Pioglitazone, Rosiglitazone	0.16 0.076	4829 77999	Rosiglitazone: 1999 (FDA), 2000 (EMA)	Edema, it should be avoided in patients with heart failure. These agents can cause or exacerbate CHF contra indicated in patients with NYHA class III or IV heart failure.
Amylin analogue	Slowing of gastric emptying, suppression of elevated glucagon, stimulation of satiety.	Pramlintide	1*	16132446	Pramlintide: 2005 (FDA)	Approved for type 1 and 2 diabetes, nausea, hypoglycemia when combined with other anti-diabetic drugs (e.g. insulin).
GLP-1 agonists	Stimulation of glucose dependent insulin release, suppression of elevated glucagon levels, reduction of gastrointestinal motility.	Exenatide, Liraglutide, Exenatide extended-release, Lixisenatide, Albiglutide, Dulaglutide	1* 1* 1* 1* 1* 1*	2* 2* 2* 2* 2* 2*	Exenatide: 2005 (FDA), 2006 (EMA), Liraglutide: 2010 (FDA), 2009 (EMA), Exenatide ER: 2012 (FDA), Lixisenatide: 2013 (EMA), Albiglutide: 2014 (FDA, EMA), Dulaglutide: 2014 (FDA)	Only injectable drug, weight loss, nausea, vomiting, diarrhea and acute pancreatitis. Risk for medullary thyroid cancer, pancreatitis or pancreatic cancer. Not confirmed in clinical trials by FDA and EMA. Many oral GLP-1 agents are under trail for TD. ORMD-0901 NN9924, NN9926, NN9927, NN9928, TTP054, ZYOG1, NN9924, ORMD-0901, TTP054 have reached Phase 2.

Table 1. contd....

Therapeutic Class of Compound	Mechanism of Action	Approved Drugs	Potency (μM)	Pubchem CID	Date of First Compound Approved	Adverse Effects and/or Comments
DPP4 inhibitor	Slow inactivation of incretin hormones.	Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin	0.018 0.034 0.0006 0.001 0.01	4369359 6918537 11243969 10096344 11450633	Sitagliptin: 2006 (FDA), 2007 (EMA), Vildagliptin: 2008 (EMA), Saxagliptin: 2009 (FDA, EMA), Linagliptin: 2011 (FDA), Alogliptin: 2013 (FDA)	Risk for medullary thyroid cancer, pancreatitis or pancreatic cancer. Not confirmed in clinical trials by FDA and EMA. Few agents are under clinical: ARI-2243 (Phase 1), Teneeligliptin (Phase 1), Omarigliptin (Phase 3), Trelagliptin (Phase 3).
Bile acid sequestrant	Possibly activation of the farnesoid X receptor / bile acid receptor.	Colesevelam	1*	160051	Colesevelam: 2008 (FDA)	Constipation, nausea and dyspepsia. Primary a lipid lowering drug with additional glucose lowering effects. Mechanism of action for diabetes control is unknown.
Dopamine agonist	Central modification of insulin resistance.	Bromocriptine	0.017	31101	Bromocriptine: 2009 (FDA)	Orthostatic hypotension, nausea. Mechanism of action for diabetes control is unknown.
SGLT2 inhibitor	Reduction of the renal threshold for glucose excretion.	Dapagliflozin, Canagliflozin, Empagliflozin	0.003 0.19 1*	9887712 24812758 11949646	Dapagliflozin: 2012 (EMA), 2014 (FDA), Canagliflozin: 2013 (FDA), Empagliflozin: 2014 (FDA, EMA)	Genital infections and possible diuretic effects. Other favorable effects of SGLT2 inhibitors include a reduction in both body weight and blood pressure. Still some agents are under trails to improve the effects, e.g. Ertugliflozin (Phase 3), EGT0001442 (Phase 2), luseogliflozin (TS-071) (Phase 1).

1* There is no biological assay report available to get potency value, and 2* there is no PubChem CID available to refer.

calculations using Glide [32]. They synthesized the ligands in moderate yields using N-(2,3,4,6-tetra-O-acetyl-b-D-glucopyranosyl)-tetrazole-5-carboxamide as a starting material. Performance of kinetics experiments against rabbit muscle glycogen phosphorylase b revealed that ligands were low- μM GP inhibitors, while the phenyl analogue ($K_i = 1 \mu\text{M}$) is one of the most potent N-(b-D-glucopyranosyl)-heteroaryl-carboxamide-type inhibitors of the GP catalytic site that has been discovered. Based on QM and QM/MM studies, the potency of the ligands was predicted to arise from favorable intra- and intermolecular hydrogen bonds formed by the most stable solution phase tautomeric state of the 1,2,4-triazole in a conformational dynamic system. ADMET property predictions showed their promising pharmacokinetic activity without any toxicity effect and highlighted the benefits of a computationally-led approach to GP inhibitor design for diabetes [67].

Fig. (4). Structure and biological activity for the most potent hit [3-(1-hydrazinyl-1-(phenylamino)ethyl)-4-hydroxy-1-methylquinolin-2(1H)-one] identified in the structure-based virtual screening strategy yields an IC_{50} of $0.73 \mu\text{M}$.

Fig. (5). Structure of the top scored designed ligand based on scaffold hopping protocol and pharmacophore mapping (Fit value = 6.91, activity predicted = 0.130) shows $\text{IC}_{50} = 7.54 \pm 0.40 \mu\text{M}$ on testing along with the STZ-s model results at 5 hours = 25.9 and 24 hours = 28.4 in terms of improvement in glucose tolerance on fasting blood glucose (2-Deoxy-D-[3H]-glucose uptake at 10 mg = 62.50%).

5. FUTURE DIRECTIONS AND CHALLENGES

Twelve classes of anti-diabetic drugs are currently available and approved (Table 1). There are ten more classes that have new mechanisms of action, which are in various phases of clinical trials (Table 2). Patients with type 2 diabetes have a multi-drug regimen that must be taken daily. To reduce the burden, a once-weekly regimen rather than once-daily formulations will show potential. The once-weekly DPP4 inhibitors omarigliptin and trelagliptin are currently in phase 3 clinical development. GLP-1 agonists are among the most potent drugs for the treatment of type 2 diabetes. However, all currently-available compounds are administered *via* injection, which can be a barrier for use by some patients, and an alternative route of administration is

Fig. (6). Schematic representation of protein secondary structure complex used in the case studies. (A) Crystallographic structure of GK complexed with 6-((2S)-3-cyclopentyl-2-[4-(trifluoromethyl)-1H-imidazol-1-yl]propanoyl)amino)pyridine-3-carboxylic acid molecule (PDB id: 3VF6, 1.86 Å). (B) The crystal structure of murine 11 β -HSD1 complexed with corticosterone molecule (PDB id: 1Y5R, 3.0 Å). (C) Crystallographic structure of DPP-IV complexed with 5-aminomethyl-6-(2,4-dichloro-phenyl)-2-(3,5-dimethoxy-phenyl)-pyrimidin-4-ylamine (PDB id: 1RWQ, 2.2 Å). (D) Crystallographic structure of PTP1B complexed with bis (Para-Phosphophenyl) methane (BPPM) molecule (PDB id: 1AAX, 1.9 Å). (E) Crystallographic structure of PTP1B complexed with bis (Para-Phosphophenyl) methane (BPPM) molecule (PDB id: 1AAX, 1.9 Å).

desired. Some oral agents have reached phase 2 development, and these compounds may show good tolerability and effectiveness compared with injectable GLP-1 agonists and may be considered for future treatment of type 2 diabetes. An effective class is SGLT2 inhibitors that block SGLT1 activity in the small intestine and improve the level of glucose due to decreased intestinal absorption of glucose. The SGLT1 transporter is responsible for glucose and galactose absorption in the gastrointestinal tract, to a smaller extent, and glucose reabsorption in the kidneys. Systolic (but not diastolic) blood pressure and weight are also significantly reduced in the developing agents are helpful to produce effective drugs in future as mentioned in Table 2. This mini-review focuses on therapeutic classes that provide novel compounds that show improved safety and tolerability profiles for known adverse effects related to marketed agents such as gastrointestinal side effects, hypoglycemic risk and weight gain. Further optimization and clinical studies will help to generate a useful drug in a short period of time from these compounds. These agents may potentially control glucose levels and improve outcomes in patients with type 2 diabetes. We expect computer-aided drug design techniques to contribute to improvement of the compounds and acceleration of novel diabetes drug development.

The high prevalence of diabetes, especially among the aging population, comes at a considerable economic cost.

Computer-aided drug design approaches mainly focus on the structural properties of a drug target and its possible binder to find or design a chemical that could bind the target. However, these approaches do not include processes before and after drug-receptor interactions, and the success rate of new drug candidates is still low. To solve this problem, a complete understanding and knowledge of mechanisms of drug action in early stages of the drug design process will be helpful to drug design experts. Therapeutic (antibodies studies)-based drug design and computational methods for improving the affinity, selectivity and stability of the protein-based therapeutics have been developed. Thus, the conventional target- and structure-based approaches can be regarded as a part of the efforts toward target/therapeutic mechanism-based drug design. Previous methods were time consuming. Bringing a new drug to market from scratch will typically take 10 to 15 years and the cost can be more than two billion dollars. A fusion of techniques and the technology to support new methods will accelerate the process of drug discovery, hence reduce the cost and increase the overall efficiency of therapies. Such integration of different disciplines and new technologies will be challenging but the task can be accomplished.

Drug design approaches should include consideration of *in silico* methods to estimate the absorption, distribution, metabolism, excretion and toxicity (ADMET) profile into the

Table 2. Drugs under development for type 2 diabetes.

Therapeutic Class of Compound	Mechanism of Action	Adverse Effects and/or Comments
11 beta-hydroxysteroid dehydrogenase type 1 inhibitor	Improves lipid profiles, fasting glucose levels and hepatic insulin sensitivity.	Risk of glucose intolerance, insulin resistance, dyslipidemia, and hypertension. Some agents are under trails. There are no long-term studies available beyond 3 months: PF-00915275 (Phase 1), INCB13739 (Phase 2), MK-0916 (Phase 2).
Glycogen phosphorylase inhibitor	Potential target of hepatic glucose production.	In early development: oral agents have shown promising results in animals and humans.
Glucokinase activator	Activate key enzyme to increase hepatic glucose metabolism.	Hyperlipidemia, hyperglycemia and Cardiovascular risk. Several drugs are currently in phase 2 clinical trials: PF-04937319 (Phase 2), AZD1656 (Phase 2).
G protein-coupled receptor 119 agonist	Activation induces insulin release and increases secretion of glucagon-like peptide 1 and gastric inhibitory peptide.	Low potential for hypoglycemia. Several agents are in clinical trials: DS-8500 (Phase 2), MBX2982 (Phase 2), GSK1292263 (Phase 2).
PTP1B inhibitor	Negatively regulates insulin in a signal pathway that helps to increase leptin and insulin release.	Reduces adipose tissue storage of triglyceride under conditions of over-nutrition and was not associated with any obvious toxicity. No weight gain, indicating another substantial advantage for diabetic patients, who are frequently obese and at high cardiovascular risk. Some agents are currently in clinical trials: TTP814 (Phase 1/2), ISIS-PTP1BRx (Phase 2).
Glucagon-receptor antagonist	Block glucagon from binding to hepatic receptors, thereby decreasing gluconeogenesis.	Low potential for hypoglycemia. Several agents are under trails: BAY 27-9955 (Phase 1), LGD-6972 (Phase 1), MK-0893 (Phase 2), MK-3577 (Phase 2), LY-2409021 (Phase 2).
Hepatic carnitine palmitoyltransferase 1 (CPT1) inhibitors	CPT1 is a mitochondrial enzyme involved in fatty acid metabolism and, it makes CPT1 important in many metabolic disorders such as diabetes. Inhibition decreases gluconeogenesis.	Since its crystal structure is not known, its exact mechanism of action remains to be determined. Only limited data available. One agent is in clinical trials: Teglicar (Phase 2).
Diacylglycerol acyltransferase (DGAT)-1 inhibitors	Inhibition of DGAT-1 enzyme responsible for final step in triglyceride synthesis – weight loss, improved insulin sensitivity, decreased cholesterol and triglycerides.	Gastrointestinal side effects (nausea, diarrhea, vomiting). Several agents are in clinical trials: DS-7250 (Phase 2), P7435 (Phase 1).
Sirtuin1 (SIRT1) activators	Enhance glucose production and lipid metabolism, insulin signaling and pancreatic insulin secretion.	SIRT1 activation improves glucose homeostasis and insulin resistance. Very early development. One agent is in clinical trials: SRT3025 (Phase 1).
Glucocorticoid receptor antagonist	Liver specific glucocorticoid receptor antagonist; reduction of hepatic glucose production.	Early in development, Only limited data is available. One agent is in clinical trials: ISIS-GCGRx (Phase 1).

early stages of drug design process. Once a model is built, a number of new structures can be tested in a short time and side effects can be predicted for a given structure. *In silico* predictions can be used as a pre-screen and followed up by *in vitro* or *in vivo* testing. In other words, the results can help to prioritize *in vitro* assays. If *in vivo* results obtained from animal studies might not be good in comparison with humans, till then *in silico* and *in vitro* profiling can help to identify and correct previous issues [68]. One advantage of *in silico* predictions is to provide a predicted profile that is validated later by *in vitro* experiment. This will be helpful to design new chemical entities with improved efficacy.

CADD approach has some challenges. First, docking programs can produce accurate binding pose of ligands in 80% of crystal structures. Other 20% cases are incorrectly

bounded [64]. Next challenge is how to treat protein flexibility. Protein structures are treated as rigid bodies in most docking programs, whereas in real life proteins are dynamic and flexible entities that may often change their confirmation to fit the binding ligand, as phenomenon known as ‘induced fit’ method [69]. Some docking programs are at early stage to consider certain degree of protein flexibility. Third, there is no general rule on how to treat water molecules, although they are ignored or deleted frequently to reduce the complexity. The ideal approach is to consider every water molecule in the binding site. The local environment and hydrogen bonds were generated by the water molecule [70]. Fourth, prediction of binding free energy has difficulties. Free energy perturbation approaches were thought promising, and linear interaction energy methods have been applied in certain systems [71], but there

is need to prove the methods for more general cases. Fifth, there have been many efforts to get scoring functions for structure-based virtual screening over the last decade. However, these are only capable of yielding 'enrichment' and rarely give a good correlation values with observed binding affinities. The all challenges focus the underlying complexity of molecular recognition. It should be noted that drugs based on oligosaccharides and carbohydrate-protein interaction have not been developed because of the lack of appropriate models. As more structural information will come in the field, CADD will have a whole new arena for discovery.

The mechanisms of blood sugar in a human body are a highly complex with many interacting parameters, and sometimes the reaction of the system to a new drug cannot be predicted. Major factors associated with the development of diabetes and its complications are generally understood, but scientists do not yet understand the genetic, immunologic and metabolic differences among patients that would allow them to accurately predict which patients will progress to diabetes, which patients will respond to specific drugs and which patients will be susceptible to serious drug side effects.

For decades, biomedical sciences have not been sufficiently accelerated due to technical limitations, but now the time has come to develop new techniques and go beyond existing approaches. New techniques will allow researchers to answer some of the most interesting questions in the biomedical sciences today. We expect computer-aided drug design techniques to improve this situation.

LIST OF ABBREVIATIONS

ADMET	=	Absorption, Distribution, Metabolism, Excretion and Toxicity
Akt2	=	AKT2 are the principal isoform responsible of the regulation of glucose uptake.
AMG-131	=	A selective Modulator PPAR- γ , a potential therapeutic agent for the treatment of type 2 diabetes
AMPK	=	Adenosine Monophosphate-Activated Protein Kinase
CHF	=	Congestive Heart Failure
DPP	=	Dipeptidyl peptidase
EMA	=	European Medicines Agency
GKA	=	Glucokinase Activator
GLP	=	Glucagon-Like Peptide-1 receptor agonists
GP	=	Glycogen phosphorylase
FDA	=	Food and Drug Administration
HIT	=	A compound which has the desired activity in a screened compound
HIV	=	Human Immunodeficiency Virus

HPLC	=	High-Performance Liquid Chromatography
INT	=	A selective PPAR γ modulator that enhances Insulin Sensitivity
IRS 1-2	=	Insulin Receptor Substrate 1, Insulin receptor substrate 2
MDPI	=	Molecular Diversity Preservation International
MM	=	Molecular Mechanics
MS/MS	=	Tandem Mass Spectrometry
NCI	=	National Cancer Institute
NIH	=	National Institutes of Health
NPH	=	Neutral Protamine Hagedorn, an intermediate-acting insulin
NYHA	=	New York Heart Association
PDB	=	Protein Data Bank
PI3K	=	Phosphoinositide 3-Kinase
PLP	=	Piecewise Linear Potential scoring function
PPAR- α	=	Peroxisome Proliferator-Activated Receptor alpha
PTP1B	=	Protein Tyrosine Phosphatases-1B
PTPN1	=	Tyrosine-Protein Phosphatase Non-receptor type 1/ Protein tyrosine phosphatases-1B
QM	=	Quantum Mechanics
QSAR	=	Quantitative Structure-Activity Relationship
SGLT	=	Sodium-dependent Glucose Cotransporters/ sodium-glucose Linked Transporter
STZ	=	Streptozotocin

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The authors thank Prof. K. Nakamura for valuable discussions and the Otsuka Toshimi Scholarship Foundation, Japan, for financial assistance for this work.

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