Review

Antidiabetic Drugs and Target Prediction on Human for Type 2 Diabetes Mellitus: A Minireview of Pharmacological Profile

David Calderon Guzman , Norma Osnaya Brizuela , Armando Valenzuela Peraza , Hugo Juarez Olguin * , Maribel Ortiz Herrera , Ernestina Hernandez Garcia

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Antidiabetic Drugs and Target Prediction on Human for Type 2 Diabetes Mellitus: A Minireview of Pharmacological Profile

Running Title: Diabetes and Drug Target Prediction on Human

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Abstract

With the advent of Covid-19, it is necessary to repurpose new treatment alternatives, either in the form of an effective single dose of these antidiabetic drug agents or an efficacious combination of them for elderly population with or had suffered this condition. Such new treatment alternatives would prevent the development of the common comorbidities, such as heart failure, nephropathy, neuropathy and retinopathy. This mini-review has the objective of predicting the targets of bioactive small molecules in human using healthcare applied artificial intelligence. Method. The tool is a tuned algorithm, with novel data in web interface. Results. Information figures of Swiss Target Prediction, which allow predictions on therapy combinations and probable side effects, were reordered. This tool is useful to understand the molecular mechanisms underlying a given phenotype or bioactivity, to rationalize possible favorable or unfavorable side effects, to predict off-targets of known molecules and to clear the way to drug repurposing. Predictions are done using a ligand-based approach, based on the similarity between a query molecule and the known ligands of a large collection of protein targets. Conclusion. The result of this study highlighted crucial recommendations for the use of some of the antidiabetic agent groups in diabetic patients, which would also reduce the cost of their therapies. This is very important for patients who, due to their ill condition, are obliged to take medicine for a long period and whose life depends on it.

Keywords: antidiabetic drugs; artificial intelligence; COVID-19; diabetes; drug targets

Introduction

Diabetes is a chronic metabolic disease with high magnitude of morbidity and mortality, which heralds it as one of the biggest problems of public health concern in the world. The number of people with diabetes and pre-diabetes is growing exponentially. Due to its high and increasing incidence, the associated healthcare costs, and threatening medical complications, it is considered as one of the priority non-communicable diseases [1]. The prevalence of type 2 diabetes mellitus (T2DM) is internationally ever-growing (Figure 1).

Therefore, prevention, diagnosis and control of insulin resistance and T2DM are of increasing importance [2]. It is pertinent to design a proper multifactorial management of patients with type 2 diabetes that aims at controlling blood pressure, hyperglycemia and dyslipidemia by using both lifestyle changes (reduction of sodium and fat intake, regular physical activity, weight loss in overweight patients, smoking cessation) and drug therapy [3].

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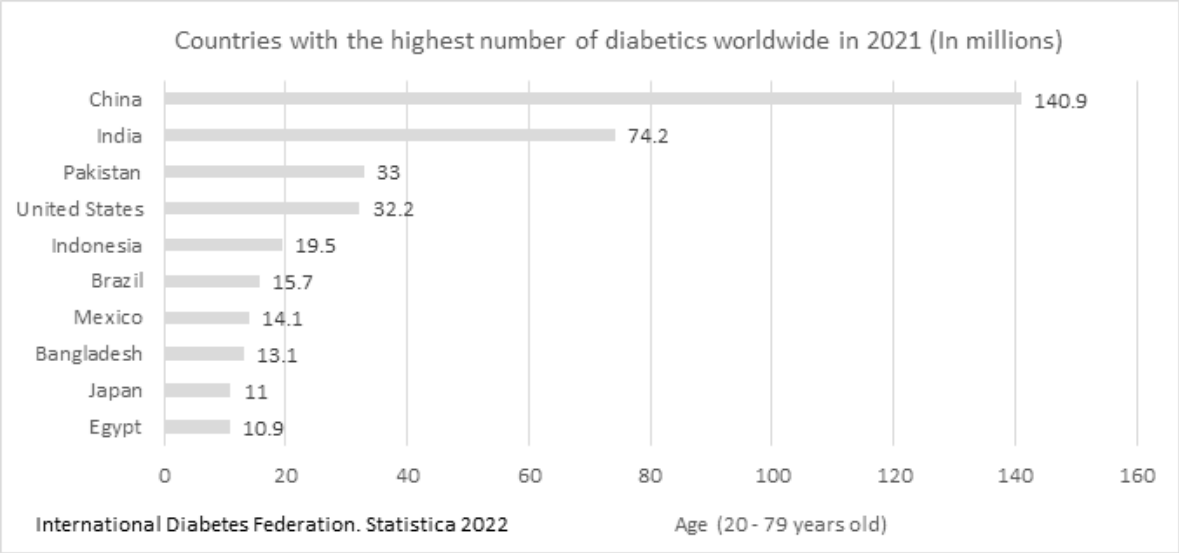

Figure 1. Prevalence of diabetes mellitus in worldwide.

Glycemia and insulin resistance are important regulators of multiple physiological processes and their dysregulation has wide-ranging consequences. During treatment, the patients may undergo rapid changes in their condition or suffer diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar status (HHS) [4]. A strict glycemic control based on the maintenance of fasting plasma glucose (FPG) at between 4.4-6.1 mmol/L and 2-hour postprandial plasma glucose (2 h PG) at 6.1-7.8 mmol/L) should be instituted. For the common type patients, FPG should be between 6.1 and 7.8 mmol/L and 2 h PG, between 7.8 and10.0 mmol/L.

Diabetes During Covid Time

The current outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) constitutes a notable challenge for diabetic patients. People with diabetes have a higher risk of developing different infectious diseases; and hence, increased mortality rate [5]. Diabetic patients who suffered from coronavirus disease 2019 (COVID-19) experienced higher mortality and higher proportion of critically ill condition [6], as opposed to non-diabetic infected patients. This difference in severity may be associated to the effects of hyperglycemia on systemic inflammatory responses and immune system dysfunction. In addition, age, environmental conditions, socioeconomic status, comorbidities and interventional timing increase the risks for severe infection, morbidity and mortality in these patients [7]. Elderly people and patients with comorbidities suffer severe coronavirus disease.

Patients with hipoglycemic, hypolipidemic and antiatherogenic effects, the prevalence of diabetes and obesity, as well as high human development index, and location at < 500 or > 2000 above sea level were associated with higher mortality rate in COVID-19 disease [8]. Therefore, diabetes and hypertension are the main cause of adult mortality worldwide, due more than 70% of adult population living in areas with high social marginality suffer diabetes, hypertension and obesity [9], respect clinical data.

Effect of Nutritional State

In fact, malnutrition is a common event among severe patients, such as elderly adults and patients with comorbidity that suffered coronavirus disease 2019 (COVID-19). The controlling nutritional status (CONUT) score, which comprises serum albumin level, cholesterol level and lymphocytes count, as well as a combined CONUT-lactate dehydrogenase-C-reactive protein score expressed a predictive capacity even superior to that of NRS-2002 (0.81% and 0.92% vs. 0.79%) in midlife and elder COVID-19 patients [10]. This author suggests that older males with severe

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inflammation, gastrointestinal symptoms and pre-existing comorbidities (diabetes, obesity or hypertension) are more prone to malnutrition and subsequently poor COVID-19 prognosis, both during the acute phase and during convalescence. Also, the epidemic of diabetes and dementia are more in older adults. The risk for dementia appears to increase in patients with diabetes, and patients with both dementia and diabetes appear to be at greater risk for severe hypoglycemia [11].

Significant endothelial cell loss has been reported in long-term disease and in cases of poor metabolic control, and corneal thickness may increase in diabetic patients [12], and as the prevalence of malnutrition is high in patients with cancer, and systematic screening for its treatment of malnutrition is necessary. The prevalence of malnutrition by disease site is as follows: head and neck, 48.9%; leukemia/lymphoma, 34.0%; lung, 45.3%; colon/rectum, 39.3%; esophagus and/or stomach, 60.2%; pancreas, 66.7%; breast, 20.5%; ovaries/uterus, 44.8%; and prostate, 13.9%. [13], and cancer is the main disorder in old patients.

Diabetes and Hypertension

The association between diabetes mellitus and hypertension has been described in 60 to 65% of diabetics, and hypertension is two to three times more common among diabetics compared with non-diabetics [14]. Aging process induces changes in renal physiology such as glomerular filtration rate reduction, and alteration in water and electrolytes handling [15], making the old person frail, and finding association between cardiovascular disorders and falls in older adults. Indeed, several cardiovascular disorders, including stroke, coronary artery disease, valvular heart disease, arterial stiffness, arrhythmia, orthostatic hypotension, and carotid sinus hypersensitivity, were consistently associated with falls [16], heart failure prevalence will more than 10% of persons over the age of 70 years in an age-dependent manner. The prevalence is up to 74% in older individuals over the age of 80 years or those over 70 years old with a high burden of comorbidities and chronic diseases [17].

On the other hand, chronic overconsumption of animal fats causes diabetes mellitus and obesity. The underlying molecular mechanisms encompass leptin resistance, a decrease in rewarding effects of physical activities, xanthine oxidase-induced oxidative stress in vasculature and peripheral tissue, impaired activation of incretin signaling and deviation in food preference [18]. Hyperuricemia can lead to cardiovascular and renal complications in patients with diabetes [19].

High-fat feeding and hyperglycemia, key risk factors for the development of metabolic syndrome (MetS), are being increasingly associated with higher risk of developing dementia and cognitive decline. Despite the effect of high fat-feeding and hyperglycemia on the levels of systemic inflammatory cytokines, gliosis in the hippocampus and immune infiltration in cerebral hemispheric tissue [20], hyperglycemia alone preferentially induces an increase in microglial numbers and astrocytosis in the hippocampus. In addition, it is associated with the peripheral recruitment of leukocytes to the cerebrovasculature, but not with systemic inflammation.

Changes in glucose levels induce neuroendocrine response, which works to prevent or correct glycemia. The main area of the brain that regulates glycemic homeostasis is the hypothalamus; consequently, metabolic diseases such as obesity and diabetes are related to imbalance of this control [21,22]. The multi-resultant effects of this imbalance are the induction of oxidative damage, production of hyperglycemia, heart failure, increased brain oxidative stress, impaired brain mitochondrial function, increased brain apoptosis, increased tau protein expression, increased phosphorylation of tau protein expression and amyloid beta levels, and decreased dendritic spine density [23]. Free radicals are normally generated in many cellular metabolic pathways as reactive oxygen species (ROS), or Nitrogen Oxygen Species (NOS). These radicals may interact with various cellular components and induce cell injury. Oxidative stress results when there is a serious imbalance between generation of free radicals and the antioxidant capacity, or disturbance of glutathione homeostasis in the body. When free radicals exceed the antioxidant capacity, cell injury causes diverse physiological and pathologic changes, including the presence of clinical disorders [24], in elderly.

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Antidiabetic Drugs

Antidiabetic drugs allow the optimization of diabetes treatment and provide opportunities to improve the management of the disease (a condition that can be treated and controlled, but has no cure yet). In addition, these drugs can reduce the complications associated with this disorder. Currently, the main groups of antidiabetic agents include:

1. Alpha-glucosidase inhibitors (acarbose, miglitol) [25].
2. Dipeptidyl peptidase 4 (DPP-4) inhibitors (alogliptan, linagliptan, saxagliptin, sitagliptin) [26].
3. Meglitinides (nateglinide, repaglinide) [27].
4. Non-sulfonylureas (metformin) [28].
5. Sodium-Glucose-co Transporter 2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) [29,30].
6. Sulfonylureas (glimepiride, glipizide, glyburide, tolazamide, tolbutamide, gliclazide) [31].
7. Thiazolidinediones (rosiglitazone, pioglitazone) [32].

Type 2 diabetes pharmacotherapy with a single agent does not generally provide durable glycemic control. Hence, the mainstay choice is to add a second-line or third-line agents once unfavorable side effects appear or when glycemic control with monotherapy deteriorates. In fact, polypharmacy and less malnutrition problems improve the health and well-being of older adults.

Predicting the Targets of Antidiabetic Agents

With artificial intelligence applications in healthcare at predicting the targets of antidiabetic agents in human, we used the tool of a tuned algorithm, with novel data in web interface. This study used figures to reorder the information of Swiss Target Prediction that allow predictions on combination therapy and probable side effects. This tool helps to understand the molecular mechanisms underlying a given phenotype or bioactivity, rationalize possible favorable or unfavorable side effects, predict off-targets of known molecules and clear the way to drug repurposing.

Predictions are done using a ligand-based approach, which considers the similarity between a query molecule and the known ligands of a large collection of protein targets as explained below (Tables 1–21).

Group 1. Alpha-glucosidase inhibitors (AGIs) and Target Predictions with Artificial Intelligence. The AGIs are ligand-based inhibitors whose mechanism of actions is to halt, in small intestine, the absorption of carbohydrates. AGIs perform this function by inhibiting enzymes, such as glucoamylase, sucrase, maltase and isomaltase that convert complex non-absorbable carbohydrates into simple absorbable carbohydrates; thus, halting the absorption of elements. Currently, there are two know available AGIs with 80% main target prediction.

Acarbosa

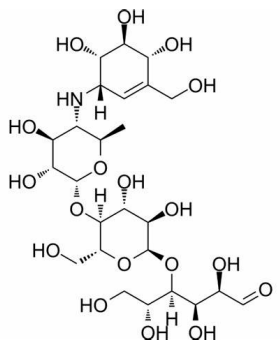

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Table 1. Acarbosa.

Target	Target Class	Probability*
Pancreatic alpha-amylase	Hydrolase	0.844359912
AMY1C	Enzyme	0.767817837
Lysosomal alpha-glucosidase	Hydrolase	0.767817837
Sucrase-isomaltase	Enzyme	0.369201611
Maltase-glucoamylase	Hydrolase	0.264198975
Trehalase	Enzyme	0.084065592
Cyclin-dependent kinase 1	Kinase	0.074564954
Carbonic anhydrase II	Lyase	0.074564954
Carbonic anhydrase I	Lyase	0.074564954
Carbonic anhydrase XII	Lyase	0.074564954
Carbonic anhydrase IX	Lyase	0.074564954

Miglitol

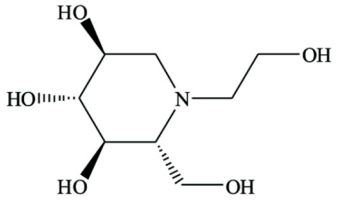

Table 2. Miglitol.

Target	Target Class	Probability*
Maltase-glucoamylase	Hydrolase	1
Lysosomal alpha-glucosidase	Hydrolase	1
Sucrase-isomaltase	Enzyme	1
Alpha-L-fucosidase I	Enzyme	0.440152276
Beta-glucocerebrosidase	Enzyme	0.409951926
Neutral alpha-glucosidase AB	Enzyme	0.389384066
Alpha-galactosidase A	Enzyme	0.369032376
Alpha-L-fucosidase 2	Enzyme	0.369032376
Ceramide glucosyltransferase	Transferase	0.337981759
Beta-glucosidase	Enzyme	0.328089366
Neutral alpha-glucosidase C	Enzyme	0.287108994
Beta-galactosidase	Hydrolase	0.225492374
Beta-mannosidase (by homology)	Enzyme	0.061914931
Liver glycogen phosphorylase	Enzyme	0.061914931
Glycogen debranching enzyme	Enzyme	0.051713312
Lysosomal alpha-mannosidase	Enzyme	0.051713312
Lanosterol synthase	Enzyme	0.041470299
Endoplasmic reticulum mannosyl-oligosaccharide 1,2-alpha-mannosidase	Enzyme	0.031226558
Vesicular acetylcholine transporter	Electrochemical transporter	0.031226558
Phospholipase A2 group IIA	Enzyme	0.031226558
Phospholipase A2 group 1B	Enzyme	0.031226558
Polyadenylate-binding protein 1	Unclassified protein	0.031226558

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Group 2. Dipeptidyl peptidase 4 inhibitors (DPP-49) and Target Predictions with Artificial Intelligence. DPP-4 inhibitors: These substances inhibit DPP-4 activity in peripheral plasma. In the peripheral circulations, DPP-4 inactivates the incretin hormone glucagon-like peptide-1 (GLP-1), that stimulates insulins secretion. Therefore, these inhibitors prevent this inactivation, and thereby, makes it possible the GLP-1 stimulation of insulin secretion. Presently, there are four available antidiabetic DPP-4 inhibitor agents with 66.7% to 80% main target prediction.

Alogliptin Benzoate

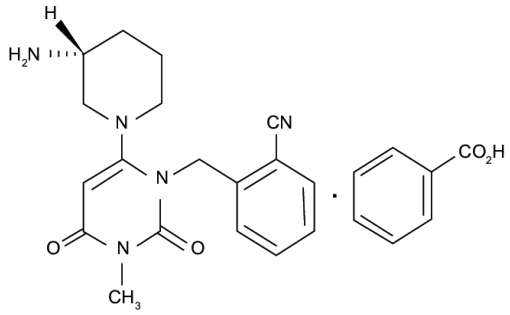

Table 3. Alogliptin Benzoate.

Target	Target Class	Probability*
Dipeptidyl peptidase IV	Protease	1
Poly [ADP-ribose] polymerase-1	Enzyme	0.097239989
Dipeptidyl peptidase VIII	Protease	0.097239989
Cyclin-dependent kinase 4/cyclin D1	Kinase	0.097239989
Cyclin-dependent kinase 2/cyclin E	Other cytosolic protein	0.097239989
Serine/threonine-protein kinase PIM1	Kinase	0.097239989
Protein kinase C theta	Kinase	0.097239989
Acetylcholine receptor; alpha1/beta1/delta/gamma	Ligand-gated ion channel	0.097239989
Neuronal acetylcholine receptor; alpha3/beta4	Ligand-gated ion channel	0.097239989
Protein kinase C delta	Kinase	0.097239989
Protein kinase C alpha	Kinase	0.097239989
Delta opioid receptor	Family A G protein-coupled receptor	0.097239989
Dipeptidyl peptidase II	Protease	0.097239989
Serotonin 1f (5-HT1f) receptor	Family A G protein-coupled receptor	0.097239989
Serotonin 1b (5-HT1b) receptor	Family A G protein-coupled receptor	0.097239989
Serotonin 1d (5-HT1d) receptor	Family A G protein-coupled receptor	0.097239989
Mu opioid receptor	Family A G protein-coupled receptor	0.097239989
Serotonin 5a (5-HT5a) receptor (by homology)	Family A G protein-coupled receptor	0.097239989
Bromodomain-containing protein 4	Reader	0.097239989
Muscarinic acetylcholine receptor M2 (by homology)	Family A G protein-coupled receptor	0.097239989

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Poly [ADP-ribose] polymerase 3	Enzyme	0.097239989
Protein kinase C epsilon	Kinase	0.097239989
Protein kinase C eta	Kinase	0.097239989
PDZ-binding kinase	Kinase	0.097239989
Caspase-3	Protease	0.097239989
Caspase-7	Protease	0.097239989
Serine/threonine-protein kinase AKT	Kinase	0.097239989
Serine/threonine-protein kinase AKT	Kinase	0.097239989
Kinesin-like protein 1	Other cytosolic protein	0.097239989
Dipeptidyl peptidase IX	Protease	0.097239989
Neurokinin 1 receptor (by homology)	Family A G protein-coupled receptor	0.097239989
Retinoid X receptor alpha	Nuclear receptor	0.097239989
Norepinephrine transporter	Electrochemical transporter	0.097239989
Serotonin transporter	Electrochemical transporter	0.097239989
Serine/threonine-protein kinase PIM2	Kinase	0.097239989
Serine/threonine-protein kinase WEE1	Kinase	0.097239989
Dopamine transporter	Electrochemical transporter	0.097239989
Trace amine-associated receptor 1 (by homology)	Family A G protein-coupled receptor	0.097239989
Tyrosyl-DNA phosphodiesterase 1	Enzyme	0.097239989
Dual specificity protein kinase TTK	Kinase	0.097239989
Poly [ADP-ribose] polymerase 2	Enzyme	0.097239989
Serotonin 3a (5-HT3a) receptor	Ligand-gated ion channel	0.097239989
Rho-associated protein kinase 2	Kinase	0.097239989
Inhibitor of apoptosis protein 3	Other cytosolic protein	0.097239989
CaM kinase II	Kinase	0.097239989
Protein farnesyltransferase	Enzyme	0.097239989
Complement factor D	Protease	0.097239989
Cyclin-dependent kinase 1	Kinase	0.097239989
Serotonin 4 (5-HT4) receptor	Family A G protein-coupled receptor	0.097239989
Dopamine D1 receptor	Family A G protein-coupled receptor	0.097239989
GABA-A receptor; alpha-1/beta-2/gamma-2	Ligand-gated ion channel	0.097239989
Maternal embryonic leucine zipper kinase	Kinase	0.097239989
CDK2/Cyclin A	Kinase	0.097239989
Protein kinase C beta	Kinase	0.097239989
Ribosomal protein S6 kinase alpha 2	Kinase	0.097239989
Inhibitor of nuclear factor kappa B kinase beta subunit	Kinase	0.097239989
Serotonin 1e (5-HT1e) receptor	Family A G protein-coupled receptor	0.097239989
Cyclooxygenase-1	Oxidoreductase	0.097239989
C-C chemokine receptor type 2	Family A G protein-coupled receptor	0.097239989
Melanocortin receptor 4	Family A G protein-coupled receptor	0.097239989

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Transient receptor potential cation channel subfamily M member 8	Voltage-gated ion channel	0.097239989
Tyrosine-protein kinase ABL	Kinase	0.097239989
Dopamine D5 receptor	Family A G protein-coupled receptor	0.097239989
Dopamine D4 receptor	Family A G protein-coupled receptor	0.097239989
Phosphodiesterase 4D	Phosphodiesterase	0.097239989
Mucosa-associated lymphoid tissue lymphoma translocation protein 1	Hydrolase	0.097239989
Tyrosine-protein kinase receptor UFO	Kinase	0.097239989
Proto-oncogene tyrosine-protein kinase MER	Kinase	0.097239989
Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4	Voltage-gated ion channel	0.097239989
Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1	Voltage-gated ion channel	0.097239989
Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 2	Voltage-gated ion channel	0.097239989
Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 3	Voltage-gated ion channel	0.097239989
Probable G-protein coupled receptor 142	Family A G protein-coupled receptor	0.097239989
Serine/threonine-protein kinase Aurora-B	Kinase	0.097239989
Dipeptidyl peptidase I	Protease	0.097239989
Renin	Protease	0.097239989
WD repeat-containing protein 5	Unclassified protein	0.097239989
CDC7/DBF4 (Cell division cycle 7-related protein kinase/Activator of S phase kinase)	Kinase	0.097239989
Kappa Opioid receptor	Family A G protein-coupled receptor	0.097239989
Sigma opioid receptor	Membrane receptor	0.097239989
Cyclin-dependent kinase 9	Kinase	0.097239989
Urokinase-type plasminogen activator	Protease	0.097239989
Tyrosine-protein kinase receptor TYRO3	Kinase	0.097239989
Baculoviral IAP repeat-containing protein 2	Enzyme	0.097239989
Cyclin-dependent kinase 2	Kinase	0.097239989
Cyclin-dependent kinase 4	Kinase	0.097239989
Amine oxidase, copper containing	Enzyme	0.097239989
Phosphodiesterase 10A	Phosphodiesterase	0.097239989
Tyrosine-protein kinase receptor FLT3	Kinase	0.097239989
Peptide N-myristoyltransferase 1	Enzyme	0.097239989
Protein kinase N2	Kinase	0.097239989
Prolyl endopeptidase	Protease	0.097239989
Rho-associated protein kinase 1	Kinase	0.097239989
DNA-directed RNA polymerase I subunit RPA1	Enzyme	0.097239989
Cell division control protein 42 homolog	Unclassified protein	0.097239989
Peregrin	Reader	0.097239989
Butyrylcholinesterase	Hydrolase	0.097239989
Dual specificity phosphatase Cdc25C	Phosphatase	0.097239989
Cathepsin S	Protease	0.097239989
Cathepsin G	Protease	0.097239989

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Linagliptin

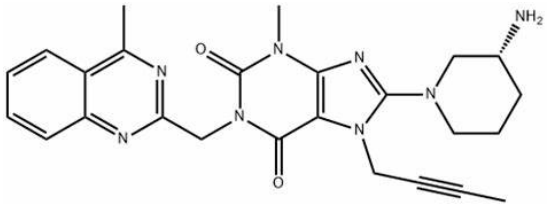

Table 4. Linagliptin.

Target	Target Class	Probability*
Muscarinic acetylcholine receptor M1	Family A G protein-coupled receptor	1
Dipeptidyl peptidase IV	Protease	1
Fibroblast activation protein alpha	Protease	1
Cyclin-dependent kinase 4	Kinase	0.110612204
Dipeptidyl peptidase IX	Protease	0.110612204
MAP kinase p38 alpha	Kinase	0.110612204
C-C chemokine receptor type 8	Family A G protein-coupled receptor	0.110612204
Tyrosine-protein kinase ABL	Kinase	0.110612204
Platelet-derived growth factor receptor beta	Kinase	0.110612204
Thrombin and coagulation factor X	Protease	0.110612204
Melanin-concentrating hormone receptor 1	Family A G protein-coupled receptor	0.110612204
Gonadotropin-releasing hormone receptor	Family A G protein-coupled receptor	0.110612204
Cyclin-dependent kinase 6	Kinase	0.110612204
Phosphoenolpyruvate carboxykinase cytosolic	Enzyme	0.110612204
Neuropeptide Y receptor type 1	Family A G protein-coupled receptor	0.110612204
Protein Mdm4	Unclassified protein	0.110612204
Bradykinin B2 receptor	Family A G protein-coupled receptor	0.110612204
Bradykinin B1 receptor	Family A G protein-coupled receptor	0.110612204
p53-binding protein Mdm-2	Other nuclear protein	0.110612204
Thrombin	Protease	0.110612204
Serine/threonine-protein kinase PIM1	Kinase	0.110612204
Serine/threonine-protein kinase PIM2	Kinase	0.110612204
Serine/threonine-protein kinase PIM3	Kinase	0.110612204
Leukocyte elastase	Protease	0.110612204
Trypsin I	Protease	0.110612204
NAD-dependent deacetylase sirtuin 1	Eraser	0.110612204
Receptor protein-tyrosine kinase erbB-2	Kinase	0.110612204
Insulin-like growth factor I receptor	Kinase	0.110612204
Serine/threonine-protein kinase AKT	Kinase	0.110612204
Bromodomain-containing protein 4	Reader	0.110612204
Vasopressin V1b receptor	Family A G protein-coupled receptor	0.110612204
Cat eye syndrome critical region protein 2	Reader	0.110612204

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Bromodomain-containing protein 9	Reader	0.110612204
Sonic hedgehog protein (by homology)	Unclassified protein	0.110612204
CREB-binding protein/p53	Writer	0.110612204
Matrix metalloproteinase 1	Protease	0.110612204
Somatostatin receptor 5	Family A G protein-coupled receptor	0.110612204
Somatostatin receptor 3	Family A G protein-coupled receptor	0.110612204
C-C chemokine receptor type 4	Family A G protein-coupled receptor	0.110612204
Tryptase beta-1	Protease	0.110612204
Insulin receptor	Kinase	0.110612204
ALK tyrosine kinase receptor	Kinase	0.110612204
Beta-secretase 1	Protease	0.110612204
Mitogen-activated protein kinase kinase kinase 8	Kinase	0.110612204
EZH2/SUZ12/EED/RBBP7/RBBP4	Writer	0.110612204
Cyclin-dependent kinase 2	Kinase	0.110612204
Cyclin-dependent kinase 1	Kinase	0.110612204
Dual specificity mitogen-activated protein kinase kinase 1	Kinase	0.110612204
MAP kinase signal-integrating kinase 2	Kinase	0.110612204
MAP kinase-interacting serine/threonine-protein kinase MNK1	Kinase	0.110612204
Tyrosine-protein kinase receptor FLT3	Kinase	0.110612204
Arachidonate 12-lipoxygenase	Enzyme	0.110612204
Hepatocyte growth factor receptor	Kinase	0.110612204
Tyrosine-protein kinase receptor TYRO3	Kinase	0.110612204
Cyclin-dependent kinase 2/cyclin E1	Kinase	0.110612204
Estrogen receptor alpha	Nuclear receptor	0.110612204
Adenosylhomocysteinase	Enzyme	0.110612204
Cyclin T1	Other cytosolic protein	0.110612204
Tyrosine-protein kinase ITK/TSK	Kinase	0.110612204
Serine/threonine-protein kinase Aurora-A	Kinase	0.110612204
Smoothened homolog	Frizzled family G protein-coupled receptor	0.110612204
Mu opioid receptor	Family A G protein-coupled receptor	0.110612204
Delta opioid receptor	Family A G protein-coupled receptor	0.110612204
Microtubule-associated protein 2	Unclassified protein	0.110612204
Methionine aminopeptidase 1	Protease	0.110612204
Rho-associated protein kinase 2	Kinase	0.110612204
Dual specificity tyrosine-phosphorylation-regulated kinase 1B	Kinase	0.110612204
ATPase family AAA domain-containing protein 2	Reader	0.110612204
Platelet activating factor receptor	Family A G protein-coupled receptor	0.110612204
Cyclin-dependent kinase 9	Kinase	0.110612204
Protein kinase C mu	Kinase	0.110612204
Ketohexokinase	Enzyme	0.110612204

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Tyrosine-protein kinase FYN	Kinase	0.110612204
Tyrosine-protein kinase BLK	Kinase	0.110612204
Receptor protein-tyrosine kinase erbB-4	Kinase	0.110612204
Tyrosine-protein kinase BMX	Kinase	0.110612204
Sodium/calcium exchanger 1	Electrochemical transporter	0.110612204
Ephrin type-A receptor 8	Kinase	0.110612204
Tyrosine-protein kinase FRK	Kinase	0.110612204
Ephrin type-B receptor 3	Kinase	0.110612204
Dipeptidyl peptidase VIII	Protease	0.110612204
Serine/threonine-protein kinase AKT2	Kinase	0.110612204
Melanocortin receptor 4	Family A G protein-coupled receptor	0.110612204
Sigma opioid receptor	Membrane receptor	0.110612204
Serotonin 1b (5-HT1b) receptor	Family A G protein-coupled receptor	0.110612204
Serotonin 1d (5-HT1d) receptor	Family A G protein-coupled receptor	0.110612204
Platelet-derived growth factor receptor alpha	Kinase	0.110612204
Dopamine D1 receptor	Family A G protein-coupled receptor	0.110612204
TGF-beta receptor type I	Kinase	0.110612204
Receptor-interacting serine/threonine-protein kinase 3	Enzyme	0.110612204
Vascular endothelial growth factor receptor 1	Kinase	0.110612204
Vascular endothelial growth factor receptor 3	Kinase	0.110612204
Fibroblast growth factor receptor 1	Kinase	0.110612204
Transitional endoplasmic reticulum ATPase	Primary active transporter	0.110612204
Heat shock protein HSP 90-alpha	Other cytosolic protein	0.110612204
Inhibitor of apoptosis protein 3	Other cytosolic protein	0.110612204
Baculoviral IAP repeat-containing protein 2	Enzyme	0.110612204
Vasopressin V2 receptor (by homology)	Family A G protein-coupled receptor	0.110612204
Oxytocin receptor (by homology)	Family A G protein-coupled receptor	0.110612204
MAP kinase-activated protein kinase 2	Kinase	0.110612204

Saxagliptin

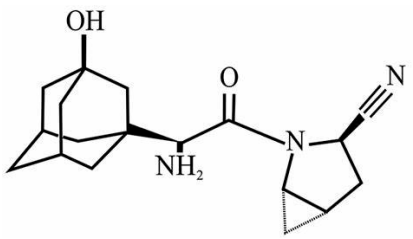

Table 5. Saxagliptin.

Target	Target Class	Probability*
Dipeptidyl peptidase IV	Protease	0.968095103

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Dipeptidyl peptidase VIII	Protease	0.959682015
Dipeptidyl peptidase IX	Protease	0.959682015
Fibroblast activation protein alpha	Protease	0.126610169
Dipeptidyl peptidase II	Protease	0.10994577
11-beta-hydroxysteroid dehydrogenase 1	Enzyme	0.101613855
Norepinephrine transporter	Electrochemical transporter	0.101613855
Serotonin transporter	Electrochemical transporter	0.101613855
Androgen Receptor	Nuclear receptor	0.101613855
11-beta-hydroxysteroid dehydrogenase 2	Enzyme	0.101613855
Lysine-specific histone demethylase 1	Eraser	0.101613855
Transient receptor potential cation channel subfamily V member 3	Voltage-gated ion channel	0.101613855
Delta opioid receptor	Family A G protein-coupled receptor	0.101613855
Prolyl endopeptidase	Protease	0.101613855
Mu opioid receptor (by homology)	Family A G protein-coupled receptor	0.101613855
Insulin-like growth factor I receptor	Kinase	0.101613855
Dopamine D1 receptor	Family A G protein-coupled receptor	0.101613855
Alpha-1a adrenergic receptor (by homology)	Family A G protein-coupled receptor	0.101613855
S-methyl-5-thioadenosine phosphorylase	Enzyme	0.101613855
Serotonin 2b (5-HT2b) receptor	Family A G protein-coupled receptor	0.101613855
Alpha-2a adrenergic receptor	Family A G protein-coupled receptor	0.101613855
Serotonin 1b (5-HT1b) receptor (by homology)	Family A G protein-coupled receptor	0.101613855
Alpha-2b adrenergic receptor	Family A G protein-coupled receptor	0.101613855
Serotonin 2a (5-HT2a) receptor	Family A G protein-coupled receptor	0.101613855
Serotonin 2c (5-HT2c) receptor	Family A G protein-coupled receptor	0.101613855
Serotonin 6 (5-HT6) receptor	Family A G protein-coupled receptor	0.101613855
Serine/threonine-protein kinase PIM1	Kinase	0.101613855
Cytochrome P450 2D6	Cytochrome P450	0.101613855
Serine/threonine-protein kinase PIM2	Kinase	0.101613855
Serine/threonine-protein kinase PIM3	Kinase	0.101613855
C-C chemokine receptor type 1	Family A G protein-coupled receptor	0.101613855
Glutamate NMDA receptor; GRIN1/GRIN2B	Ligand-gated ion channel	0.101613855
Nociceptin receptor	Family A G protein-coupled receptor	0.101613855
Beta-1 adrenergic receptor	Family A G protein-coupled receptor	0.101613855
Beta-3 adrenergic receptor	Family A G protein-coupled receptor	0.101613855

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Glutamate [NMDA] receptor subunit epsilon 2	Ligand-gated ion channel	0.101613855
Glycine transporter 1	Electrochemical transporter	0.101613855
Cathepsin S	Protease	0.101613855
Dipeptidyl peptidase I	Protease	0.101613855
Renin	Protease	0.101613855
Serotonin 7 (5-HT7) receptor	Family A G protein-coupled receptor	0.101613855
Cytochrome P450 19A1	Cytochrome P450	0.101613855
Somatostatin receptor 3	Family A G protein-coupled receptor	0.101613855
Adrenergic receptor beta	Family A G protein-coupled receptor	0.101613855
Protein kinase C theta	Kinase	0.101613855
Heat shock protein HSP 90-alpha	Other cytosolic protein	0.101613855
Neurokinin 1 receptor	Family A G protein-coupled receptor	0.101613855
Serotonin 1d (5-HT1d) receptor	Family A G protein-coupled receptor	0.101613855
Thrombin and coagulation factor X	Protease	0.101613855
Squalene synthetase (by homology)	Enzyme	0.101613855
Dual specificity mitogen-activated protein kinase kinase 1	Kinase	0.101613855
Urotensin II receptor	Family A G protein-coupled receptor	0.101613855
Cytochrome P450 51	Cytochrome P450	0.101613855
P-glycoprotein 1	Primary active transporter	0.101613855
Cathepsin K	Protease	0.101613855
Neuronal acetylcholine receptor; alpha3/alpha6/beta2/beta3	Ligand-gated ion channel	0.101613855
Egl nine homolog 1	Oxidoreductase	0.101613855
Sodium channel protein type V alpha subunit	Voltage-gated ion channel	0.101613855
Dopamine D5 receptor	Family A G protein-coupled receptor	0.101613855
Cyclin-dependent kinase 4/cyclin D1	Kinase	0.101613855
Cyclin-dependent kinase 2/cyclin E	Other cytosolic protein	0.101613855
Calcium sensing receptor	Family C G protein-coupled receptor	0.101613855
Steryl-sulfatase	Enzyme	0.101613855
Prostanoid EP2 receptor	Family A G protein-coupled receptor	0.101613855
Prostanoid EP3 receptor	Family A G protein-coupled receptor	0.101613855
Peptide N-myristoyltransferase 1	Enzyme	0.101613855
Poly [ADP-ribose] polymerase-1	Enzyme	0.101613855
Phosphodiesterase 10A	Phosphodiesterase	0.101613855
Histamine H4 receptor	Family A G protein-coupled receptor	0.101613855
Serine/threonine-protein kinase ILK-1	Kinase	0.101613855
CaM kinase II	Kinase	0.101613855
Protein kinase C alpha	Kinase	0.101613855

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Voltage-gated potassium channel subunit Kv1.5	Voltage-gated ion channel	0.101613855
Synaptic vesicular amine transporter (by homology)	Electrochemical transporter	0.101613855
Histamine H1 receptor	Family A G protein-coupled receptor	0.101613855
Muscarinic acetylcholine receptor M5	Family A G protein-coupled receptor	0.101613855
Alpha-1d adrenergic receptor	Family A G protein-coupled receptor	0.101613855
Muscarinic acetylcholine receptor M3	Family A G protein-coupled receptor	0.101613855
Liver glycogen phosphorylase	Enzyme	0.101613855
Phenylethanolamine N-methyltransferase	Enzyme	0.101613855
Neurokinin 2 receptor	Family A G protein-coupled receptor	0.101613855
Melanocortin receptor 4	Family A G protein-coupled receptor	0.101613855
Tyrosine-protein kinase JAK1	Kinase	0.101613855
p53-binding protein Mdm-2	Other nuclear protein	0.101613855
Protein arginine N-methyltransferase 6	Writer	0.101613855
Carbonic anhydrase II	Lyase	0.101613855
Carbonic anhydrase I	Lyase	0.101613855
Protein arginine N-methyltransferase 8	Writer	0.101613855
Carbonic anhydrase IX	Lyase	0.101613855
C-C chemokine receptor type 3	Family A G protein-coupled receptor	0.101613855
Phospholipase A2 group IIC	Enzyme	0.101613855
Group X secretory phospholipase A2	Enzyme	0.101613855
Cathepsin D	Protease	0.101613855
Beta-secretase 1	Protease	0.101613855
Mitogen-activated protein kinase kinase kinase 12	Enzyme	0.101613855
Rho-associated protein kinase 2	Kinase	0.101613855
Phosphodiesterase 9A	Phosphodiesterase	0.101613855
Phosphodiesterase 1C	Phosphodiesterase	0.101613855
Voltage-gated potassium channel subunit Kv1.3	Voltage-gated ion channel	0.101613855
Glucocorticoid receptor	Nuclear receptor	0.101613855

Sitagliptin

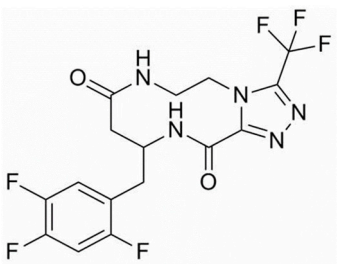

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Table 6. Sitagliptin.

Target	Target Class	Probability*
Dipeptidyl peptidase IV	Protease	1
Dipeptidyl peptidase VIII	Protease	1
Fibroblast activation protein alpha	Protease	1
Dipeptidyl peptidase IX	Protease	1
Dipeptidyl peptidase II	Protease	0.115736675
Glycine transporter 1	Electrochemical transporter	0.115736675
Chymase	Protease	0.115736675
C-C chemokine receptor type 2	Family A G protein-coupled receptor	0.115736675
Serotonin transporter	Electrochemical transporter	0.115736675
Histone-arginine methyltransferase CARM1 (by homology)	Writer	0.115736675
Leukocyte elastase	Protease	0.115736675
CaM kinase II	Kinase	0.115736675
Glycine transporter 2	Electrochemical transporter	0.115736675
5-lipoxygenase activating protein	Other cytosolic protein	0.115736675
Cyclooxygenase-2	Oxidoreductase	0.115736675
Gonadotropin-releasing hormone receptor	Family A G protein-coupled receptor	0.115736675
G-protein coupled bile acid receptor 1	Family A G protein-coupled receptor	0.115736675
Beta amyloid A4 protein	Membrane receptor	0.115736675
Cyclin-dependent kinase 2/cyclin A	Other cytosolic protein	0.115736675
Histone deacetylase 4	Eraser	0.115736675
Interleukin-1 receptor-associated kinase 4	Kinase	0.115736675
Metabotropic glutamate receptor 1	Family C G protein-coupled receptor	0.115736675
Histone-lysine N-methyltransferase SETD7	Writer	0.115736675
C-C chemokine receptor type 1	Family A G protein-coupled receptor	0.115736675

Group 3. Meglitinides and Target Predictions with Artificial Intelligence. These substances work to reduce blood glucose levels by stimulating endogenous insulin production. The dosing strategy depends on the level of hemoglobin A1c. The recommended starting dose for A1c level below 8% (64 mmol/mol) is 0.5mg pre-prandial and for A1c level above 8% is 1 to 2mg. Two meglitinides are currently available with 73.3% to 86.6% main target prediction.

Nateglinide

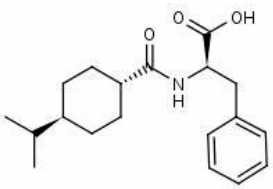

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Table 7. Nateglinide.

Target	Target Class	Probability*
Solute carrier family 22 member 6 (by homology)	Electrochemical transporter	0.921392246
Epoxide hydratase	Protease	0.251528881
Ephrin type-A receptor 2	Kinase	0.22658196
Neprilysin	Protease	0.218248072
Angiotensin-converting enzyme	Protease	0.151564691
Carboxypeptidase A1	Protease	0.134939009
Angiotensin-converting enzyme 2	Protease	0.134939009
11-beta-hydroxysteroid dehydrogenase 1	Enzyme	0.126610169
Protein-tyrosine phosphatase 1B	Phosphatase	0.118277085
T-cell protein-tyrosine phosphatase	Phosphatase	0.118277085
Calpain 1	Protease	0.118277085
11-beta-hydroxysteroid dehydrogenase 2	Enzyme	0.10994577
Protein-tyrosine phosphatase 1C	Phosphatase	0.10994577
Endothelin-converting enzyme 1	Protease	0.101613855
Matrix metalloproteinase 2	Protease	0.101613855
Alkaline ceramidase 2	Enzyme	0.101613855
Gamma-secretase	Protease	0.101613855
MAP kinase ERK2	Kinase	0.101613855
Integrin alpha-4/beta-1	Membrane receptor	0.101613855
Matrix metalloproteinase 3	Protease	0.101613855
Matrix metalloproteinase 1	Protease	0.101613855
Chymase	Protease	0.101613855
Estradiol 17-beta-dehydrogenase 2	Enzyme	0.101613855
Cyclooxygenase-2	Oxidoreductase	0.101613855
Neurotensin receptor 1	Family A G protein-coupled receptor	0.101613855
Histone deacetylase 6	Eraser	0.101613855
Histone deacetylase 1	Eraser	0.101613855
Inhibitor of apoptosis protein 3	Other cytosolic protein	0.101613855
Beta secretase 2	Protease	0.101613855
Beta-secretase 1	Protease	0.101613855
Chromobox protein homolog 7	Reader	0.101613855
Protein farnesyltransferase	Enzyme	0.101613855
Baculoviral IAP repeat-containing protein 2	Enzyme	0.101613855
Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	Enzyme	0.101613855
HLA class I histocompatibility antigen A-3	Surface antigen	0.101613855
Cathepsin D	Protease	0.101613855
Oxytocin receptor	Family A G protein-coupled receptor	0.101613855
E3 SUMO-protein ligase CBX4	Enzyme	0.101613855
Retinoic acid receptor beta	Nuclear receptor	0.101613855
Retinoic acid receptor alpha	Nuclear receptor	0.101613855
G protein-coupled receptor 44	Family A G protein-coupled receptor	0.101613855
Cathepsin (B and K)	Protease	0.101613855

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Cannabinoid receptor 1	Family A G protein-coupled receptor	0.101613855
Cathepsin G	Protease	0.101613855
Neurokinin 2 receptor	Family A G protein-coupled receptor	0.101613855
Aminopeptidase N	Protease	0.101613855
Aminopeptidase B (by homology)	Protease	0.101613855
Leucine aminopeptidase	Protease	0.101613855
Group X secretory phospholipase A2	Enzyme	0.101613855
Matrix metalloproteinase 9	Protease	0.101613855
Integrin alpha-4/beta-7	Membrane receptor	0.101613855
Oxoeicosanoid receptor 1	Family A G protein-coupled receptor	0.101613855
Tyrosyl-tRNA synthetase	Enzyme	0.101613855
Lysine-specific demethylase 5A	Eraser	0.101613855
Lysine-specific demethylase 5B	Eraser	0.101613855
Lysine-specific demethylase 2B	Eraser	0.101613855
Acyl-CoA:dihydroxyacetonephosphateacyltransferase	Enzyme	0.101613855
Prostanoid EP4 receptor	Family A G protein-coupled receptor	0.101613855
Serotonin transporter	Electrochemical transporter	0.101613855
Mu opioid receptor	Family A G protein-coupled receptor	0.101613855
Delta opioid receptor	Family A G protein-coupled receptor	0.101613855
Prostanoid EP1 receptor	Family A G protein-coupled receptor	0.101613855
Aldose reductase (by homology)	Enzyme	0.101613855
MAP kinase p38 alpha	Kinase	0.101613855
Solute carrier family 22 member 12	Electrochemical transporter	0.101613855
Atrial natriuretic factor	Unclassified protein	0.101613855
N-acylsphingosine-amidohydrolase	Enzyme	0.101613855
Leukotriene A4 hydrolase	Protease	0.101613855
Kappa Opioid receptor	Family A G protein-coupled receptor	0.101613855
Matrix metalloproteinase 8	Protease	0.101613855
Integrin alpha-4	Membrane receptor	0.101613855
Transient receptor potential cation channel subfamily M member 8	Voltage-gated ion channel	0.101613855
Progesterone receptor	Nuclear receptor	0.101613855
Lysosomal protective protein	Protease	0.101613855
Aldo-keto-reductase family 1 member C3	Enzyme	0.101613855
Aldo-keto reductase family 1 member C2	Enzyme	0.101613855
C-C chemokine receptor type 5	Family A G protein-coupled receptor	0.101613855
Dihydroorotate dehydrogenase	Oxidoreductase	0.101613855
Retinoid X receptor alpha	Nuclear receptor	0.101613855
Cytochrome P450 26A1	Cytochrome P450	0.101613855

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Endothelin receptor ET-A	Family A G protein-coupled receptor	0.101613855
Cathepsin L	Protease	0.101613855
Oligopeptide transporter small intestine isoform	Electrochemical transporter	0.101613855
Cathepsin E	Protease	0.101613855
Cholecystokinin B receptor	Family A G protein-coupled receptor	0.101613855
Cyclooxygenase-1	Oxidoreductase	0.101613855
Group IIE secretory phospholipase A2	Enzyme	0.101613855
Group IIF secretory phospholipase A2	Enzyme	0.101613855
Group IID secretory phospholipase A2	Enzyme	0.101613855
Phospholipase A2 group 1B (by homology)	Enzyme	0.101613855
c-Jun N-terminal kinase 1	Kinase	0.101613855
Formyl peptide receptor 1	Family A G protein-coupled receptor	0.101613855
Dual specificity protein phosphatase 3	Phosphatase	0.101613855
Gamma-amino-N-butyrate transaminase (by homology)	Transferase	0.101613855
Insulin-like growth factor I receptor	Kinase	0.101613855
Histone deacetylase 8	Eraser	0.101613855
Cathepsin (V and K)	Protease	0.101613855
Phospholipase A2 group IIA	Enzyme	0.101613855
Transitional endoplasmic reticulum ATPase	Primary active transporter	0.101613855
Phosphodiesterase 3	Phosphodiesterase	0.101613855

Rapaglinide

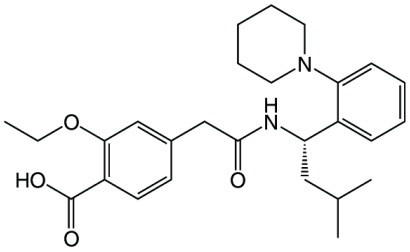

Table 8. Rapaglinide.

Target	Target Class	Probability*
Sulfonylurea receptor 1	Primary active transporter	0.989973857
Solute carrier family 22 member 1	Electrochemical transporter	0.989973857
Hematopoietic prostaglandin D synthase	Transferase	0.100634432
Vasopressin V2 receptor	Family A G protein-coupled receptor	0.100634432
Cytosolic phospholipase A2	Enzyme	0.100634432
Retinoid X receptor alpha	Nuclear receptor	0.100634432
ADAMTS5	Protease	0.100634432
Matrix metalloproteinase 14	Protease	0.100634432
Peroxisome proliferator-activated receptor delta	Nuclear receptor	0.100634432
Sphingosine 1-phosphate receptor Edg-1	Family A G protein-coupled receptor	0.100634432

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Neurotensin receptor 1	Family A G protein-coupled receptor	0.100634432
Epoxide hydrolase 1	Protease	0.100634432
Phosphodiesterase 4D	Phosphodiesterase	0.100634432
Phosphodiesterase 4C	Phosphodiesterase	0.100634432
11-beta-hydroxysteroid dehydrogenase 1	Enzyme	0.100634432
Thromboxane-A synthase	Cytochrome P450	0.100634432
Arachidonate 5-lipoxygenase	Oxidoreductase	0.100634432
Prostaglandin E synthase	Enzyme	0.100634432
Retinoid X receptor gamma (by homology)	Nuclear receptor	0.100634432
Heat shock protein HSP 90-alpha	Other cytosolic protein	0.100634432
Cathepsin (B and K)	Protease	0.100634432
Plasma kallikrein	Protease	0.100634432
Complement factor D	Protease	0.100634432
Sphingosine 1-phosphate receptor Edg-6	Family A G protein-coupled receptor	0.100634432
Matrix metalloproteinase 8	Protease	0.100634432
Kelch-like ECH-associated protein 1	Unclassified protein	0.100634432
Dual specificity phosphatase Cdc25A	Phosphatase	0.100634432
Retinoid X receptor beta	Nuclear receptor	0.100634432
Macrophage migration inhibitory factor	Enzyme	0.100634432
Cysteinyl leukotriene receptor 1	Family A G protein-coupled receptor	0.100634432
Alpha-2b adrenergic receptor	Family A G protein-coupled receptor	0.100634432
Adenosine A1 receptor	Family A G protein-coupled receptor	0.100634432
Adenosine A3 receptor	Family A G protein-coupled receptor	0.100634432
Nitric oxide synthase, inducible	Enzyme	0.100634432
Purinergic receptor P2Y12	Family A G protein-coupled receptor	0.100634432
Ubiquitin-like domain-containing CTD phosphatase 1	Enzyme	0.100634432
Retinoic acid receptor alpha	Nuclear receptor	0.100634432
Monoacylglycerol lipase ABHD6 (by homology)	Enzyme	0.100634432
Low molecular weight phosphotyrosine protein phosphatase	Phosphatase	0.100634432
Peptidyl-glycine alpha-amidating monooxygenase	Enzyme	0.100634432
Vasopressin V1a receptor	Family A G protein-coupled receptor	0.100634432
Ileal bile acid transporter	Electrochemical transporter	0.100634432
Translocator protein (by homology)	Membrane receptor	0.100634432
Serine/threonine-protein phosphatase	Phosphatase	0.100634432
Endothelin-converting enzyme 1	Protease	0.100634432
Leukotriene B4 receptor 1	Family A G protein-coupled receptor	0.100634432
Cytochrome P450 26A1	Cytochrome P450	0.100634432

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Serine/threonine-protein kinase Aurora-B	Kinase	0.100634432
Phospholipase A2 group IIA	Enzyme	0.100634432
Gamma-secretase	Protease	0.100634432
Carboxypeptidase B	Protease	0.100634432
Cytochrome P450 26B1	Cytochrome P450	0.100634432
Cathepsin G	Protease	0.100634432
Tumour suppressor p53/oncoprotein Mdm2	Transcription factor	0.100634432
Thrombopoietin receptor	Membrane receptor	0.100634432
Inhibitor of nuclear factor kappa B kinase beta subunit	Kinase	0.100634432
SUMO-activating enzyme	Enzyme	0.100634432
Hexokinase type IV	Enzyme	0.100634432
Anandamide amidohydrolase	Enzyme	0.100634432
Fatty acid binding protein epidermal	Fatty acid binding protein family	0.100634432
Prostanoid EP3 receptor	Family A G protein-coupled receptor	0.100634432
Prostaglandin E synthase 2	Enzyme	0.100634432
c-Jun N-terminal kinase 1	Kinase	0.100634432
Phosphodiesterase 2A	Phosphodiesterase	0.100634432
Transitional endoplasmic reticulum ATPase	Primary active transporter	0.100634432
Sn1-specific diacylglycerol lipase alpha	Enzyme	0.100634432
Prostanoid EP4 receptor	Family A G protein-coupled receptor	0.100634432
Lysine-specific demethylase 5C	Eraser	0.100634432
Casein kinase II alpha	Kinase	0.100634432
Presenilin 1	Other ion channel	0.100634432
Vascular endothelial growth factor receptor 2	Kinase	0.100634432
Urokinase plasminogen activator surface receptor	Membrane receptor	0.100634432
Lysosomal protective protein	Protease	0.100634432
Somatostatin receptor 3	Family A G protein-coupled receptor	0.100634432
Toll-like receptor 4	Toll-like and Il-1 receptors	0.100634432
Adenosine A2a receptor	Family A G protein-coupled receptor	0.100634432
Free fatty acid receptor 1	Family A G protein-coupled receptor	0.100634432
Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	Enzyme	0.100634432
Apelin receptor	Family A G protein-coupled receptor	0.100634432
Glycogen synthase kinase-3 alpha	Kinase	0.100634432
L-lactate dehydrogenase A chain	Enzyme	0.100634432
LIM domain kinase 2	Kinase	0.100634432
Cyclooxygenase-1	Oxidoreductase	0.100634432
Cyclooxygenase-2 (by homology)	Oxidoreductase	0.100634432

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6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3	Enzyme	0.100634432
Dual specificity phosphatase Cdc25C	Phosphatase	0.100634432
Adenosine A2b receptor	Family A G protein-coupled receptor	0.100634432
Aldo-keto-reductase family 1 member C3	Enzyme	0.100634432
Dual specificity phosphatase Cdc25B	Phosphatase	0.100634432
G protein-coupled receptor 44	Family A G protein-coupled receptor	0.100634432
Oxoeicosanoid receptor 1	Family A G protein-coupled receptor	0.100634432
Serine/threonine-protein kinase PIM1	Kinase	0.100634432
Plasminogen activator inhibitor-1	Secreted protein	0.100634432
HMG-CoA reductase (by homology)	Oxidoreductase	0.100634432
Taste receptor type 2 member 31	Taste family G protein-coupled receptor	0.100634432
DNA polymerase beta (by homology)	Enzyme	0.100634432
PI3-kinase p110-beta subunit	Enzyme	0.100634432
Prolyl endopeptidase	Protease	0.100634432
Cathepsin (V and K)	Protease	0.100634432
Gonadotropin-releasing hormone receptor	Family A G protein-coupled receptor	0.100634432

GROUP 4. Non-sulfonylureas and Target Predictions with Artificial Intelligence. It inhibits the amount of glucose produced by the liver, increases the insulin-receptor binding and stimulates tissue uptake of glucose. One antidiabetic agent of this class is currently available (86.6% main target prediction).

Metformin

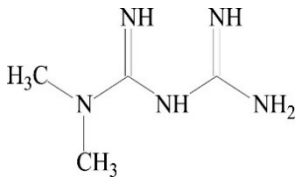

Table 9. Metformin.

Target	Target Class	Probability*
Thrombin	Protease	0.02383274
Urokinase-type plasminogen activator	Protease	0
Histamine H4 receptor	Family A G protein-coupled receptor	0
D-amino-acid oxidase	Enzyme	0
Histamine H3 receptor	Family A G protein-coupled receptor	0
Xanthine dehydrogenase	Oxidoreductase	0
Dihydrofolate reductase (by homology)	Oxidoreductase	0
Integrin alpha-V/beta-3	Membrane receptor	0
Coagulation factor IX	Protease	0
Neuronal acetylcholine receptor; alpha4/beta2	Ligand-gated ion channel	0

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S-100 protein beta chain	Other cytosolic protein	0
Beta-hexosaminidase subunit alpha	Enzyme	0
Beta-N-acetyl-D-hexosaminidase-A/B	Enzyme	0
Solute carrier family 22 member 1 (by homology)	Electrochemical transporter	0
Multidrug and toxin extrusion protein 1 (by homology)	Electrochemical transporter	0
Trypsin I	Protease	0
Indolethylamine N-methyltransferase	Enzyme	0
7,8-dihydro-8-oxoguanine triphosphatase	Enzyme	0
Thymidine phosphorylase	Enzyme	0
Dihydropyrimidine dehydrogenase	Enzyme	0
Adenosine A1 receptor (by homology)	Family A G protein-coupled receptor	0
Serotonin 5a (5-HT5a) receptor	Family A G protein-coupled receptor	0
CDC7/DBF4 (Cell division cycle 7-related protein kinase/Activator of S phase kinase)	Kinase	0
Nitric oxide synthase, inducible	Enzyme	0
Nitric-oxide synthase, endothelial	Enzyme	0
Indoleamine 2,3-dioxygenase	Enzyme	0
Neuronal acetylcholine receptor protein alpha-4 subunit (by homology)	Ligand-gated ion channel	0
Estrogen receptor beta	Nuclear receptor	0
Histamine H2 receptor	Family A G protein-coupled receptor	0
Uridine phosphorylase 1 (by homology)	Enzyme	0
Carbonic anhydrase II	Lyase	0
Carbonic anhydrase I	Lyase	0
Carbonic anhydrase XII	Lyase	0
Carbonic anhydrase IX	Lyase	0
G-protein coupled receptor 84	Family A G protein-coupled receptor	0
Purine nucleoside phosphorylase	Enzyme	0
Trace amine-associated receptor 1 (by homology)	Family A G protein-coupled receptor	0
Nitric-oxide synthase, brain	Enzyme	0
Nischarin	Other cytosolic protein	0
Plasminogen	Protease	0
Thymidylate synthase	Transferase	0
Kallikrein 1	Protease	0
Methionine aminopeptidase 2	Protease	0
Phosphodiesterase 5A	Phosphodiesterase	0
Epidermal growth factor receptor erbB1	Kinase	0
Guanine deaminase	Hydrolase	0
Urokinase plasminogen activator surface receptor	Membrane receptor	0
Acetylcholinesterase	Hydrolase	0

Group 5. Sodium-Glucose-co Transporter 2 (SGLT-2) inhibitors and Target Predictions with Artificial Intelligence. SGLT2 inhibitors are the latest class of anti-hyperglycemic agents approved by Food and Drug Administration (FDA). SGLT2 inhibitors function through a novel mechanism

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consisting of reducing renal tubular glucose reabsorption. Hence, they help to reduce blood glucose without stimulating insulin release. Currently, there are four antidiabetic agents of this class with 73.3% to 86.6% main target prediction.

Canagliflozin

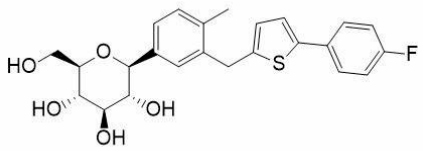

Table 10. Canagliflozin.

Target	Target Class	Probability*
Sodium/glucose cotransporter 2	Electrochemical transporter	0.830720846
Sodium/glucose cotransporter 1	Electrochemical transporter	0.778528112
Glucose transporter (by homology)	Electrochemical transporter	0.118883307
Equilibrative nucleoside transporter 1	Electrochemical transporter	0.118883307
Coagulation factor VII/tissue factor	Surface antigen	0.118883307
Adenosine A1 receptor (by homology)	Family A G protein-coupled receptor	0.118883307
Adenosine kinase	Enzyme	0.118883307
Adenosine A2a receptor	Family A G protein-coupled receptor	0.118883307
Adenosine A3 receptor	Family A G protein-coupled receptor	0.118883307
Sodium/nucleoside cotransporter 2	Electrochemical transporter	0.118883307
Adenosine A2b receptor	Family A G protein-coupled receptor	0.118883307
Purinergic receptor P2Y12 (by homology)	Family A G protein-coupled receptor	0.118883307
MAP kinase p38 alpha	Kinase	0.118883307
Tyrosine-protein kinase JAK2	Kinase	0.118883307
Glyceraldehyde-3-phosphate dehydrogenase liver	Oxidoreductase	0.118883307
Carbonic anhydrase II	Lyase	0.118883307
Carbonic anhydrase I	Lyase	0.118883307
Carbonic anhydrase IX	Lyase	0.118883307
Dual specificity mitogen-activated protein kinase kinase 1	Kinase	0.118883307
Liver glycogen phosphorylase	Enzyme	0.118883307
Interleukin-1 receptor-associated kinase 4	Kinase	0.118883307
Phosphodiesterase 5A	Phosphodiesterase	0.118883307
Bifunctional protein NCOAT	Enzyme	0.118883307
Uridine phosphorylase 1 (by homology)	Enzyme	0.118883307
DNA (cytosine-5)-methyltransferase 1	Writer	0.118883307
Beta-glucocerebrosidase	Enzyme	0.118883307
Carbonic anhydrase XII	Lyase	0.118883307
Carbonic anhydrase XIV	Lyase	0.118883307

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Heat shock cognate 71 kDa protein	Other cytosolic protein	0.118883307
78 kDa glucose-regulated protein	Unclassified protein	0.118883307
Hepatocyte growth factor receptor	Kinase	0.118883307
Galectin-3	Other cytosolic protein	0.118883307
Galectin-1	Other cytosolic protein	0.118883307
Muscle glycogen phosphorylase	Enzyme	0.118883307
Beta-glucosidase	Enzyme	0.118883307
Protein arginine N-methyltransferase 7	Writer	0.118883307
Serine/threonine-protein kinase Chk1	Kinase	0.118883307
c-Jun N-terminal kinase 1	Kinase	0.118883307
Leucyl-tRNA synthetase	Enzyme	0.118883307
MAP kinase ERK2	Kinase	0.118883307
Serine/threonine-protein kinase B-raf	Kinase	0.118883307
Epidermal growth factor receptor erbB1	Kinase	0.118883307
Dipeptidyl peptidase IV	Protease	0.118883307
Sodium channel protein type IX alpha subunit	Voltage-gated ion channel	0.118883307
NAD-dependent deacetylase sirtuin 2	Eraser	0.118883307
Alkaline phosphatase, tissue-nonspecific isozyme	Enzyme	0.118883307
Cathepsin L	Protease	0.118883307
Glutamate [NMDA] receptor PROTEIN	Ligand-gated ion channel	0.118883307
Matrix metalloproteinase 13	Protease	0.118883307
Matrix metalloproteinase 9	Protease	0.118883307
Matrix metalloproteinase 2	Protease	0.118883307
Matrix metalloproteinase 8	Protease	0.118883307
Tyrosine-protein kinase SYK	Kinase	0.118883307

Dapagliflozin

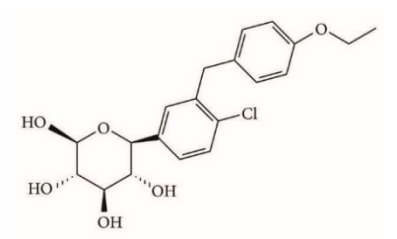

Table 11. Dapaglifozin.

Target	Target Class	Probability*
Sodium/myo-inositol cotransporter 2	Electrochemical transporter	1
Low affinity sodium-glucose cotransporter	Electrochemical transporter	1
Sodium/glucose cotransporter 2	Electrochemical transporter	1
Sodium/glucose cotransporter 1	Electrochemical transporter	1
Adenosine kinase	Enzyme	0.115736675
Adenosine A2a receptor	Family A G protein-coupled receptor	0.115736675
Adenosine A3 receptor	Family A G protein-coupled receptor	0.115736675

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Dual specificity mitogen-activated protein kinase kinase 1	Kinase	0.115736675
Platelet-derived growth factor receptor beta	Kinase	0.115736675
Tyrosine-protein kinase LCK	Kinase	0.115736675
MAP kinase p38 alpha	Kinase	0.115736675
c-Jun N-terminal kinase 3	Kinase	0.115736675
MAP kinase p38 beta	Kinase	0.115736675
Ephrin type-A receptor 5	Kinase	0.115736675
Serine/threonine-protein kinase GAK	Kinase	0.115736675
Equilibrative nucleoside transporter 1	Electrochemical transporter	0.115736675
Beta-glucosidase	Enzyme	0.115736675
Hexokinase type II	Enzyme	0.115736675
Hexokinase type I	Enzyme	0.115736675
Sodium/nucleoside cotransporter 2	Electrochemical transporter	0.115736675
78 kDa glucose-regulated protein	Unclassified protein	0.115736675
Phosphodiesterase 5A	Phosphodiesterase	0.115736675
Heat shock cognate 71 kDa protein	Other cytosolic protein	0.115736675
Coagulation factor VII/tissue factor	Surface antigen	0.115736675
Beta-glucocerebrosidase	Enzyme	0.115736675
Glucose transporter (by homology)	Electrochemical transporter	0.115736675
Epidermal growth factor receptor erbB1	Kinase	0.115736675
Uridine phosphorylase 1 (by homology)	Enzyme	0.115736675
Alkaline phosphatase, tissue-nonspecific isozyme	Enzyme	0.115736675
Muscle glycogen phosphorylase	Enzyme	0.115736675
Glyceraldehyde-3-phosphate dehydrogenase liver	Oxidoreductase	0.115736675
Glutathione S-transferase Pi	Enzyme	0.115736675
Glutathione S-transferase Mu 2	Enzyme	0.115736675
Matrix metalloproteinase 3	Protease	0.115736675
Matrix metalloproteinase 1	Protease	0.115736675
Serine/threonine-protein kinase Chk1	Kinase	0.115736675
Bifunctional protein NCOAT	Enzyme	0.115736675
Adenosine A2b receptor	Family A G protein-coupled receptor	0.115736675
Cathepsin L	Protease	0.115736675
Purinergic receptor P2Y12 (by homology)	Family A G protein-coupled receptor	0.115736675
Intercellular adhesion molecule-1	Adhesion	0.115736675
Vascular cell adhesion protein 1	Adhesion	0.115736675
Selectin E	Adhesion	0.115736675
MAP kinase ERK2	Kinase	0.115736675
Liver glycogen phosphorylase	Enzyme	0.115736675
Interleukin-1 receptor-associated kinase 4	Kinase	0.115736675
Glutamate [NMDA] receptor PROTEIN	Ligand-gated ion channel	0.115736675
Carbonic anhydrase XIV	Lyase	0.115736675
Neprilysin	Protease	0.115736675
Tyrosine-protein kinase JAK2	Kinase	0.115736675

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Mitogen-activated protein kinase kinase kinase 14	Kinase	0.115736675
GABA receptor alpha-5 subunit	Ligand-gated ion channel	0.115736675
Endoplasmic reticulum mannosyl-oligosaccharide 1,2-alpha-mannosidase	Enzyme	0.115736675
Alpha-mannosidase 2A1	Enzyme	0.115736675
Alpha-L-fucosidase I	Enzyme	0.115736675
Endothelin-converting enzyme 1	Protease	0.115736675
Glutamate receptor ionotropic kainate 1	Ligand-gated ion channel	0.115736675
Beta-galactosidase	Hydrolase	0.115736675
Cyclin-dependent kinase 1	Kinase	0.115736675
Squalene synthetase	Enzyme	0.115736675

Empagliflozin

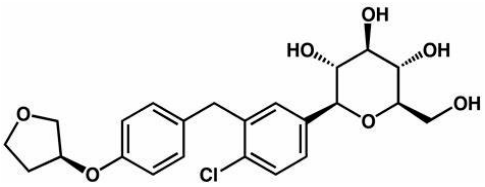

Table 12. Empagliflozin.

Target	Target Class	Probability*
Sodium/glucose cotransporter 2	Electrochemical transporter	0.995022825
Sodium/glucose cotransporter 1	Electrochemical transporter	0.995022825
Sodium/myo-inositol cotransporter 2	Electrochemical transporter	0.424564571
Low affinity sodium-glucose cotransporter	Electrochemical transporter	0.424564571
Serine/threonine-protein kinase PIM1	Kinase	0.118883307
Adenosine kinase	Enzyme	0.118883307
Equilibrative nucleoside transporter 1	Electrochemical transporter	0.118883307
Neprilysin (by homology)	Protease	0.118883307
Dual specificity mitogen-activated protein kinase kinase 1	Kinase	0.118883307
Glucose transporter (by homology)	Electrochemical transporter	0.118883307
Phosphodiesterase 5A	Phosphodiesterase	0.118883307
Coagulation factor VII/tissue factor	Surface antigen	0.118883307
Adenosine A2a receptor	Family A G protein-coupled receptor	0.118883307
Purinergic receptor P2Y12	Family A G protein-coupled receptor	0.118883307
Ceramide glucosyltransferase	Transferase	0.118883307
Beta-glucocerebrosidase	Enzyme	0.118883307
Beta-glucosidase	Enzyme	0.118883307

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Ertugliflozin

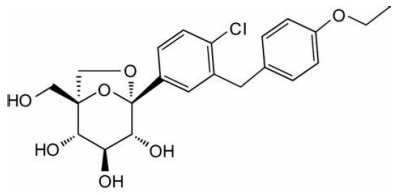

Table 13. Ertugliflozin.

Target	Target Class	Probability*
Low affinity sodium-glucose cotransporter	Electrochemical transporter	1
Sodium/glucose cotransporter 1	Electrochemical transporter	1
Sodium/glucose cotransporter 2 (by homology)	Electrochemical transporter	0.930927137
Sodium/myo-inositol cotransporter 2	Electrochemical transporter	0.214435241
Glucose transporter (by homology)	Electrochemical transporter	0.106165761
Adenosine kinase	Enzyme	0.106165761
Equilibrative nucleoside transporter 1	Electrochemical transporter	0.106165761
Dual specificity mitogen-activated protein kinase kinase 1	Kinase	0.106165761
Carbonic anhydrase II	Lyase	0.106165761
Adenosine A2a receptor	Family A G protein-coupled receptor	0.106165761
Adenosine A3 receptor	Family A G protein-coupled receptor	0.106165761
Carbonic anhydrase I	Lyase	0.106165761
Carbonic anhydrase XII	Lyase	0.106165761
Carbonic anhydrase IX	Lyase	0.106165761
Phosphodiesterase 5A	Phosphodiesterase	0.106165761
Heat shock cognate 71 kDa protein	Other cytosolic protein	0.106165761
Epidermal growth factor receptor erbB1	Kinase	0.106165761
Muscle glycogen phosphorylase	Enzyme	0.106165761
78 kDa glucose-regulated protein	Unclassified protein	0.106165761
Beta-glucocerebrosidase	Enzyme	0.106165761
Matrix metalloproteinase 3	Protease	0.106165761
Matrix metalloproteinase 9	Protease	0.106165761
Matrix metalloproteinase 1	Protease	0.106165761
ADAM17	Protease	0.106165761
Adenosine A2b receptor	Family A G protein-coupled receptor	0.106165761
Hexokinase type II	Enzyme	0.106165761
Hexokinase type I	Enzyme	0.106165761
Uridine phosphorylase 1 (by homology)	Enzyme	0.106165761
Purinergic receptor P2Y12 (by homology)	Family A G protein-coupled receptor	0.106165761
Sodium/nucleoside cotransporter 2	Electrochemical transporter	0.106165761
MAP kinase p38 alpha	Kinase	0.106165761
Coagulation factor VII/tissue factor	Surface antigen	0.106165761

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GABA receptor alpha-5 subunit	Ligand-gated ion channel	0.106165761
Carbonic anhydrase XIV	Lyase	0.106165761
Glyceraldehyde-3-phosphate dehydrogenase liver	Oxidoreductase	0.106165761
Adenosine A1 receptor	Family A G protein-coupled receptor	0.106165761
Bifunctional protein NCOAT	Enzyme	0.106165761
6-O-methylguanine-DNA methyltransferase	Enzyme	0.106165761
Beta-mannosidase	Enzyme	0.106165761
Matrix metalloproteinase 13	Protease	0.106165761
Cyclin-dependent kinase 2	Kinase	0.106165761
Cyclin-dependent kinase 1	Kinase	0.106165761
Matrix metalloproteinase 7	Protease	0.106165761
Matrix metalloproteinase 12	Protease	0.106165761
Matrix metalloproteinase 8	Protease	0.106165761
Neprilysin	Protease	0.106165761
GTPase NRas	Unclassified protein	0.106165761
Tyrosine-protein kinase SRC	Kinase	0.106165761
Endothelin-converting enzyme 1	Protease	0.106165761
Platelet-derived growth factor receptor beta	Kinase	0.106165761
Tyrosine-protein kinase LCK	Kinase	0.106165761
c-Jun N-terminal kinase 3	Kinase	0.106165761
MAP kinase p38 beta	Kinase	0.106165761
Ephrin type-A receptor 5	Kinase	0.106165761
Serine/threonine-protein kinase GAK	Kinase	0.106165761
Type-1 angiotensin II receptor (by homology)	Family A G protein-coupled receptor	0.106165761
Alpha-L-fucosidase I	Enzyme	0.106165761
Fibroblast growth factor receptor 1	Kinase	0.106165761
DNA (cytosine-5)-methyltransferase 1	Writer	0.106165761
Glutamate [NMDA] receptor PROTEIN	Ligand-gated ion channel	0.106165761
Serine/threonine-protein kinase Chk1	Kinase	0.106165761
Interleukin-1 receptor-associated kinase 4	Kinase	0.106165761
MAP kinase ERK2	Kinase	0.106165761

Group 6. Sulfonylureas and meglitinides and Target Predictions with Artificial Intelligence. This group of diabetic agents directly stimulate insulin release from pancreatic beta cells; thus, lower blood glucose concentration. Because they work by stimulating insulin secretion, they are useful only in patients with some beta cell function. Adverse effects may include weight gain and hypoglycemia. Six antidiabetic agents of this class are currently available (53.3% to 86.6% main target prediction).

Glimepiride

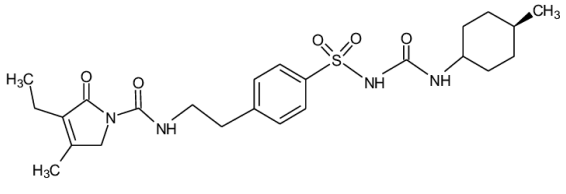

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Table 14. Glimepiride.

Target	Target Class	Probability*
Prostanoid EP4 receptor	Family A G protein-coupled receptor	0.120225751
Proteasome subunit beta type-9	Enzyme	0.120225751
Tyrosine-protein kinase BRK	Kinase	0.120225751
Tyrosine-protein kinase ABL	Kinase	0.120225751
Insulin-like growth factor I receptor	Kinase	0.120225751
Insulin receptor	Kinase	0.120225751
Cannabinoid receptor 2	Family A G protein-coupled receptor	0.120225751
Tyrosine-protein kinase SRC	Kinase	0.120225751
Vascular endothelial growth factor receptor 2	Kinase	0.120225751
PI3-kinase p110-delta subunit	Enzyme	0.120225751
PI3-kinase p110-beta subunit	Enzyme	0.120225751
PI3-kinase p110-gamma subunit	Enzyme	0.120225751
Hepatocyte growth factor receptor	Kinase	0.120225751
PI3-kinase p110-alpha subunit	Enzyme	0.120225751
Fibroblast growth factor receptor 2	Kinase	0.120225751
ALK tyrosine kinase receptor	Kinase	0.120225751
Mitogen-activated protein kinase kinase kinase 12	Enzyme	0.120225751
Acetyl-CoA carboxylase 2	Ligase	0.120225751
Cathepsin S	Protease	0.120225751
Acetyl-coenzyme A transporter 1	Electrochemical transporter	0.120225751
Phosphodiesterase 10A	Phosphodiesterase	0.120225751
c-Jun N-terminal kinase 1	Kinase	0.120225751
Poly [ADP-ribose] polymerase-1	Enzyme	0.120225751
c-Jun N-terminal kinase 2	Kinase	0.120225751
MAP kinase p38 alpha	Kinase	0.120225751
Tyrosine-protein kinase JAK2	Kinase	0.120225751
Tyrosine kinase non-receptor protein 2	Kinase	0.120225751
Fatty acid synthase	Transferase	0.120225751
Receptor protein-tyrosine kinase erbB-2	Kinase	0.120225751
Macrophage colony stimulating factor receptor	Kinase	0.120225751
Platelet-derived growth factor receptor beta	Kinase	0.120225751
Purinergic receptor P2Y12	Family A G protein-coupled receptor	0.120225751
Cyclin-dependent kinase 4	Kinase	0.120225751
Orexin receptor 2	Family A G protein-coupled receptor	0.120225751
Nicotinamide phosphoribosyltransferase	Enzyme	0.120225751
Calcium sensing receptor	Family C G protein-coupled receptor	0.120225751
Muscarinic acetylcholine receptor M2	Family A G protein-coupled receptor	0.120225751

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Muscarinic acetylcholine receptor M3	Family A G protein-coupled receptor	0.120225751
Gamma-secretase	Protease	0.120225751
Endothelin receptor ET-B	Family A G protein-coupled receptor	0.120225751
Androgen Receptor	Nuclear receptor	0.120225751
Serine/threonine-protein kinase RAF	Kinase	0.120225751
Cyclin-dependent kinase 5/CDK5 activator 1	Kinase	0.120225751
Stem cell growth factor receptor	Kinase	0.120225751
Progesterone receptor	Nuclear receptor	0.120225751
Endothelin receptor ET-A	Family A G protein-coupled receptor	0.120225751
Nerve growth factor receptor Trk-A	Kinase	0.120225751
Phosphoglycerate kinase 1	Enzyme	0.120225751
Vanilloid receptor	Voltage-gated ion channel	0.120225751
Epidermal growth factor receptor erbB1	Kinase	0.120225751
EZH2/SUZ12/EED/RBBP7/RBBP4	Writer	0.120225751
6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3	Enzyme	0.120225751
Tyrosine-protein kinase SYK	Kinase	0.120225751
Orexin receptor 1	Family A G protein-coupled receptor	0.120225751
Metabotropic glutamate receptor 5	Family C G protein-coupled receptor	0.120225751
Interleukin-1 receptor-associated kinase 4	Kinase	0.120225751
N-acylsphingosine-amidohydrolase	Enzyme	0.120225751
Beta-secretase 1	Protease	0.120225751
Dual specificity protein kinase TTK	Kinase	0.120225751
Muscle glycogen synthase	Enzyme	0.120225751
Bromodomain-containing protein 4	Reader	0.120225751
Tyrosine-protein kinase JAK3	Kinase	0.120225751
Focal adhesion kinase 1	Kinase	0.120225751
Phosphodiesterase 9A	Phosphodiesterase	0.120225751
MAP kinase ERK2	Kinase	0.120225751
P2X purinoceptor 7	Ligand-gated ion channel	0.120225751
Serine/threonine-protein kinase Aurora-B	Kinase	0.120225751
Serine/threonine-protein kinase mTOR	Kinase	0.120225751
Squalene synthetase	Enzyme	0.120225751
Phosphodiesterase 1C	Phosphodiesterase	0.120225751
Polyadenylate-binding protein 1	Unclassified protein	0.120225751
Vasopressin V2 receptor (by homology)	Family A G protein-coupled receptor	0.120225751
Gonadotropin-releasing hormone receptor	Family A G protein-coupled receptor	0.120225751
Oxytocin receptor (by homology)	Family A G protein-coupled receptor	0.120225751
3-phosphoinositide dependent protein kinase-1	Kinase	0.120225751
Rho-associated protein kinase 2	Kinase	0.120225751

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Cyclin-dependent kinase 1/cyclin B1	Other cytosolic protein	0.120225751
Cyclin-dependent kinase 2/cyclin A	Other cytosolic protein	0.120225751
Cyclin T1	Other cytosolic protein	0.120225751
Cyclin-dependent kinase 7/ cyclin H	Other cytosolic protein	0.120225751
CDK9/cyclin T1	Other cytosolic protein	0.120225751
Glycogen synthase kinase-3 beta	Kinase	0.120225751
Cyclin-dependent kinase 2	Kinase	0.120225751
CDK2/Cyclin A	Kinase	0.120225751
Protein kinase C beta	Kinase	0.120225751
Caspase-6	Protease	0.120225751
Caspase-7	Protease	0.120225751
Hexokinase type IV	Enzyme	0.120225751
TGF-beta receptor type II	Kinase	0.120225751
Caspase-1	Protease	0.120225751
GABA receptor alpha-5 subunit	Ligand-gated ion channel	0.120225751
Smoothened homolog	Frizzled family G protein-coupled receptor	0.120225751
Glycine transporter 1	Electrochemical transporter	0.120225751
Tyrosine-protein kinase ITK/TSK	Kinase	0.120225751
Serine/threonine-protein kinase Aurora-A	Kinase	0.120225751
Protein Wnt-3a	Unclassified protein	0.120225751
Estrogen receptor alpha	Nuclear receptor	0.120225751
Estrogen receptor beta	Nuclear receptor	0.120225751
Tankyrase-2	Enzyme	0.120225751
DNA-dependent protein kinase	Kinase	0.120225751

Glipizide

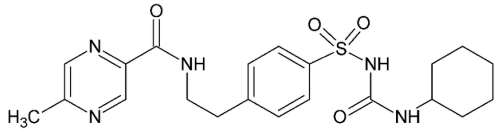

Table 15. Glipizide.

Target	Target Class	Probability*
Tyrosine-protein kinase JAK3	Kinase	0.118883307
Tyrosine-protein kinase JAK2	Kinase	0.118883307
Serotonin 7 (5-HT7) receptor	Family A G protein-coupled receptor	0.118883307
Serine/threonine-protein kinase mTOR	Kinase	0.118883307
Vascular endothelial growth factor receptor 1	Kinase	0.118883307
Platelet-derived growth factor receptor alpha	Kinase	0.118883307
Vascular endothelial growth factor receptor 2	Kinase	0.118883307
Fibroblast growth factor receptor 1	Kinase	0.118883307
Prostanoid EP3 receptor	Family A G protein-coupled receptor	0.118883307
Sodium channel protein type IX alpha subunit	Voltage-gated ion channel	0.118883307

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MAP kinase p38 alpha	Kinase	0.118883307
Bromodomain-containing protein 2	Reader	0.118883307
Bromodomain-containing protein 3	Reader	0.118883307
Phosphodiesterase 4B	Phosphodiesterase	0.118883307
CREB-binding protein/p53	Writer	0.118883307
Phosphodiesterase 5A	Phosphodiesterase	0.118883307
Platelet-derived growth factor receptor beta	Kinase	0.118883307
Inhibitor of nuclear factor kappa B kinase beta subunit	Kinase	0.118883307
Complement factor D	Protease	0.118883307
Adenosine A1 receptor (by homology)	Family A G protein-coupled receptor	0.118883307
Hepatocyte growth factor receptor	Kinase	0.118883307
Vascular endothelial growth factor receptor 3	Kinase	0.118883307
Phosphodiesterase 9A	Phosphodiesterase	0.118883307
Angiotensin II receptor	Family A G protein-coupled receptor	0.118883307
Phosphodiesterase 4A	Phosphodiesterase	0.118883307
Tyrosine-protein kinase SYK	Kinase	0.118883307
Bradykinin B1 receptor	Family A G protein-coupled receptor	0.118883307
Phosphodiesterase 10A	Phosphodiesterase	0.118883307
Insulin-like growth factor I receptor	Kinase	0.118883307
Oxytocin receptor	Family A G protein-coupled receptor	0.118883307
c-Jun N-terminal kinase 3	Kinase	0.118883307
Cathepsin S	Protease	0.118883307
MAP kinase ERK2	Kinase	0.118883307
Hypoxia-inducible factor 1 alpha	Transcription factor	0.118883307
Tyrosine kinase non-receptor protein 2	Kinase	0.118883307
Purinergic receptor P2Y12	Family A G protein-coupled receptor	0.118883307
Cyclin-dependent kinase 5/CDK5 activator 1	Kinase	0.118883307
Epidermal growth factor receptor erbB1	Kinase	0.118883307
11-beta-hydroxysteroid dehydrogenase 1	Enzyme	0.118883307
Platelet activating factor receptor	Family A G protein-coupled receptor	0.118883307
Nerve growth factor receptor Trk-A	Kinase	0.118883307
Vanilloid receptor	Voltage-gated ion channel	0.118883307
CDC7/DBF4 (Cell division cycle 7-related protein kinase/Activator of S phase kinase)	Kinase	0.118883307
Adenosine A2b receptor	Family A G protein-coupled receptor	0.118883307
Poly [ADP-ribose] polymerase-1	Enzyme	0.118883307
DNA-dependent protein kinase	Kinase	0.118883307
Cathepsin (V and K) (by homology)	Protease	0.118883307
Ribosomal protein S6 kinase 1	Kinase	0.118883307

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Serine/threonine-protein kinase Aurora-A	Kinase	0.118883307
Phosphatidylinositol 3-kinase catalytic subunit type 3	Enzyme	0.118883307
CDC7/DBF4 (Cell division cycle 7-related protein kinase/Activator of S phase kinase)	Kinase	0.118883307
c-Jun N-terminal kinase 1	Kinase	0.118883307
c-Jun N-terminal kinase 2	Kinase	0.118883307
Leucine-rich repeat serine/threonine-protein kinase 2	Kinase	0.118883307
Calcium sensing receptor	Family C G protein-coupled receptor	0.118883307
Proteasome subunit beta type-9	Enzyme	0.118883307
Serine/threonine-protein kinase Aurora-B	Kinase	0.118883307
Intercellular adhesion molecule-1	Adhesion	0.118883307
Dual specificity mitogen-activated protein kinase kinase 1	Kinase	0.118883307
Selectin E	Adhesion	0.118883307
Rho-associated protein kinase 2	Kinase	0.118883307
Cyclin-dependent kinase 2	Kinase	0.118883307
Transcription intermediary factor 1-alpha	Reader	0.118883307
GABA receptor alpha-5 subunit	Ligand-gated ion channel	0.118883307
Cytochrome P450 19A1	Cytochrome P450	0.118883307
Protein kinase C theta	Kinase	0.118883307
TGF-beta receptor type I	Kinase	0.118883307
Serine/threonine-protein kinase TNNI3K	Kinase	0.118883307
Cyclin-dependent kinase 2/cyclin E1	Kinase	0.118883307
Glycine transporter 1	Electrochemical transporter	0.118883307
Glycine transporter 2	Electrochemical transporter	0.118883307
N-acylsphingosine-amidohydrolase (by homology)	Enzyme	0.118883307
Acetyl-CoA carboxylase 2	Ligase	0.118883307
Matrix metalloproteinase 1	Protease	0.118883307
Probable protein-cysteine N-palmitoyltransferase porcupine (by homology)	Enzyme	0.118883307
Serine/threonine-protein kinase PIM1	Kinase	0.118883307
Tyrosine-protein kinase LCK	Kinase	0.118883307
Cyclin-dependent kinase 1	Kinase	0.118883307
Cyclin-dependent kinase 4	Kinase	0.118883307
Protein-tyrosine phosphatase 1B	Phosphatase	0.118883307
Serine/threonine-protein kinase PIM2	Kinase	0.118883307
Receptor protein-tyrosine kinase erbB-2	Kinase	0.118883307
Histone deacetylase 3	Eraser	0.118883307
Vasopressin V1a receptor	Family A G protein-coupled receptor	0.118883307
Histone deacetylase 2	Eraser	0.118883307

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Kappa Opioid receptor	Family A G protein-coupled receptor	0.118883307
Phosphodiesterase 3	Phosphodiesterase	0.118883307
Phosphodiesterase 3B	Phosphodiesterase	0.118883307
Histone deacetylase 1	Eraser	0.118883307
MAP kinase p38 beta	Kinase	0.118883307
Tyrosine-protein kinase BRK	Kinase	0.118883307
Sodium/glucose cotransporter 1	Electrochemical transporter	0.118883307
Smoothened homolog	Frizzled family G protein-coupled receptor	0.118883307
Corticotropin releasing factor receptor 1	Family B G protein-coupled receptor	0.118883307
Macrophage colony stimulating factor receptor (by homology)	Kinase	0.118883307
Ephrin type-A receptor 2	Kinase	0.118883307
Protein farnesyltransferase	Enzyme	0.118883307
Interleukin-8 receptor B	Family A G protein-coupled receptor	0.118883307
Acetyl-CoA carboxylase 1	Enzyme	0.118883307
Endothelin receptor ET-B	Family A G protein-coupled receptor	0.118883307

Glyburide

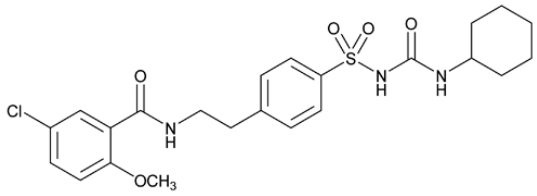

Table 16. Glyburide.

Target	Target Class	Probability*
Sulfonylurea receptor 2, Kir6.2	Primary active transporter	1
Sulfonylurea receptor 1, Kir6.2	Voltage-gated ion channel	1
Cytochrome P450 2C9	Cytochrome P450	1
Bile salt export pump	Primary active transporter	1
Sulfonylurea receptor 1	Primary active transporter	0.117389882
Phosphoglycerate kinase 1	Enzyme	0.100634432
Protein-tyrosine phosphatase 1B	Phosphatase	0.100634432
Purinergic receptor P2Y12	Family A G protein-coupled receptor	0.100634432
Bromodomain-containing protein 4	Reader	0.100634432
Orexin receptor 2	Family A G protein-coupled receptor	0.100634432
Orexin receptor 1	Family A G protein-coupled receptor	0.100634432
Nicotinamide phosphoribosyltransferase	Enzyme	0.100634432
Macrophage colony stimulating factor receptor	Kinase	0.100634432

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Platelet-derived growth factor receptor beta	Kinase	0.100634432
Tyrosine-protein kinase receptor FLT3	Kinase	0.100634432
Vascular endothelial growth factor receptor 2	Kinase	0.100634432
Multidrug resistance-associated protein 1	Primary active transporter	0.100634432
Cyclin-dependent kinase 2	Kinase	0.100634432
P-glycoprotein 1	Primary active transporter	0.100634432
Phosphodiesterase 10A (by homology)	Phosphodiesterase	0.100634432
Serine/threonine-protein kinase mTOR	Kinase	0.100634432
PI3-kinase p110-alpha subunit	Enzyme	0.100634432
Tyrosine-protein kinase JAK2	Kinase	0.100634432
Serine/threonine-protein kinase Aurora-A	Kinase	0.100634432
Smoothened homolog	Frizzled family G protein-coupled receptor	0.100634432
Diacylglycerol O-acyltransferase 1	Enzyme	0.100634432
Carbonic anhydrase II	Lyase	0.100634432
Tyrosine kinase non-receptor protein 2	Kinase	0.100634432
Stem cell growth factor receptor	Kinase	0.100634432
6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3	Enzyme	0.100634432
ALK tyrosine kinase receptor	Kinase	0.100634432
Adenosine A1 receptor (by homology)	Family A G protein-coupled receptor	0.100634432
Adenosine A2a receptor (by homology)	Family A G protein-coupled receptor	0.100634432
Adenosine A3 receptor	Family A G protein-coupled receptor	0.100634432
Bile acid receptor FXR	Nuclear receptor	0.100634432
PI3-kinase p110-delta subunit	Enzyme	0.100634432
Thymidine kinase, mitochondrial	Enzyme	0.100634432
Acetyl-coenzyme A transporter 1	Electrochemical transporter	0.100634432
Insulin receptor	Kinase	0.100634432
Hepatocyte growth factor receptor	Kinase	0.100634432
Carbonic anhydrase I	Lyase	0.100634432
Carbonic anhydrase XII	Lyase	0.100634432
Insulin-like growth factor I receptor	Kinase	0.100634432
Dual specificity mitogen-activated protein kinase kinase 1	Kinase	0.100634432
N-acylsphingosine-amidohydrolase	Enzyme	0.100634432
Glucose-dependent insulinotropic receptor	Family A G protein-coupled receptor	0.100634432
CaM kinase II	Kinase	0.100634432
5-lipoxygenase activating protein	Other cytosolic protein	0.100634432
Serine/threonine-protein kinase B-raf	Kinase	0.100634432
Protein Wnt-3a	Unclassified protein	0.100634432
Tyrosine-protein kinase JAK1	Kinase	0.100634432
Tankyrase-2	Enzyme	0.100634432

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Prostanoid EP1 receptor	Family A G protein-coupled receptor	0.100634432
Tyrosine-protein kinase SYK	Kinase	0.100634432
Phosphodiesterase 4D	Phosphodiesterase	0.100634432
CDK8/Cyclin C	Kinase	0.100634432
Poly [ADP-ribose] polymerase-1	Enzyme	0.100634432
Phosphodiesterase 9A	Phosphodiesterase	0.100634432
Acetyl-CoA carboxylase 2	Ligase	0.100634432
Cell division protein kinase 8	Kinase	0.100634432
c-Jun N-terminal kinase 1	Kinase	0.100634432
c-Jun N-terminal kinase 3	Kinase	0.100634432
Translocator protein (by homology)	Membrane receptor	0.100634432
Carbonic anhydrase IX	Lyase	0.100634432
Receptor protein-tyrosine kinase erbB-2	Kinase	0.100634432
Cyclin-dependent kinase 5/CDK5 activator 1	Kinase	0.100634432
Epidermal growth factor receptor erbB1	Kinase	0.100634432
Serine/threonine-protein kinase PIM1	Kinase	0.100634432
Dual-specificity tyrosine-phosphorylation regulated kinase 1A (by homology)	Kinase	0.100634432
Adenosine A2b receptor	Family A G protein-coupled receptor	0.100634432
Transmembrane domain-containing protein TMIGD3	Unclassified protein	0.100634432
Dual specificty protein kinase CLK1 (by homology)	Kinase	0.100634432
Dual specificity protein kinase CLK3 (by homology)	Kinase	0.100634432
Dual-specificity tyrosine-phosphorylation regulated kinase 2	Kinase	0.100634432
Calcium sensing receptor	Family C G protein-coupled receptor	0.100634432
Voltage-gated calcium channel alpha2/delta subunit 1	Calcium channel auxiliary subunit alpha2delta family	0.100634432
Caspase-6	Protease	0.100634432
Caspase-7	Protease	0.100634432
Caspase-1	Protease	0.100634432
Tyrosine-protein kinase ABL	Kinase	0.100634432
Cyclin-dependent kinase 2/cyclin E1	Kinase	0.100634432
Mitogen-activated protein kinase kinase kinase 12	Enzyme	0.100634432
Metabotropic glutamate receptor 1	Family C G protein-coupled receptor	0.100634432
c-Jun N-terminal kinase 2	Kinase	0.100634432
Steroidogenic factor 1	Nuclear receptor	0.100634432
Eukaryotic translation initiation factor 2-alpha kinase 3	Kinase	0.100634432
Tyrosine-protein kinase SRC	Kinase	0.100634432
DNA-dependent protein kinase	Kinase	0.100634432
Fibroblast growth factor receptor 2	Kinase	0.100634432

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Corticotropin releasing factor receptor 1	Family B G protein-coupled receptor	0.100634432
Nerve growth factor receptor Trk-A	Kinase	0.100634432
PI3-kinase p110-beta subunit	Enzyme	0.100634432
PI3-kinase p110-gamma subunit	Enzyme	0.100634432
Serine/threonine-protein kinase Chk1	Kinase	0.100634432
Serine/threonine-protein kinase Aurora-B	Kinase	0.100634432
Interleukin-8 receptor B	Family A G protein-coupled receptor	0.100634432
Neuronal acetylcholine receptor protein alpha-7 subunit	Ligand-gated ion channel	0.100634432
CDK2/Cyclin A	Kinase	0.100634432
Hypoxia-inducible factor 1 alpha	Transcription factor	0.100634432
MAP kinase-activated protein kinase 2	Kinase	0.100634432

Tolazamide

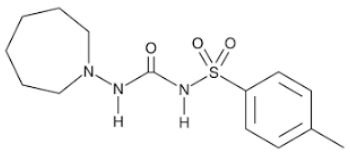

Table 17. Tolazamide.

Target	Target Class	Probability*
P2X purinoceptor 7	Ligand-gated ion channel	0.097874534
Phosphodiesterase 10A	Phosphodiesterase	0.097874534
Melatonin receptor 1B	Family A G protein-coupled receptor	0.097874534
Cytochrome P450 19A1	Cytochrome P450	0.097874534
Glutathione transferase omega 1	Enzyme	0.097874534
Vascular endothelial growth factor receptor 1	Kinase	0.097874534
Vascular endothelial growth factor receptor 2	Kinase	0.097874534
Prolyl endopeptidase	Protease	0.097874534
Orexin receptor 2	Family A G protein-coupled receptor	0.097874534
Phosphatidylinositol-5-phosphate 4-kinase type-2 gamma	Enzyme	0.097874534
MAP kinase p38 alpha	Kinase	0.097874534
Phosphodiesterase 5A	Phosphodiesterase	0.097874534
Cyclin-dependent kinase 5/CDK5 activator 1	Kinase	0.097874534
Orexin receptor 1	Family A G protein-coupled receptor	0.097874534
Bromodomain-containing protein 4	Reader	0.097874534
Bromodomain-containing protein 2	Reader	0.097874534
Bromodomain-containing protein 3	Reader	0.097874534
Cyclin-dependent kinase 2/cyclin E	Other cytosolic protein	0.097874534
Adenosine A2b receptor	Family A G protein-coupled receptor	0.097874534
Androgen Receptor	Nuclear receptor	0.097874534
Protoporphyrinogen oxidase	Oxidoreductase	0.097874534

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Epoxide hydrolase 1	Protease	0.097874534
Glycogen synthase kinase-3 beta	Kinase	0.097874534
Cyclin-dependent kinase 2	Kinase	0.097874534
Hepatocyte growth factor receptor	Kinase	0.097874534
Nitric oxide synthase, inducible	Enzyme	0.097874534
Metabotropic glutamate receptor 5 (by homology)	Family C G protein-coupled receptor	0.097874534
Voltage-gated potassium channel subunit Kv1.3	Voltage-gated ion channel	0.097874534
c-Jun N-terminal kinase 1	Kinase	0.097874534
c-Jun N-terminal kinase 3	Kinase	0.097874534
Glutaminyl-peptide cyclotransferase	Enzyme	0.097874534
Plectin	Unclassified protein	0.097874534
Adenosine A1 receptor	Family A G protein-coupled receptor	0.097874534
Adenosine A2a receptor	Family A G protein-coupled receptor	0.097874534
Beta-secretase 1	Protease	0.097874534
Long-chain fatty acid transport protein 1	Electrochemical transporter	0.097874534
Dopamine transporter	Electrochemical transporter	0.097874534
Beta secretase 2	Protease	0.097874534
Protein kinase C gamma (by homology)	Kinase	0.097874534
ALK tyrosine kinase receptor	Kinase	0.097874534
GABA receptor alpha-5 subunit	Ligand-gated ion channel	0.097874534
Butyrylcholinesterase	Hydrolase	0.097874534
Cathepsin K	Protease	0.097874534
Glycogen synthase kinase-3 alpha	Kinase	0.097874534
Potassium channel subfamily K member 3	Voltage-gated ion channel	0.097874534
Cyclin-dependent kinase 1/cyclin B	Other cytosolic protein	0.097874534
Adenosine A3 receptor	Family A G protein-coupled receptor	0.097874534
Cyclin-dependent kinase 4	Kinase	0.097874534
Hydroxycarboxylic acid receptor 2	Family A G protein-coupled receptor	0.097874534
Insulin-like growth factor I receptor	Kinase	0.097874534
Transthyretin	Secreted protein	0.097874534
NAD-dependent deacetylase sirtuin 1	Eraser	0.097874534
Tyrosine-protein kinase JAK3	Kinase	0.097874534
C5a anaphylatoxin chemotactic receptor	Family A G protein-coupled receptor	0.097874534
Tyrosine-protein kinase JAK2	Kinase	0.097874534
Protein tyrosine kinase 2 beta	Kinase	0.097874534
ADAMTS5	Protease	0.097874534
ADAMTS4	Protease	0.097874534
Matrix metalloproteinase 3	Protease	0.097874534
ADAM17	Protease	0.097874534
Prostanoid EP2 receptor	Family A G protein-coupled receptor	0.097874534
Progesterone receptor	Nuclear receptor	0.097874534

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SUMO-activating enzyme	Enzyme	0.097874534
Inosine-5′-monophosphate dehydrogenase 2	Oxidoreductase	0.097874534
Tyrosine-protein kinase SYK	Kinase	0.097874534
Cathepsin (B and K)	Protease	0.097874534
Estrogen receptor beta	Nuclear receptor	0.097874534
Nerve growth factor receptor Trk-A	Kinase	0.097874534
Cathepsin S	Protease	0.097874534
Fibroblast growth factor receptor 1	Kinase	0.097874534
Hexokinase type IV	Enzyme	0.097874534
Estrogen receptor alpha	Nuclear receptor	0.097874534
Anandamide amidohydrolase	Enzyme	0.097874534
Cathepsin (V and K) (by homology)	Protease	0.097874534
c-Jun N-terminal kinase 2	Kinase	0.097874534
Arylamine N-acetyltransferase 1	Enzyme	0.097874534
Cholecystokinin A receptor	Family A G protein-coupled receptor	0.097874534
Platelet-derived growth factor receptor beta	Kinase	0.097874534
GABA receptor alpha-1 subunit	Ligand-gated ion channel	0.097874534
Epidermal growth factor receptor erbB1	Kinase	0.097874534
Platelet activating factor receptor	Family A G protein-coupled receptor	0.097874534
Phosphodiesterase 4B	Phosphodiesterase	0.097874534
Cholecystokinin B receptor	Family A G protein-coupled receptor	0.097874534
Voltage-gated L-type calcium channel alpha-1C subunit	Voltage-gated ion channel	0.097874534
Induced myeloid leukemia cell differentiation protein Mcl-1	Other cytosolic protein	0.097874534
Serotonin transporter	Electrochemical transporter	0.097874534
Serine/threonine-protein kinase Chk2	Kinase	0.097874534
Liver glycogen phosphorylase	Enzyme	0.097874534
Serine/threonine-protein kinase PLK4	Kinase	0.097874534
Serine/threonine-protein kinase Aurora-A	Kinase	0.097874534
Serine/threonine-protein kinase RIPK2	Kinase	0.097874534
Isocitrate dehydrogenase [NADP] cytoplasmic	Enzyme	0.097874534
Potassium channel subfamily K member 9	Voltage-gated ion channel	0.097874534
Tyrosine-protein kinase SRC	Kinase	0.097874534
Focal adhesion kinase 1	Kinase	0.097874534
Poly [ADP-ribose] polymerase-1	Enzyme	0.097874534
MAP kinase-interacting serine/threonine-protein kinase MNK1	Kinase	0.097874534
Tankyrase-2	Enzyme	0.097874534
Glucagon-like peptide 1 receptor	Family B G protein-coupled receptor	0.097874534
Stem cell growth factor receptor	Kinase	0.097874534

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Tolbutamide

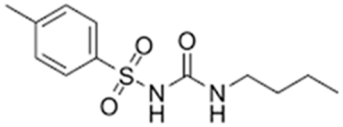

Table 18. Tolbutamide.

Target	Target Class	Probability*
Fructose-1,6-bisphosphatase	Enzyme	0.098947479
Carbonic anhydrase II	Lyase	0.071715932
Carbonic anhydrase I	Lyase	0.071715932
Carbonic anhydrase XII	Lyase	0.071715932
Carbonic anhydrase IX	Lyase	0.071715932
Adenosine A1 receptor	Family A G protein-coupled receptor	0.053556076
Adenosine A2a receptor	Family A G protein-coupled receptor	0.053556076
Adenosine A2b receptor	Family A G protein-coupled receptor	0.053556076
Adenosine A3 receptor	Family A G protein-coupled receptor	0.053556076
P2X purinoceptor 7	Ligand-gated ion channel	0.053556076
MAP kinase p38 alpha	Kinase	0.053556076
NAD-dependent protein deacylase sirtuin-5, mitochondrial	Eraser	0.053556076
NAD-dependent deacetylase sirtuin 2	Eraser	0.053556076
NAD-dependent deacetylase sirtuin 1	Eraser	0.053556076
Orexin receptor 2	Family A G protein-coupled receptor	0.053556076
Orexin receptor 1	Family A G protein-coupled receptor	0.053556076
Cyclin-dependent kinase 2/cyclin E	Other cytosolic protein	0.053556076
Cyclin-dependent kinase 1/cyclin B	Other cytosolic protein	0.053556076
Estrogen receptor beta	Nuclear receptor	0.053556076
Cytochrome P450 19A1	Cytochrome P450	0.053556076
Cathepsin K	Protease	0.053556076
Cathepsin S	Protease	0.053556076
Tyrosine-protein kinase ITK/TSK	Kinase	0.053556076
Glutathione transferase omega 1	Enzyme	0.053556076
Cathepsin (V and K) (by homology)	Protease	0.053556076
Glutaminyl-peptide cyclotransferase	Enzyme	0.053556076
G-protein coupled receptor kinase 2	Kinase	0.053556076
Tyrosine-protein kinase JAK3	Kinase	0.053556076
Nerve growth factor receptor Trk-A	Kinase	0.053556076
Tyrosine-protein kinase JAK2	Kinase	0.053556076
Cyclin-dependent kinase 5/CDK5 activator 1	Kinase	0.053556076
Arachidonate 5-lipoxygenase	Oxidoreductase	0.053556076
Vascular endothelial growth factor receptor 2	Kinase	0.053556076

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Metabotropic glutamate receptor 5 (by homology)	Family C G protein-coupled receptor	0.053556076
Fibroblast growth factor receptor 1	Kinase	0.053556076
Serine/threonine-protein kinase Aurora-B	Kinase	0.053556076
Cyclin-dependent kinase 2	Kinase	0.053556076
Signal transducer and activator of transcription 5B	Transcription factor	0.053556076
Bromodomain-containing protein 4	Reader	0.053556076
Bromodomain-containing protein 2	Reader	0.053556076
Phenylalanyl-tRNA synthetase mitochondrial	Enzyme	0.053556076
Androgen Receptor	Nuclear receptor	0.053556076
Heat shock protein HSP 90-alpha	Other cytosolic protein	0.053556076
Inosine-5′-monophosphate dehydrogenase 2	Oxidoreductase	0.053556076
Insulin-like growth factor I receptor	Kinase	0.053556076
Fatty acid desaturase 1	Enzyme	0.053556076
Endothelin receptor ET-A (by homology)	Family A G protein-coupled receptor	0.053556076
Induced myeloid leukemia cell differentiation protein Mcl-1	Other cytosolic protein	0.053556076
Protein tyrosine kinase 2 beta	Kinase	0.053556076
Nuclear receptor subfamily 4 group A member 1	Nuclear receptor	0.053556076
Glucagon-like peptide 1 receptor	Family B G protein-coupled receptor	0.053556076
Integrin alpha-4/beta-7	Membrane receptor	0.053556076
c-Jun N-terminal kinase 1	Kinase	0.053556076
c-Jun N-terminal kinase 3	Kinase	0.053556076
c-Jun N-terminal kinase 2	Kinase	0.053556076
Arylamine N-acetyltransferase 1	Enzyme	0.053556076
GABA receptor alpha-5 subunit	Ligand-gated ion channel	0.053556076
Dual-specificity tyrosine-phosphorylation regulated kinase 1A (by homology)	Kinase	0.053556076
MAP kinase-activated protein kinase 2	Kinase	0.053556076
Cyclin-dependent kinase 1	Kinase	0.053556076
Tyrosine-protein kinase TYK2	Kinase	0.053556076
Cathepsin (B and K)	Protease	0.053556076
Plectin	Unclassified protein	0.053556076
Prostanoid EP2 receptor	Family A G protein-coupled receptor	0.053556076
Epoxide hydrolase 1	Protease	0.053556076
Protein farnesyltransferase	Enzyme	0.053556076
Tyrosine-protein kinase LCK	Kinase	0.053556076
Poly [ADP-ribose] polymerase-1	Enzyme	0.053556076
Serine/threonine-protein kinase Aurora-A	Kinase	0.053556076
Cyclin-dependent kinase 2/cyclin E1	Kinase	0.053556076
Tyrosine-protein kinase receptor FLT3	Kinase	0.053556076
Kinesin-1 heavy chain/ Tyrosine-protein kinase receptor RET	Kinase	0.053556076
Fibroblast growth factor receptor 3	Kinase	0.053556076
Phosphodiesterase 10A	Phosphodiesterase	0.053556076
Muscle, skeletal receptor tyrosine protein kinase	Kinase	0.053556076

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Cyclin-dependent kinase 2/cyclin A	Other cytosolic protein	0.053556076
Glycogen synthase kinase-3 beta	Kinase	0.053556076
Tyrosine-protein kinase SRC	Kinase	0.053556076
Cholecystokinin B receptor	Family A G protein-coupled receptor	0.053556076
Hormone sensitive lipase	Enzyme	0.053556076
Tankyrase-2	Enzyme	0.053556076
Amine oxidase, copper containing	Enzyme	0.053556076
Voltage-gated L-type calcium channel alpha-1C subunit	Voltage-gated ion channel	0.053556076
Estrogen receptor alpha	Nuclear receptor	0.053556076
Cathepsin D	Protease	0.053556076
Hexokinase type IV	Enzyme	0.053556076
Cathepsin L	Protease	0.053556076
MAP kinase-interacting serine/threonine-protein kinase MNK1	Kinase	0.053556076
Bromodomain-containing protein 3	Reader	0.053556076
Monoamine oxidase B	Oxidoreductase	0.053556076
GABA-A receptor; alpha-5/beta-3/gamma-2	Ligand-gated ion channel	0.053556076
Ephrin receptor	Kinase	0.053556076
Axin1/beta-catenin	Unclassified protein	0.053556076
Vascular endothelial growth factor receptor 3	Kinase	0.053556076
ADAMTS5	Protease	0.053556076
Phosphorylase kinase gamma subunit 2	Kinase	0.053556076
Tyrosine-protein kinase SYK	Kinase	0.053556076
Focal adhesion kinase 1	Kinase	0.053556076
Mitogen-activated protein kinase kinase kinase 9	Kinase	0.053556076
ALK tyrosine kinase receptor	Kinase	0.053556076

Gliclazide

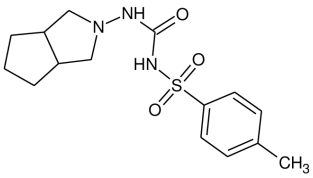

Table 19. Gliclazide.

Target	Target Class	Probability*
Phosphodiesterase 10A	Phosphodiesterase	0.111501865
P2X purinoceptor 7	Ligand-gated ion channel	0.111501865
Cytochrome P450 19A1	Cytochrome P450	0.111501865
Bromodomain-containing protein 4	Reader	0.111501865
Tyrosine-protein kinase JAK2	Kinase	0.111501865
Matrix metalloproteinase 9	Protease	0.111501865
Matrix metalloproteinase 2	Protease	0.111501865
Matrix metalloproteinase 14	Protease	0.111501865
Adenosine A2a receptor	Family A G protein-coupled receptor	0.111501865

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Adenosine A2b receptor	Family A G protein-coupled receptor	0.111501865
Metabotropic glutamate receptor 5 (by homology)	Family C G protein-coupled receptor	0.111501865
Butyrylcholinesterase	Hydrolase	0.111501865
Adenosine A1 receptor (by homology)	Family A G protein-coupled receptor	0.111501865
Protein tyrosine kinase 2 beta	Kinase	0.111501865
Androgen Receptor	Nuclear receptor	0.111501865
Epoxide hydrolase 1	Protease	0.111501865
MAP kinase p38 alpha	Kinase	0.111501865
Melatonin receptor 1B	Family A G protein-coupled receptor	0.111501865
Adenosine A3 receptor	Family A G protein-coupled receptor	0.111501865
Cathepsin (B and K)	Protease	0.111501865
Orexin receptor 2	Family A G protein-coupled receptor	0.111501865
Orexin receptor 1	Family A G protein-coupled receptor	0.111501865
Glutathione transferase omega 1	Enzyme	0.111501865
Hepatocyte growth factor receptor	Kinase	0.111501865
Glutaminyl-peptide cyclotransferase	Enzyme	0.111501865
Bromodomain-containing protein 2	Reader	0.111501865
Bromodomain-containing protein 3	Reader	0.111501865
Tyrosine-protein kinase JAK3	Kinase	0.111501865
Serine/threonine-protein kinase Aurora-B	Kinase	0.111501865
Cathepsin K	Protease	0.111501865
Nerve growth factor receptor Trk-A	Kinase	0.111501865
Cathepsin S	Protease	0.111501865
Cyclin-dependent kinase 2	Kinase	0.111501865
GABA receptor alpha-5 subunit	Ligand-gated ion channel	0.111501865
Cyclin-dependent kinase 5/CDK5 activator 1	Kinase	0.111501865
Cathepsin (V and K)	Protease	0.111501865
Cathepsin L	Protease	0.111501865
Nitric oxide synthase, inducible	Enzyme	0.111501865
NAD-dependent deacetylase sirtuin 1	Eraser	0.111501865
Cyclin-dependent kinase 2/cyclin E	Other cytosolic protein	0.111501865
Glycogen synthase kinase-3 beta	Kinase	0.111501865
Poly [ADP-ribose] polymerase-1	Enzyme	0.111501865
Cyclin-dependent kinase 4	Kinase	0.111501865
Cathepsin G	Protease	0.111501865
Tankyrase-2	Enzyme	0.111501865
Serine/threonine-protein kinase Aurora-A	Kinase	0.111501865
Vascular endothelial growth factor receptor 1	Kinase	0.111501865
Cyclin-dependent kinase 2/cyclin E1	Kinase	0.111501865
Tyrosine-protein kinase receptor FLT3	Kinase	0.111501865

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Kinesin-1 heavy chain/ Tyrosine-protein kinase receptor RET	Kinase	0.111501865
GABA-A receptor; alpha-5/beta-3/gamma-2	Ligand-gated ion channel	0.111501865
Tyrosine-protein kinase LCK	Kinase	0.111501865
Fibroblast growth factor receptor 3	Kinase	0.111501865
Vascular endothelial growth factor receptor 2	Kinase	0.111501865
Prolyl endopeptidase	Protease	0.111501865
Muscle, skeletal receptor tyrosine protein kinase	Kinase	0.111501865
Phosphodiesterase 5A	Phosphodiesterase	0.111501865
Dopamine transporter	Electrochemical transporter	0.111501865
Beta amyloid A4 protein	Membrane receptor	0.111501865
Beta secretase 2	Protease	0.111501865
Beta-secretase 1	Protease	0.111501865
c-Jun N-terminal kinase 1	Kinase	0.111501865
c-Jun N-terminal kinase 3	Kinase	0.111501865
Insulin-like growth factor I receptor	Kinase	0.111501865
Insulin receptor	Kinase	0.111501865
Phosphodiesterase 4B	Phosphodiesterase	0.111501865
Phosphodiesterase 7A	Phosphodiesterase	0.111501865
Fibroblast growth factor receptor 1	Kinase	0.111501865
Cyclin-dependent kinase 1/cyclin B	Other cytosolic protein	0.111501865
Dual-specificity tyrosine-phosphorylation regulated kinase 1A (by homology)	Kinase	0.111501865
Arachidonate 5-lipoxygenase	Oxidoreductase	0.111501865
Tyrosine-protein kinase SRC	Kinase	0.111501865
Signal transducer and activator of transcription 5B	Transcription factor	0.111501865
Epidermal growth factor receptor erbB1	Kinase	0.111501865
Inosine-5′-monophosphate dehydrogenase 2	Oxidoreductase	0.111501865
SUMO-activating enzyme	Enzyme	0.111501865
Anandamide amidohydrolase	Enzyme	0.111501865
Hydroxycarboxylic acid receptor 2	Family A G protein-coupled receptor	0.111501865
Induced myeloid leukemia cell differentiation protein Mcl-1	Other cytosolic protein	0.111501865
Sodium channel protein type V alpha subunit	Voltage-gated ion channel	0.111501865
Long-chain fatty acid transport protein 1	Electrochemical transporter	0.111501865
Alpha-1d adrenergic receptor	Family A G protein-coupled receptor	0.111501865
Alpha-1a adrenergic receptor	Family A G protein-coupled receptor	0.111501865
Tyrosine-protein kinase SYK	Kinase	0.111501865
Serine/threonine-protein kinase PLK1	Kinase	0.111501865
Serine/threonine-protein kinase PLK2	Kinase	0.111501865
Cholecystokinin A receptor	Family A G protein-coupled receptor	0.111501865

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C5a anaphylatoxin chemotactic receptor	Family A G protein-coupled receptor	0.111501865
Cholecystokinin B receptor	Family A G protein-coupled receptor	0.111501865
Potassium channel subfamily K member 3	Voltage-gated ion channel	0.111501865
Potassium channel subfamily K member 9	Voltage-gated ion channel	0.111501865
Peroxisome proliferator-activated receptor gamma	Nuclear receptor	0.111501865
Estrogen receptor beta	Nuclear receptor	0.111501865
Tumor necrosis factor receptor R1	Membrane receptor	0.111501865
Nuclear receptor subfamily 4 group A member 1	Nuclear receptor	0.111501865
Platelet activating factor receptor	Family A G protein-coupled receptor	0.111501865
ADAMTS5	Protease	0.111501865
Serotonin transporter	Electrochemical transporter	0.111501865
ADAMTS4	Protease	0.111501865
Leukocyte elastase	Protease	0.111501865

Group 7. Thiazolidinediones and Target Predictions with Artificial Intelligence. This class of antidiabetic agents increases insulin sensitivity by acting on adipose, muscle and liver, in a lesser extent, to increase glucose utilization and decrease glucose production. Two thiazolidinediones are currently available (59.8% to 66.5% main target prediction).

Rosiglitazone

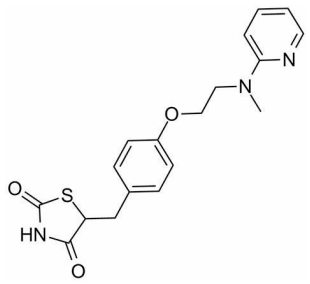

Table 20. Rosiglitazone.

Target	Target Class	Probability*
Peroxisome proliferator-activated receptor gamma	Nuclear receptor	1
Thromboxane-A synthase	Cytochrome P450	0.843606914
Monoamine oxidase B	Oxidoreductase	0.843606914
Carbonic anhydrase II	Lyase	0.843606914
Type-1 angiotensin II receptor (by homology)	Family A G protein-coupled receptor	0.843606914
Peroxisome proliferator-activated receptor alpha	Nuclear receptor	0.843606914
Peroxisome proliferator-activated receptor delta	Nuclear receptor	0.843606914
Bile salt export pump	Primary active transporter	0.843606914

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Free fatty acid receptor 1	Family A G protein-coupled receptor	0.097239989
15-hydroxyprostaglandin dehydrogenase [NAD+]	Enzyme	0.097239989
Matrix metalloproteinase 8	Protease	0.097239989
Phospholipase A2 group IIA	Enzyme	0.097239989
Macrophage colony stimulating factor receptor	Kinase	0.097239989
Matrix metalloproteinase 3	Protease	0.097239989
Glucocorticoid receptor	Nuclear receptor	0.097239989
Tyrosine-protein kinase LCK	Kinase	0.097239989
Ileal bile acid transporter	Electrochemical transporter	0.097239989
Prostanoid DP receptor	Family A G protein-coupled receptor	0.097239989
Cyclin-dependent kinase 9	Kinase	0.097239989
Calpain 1	Protease	0.097239989
Calpain 2	Protease	0.097239989
MAP kinase p38 alpha	Kinase	0.097239989
Methionyl-tRNA synthetase	Enzyme	0.097239989
Dihydroorotate dehydrogenase	Oxidoreductase	0.097239989
Endothelin receptor ET-A	Family A G protein-coupled receptor	0.097239989
Epoxide hydratase	Protease	0.097239989
Hydroxycarboxylic acid receptor 2	Family A G protein-coupled receptor	0.097239989
Lysine-specific demethylase 4C	Eraser	0.097239989
Protein-tyrosine phosphatase 1B	Phosphatase	0.097239989

Pioglitazone.HCl

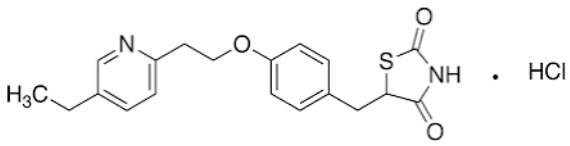

Table 21. Pioglitazone.HCl.

Target	Target Class	Probability*
Monoamine oxidase B	Oxidoreductase	0.938790203
Carbonic anhydrase II	Lyase	0.938790203
Peroxisome proliferator-activated receptor gamma	Nuclear receptor	0.938790203
Peroxisome proliferator-activated receptor alpha	Nuclear receptor	0.938790203
Bile salt export pump	Primary active transporter	0.938790203
Thromboxane-A synthase	Cytochrome P450	0.097239989
Type-1 angiotensin II receptor (by homology)	Family A G protein-coupled receptor	0.097239989
Peroxisome proliferator-activated receptor delta	Nuclear receptor	0.097239989

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15-hydroxyprostaglandin dehydrogenase [NAD+]	Enzyme	0.097239989
Free fatty acid receptor 1	Family A G protein-coupled receptor	0.097239989
Macrophage colony stimulating factor receptor	Kinase	0.097239989
Vanilloid receptor	Voltage-gated ion channel	0.097239989
Dihydroorotate dehydrogenase	Oxidoreductase	0.097239989
Epoxide hydratase	Protease	0.097239989
Hexokinase type IV	Enzyme	0.097239989
Bombesin receptor subtype-3	Family A G protein-coupled receptor	0.097239989
Phosphodiesterase 10A (by homology)	Phosphodiesterase	0.097239989
Adenosine A3 receptor	Family A G protein-coupled receptor	0.097239989
Cyclin-dependent kinase 9	Kinase	0.097239989
Alpha-2b adrenergic receptor	Family A G protein-coupled receptor	0.097239989
Epidermal growth factor receptor erbB1	Kinase	0.097239989
Norepinephrine transporter	Electrochemical transporter	0.097239989
Glycogen synthase kinase-3 beta	Kinase	0.097239989
Induced myeloid leukemia cell differentiation protein Mcl-1	Other cytosolic protein	0.097239989
Adenosine A1 receptor	Family A G protein-coupled receptor	0.097239989
Tyrosine-protein kinase LCK	Kinase	0.097239989
Ileal bile acid transporter	Electrochemical transporter	0.097239989
Receptor protein-tyrosine kinase erbB-2	Kinase	0.097239989
Beta-3 adrenergic receptor	Family A G protein-coupled receptor	0.097239989
Cytochrome P450 3A4	Cytochrome P450	0.097239989
Phospholipase A2 group IIA	Enzyme	0.097239989
Cathepsin (V and K)	Protease	0.097239989
Cathepsin L	Protease	0.097239989
Aldo-keto-reductase family 1 member C3	Enzyme	0.097239989
Caspase-3	Protease	0.097239989
MAP kinase p38 alpha	Kinase	0.097239989
Caspase-6	Protease	0.097239989
Caspase-7	Protease	0.097239989
Caspase-8	Protease	0.097239989
Ghrelin receptor	Family A G protein-coupled receptor	0.097239989
Apoptosis regulator Bcl-X	Other ion channel	0.097239989
Apoptosis regulator Bcl-2	Other ion channel	0.097239989
Caspase-2	Protease	0.097239989

Molecules or natural substances in the body are target specific receptors on the surface of cells. It substances bind with the receptor on a cell and stimulate the receptor to perform its function, which is to produce or to inhibit a specific action in the cell. Antidiabetic agents can also target and bind

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with these receptors. Then this drugs act as agonists, stimulating the receptor in the same way that the body's natural substances do. Others act as antagonists, blocking the action of the natural substance on the receptor. Each type of receptor has many subtypes, and this antidiabetic drugs may act on one or several subtypes of receptors [33].

Expectance and Conclusions

Polypharmacy is widespread among older people with diabetes and exists evidence for an association between polypharmacy and many adverse outcomes, including adverse drug events and disability [34]. Doses of drugs in Elderly polypharmacy varies with ailments, age, sex and weight. With increasing age there is an increased prevalence of disease for which medication may be indicated and increased drug toxicity [35]. Drug toxicity in old age is influenced by changes in the quantity, affinity and responsiveness of drug targets, physiological reserve and response to injury. Drug-induced liver injury (DILI) is an important cause of hospitalization and of medication deregistration [36]. However, The World Health Organization (WHO) has listed 525 different drugs, that can lead to acute pancreatitis cases, as a medication side-effect [37].

Oral antidiabetic agents work in various ways to reduce blood sugar levels in people with type 2 diabetes. Some stimulate pancreatic insulin secretion, others improve the responsiveness of cells to insulin or prevent glucose production by the liver, while other groups inhibit or slow down glucose absorption after meals. However, previous experience has allowed us to formulate recommendations for the use of some groups of antidiabetic agents in diabetic patients. It is pertinent to highlight that it should not be forgotten that the selection of medications with high therapeutics effects and low cost is of paramount importance for patients that take medicine for a longer period and whose lives depend on it. This is an invaluable information for the maximization of antidiabetic agents for the benefit of the patients.

Declarations: Ethics approval and consent to participate: Not applicable

Consent for publication: As any identifiable information (image, face, name etc.) of participant is not revealed in the submission, for that Consent is not applicable.

Availability of data and material: All data generated or analyzed during this study are included in this published article. Besides, any additional data/files may be obtained from the corresponding author. Conflict of interests: The authors declare that there are no conflicts of interests.

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Authors' information: All participating authors are qualified as medical science researcher, recognized by the Health Ministry of Mexico.

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