Supplementary information

A computational study on role of 6-(hydroxymethyl)-3-[3,4,5-trihydroxy-6-[(3,4,5-trihydroxyoxan-2-yl)oxymethyl]oxan-2-yl]oxyoxane-2,4,5-triol in the regulation of blood glucose level

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Description of protein targets

DPP-IV, type II transmembrane serine protease, plays a major role in maintaining glucose homeostasis through two important incretins such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) (Aertgeerts et al., 2004; Semighini et al., 2011). GLP-1, stimulates the insulin biosynthesis and secretion, promotes the proliferation of pancreatic β cells, inhibits glucagon release, and delays gastric emptying (Meng et al., 2010), while GIP influence only on insulintropic effect. DPP-IV inactivates these incretins by cleaving GLP-1 (7-36) and GIP (1-42) to GLP-1 (9-36) and GIP (3-42), thereby increase the blood glucose level (Figure 3) (Pei et al., 2006). Inhibition of DPP-IV will help in the prolonging GLP-1 and GIP action for the treatment of type 2 diabetes.

PTP1B, a crucial modulator of tyrosine phosphorylation-dependent cellular events and expressed widely in insulin-sensitive tissues (Rao, Ramachandran, & Bajaj, 2006). The insulin signaling pathway plays a vital role in controlling glucose level through uptake of glucose into the peripheral tissues. In general, Insulin binds to the insulin receptor and invokes a cascade of phosphorylation events in the glucose uptake mechanism (G. Liu et al., 2003). The activation of the insulin receptor in insulin signaling pathway is reversed by PTP1B (Figure 3). It dephosphorylates phosphorylated tyrosine (Tyr(P)) residues in the kinase regulatory domain of the insulin receptor and act as a negative regulator of insulin signaling pathway that leads to reduced insulin sensitivity, glycemic control, and obesity (Ala, Gonneville, Hillman, Becker-Pasha, Wei, et al., 2006). Insulin resistance has been linked with the elevated level of PTP1B in muscle and adipose tissue (Pei et al., 2003). Inhibiting negative action of PTP1B has been recognized as the effective therapeutic approach to enhance insulin-stimulated glucose transport for the treatment of diabetes (Brandão, Hengge, & Johnson, 2010). Thus, PTP1B has been used as the effective target for the diabetes treatment.

PEPCK, a lyase family enzyme, involves in the metabolic pathway of gluconeogenesis. It catalyzes the first committed step in hepatic gluconeogenesis, where it converts oxaloacetate (OAA) into phosphoenolpyruvate and carbon dioxide. During fasting, glucagon, glucocorticoids, and catecholamines induce PEPCK expression, while glucose-induced insulin secretion inhibits the PEPCK expression upon feeding (Figure 3)

(Quinn & Yeagley, 2005). Normally gluconeogenesis maintains blood glucose levels during fasting; however, over expression of PEPCK leads to hyperglycemia in diabetic condition. PEPCK inhibitors control the blood glucose during diabetes. Thus, PEPCK has been considered as the potential therapeutic target for the treatment of diabetes (Foley et al., 2003).

GSK-3B is a negative regulator of many signaling pathways and implicated in pathological conditions such as diabetes and Alzheimer's disease (Coffman et al., 2011). Insulin stimulates the glycogen synthesis by inhibiting GSK-3B through PKB/AKT pathway that reduces the phosphorylation of glycogen synthase level for active conversation of glucose into glycogen (Figure 3) (Ali, Hoeflich, & Woodgett, 2001), while in diabetic condition inhibits the activity of glycogen synthase was found to be overexpressed (Shin et al., 2007). Thus, GSK-3B has been recognized as the target for diabetes, inhibiting GSK-3B represents a promising therapeutic approach for the treatment of diabetes and many other diseases.

GK is a member of hexokinase family which is predominantly expressed in the brain, pancreatic β -cells, liver, and gut. In pancreatic β -cells, it acts as the rate-limiting enzyme in glucose-stimulated insulin secretion in the pancreas and it is responsible for the phosphorylation of glucose during the conversion of glucose to glucose 6-phosphate in the first step of glucose utilization (Figure 3) (Cheruvallath et al., 2013; Hinklin et al., 2014). It serves as a glucose sensor in the maintenance of the plasma glucose homeostasis by enhancing insulin secretion from pancreatic β -cells and glucose metabolism in the liver. Therefore, activation of GK with a small molecule is promising therapeutic approach for the treatment of diabetes (Nishimura et al., 2009).

Figure S1. 2D interaction obtained through extra precision docking for SID 242078875 with DPP-IV (a), PTP1B (b), PEPCK (c), GSK-3B (d), and GK (e).

Figure S2. 2D interaction obtained through QPLD for SID 242078875 with DPP-IV (a), PTP1B (b), PEPCK (c), GSK-3B (d), and GK (e).

Figure S3. Comparison of docking scores of SID 242078875 with experimentally validated DPP-IV inhibitors (a), PTP1B inhibitors (b), PEPCK inhibitors (c), GSK-3B inhibitors (d), and GK agonists (e). The number in the graph represents the active compounds, which is mentioned in table S1-S5.

Figure S4. Total energy of molecular dynamics simulation system

Figure S5. Potential energy of molecular dynamics simulation system

Figure S6. Pressure of molecular dynamics simulation system

Figure S7. Temperature of molecular dynamics simulation system

Table S1: Potent DPP-IV inhibitors and the interacting residues of DPP-IV with respective compound.

Compound name	Hydrogen bond Interaction(s)	PDB IDs	IC ₅₀ (nM)	Re-docking Score	2D interaction diagram	Reference
Anagliptin	Glu205, Glu206, Tyr547	3WQH	3.3	-9.482		Watanabe et al., 2015
1-(cis-1-phenyl-4-{[(2E)-3-phenylprop-2-en-1-yl]oxy}cyclohexyl)methanamine	Glu205, Glu206, Tyr547	4N8D	11900	-5.294		Namoto et al., 2014

1-[cis-4-(aminomethyl)-4-(3-chlorophenyl) cyclohexyl]piperidin- 2-one	Glu205, Glu206, Tyr662	4N8E	20	-4.794		Namoto et al., 2014
(2R,3S,5R)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4- c]pyrazol-5(4H)-yl]-2-(2,4,5-trifluorophenyl)tetrahydro-2H-pyran-3-amine	Glu205, Glu206	4PNZ	1.6	-6.076		Biftu et al., 2014

4-(2,4,5-trifluorophenyl)butane-1,3-diamines	Glu205, Glu206	4J3J	31	-5.798		Zhu et al., 2013
2-[3-(aminomethyl)-4-(2,4-dichlorophenyl)- 2-methyl-5-oxo-5,7-dihydro-6H-pyrrolo[3,4- b]pyridin-6-yl]-N,N-dimethylacetamide	Glu205, Glu206, Tyr547, Ser630	4JH0	0.94	-6.536		Devasthale et al., 2013

3-(aminomethyl)-4-(2,4-dichlorophenyl)-6-(2-methoxyethyl)-2-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	Glu205, Glu206, Tyr547	4LKO	8.3	-5.418		Devasthale et al., 2013
{(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone	Glu205, Glu206	3VJK	0.37	-4.651		Yoshida et al., 2012

6-[(3s)-3-aminopiperidin-1-yl]-5-benzyl-4-oxo-3-(quinolin-4-ylmethyl)-4,5-dihydro-3h- pyrrolo[3,2-d]pyrimidine-7-carbonitrile	Glu205, Glu206, Tyr631	4A5S	4	-8.039		Sutton et al., 2012
7-amino-6-(aminomethyl)-5-(2-bromophenyl)- 1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)- dione	Glu205, Glu206, Tyr662, Tyr631, Tyr630	4G1F	17	-6.248		Lam et al., 2012

2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl- 2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzonitrile	Arg125, Glu205, Glu206, Ser630	3G0B	68	-4.637		Z. Zhang et al., 2011
7-(2-chlorobenzyl)-1,3-dimethyl-8-piperazin- 1-yl-3,7-dihydro-1H-purine-2,6-dione	Glu205, Glu206, Ser630	3G0C	2000	-4.807		Z. Zhang et al., 2011

2-({8-[(3R)-3-aminopiperidin-1-yl]-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7h-purin-7-yl}methyl)benzonitrile	Arg125, Glu205, Glu206, Ser630	3G0D	5	-5.863		Z. Zhang et al., 2011
2-({2-[(3R)-3-aminopiperidin-1-yl]-5-bromo-6-oxopyrimidin-1(6H)-yl}methyl)benzonitrile	Arg125, Glu205, Glu206, Ser630	3G0G	5	-4.624		Z. Zhang et al., 2011

[5-(aminomethyl)-6-(2,2-dimethylpropyl)-2-ethyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid	Arg125, Glu205, Glu206, Tyr547, Ser630, Tyr662, His740,	3O95	5.3	-6.317		Miyamoto et al., 2011
5-(aminomethyl)-2-methyl-4-(4-methylphenyl)- 6-(2-methylpropyl)pyridine-3-carboxic acid	Glu205, Glu206, Tyr547, Ser630, Tyr662	3O9V	18	-6.318		Miyamoto et al., 2011

2- {[3-(aminomethyl)-2-(2-methylpropyl)-1-oxo-4-phenyl-1,2-dihydroisoquinolin-6-yl]oxy}acetamide	Glu205, Glu206, Trp629, Tyr662	3OPM	240	-6.881		Banno et al., 2011
3-(aminomethyl)-4-(2,4-dichlorophenyl)-6-(2-methoxyethyl)-2-methyl-5,6-dihydro-7H-pyrrolo[3,4-b]pyridin-7-one	Glu205, Glu206	3SWW	4	-4.067		Wang et al., 2011

Alogliptin	Glu205, Tyr631	2ONC	13	-6.066		Feng et al., 2007
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<p>4-bromo-3-(carboxymethoxy)-5-{3-[cyclohexyl(methylcarbamoyl)amino]phenyl}thiophene-2-carboxylic acid</p>	<p>Lys120, Phe182, Arg221, Gln266</p>	<p>2ZMM</p>	<p>25</p>	<p>-9.011</p>		<p>Wan et al., 2008</p>
<p>4-bromo-3-(carboxymethoxy)-5-{3-[cyclohexyl(phenylcarbonyl)amino]phenyl}thiophene-2-carboxylic acid</p>	<p>Lys120, Phe182, Arg221, Gln266</p>	<p>2ZN7</p>	<p>13</p>	<p>-11.952</p>		<p>Wan et al., 2008</p>

N-[(1S)-1-(4-benzyl-1H-imidazol-2-yl)-2-{4- [(5S)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenyl}ethyl]- 3-(trifluoromethyl)benzenesulfonamide	Tyr46, Asp48, Phe182, Ser216, Ala217, Ile219, Gly220, Gln266	2VEV	300	-6.358		Douty et al., 2008
N-[(1S)-2-{4-[(5S)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenyl}-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-3-(trifluoromethyl) benzenesulfonamide	Asp48, Lys120, Phe182, Cys215, Ser216, Ala217, Gly220, Arg221, Gln266	2VEU	100	-6.546		Douty et al., 2008
N-{(1S)-2-{4-[(5S)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenyl}-1-[(4R)-4-(2-phenylethyl)-4,5-dihydro-1H-imidazol-2-yl]ethyl}-3-fluorobenzenesulfonamide	Asp48, Phe182, Ser216, Ala217, Gly220, Gln266	2VEX	180	-5.928		Douty et al., 2008

N-{(1S)-2-{4-[(5S)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenyl}-1-[4-(3-phenylpropyl)-1H-imidazol-2-yl]ethyl}-3-fluorobenzenesulfonamide	Asp48, Phe182, Ser216, Ala217, Gly220, Gln266	2VEY	43	-8.059		Douty et al., 2008
{[5-(3-{[1-(benzylsulfonyl)piperidin-4-yl]amino}phenyl)-4-bromo-2-(2h-tetrazol-5-yl)-3-thienyl]oxy}acetic acid	Tyr46, Lys120, Phe182, Arg221,	2NT7	300	-12.466		Wan et al., 2007
4-bromo-3-(carboxymethoxy)-5-[3-(cyclohexylamino)phenyl]thiophene-2-carboxylic acid	Lys120, Phe182, Arg221, Gln266	2QBS	210	-8.354		Wilson et al., 2007

4-bromo-3-(carboxymethoxy)-5-{3-[(3,3,5,5-tetramethylcyclohexyl)amino]phenyl}thiophene-2-carboxylic acid	Lys120, Phe182, Arg221, Gln266	2QBQ	36	-10.506		Wilson et al., 2007
5-(3-{[1-(benzylsulfonyl)piperidin-4-yl]amino}phenyl)-4-bromo-3-(carboxymethoxy) thiophene-2-carboxylic acid	Lys120, Phe182, Arg221, Gln266	2QBP	4	-13.200		Wilson et al., 2007

5-[3-(benzylamino)phenyl]-4-bromo-3-(carboxymethoxy)thiophene-2-carboxylic acid	Lys120, Phe182, Arg221, Gln266	2QBR	470	-9.477		Wilson et al., 2007
(3R)-methylcarbamoyl-7-sulfoamino-3,4-dihydro- 1h-isoquinoline-2-carboxylic acid benzyl ester	Phe182, Ser216, Ala217, Gly220, Arg221	2F6V	37000	-6.935		Klopfenstein et al., 2006
(5S)-5-{4-[(2S)-2-(1H-benzimidazol-2-yl)-2-(1,3-benzothiazol-2-ylamino)ethyl]phenyl}isothiazolidin-3-one 1,1-dioxide	Asp48, Phe182, Ser216, Ala217, Gly220, Arg221, Gln266	2CNF	240	-4.623		Ala, Gonneville, Hillman, Becker-Pasha, Yue, et al., 2006

3-[3-(3(S)-methylcarbamoyl-7-sulfoamino-3,4,- dihydro-1h-isoquinolin-2-yl)-3-oxo-propyl]- benzoic acid	Phe182, Ser216, Ala217, Gly220, Arg221, Arg254	2F71	2500	-10.625		Klopfenstein et al., 2006
4-bromo-3-(carboxymethoxy)-5-(4-hydroxyphenyl)thiophene- 2-carboxylic acid	Asp48, Lys120, Phe182, Arg221, Gln266	2H4G	300	-11.288		Wan et al., 2006
4-bromo-3-(carboxymethoxy)-5-phenylthiophene- 2-carboxylic acid	Lys120, Phe182, Arg221, Gln266	2H4K	3200	-11.214		Wan et al., 2006

4-bromo-3-(carboxymethoxy)thiophene-2-carboxylic acid	Lys120, Phe182, Arg221, Gln266	2HB1	160000	-10.411		Wan et al., 2006
6- {[1-(benzylsulfonyl)piperidin-4-yl]amino}- 3-(carboxymethoxy)thieno[3,2-b][1]benzothiophene- 2-carboxylic acid	Phe182, Lys120, Arg221, Gln266	2B07	370	-11.617		Moretto et al., 2006
Methyl 2- {[5-({3-chloro-4-[(5s)-1,1-dioxido-3-oxo-1,2,4-thiazolidin-5-yl]-n-(phenylsulfonyl)-1-phenylalanyl}amino)pentyl]oxy}-6-hydroxybenzoate	Arg24, Asp48, Phe182, Ser216, Ala217, Ile219, Gly220, Arg221, Gln262, Arg254, Gln266	2CNI	21	-8.863		Ala, Gonneville, Hillman, Becker-Pasha, Yue, et al., 2006

N-({4-[difluoro(phosphono)methyl]phenyl}acetyl)-1-phenylalanyl-4-[difluoro(phosphono)methyl]-1-phenylalaninamide	Arg47, Asp48, Cys215, Ser216, Ala217, Ile219, Gly220, Arg221, Gln266	2CNE	1.7	-9.989		Ala, Gonneville, Hillman, Becker-Pasha, Yue, et al., 2006
N-[(1S)-1-(1H-benzimidazol-2-yl)-2-{4-[(5s)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenyl}ethyl]-4-methyl-3,4-dihydro-2h-1,4-benzoxazine-7- sulfonamide	Asp48, Phe182, Ser216, Ala217, Ile219, Gly220, Gln266	2CNH	59	-6.797		Ala, Gonneville, Hillman, Becker-Pasha, Yue, et al., 2006

N-{(1S)-2-{4-[(5R)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenyl}-1-[5-(trifluoromethyl)-1h-benzimidazol-2-yl]ethyl}-2,2,2-trifluoroacetamide	Asp48, Phe182, Ser216, Ala217, Gly220, Gln266	2CNG	110	-5.883		Ala, Gonneville, Hillman, Becker-Pasha, Yue, et al., 2006
N-acetyl-l-phenylalanyl-4-[difluoro(phosphono)methyl]-l-phenylalaninamide	Asp48, Phe182, Cys215, Ser216, Als217, Ile219, Gly220	2CMC	1750	-10.584		Ala, Gonneville, Hillman, Becker-Pasha, Yue, et al., 2006

[[4-(aminomethyl)phenyl]amino]oxo-acetic acid	Ser216, Gly220, Arg221	1WAX	86000	-13.417		Hartshorn et al., 2005
1,2,5-thiadiazolidin-3-one-1,1-dioxide	Phe182, Cys215 Ser216, Ala217, Ile219, Gly220, Gln266	2BGE	2470	-4.957		Black et al., 2005

Table S3: Potent PEPCK inhibitors and the interacting residues of PEPCK with respective compound.

Compound name	Hydrogen bond Interaction(s)	PDB IDs	IC ₅₀ (nM)	Re-docking Score	2D interaction diagram	Reference
N-(4-{[3-butyl-1-(2-fluorobenzyl)-2,6-dioxo- 2,3,6,7-tetrahydro-1h-purin-8-yl]methyl}phenyl)- 1-methyl-1h-imidazole-4-sulfonamide	Asn292, Phe517, Phe530, Asn533	2GMV	630	-11.247		Pietranico et al., 2007
N-[4-(1-allyl-3-butyl-2,6-dioxo-2,3,6,7-tetrahydro- 1h-purin-8-ylmethyl)-phenyl]-acetamide	Asn292, Phe517, Phe530, Asn533	1M51	18200	-8.281		Foley et al., 2003

<p>N-{4-[1-(2-fluorobenzyl)-3-butyl-2,6-dioxo- 2,3,6,7-tetrahydro-1h-purin-8-ylmethyl]-phenyl}- acetamide</p>	<p>Asn292, Phe530, Asn533</p>	<p>1NHX</p>	<p>2110</p>	<p>-5.835</p>		<p>Foley et al., 2003</p>
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Table S4: Potent GSK-3B inhibitors and the interacting residues of GSK-3B with respective compound.

Compound name	Hydrogen bond Interaction(s)	PDB IDs	IC ₅₀ (nM)	Re-docking Score	2D interaction diagram	Reference
2-{2-[(cyclopropylcarbonyl)amino]pyridin-4-yl}-4-methoxypyrimidine-5-carboxamide	Lys85, Val135	4PTG	5.9	-10.434		Sivaprakasam et al., 2015

2-{2-[(cyclopropylcarbonyl)amino]pyridin-4-yl}-4-oxo-4H-1lambda~4~,3-thiazole-5-carboxamide	Lys85, Val135	4PTC	1.1	-9.176		Sivaprakasam et al., 2015
N-[4-(isoquinolin-7-yl)pyridin-2-yl]cyclopropanecarboxamide	Lys85, Val135	4PTE	74	-10.012		Sivaprakasam et al., 2015

3,6-Diamino-4-(2-chlorophenyl)thieno[2,3- b]pyridine-2,5-dicarbonitrile	Val135. Asp200	3ZDI	13	-5.538		Fugel et al., 2013
6-chloro-N-cyclohexyl-4-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-amine	Asp133, Val135	4IQ6	0.9	-9.301		Fugel et al., 2013

(5Z)-5-(1,3-benzodioxol-5-ylmethylidene)-3-methyl-2-(propan-2-ylamino)imidazol-4-one	Lys85, Val135	4B7T	380	-7.637		Tahtouh et al., 2012
2-amino-5-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-n-[4-(pyrrolidin-1-ylmethyl)pyridin-3-yl]pyridine-3-carboxamide	Lys85, Val135	4ACG	22	-9.258		Berg et al., 2012
3-amino-6-(4-{[2-(dimethylamino)ethyl]sulfamoyl}phenyl)-n-pyridin-3-ylpyrazine-2-carboxamide	Lys85, Val135	4ACC	220	-7.050		Berg et al., 2012

3-amino-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-n-pyridin-3-ylpyrazine-2-carboxamide	Lys85, Val135	4ACD	20	-6.435		Berg et al., 2012
5-(4-methoxyphenyl)-n-(pyridin-4-ylmethyl)-1,3-oxazole-4-carboxamide	Val135	4AFJ	7.1	-8.053		Gentile et al., 2012

2-(4-pyridinyl)furo[3,2-c]pyridin-4(5h)-one	Lys85, Val135	3ZRK	6.9	-7.555		Gentile et al., 2012
4-(4-hydroxy-3-methylphenyl)-6-phenylpyrimidin-2(5H)-one	Lys85, Asp133, Val135	3Q3B	17.2	-7.605		Coffman et al., 2011

7-(4-hydroxyphenyl)-2-pyridin-4-yl-5h-thieno[3,2-c]pyridin-4-one	Lys85, Val135	3ZRM	6.9	-7.418		Gentile et al., 2011
7-bromo-2-pyridin-4-yl-5h-thieno[3,2-c]pyridin-4-one	Lys85, Val135	3ZRL	6.8	-7.309		Gentile et al., 2011

Ruthenium pyridocarbazole	Asp133, Val135	3M1S	1.0	-1.587		Atila-Gokcumen, Di Costanzo, & Meggers, 2011
(4E)-4-[(4-chlorophenyl)hydrazono]-5-(3,4-dimethoxyphenyl)-2,4-dihydro-3H-pyrazol-3-one	Asp133, Val135, Asp200	3L1S	2	-8.568		Arnost et al., 2010

2-(1,3-benzodioxol-5-yl)-5-[(3-fluoro-4-methoxybenzyl)sulfanyl]-1,3,4-oxadiazole	Phe67, Val135	3F7Z	65	-8.412		Saitoh, Kunitomo, Kimura, Hayase, et al., 2009
2-methyl-5-(3-{4-[(S)-methylsulfinyl]phenyl}-1-benzofuran-5-yl)-1,3,4-oxadiazole	Lys85	3GB2	35	-6.688		Saitoh, Kunitomo, Kimura, Hayase, et al., 2009

5-[1-(4-methoxyphenyl)-1H-benzimidazol-6-yl]-1,3,4-oxadiazole-2(3H)-thione	Val135	3F88	2.3	-8.222		Saitoh, Kunitomo, Kimura, Hayase, et al., 2009
N-[(1S)-2-hydroxy-1-phenylethyl]-4-[5-methyl-2-(phenylamino)pyrimidin-4-yl]-1H-pyrrole-2-carboxamide	Lys85, Val135, Asp200	2X39	7	-10.238		Aronov et al., 2009

Ruthenium pyridocarbazole

Asp133, Val135

2JLD

180

-5.004

Atila-Gokcumen et al., 2008

2-(2,4-dichloro-phenyl)-7-hydroxy-1h-benzimidazole-4-carboxylic acid [2-(4-methanesulfonylamino-phenyl)-ethyl]-amide	Asp133, Val135, Gln185, Arg220	2O5K	15	-7.943		Shin et al., 2007
Bis-(indole)maleimide pyridinophane	Val135	2OW3	3	-10.626		H.-C. Zhang et al., 2007

(Z)-1h,1'h-[2,3]biindolylidene-3,2'-dione- 3-oxime	Asp133, Val135	1Q41	22	-10.369		Bertrand et al., 2003
2-chloro-5-[4-(3-chloro-phenyl)-2,5-dioxo-2,5-dihydro-1h-pyrrol-3-ylamino]-benzoic acid	Asp133, Val135, Arg141, Gln185	1Q4L	160	-11.792		Bertrand et al., 2003

6-bromoindirubin-3'-oxime	Asp133, Val135	1UV5	17	-10.754		Meijer et al., 2003
9-nitro-5,12-dihydro-7h-benzo[2,3] azepino[4,5-b]indol-6-one	Gln185, Val135	1Q3W	4	-8.460		Bertrand et al., 2003

N-(4-methoxybenzyl)-n'-(5-nitro-1,3-thiazol-2-yl)urea	Val135, Pro136, Arg141	1Q5K	104	-7.137		Bhat et al., 2003
Phosphoaminophosphonic acid-adenylate ester	Lys85, Lys183, Gln185, Val135	1PYX	15	-7.055		Bertrand et al., 2003

Staurosporine	Asp133, Val135	1Q3D	15	-7.978		Bertrand et al., 2003
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Table S5: Potent GK agonists and the interacting residues of GK with respective compound.

Compound name	Hydrogen bond Interaction(s)	PDB IDs	EC ₅₀ (nM)	Re-docking Score	2D interaction diagram	Reference
1-{3-[(2-ethylpyridin-3-yl)oxy]-5-(pyridin-2-ylsulfanyl)pyridin-2-yl}-3-methylurea	Arg63, Tyr214	4RCH	88	-5.395		Hinklin et al., 2014
(2S)-3-cyclohexyl-2-(6-fluoro-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-N-(1,3-thiazol-2-yl)propanamide	Arg63, Tyr99	4ISF	30	-12.569		Cheruvallath et al., 2013

(2S)-3-cyclohexyl-2-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-N-(1,3-thiazol-2-yl)propanamide	Arg63, Tyr99, Tyr214	4ISE	4000	-11.432		Cheruvallath et al., 2013
(2S)-3-cyclohexyl-2-[4-(methylsulfonyl)-2-oxopiperazin-1-yl]-N-(1,3-thiazol-2-yl)propanamide	Arg63, Tyr214	4ISG	1600	-11.339		Cheruvallath et al., 2013

3-(benzyloxy)-5-methyl-N-(4-methyl-1,3-thiazol-2-yl)pyridin-2-amine	Arg63, Tyr214	4MLH	2640	-10.037		Hinklin et al., 2013
3-(benzyloxy)-N-(4-methyl-1,3-thiazol-2-yl)pyridin-2-amine	Arg63, Tyr214	4MLE	4940	-5.491		Hinklin et al., 2013

(2S)-3-cyclopentyl-N-(5-methylpyridin-2-yl)-2-[2-oxo-4-(trifluoromethyl) pyridin-1(2H)- yl]propanamide	Arg63	3VEV	691	-12.109		Liu et al., 2012
6-({(2S)-3-cyclopentyl-2-[4-(trifluoromethyl)- 1H-imidazol-1-yl]propanoyl} amino)pyridine- 3-carboxylic acid	Arg63	3VF6	92	-12.357		Liu et al., 2012

N,N-dimethyl-5-({2-methyl-6-[(5-methylpyrazin- 2-yl)carbamoyl]-1-benzofuran-4-yl}oxy)pyrimidine- 2-carboxamide	Arg63	4DHY	172	-9.577		Liu et al., 2012
(2R)-3-cyclopentyl-N-(5-methoxy[1,3]thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(4-methylpiperazin- 1-yl)sulfonyl]phenyl}propanamide	Arg63, Ser69	3IMX	39	-14.755		Bebernitz et al., 2009

1-({5-[4-(methylsulfonyl)phenoxy]-2-pyridin- 2-yl-1H-benzimidazol-6-yl}methyl)pyrrolidine- 2,5-dione	Arg63, Gln98	3H1V	160	-9.222		Takahashi et al., 2009
2-(methylamino)-N-(4-methyl-1,3-thiazol-2- yl)-5-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]benzamide	Arg63	3GOI	250	-10.051		Mitsuya et al., 2009

2-amino-N-(4-methyl-1,3-thiazol-2-yl)-5-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]benzamide	Arg63, Tyr214, Tyr215	3FR0	140	-11.121		Nishimura et al., 2009
3-[(4-fluorophenyl)sulfanyl]-N-(4-methyl-1,3-thiazol-2-yl)-6-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]pyridine-2-carboxamide	Arg63	3A0I	1070	-9.864		Mitsuya et al., 2009

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