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Targeted Trigonelline Derivatives as Anti-Diabetic Agents: In-Silico Evaluation of Drug-Likeness, Safety and Efficacy

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ABSTRACT

One of the most common metabolic disorders worldwide today is Type 2 diabetes mellitus. It is characterized by symptoms as a recognizable cause of metabolic distress, symptom and pathology. It is thought to be a heterogeneous and progressive group of disorder in which beta cell dysfunction is accompanied by lactic acidosis representing a number of metabolic pathways implicated in insulin metabolism and associated with cardiovascular pathophysiology. A high rate of diabetes-related mortality and morbidity is associated with it. Fenugreek, a spice, has been extensively used as an antidiabetic and hypolipidemic agent. It has also been used to treat diabetic complications, central nervous system (CNS) and cardiovascular (CVS) disorders. The pharmacological properties and mechanisms of a major alkaloid component of fenugreek- Trigonelline, have been thoroughly evaluated, especially with regard to its pharmacokinetics and toxicity. The present insilico study using CADD was designed to evaluate the useful effects of trigonelline hybrids against T2DM. Several amino acid derivatives of trigonelline were made and computational tools like Swiss ADME, Discovery studio Biovia and PyRx were used to evaluate the derivatives for binding affinity to key diabetic targets, drug likeness, ADME properties and potential off target effects. These findings paved the path for more preclinical and clinical research by indicating a final list of potent trigonelline-based compounds with promising anti-diabetic qualities. These results highlight trigonelline derivatives' potential as a new class of antidiabetic drugs and highlight the value of insilico approaches in the drug discovery process for complicated conditions like type 2 diabetes.

Keywords: *T2DM, Trigonelline, insilico study, CADD, computational tools, antidiabetic*

INTRODUCTION

Diabetes mellitus is a metabolic disorder chronic in nature. It is characterized by elevated blood glucose levels due to defects in insulin secretion or insulin action or both. The two primary forms are Type 1 diabetes mellitus (T1DM) which is caused due to autoimmune destruction of pancreatic β-cells, and Type 2 diabetes mellitus (T2DM), which is associated with resistance of insulin and relative insulin deficiency. [1]

Classification:

Diabetes is categorized into several types based on its etiology and pathophysiology, the most common being- Type 1 diabetes (T1DM), Type 2 diabetes (T2DM) and gestational diabetes mellitus (GDM). There are also rarer forms, including monogenic diabetes and secondary diabetes.

1. **Type 1 diabetes mellitus.** An autoimmune disease in which blood glucose levels are abnormally elevated due to destruction of the pancreatic insulin-secreting β-cells, leading to absolute insulin deficiency and a requirement for lifelong insulin treatment is known as T1DM. T1DM is typically identified in children and young adults, although it can occur at any age. The cause of T1DM is not exactly known, but it is assumed that genetic susceptibility, environmental influences like viral infections, and autoimmune triggers may lead to the disease. It contributes to just some 5-10% of the total cases of diabetes. The main characteristics constitute its mild onset, easy loss of weight,polydipsia, polyuria and continued elevation of blood sugar(hyperglycemia). Without insulin treatment it may progress on to lead to complications as diabetic ketoacidosis (DKA).
2. **Type 2 diabetes mellitus.** More than 90% of all cases of diabetes are accounted to Be T2DM. It is characterized chiefly by a combination of insulin resistance and a relative deficiency of insulin secretion. While T1DM is more acute in nature, T2DM generally has an insidious onset and is strongly associated with lifestyle changes, obesity, lack of exercise, and some degree of unhealthy eating habits.The pathophysiology of T2DM is combined with several environmental and genetic factors that lead to a gradual onset of β-cell dysfunction. The early stage of the disease is often asymptomatic, which makes timely diagnosis and management difficult. Microvascular

complications like retinopathy, nephropathy, neuropathy and macrovascular complications like cardiovascular diseases can gradually be caused due to chronic hyperglycemia. Prevention strategies include lifestyle changes to keep a healthy weight, the promotion of regular physical activity, and balanced nutrition. All these will go a long way in curbing the growth of T2DM globally. [4,5,6]

3. **Gestational Diabetes Mellitus (GDM).** A transitory form of diabetes arising in pregnant women is known as GDM. These women do not have a previous history of diabetes. It occurs because of hormonal changes that make one insulin ineffective combined with inadequate response in insulin secretions. Dangers such as preeclampsia, macrosomia and an increased risk of T2DM later in life are possessed for both the mother and fetus. Early screening and management-rechanges, physical activity, and at times, insulin therapy-emphasize a lower risk for complications. [7,8]
4. **Monogenic Diabetes:**
   1. Monogenic includes MODY and is characterized by certain atypical mutations in single genes that affect insulin production and/or function. Rare in occurrence, and often classified under T1DM or T2DM, they have a distinct genetic and clinical aspect.[9]
5. **Secondary Diabetes**:
   2. This form of the disease manifests either because of other coexisting conditions that can have effects on diabetes or due to other conditions such as pancreatic diseases (e.g., pancreatitis), endocrinopathies (e.g., Cushing's syndrome), or the application of certain specific drugs (e.g., glucocorticoids). [10]

With an estimated 382 million individuals affected in 2013, the global prevalence of diabetes has reached pandemic proportions, a number projected to exceed 590 million by 2035.[11] According to WHO this surge is largely attributed to lifestyle factors such as poor diet and physical inactivity, leading to increased obesity rates. The prevalence of diabetes in low- and middle-income countries is seen to be increasing more rapidly than in high-income countries.

Pathophysiology of Diabetes:
All pathophysiological mechanisms that form the basis of any effective therapeutic treatment and management approaches are included in the study of diabetes.

Normal Glucose Homeostasis:
Insulin and glucagon, secreted by the pancreas help regulate the blood glucose levels in healthy individuals by maintaining a balance. Insulin production occurs mainly from β-cells of islets of Langerhans. This hormone allows for cellular uptake of glucose, promotes hepatic glycogen synthesis, and inhibits gluconeogenesis and lipolysis. Opposing it, glucagon produced by the α cells supports glucose manufacture by the liver in fasting states. Disturbances of this balance result in hyperglycemia, the hallmark feature of diabetes.[12]

Pathophysiology of type 1 diabetes mellitus:
T1DM types involves the destruction of the pancreatic β-cells causing absolute deficiency of insulin representing one of the autoimmune processes.

1. Autoimmune Mechanisms: The immune system itself mistakenly believes it is killing the β-cells; this is mediated by cell-mediated immunity, with the central role later being attributed to T-cells. There are autoantibodies that can be routinely tested for in patients, the most relevant ones being those against glutamic acid decarboxylase (GAD65) and more recently insulin.[13]
2. Loss of Insulin Secretion: The destruction of β-cells prevents insulin production, causing glucose to build up in the blood. The result is osmotic diuresis, dehydration, and electrolyte balance disturbance.[14]
3. Ketogenesis and Ketoacidosis: Without insulin, lipolysis is improperly controlled, which dramatically raises free fatty acid release and fosters the production of ketone bodies in the liver. Excessive quantities of ketone bodies lead to the molecular form of diabetic emergency, the diabetic ketoacidosis (DKA).[15]

Pathophysiology of type 2 diabetes mellitus:
Type 2 diabetes mellitus is caused due to insulin resistance and reduction in β-cell function, being most often determined by genetic and environmental factors.

1. Insulin Resistance: Factors like obesity, inflammation and lipotoxicity contribute to high resistance in peripheral tissues, like skeletal muscle, adipose tissue and liver where the cells fail to adequately respond to insulin.
2. Obesity and inflammation: Pro-inflammatory cytokines as TNF-α and IL-6 are secreted by adipose tissue whereas it down-regulates adiponectin secretion impairing insulin signal transduction pathways.
3. Ectopic fat deposition: Lipid accretion in the liver and pancreas non adipose tissues aggravates the state of resistance of insulin and impairment in β-cell activity.
4. β-cell dysfunction: Protracted insulin resistance results in hyperinsulinemia, which in turn exerts stress on β-cells. With the passage of time, their ability to compensate breaks down and they fail to secrete sufficient insulin in relation to glucose levels.

5. Hepatic glucose overproduction: Insulin resistance in the liver allows for unapplied gluconeogenesis and glycogenolysis, further contributing to hyperglycemia. [16]

Pathophysiology of Gestational Diabetes Mellitus (GDM):
Gestational diabetes mellitus occurs due to hormonal changes that, occur during pregnancy leading to increase in insulin resistance.

3. Placental Hormones: It includes the human placental lactogen, progesterone, and cortisol, which interfere with insulin action and increase blood glucose values.
4. Compensatory β-Cell Function: Most often, β-cell function working in a compensatory way will increase the level of secretion of insulin, counteracting insulin resistance. However, if this compensation fails, GDM develops.
5. Maternal and Fetal Complications: Raised maternal glucose crosses the placenta, resulting in fetal hyperinsulinemia, macrosomia, and increased risk for neonatal hypoglycemia [17]

Complications Arising from Diabetes Pathophysiology:
Severe complications, including cardiovascular diseases, neuropathy, nephropathy, and retinopathy, significantly contributing to global morbidity and mortality are associated with diabetes.[18]
Hyperglycemia in diabetes is responsible for inducing a series of complications via multiple mechanisms such as:

1. Experimental evidence from various studies showed that continuous exposure of the tissues to high glucose permits polyols (such as sorbitol) to build up. Sorbitol accumulation could lead to oxidative stress and eventual development of complications, including neuropathy.
2. AGEs, which damage proteins, lipids, and DNA are formed due to Chronic hyperglycemia which leads to the further worsening of vascular and tissue injury.
3. Through hyperglycemia such as factors affecting PKC, vascular function is impaired, leading to inflammation, thrombosis, and angiogenesis.

Despite the availability of different pharmacological treatments, attaining and sustaining glucose levels under control is a continuing challenge for many patients. These aspects are stimulating increasing interest in alternative and complementary therapies: one of the more sophisticated features of interest is the medicinal plants capable of antidiabetic properties. Herbal medicine has a long record of use for managing diabetes, primarily where access to standard treatments is not readily available. Medicinal plants continue to be excellent sources of bioactive compounds capable of modulating glucose metabolism through different pathways. Among the many antidiabetic plants are such notable examples as Gymnema sylvestre, Momordica charantia and Trigonella foenum-graecum that exhibit hypoglycemic and, in some cases, hypolipidemic effects in diabetic patients.[19]

The therapeutic potential of these herbal representatives is attributed to their various means, such as insulin secretion; insulin sensitivity induction; inhibition of carbohydrate digesting enzymes; regulation of glucose uptake in tissues. For example, bitter melon contains insulin-mimicking bioactive compounds that help in glucose uptake.[20] Similarly, Gymnema sylvestre has been shown to promote regeneration of pancreatic β-cells and inhibits glucose absorption into the intestine.[21]

Fenugreek (Trigonella foenum-graecum) is a medicinal plant widely cultivated in parts of Asia, North Africa, and the Mediterranean region. It has long been exploited for its therapeutic properties. Bioactive compounds like alkaloids, saponins, flavonoids, and amino acids that are attributed to its wide medicinal applications are found mainly in the seeds and leaves of fenugreek. Also, fenugreek may have demonstrated widely researched benefits regarding the management of diabetes.[22]

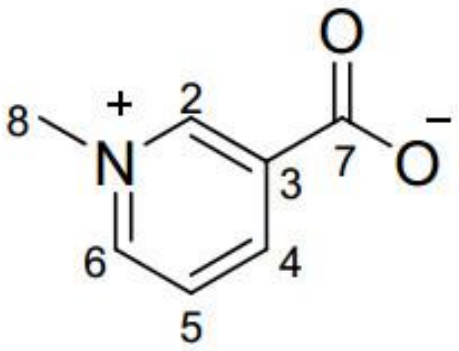
Role of fenugreek in treating diabetes:

- **HypoglycemicProperties:**Fenugreekseeds possess significant hypoglycemicactivityand thus hold great promise a s an emerging herbal remedy for diabetes. These effects can be largely due to their rich content of soluble dietary fibers, galactomannan, and bioactive compounds like trigonelline, 4-hydroxyisoleucine, and diosgenin
- **Anti-inflammatory and Antioxidant Effects:**The development of diabetes and its complications were triggered by chronic inflammation and oxidative stress. Fenugreek contains large amounts of flavonoids and polyphenolic compounds, leading to a reduction in oxidative damage and pro-inflammatory cytokine levels, improving insulin resistance and preserving β-cell function. [23,24]

Relevance of fenugreek in modern drug development:
Recent studies consider Fenugreek safe for ingestion, with negligible side effects associated with moderate use. Its low cost and easy availability make it even more attractive to low- and middle-income countries undergoing rapid diabetes exposition. The diverse phytochemical contents and better carbohydrate-lowering effect on diabetes make Fenugreek a leading candidate in search of novel therapeutic agents. The unique bioactive components of Fenugreek, most notably trigonelline, offer vast prospects for the explorative study of novel antidiabetic agents.

Trigonelline is a naturally occurring alkaloid principally found in fenugreek (*Trigonella foenum-graecum*), which has received considerable acclaim for its potential antidiabetic qualities. Through extensive research, trigonelline has been shown to ameliorate diabetes through various mechanisms, such as regulation of insulin release, decrease in oxidative stress, and enhancement of glucose tolerance and insulin sensitivity. [25,26]

Computer-assisted drug design (CADD) and molecular docking studies have come to play an important role in finding new antidiabetic agents. The use of these modern computational methods helps the identification and optimization of bioactive compounds through their interaction with certain biological targets. In the context of trigonelline derivatives, molecular docking studies were put to use to gain insight into the inhibitory actions of specific enzymes involved in glycogen metabolism and insulin signaling [27]. Considering the various antidiabetic effects of trigonelline itself, preparations and optimizations of its hybrids with a view toward improving potency and selectivity are gaining grounds with much interest. The modeling of interactions between trigonelline hybrids and different molecular targets in diabetes pathophysiology are facilitated by the pivotal role of Computational-Aided Drug Design and Molecular Docking studies. Such approaches minimize the time taken for drug development, additionally providing an insight into the structural requirements for optimal activity. This, alongside the integration of its natural antidiabetic properties with advanced computational techniques, has much potential in the development of novel therapeutic agents. The discoveries made through ongoing research in the development of trigonelline derivatives and with the assistance of CADD and docking studies may witness the discovery of diabetes treatment extensions. [28]. Trigonelline hybrids were thus designed by addition of amino acids at position 3 of trigonelline molecule. [29]



TRIGONELLINE

MATERIALS AND METHODS:

Potential Anti-Diabetic Compounds:

Due to its well-established antidiabetic properties, trigonelline was chosen as the study's lead compound. Using computational tools and techniques, a number of trigonelline amino acid hybrids were designed and analysed.

Ligand design Using ChemDraw 12.0 Software:

The chemical structures of trigonelline and its hybrids were designed and drawn using ChemDraw 12.0 software by attaching different amino acids. The software was used to generate two-dimensional (2D) structures for further computational analysis. [30]

Protein Target Data retrieval from RCSB.org:

The RCSB Protein Data Bank (PDB) (www.rcsb.org) was used to obtain the three-dimensional (3D) crystal structures of protein targets relevant to diabetes treatment. Specific protein target included dipeptidyl peptidase-4 (DPP-4). This target was selected based on its pivotal roles in glucose metabolism, insulin sensitivity and carbohydrate breakdown. The protein chosen in this case was **3et0**. [31,32]

Swiss ADME study:

The SwissADME tool (http://www.swissadme.ch/) was used to evaluate the pharmacokinetic properties of the designed trigonelline derivative ligands. Parameters analyzed included:

- **Drug likeness:** To assess drug-likeness by evaluating molecular weight, hydrogen bond donors/acceptors, and lipophilicity.
- **Absorption and Distribution:** Prediction of water solubility, gastrointestinal absorption and blood-brain barrier (BBB) permeability.
- **Pharmacokinetics:** Evaluation of cytochrome P450 enzyme interactions for metabolism predictions.

This analysis ensured that only ligands with favorable ADME properties were considered for further studies. [33]

ProTox Toxicity Study:
Toxicity predictions were carried out using the ProTox 3.0 [34]. The tool provided insights into the toxicological profile of the ligands, including:

- LD50 Values (Median Lethal Dose): Used to estimate acute toxicity levels.
- Toxicological Classifications: Identification of potential risks such as hepatotoxicity, mutagenicity and carcinogenicity.
- Toxicological Pathways**:** Mechanisms of adverse effects were analyzed to ensure the safety of the designed derivatives.

Adverse Drug Reactions Prediction by ADVER-PreD:
The ADVER-PreD tool was employed to predict potential adverse drug reactions (ADRs) associated with the ligands [35, 36] This analysis focused on:

- Identifying possible off-target effects that could lead to unwanted side effects.

Evaluating the safety profile of the compounds during early-stage drug design.

The data obtained helped prioritize ligands with minimal ADR risks for further docking and biological evaluations.

Prediction of biological activity by PASS Online:
The PASS Online tool (http://www.way2drug.com/passonline/) was used for the potential biological activity prediction of trigonelline derivatives. This tool provides a probability score (Pa and Pi) for various pharmacological effects. Ligands with high probabilities for antidiabetic activities and low probabilities for adverse effects were selected for docking studies.

Valuable insights were gained into the functional potential of the designed compounds. [37]

Preparation of protein by Biovia discovery studio:
Protein was prepared for further docking studies. Water molecules and other non-essential entities were removed during the protein preparation process to enhance docking accuracy Proteins were pre-processed by removing non-essential entities, adding hydrogen atoms and assigning charges.PDBQT format was used to store the ligands.[38]

Docking Simulation by PyRx- Open Babel software:
Molecular docking simulations were conducted using PyRx, an open-source virtual screening tool integrated with Open Babel for file format conversion.[39]. The workflow involved:

Docking Protocol:
Docking simulations were conducted to predictbinding affinities and interaction patterns of the ligands with the active sites of the target proteins.

Scoring Function: Binding affinities were assessed using AutoDock Vina's scoring function, where more negative docking scores indicated stronger binding.
This step helped identify compounds with the highest potential as inhibitors or activators of diabetes-related targets.

Visualization of Docked Molecules:
The analysis of docked complexes were carried out using BIOVIA Discovery Studio for a detailed interpretation of the interactions. High-affinity models were further examined to evaluate structural compatibility with the target proteins. Two-dimensional (2D) interaction diagrams were generated to illustrate the binding interactions, which provided a clear understanding of ligand-protein interactions. These visualizations were critical for validating the docking results and supporting the selection of lead compounds for further development.

RESULTS AND DISCUSSION:

Design of amino acid hybrids of the molecule:
Trigonelline-amino acid hybrid molecules were designed which are 20 in number as presented below in the table- Table 1

Table 1 (Trigonelline amino acid hybrids):

6. MOLECULE	7. IUPAC NAME	8. MOLECULE	9. IUPAC NAME
10. PPS 0	11. 1-methylpyridin-1-ium-3-carboxylate 12.	13. PPS 11	14. 3-((1-carboxy-3-methylbutyl)carbamoyl)-1-methylpyridin-1-ium
15. PPS 1	16. 3-((1-carboxyethyl)carbamoyl)-1-methylpyridin-1-ium	17. PPS 12	18. 3-((5-amino-1-carboxypentyl)carbamoyl)-1-methylpyridin-1-ium
19. PPS 2	20. 3-((1-carboxy-4-guanidinobutyl) 21. carbamoyl)-1-methyl pyridin-1-ium	22. PPS 13	23. 3-((1-carboxy-3-(methylthio)propyl)carbamoyl)-1-methylpyridin-1-ium
24. PPS 3	25. 3-((3-amino-1-carboxy-3-oxopropyl)carbamoyl)-1-methylpyridin-1-ium	26. PPS 14	27. 3-((1-carboxy-2-phenylethyl)carbamoyl)-1-methylpyridin-1-ium
28. PPS 4	29. 3-((1,2-dicarboxyethyl)carbamoyl)-1-methylpyridin-1-ium	30. PPS 15	31. 3-(2-carboxypyrrolidine-1-carbonyl)-1-methylpyridin-1-ium
32. PPS 5	33. 3-((1-carboxy-2-mercaptoethyl)carbamoyl)-1-methylpyridin-1-ium	34. PPS 16	35. 3-((1-carboxy-2-hydroxyethyl)carbamoyl)-1-methylpyridin-1-ium
36. PPS 6	37. 3-((1,3-dicarboxypropyl)carbamoyl)-1-methylpyridin-1-ium	38. PPS 17	39. 3-((1-carboxy-2-hydroxypropyl)carbamoyl)-1-methylpyridin-1-ium
40. PPS 7	41. 3-((4-amino-1-carboxy-4-oxobutyl)carbamoyl)-1-methylpyridin-1-ium	42. PPS 18	43. (S)-3-((1-carboxy-2-(1H-indol-3-yl)ethyl)carbamoyl)-1-methylpyridin-1-ium
44. PPS 8	45. 3-((carboxymethyl)carbamoyl)-1-methylpyridin-1-ium	46. PPS 19	47. 3-((1-carboxy-2-(4-hydroxyphenyl)ethyl)carbamoyl)-1-methylpyridin-1-ium
48. PPS 9	49. 3-((1-carboxy-2-(1H-imidazol-4-yl)ethyl)carbamoyl)-1-methylpyridin-1-ium	50. PPS 20	51. 3-((1-carboxy-2-methylpropyl)carbamoyl)-1-methylpyridin-1-ium
52. PPS 10	53. 3-((1-carboxy-2-methylbutyl)carbamoyl)-1-methylpyridin-1-ium	54.	55.

Physicochemical, Pharmacokinetics and Drug-Likeness Study:

Swiss ADME was used to determine the Physicochemical, Pharmacokinetics and Drug-Likeness properties of the hybrid molecules as shown in table 2,3 and 4 respectively.

Table 2 (Physicochemical Properties):

56. OLECULE	57. FORMULA	58. W	59. HEAVY ATOMS	60. AROMATIC HEAVY ATOMS	61. FRACTION CSP3	62. ROTATABLE BONDS	63. H-BOND ACCEPTORS	64. H-BOND DONORS	65. R	66. PSA
67. PS 0	68. C7H7NO2	69. 37.14	70. 10	71. 6	72. 0.14	73. 1	74. 2	75. 0	76. 5.05	77. 4.01
78. PS 1	79. C10H13N2O3+	80. 09.22	81. 15	82. 6	83. 0.3	84. 4	85. 3	86. 2	87. 4.42	88. 0.28
89. PS 2	90. C13H20N5O3+	91. 94.33	92. 21	93. 6	94. 0.38	95. 9	96. 4	97. 5	98. 7.94	99. 32.18
100. PS 3	101. C11H14N3O4+	102. 52.25	103. 18	104. 6	105. 0.27	106. 6	107. 4	108. 3	109. 2.13	110. 13.37
111. PS 4	112. C11H13N2O5+	113. 53.23	114. 18	115. 6	116. 0.27	117. 6	118. 5	119. 3	120. 0.99	121. 07.58
122. PS5	123. C10H13N2O3S+	124. 41.29	125. 16	126. 6	127. 0.3	128. 5	129. 3	130. 2	131. 2.34	132. 09.08
133. PS6	134. C12H15N2O5+	135. 67.26	136. 19	137. 6	138. 0.33	139. 7	140. 5	141. 3	142. 5.8	143. 07.58
144. PS7	145. C12H16N3O4+	146. 66.27	147. 19	148. 6	149. 0.33	150. 7	151. 4	152. 3	153. 6.94	154. 13.37

155. PS8	156. C9H11N2O3+	157. 95.2	158. 14	159. 6	160. 0.22	161. 4	162. 3	163. 2	164. 9.61	165. 0.28	
166. PS9	167. C13H15N4O3+	168. 75.28	169. 20	170. 11	171. 0.23	172. 6	173. 4	174. 3	175. 1.05	176. 8.96	
177. PS10	178. C13H15N4O3+	179. 75.28	180. 20	181. 11	182. 0.23	183. 6	184. 4	185. 3	186. 1.05	187. 8.96	
188. PS11	189. C13H19N2O3+	190. 51.3	191. 18	192. 6	193. 0.46	194. 6	195. 3	196. 2	197. 8.84	198. 0.28	
199. PS12	200. C13H20N3O3+	201. 66.32	202. 19	203. 6	204. 0.46	205. 8	206. 4	207. 3	208. 1.54	209. 6.3	
210. PS13	211. C12H17N2O3S+	212. 69.34	213. 18	214. 6	215. 0.42	216. 7	217. 3	218. 2	219. 1.62	220. 5.58	
221. PS14	222. C16H17N2O3+	223. 85.32	224. 21	225. 12	226. 0.19	227. 6	228. 3	229. 2	230. 8.9	231. 0.28	
232. PS15	233. C12H15N2O3+	234. 35.26	235. 17	236. 6	237. 0.42	238. 3	239. 3	240. 1	241. 5.92	242. 1.49	
243. PS16	244. C10H13N2O4+	245. 25.22	246. 16	247. 6	248. 0.3	249. 5	250. 4	251. 3	252. 5.58	253. 0.51	
254. PS17	255. C11H15N2O4+	256. 39.25	257. 17	258. 6	259. 0.36	260. 5	261. 4	262. 3	263. 0.38	264. 0.51	
265. PS18	266. C18H18N3O3+	267. 24.35	268. 24	269. 15	270. 0.17	271. 6	272. 3	273. 3	274. 0.76	275. 6.07	
276. PS19	277. C16H17N2O4+	278. 01.32	279. 22	280. 12	281. 0.19	282. 6	283. 4	284. 3	285. 0.93	286. 0.51	
287. PS20	288. C12H17N2O3+	289. 37.27	290. 17	291. 6	292. 0.42	293. 5	294. 3	295. 2	296. 4.03	297. 0.28	

Table 3 Pharmacokinetic Properties:

298. MOLECULE	299. GI ABSORPTION	300. BBB PERMEANT	301. GP SUBSTRATE	302. CYP1A2 INHIBITOR	303. CYP2C19 INHIBITOR	304. CYP2C9 INHIBITOR	305. CYP2D6 INHIBITOR	306. CYP3A4 INHIBITOR	307. LOGKP (CM/S)
308. PPS-0	309. High	310. No	311. o	312. No	313. No	314. No	315. No	316. No	317. -6.77
318. PPS-1	319. High	320. No	321. o	322. No	323. No	324. No	325. No	326. No	327. -7.39
328. PPS-2	329. Low	330. No	331. o	332. No	333. No	334. No	335. No	336. No	337. -8.5
338. PPS-3	339. High	340. No	341. o	342. No	343. No	344. No	345. No	346. No	347. -8.73
348. PPS-4	349. High	350. No	351. o	352. No	353. No	354. No	355. No	356. No	357. -8.28
358. PPS-5	359. High	360. No	361. o	362. No	363. No	364. No	365. No	366. No	367. -7.64
368. PPS-6	369. High	370. No	371. o	372. No	373. No	374. No	375. No	376. No	377. -8.11
378. PPS-7	379. High	380. No	381. o	382. No	383. No	384. No	385. No	386. No	387. -8.57
388. PPS-8	389. High	390. No	391. o	392. No	393. No	394. No	395. No	396. No	397. -7.6
398. PPS-9	399. High	400. No	401. o	402. No	403. No	404. No	405. No	406. No	407. -7.97
408. PPS-10	409. High	410. No	411. o	412. No	413. No	414. No	415. No	416. No	417. -7.97
418. PPS-11	419. High	420. No	421. o	422. No	423. No	424. No	425. No	426. No	427. -6.71
428. PPS-12	429. High	430. No	431. o	432. No	433. No	434. No	435. No	436. No	437. -9.53

438. PPS-13	439. High	440. No	441. o	442. No	443. No	444. No	445. No	446. No	447. -7.3
448. PPS-14	449. High	450. No	451. es	452. No	453. No	454. No	455. No	456. No	457. -6.73
458. PPS-15	459. High	460. No	461. o	462. No	463. No	464. No	465. No	466. No	467. -7.34
468. PPS-16	469. High	470. No	471. o	472. No	473. No	474. No	475. No	476. No	477. -8.23
478. PPS-17	479. High	480. No	481. o	482. No	483. No	484. No	485. No	486. No	487. -8.02
488. PPS-18	489. High	490. No	491. es	492. No	493. No	494. No	495. No	496. No	497. -7.36
498. PPS-19	499. High	500. No	501. es	502. No	503. No	504. No	505. No	506. No	507. -7.08
508. PPS-20	509. High	510. No	511. o	512. No	513. No	514. No	515. No	516. No	517. -6.88

Table 4 Drug-Likeness Studies:

518. MOLECULE	519. LIPINSKI VIOLATIONS	520. GHOSE VIOLATIONS	521. VEBER VIOLATIONS	522. EGAN VIOLATIONS	523. MUEGGE VIOLATIONS	524. BIO AVAILABILITY SCORE
525. PPS0	526. 0	527. 4	528. 0	529. 0	530. 1	531. 0.55
532. PPS1	533. 0	534. 0	535. 0	536. 0	537. 0	538. 0.55
539. PPS2	540. 0	541. 1	542. 0	543. 1	544. 0	545. 0.55
546. PP3	547. 0	548. 1	549. 0	550. 0	551. 0	552. 0.55
553. PPS4	554. 0	555. 1	556. 0	557. 0	558. 0	559. 0.56
560. PPS5	561. 0	562. 0	563. 0	564. 0	565. 0	566. 0.55
567. PPS6	568. 0	569. 1	570. 0	571. 0	572. 0	573. 0.56
574. PPS7	575. 0	576. 1	577. 0	578. 0	579. 0	580. 0.55
581. PPS8	582. 0	583. 1	584. 0	585. 0	586. 1	587. 0.55
588. PPS9	589. 0	590. 0	591. 0	592. 0	593. 0	594. 0.55
595. PPS10	596. 0	597. 0	598. 0	599. 0	600. 0	601. 0.55
602. PPS11	603. 0	604. 0	605. 0	606. 0	607. 0	608. 0.55
609. PPS12	610. 0	611. 0	612. 0	613. 0	614. 1	615. 0.55
616. PPS13	617. 0	618. 0	619. 0	620. 0	621. 0	622. 0.55
623. PPS14	624. 0	625. 0	626. 0	627. 0	628. 0	629. 0.55
630. PPS15	631. 0	632. 0	633. 0	634. 0	635. 0	636. 0.55
637. PPS16	638. 0	639. 1	640. 0	641. 0	642. 0	643. 0.55
644. PPS17	645. 0	646. 1	647. 0	648. 0	649. 0	650. 0.55
651. PPS18	652. 0	653. 0	654. 0	655. 0	656. 0	657. 0.55
658. PPS19	659. 0	660. 0	661. 0	662. 0	663. 0	664. 0.55
665. PPS20	666. 0	667. 0	668. 0	669. 0	670. 0	671. 0.55

Toxicity Prediction:

Various types of toxicities are caused which are majorly classified as organ toxicity and toxicity end points which were determined by Protox 3.0 as shown in table 5 and 6 respectively.

.

Table 5 Organ Toxicity:

672. NAME	673. LD50 674. (MG/KG)	675. TOXICITY CLASS	676. ORGAN TOXICITY				
			677. HEPATOTOXICITY	678. NEUROTOXICITY	679. NEPHROTOXICITY	680. RESPIRATORY TOXICITY	681. CARDIOTOXICITY
682. PS 0	683. 3720	684. 5	685. Inactive (0.60)	686. Active (0.76)	687. Inactive (0.59)	688. Active (0.69)	689. Inactive (0.75)
690. PS-1	691. 3500	692. 5	693. Inactive (0.65)	694. Active (0.56)	695. Active (0.50)	696. Active (0.74)	697. Inactive (0.68)
698. PS-2	699. 3500	700. 5	701. Inactive (0.85)	702. Active (0.58)	703. Active (0.51)	704. Active (0.76)	705. Inactive (0.58)
706. PS-3	707. 3500	708. 5	709. Inactive (0.68)	710. Active (0.57)	711. Inactive (0.51)	712. Active (0.74)	713. Active (0.52)
714. PS-4	715. 3500	716. 5	717. Inactive (0.67)	718. Active (0.56)	719. Active (0.51)	720. Active (0.74)	721. Inactive (0.52)
722. PS-5	723. 3500	724. 5	725. Inactive (0.75)	726. Active (0.56)	727. Active (0.52)	728. Active (0.78)	729. Inactive (0.64)
730. PS-6	731. 3500	732. 5	733. Inactive (0.66)	734. Active (0.54)	735. Active (0.53)	736. Active (0.74)	737. Inactive (0.56)
738. PS-7	739. 3500	740. 5	741. Inactive (0.67)	742. Active (0.56)	743. Inactive (0.50)	744. Active (0.76)	745. Inactive (0.51)
746. PS-8	747. 3500	748. 5	749. Inactive (0.81)	750. Active (0.59)	751. Active (0.51)	752. Active (0.75)	753. Inactive (0.63)
754. PS-9	755. 3500	756. 5	757. Inactive (0.61)	758. Active (0.68)	759. Active (0.54)	760. Active (0.78)	761. Inactive (0.58)
762. PS-10	763. 3500	764. 5	765. Inactive (0.66)	766. Active (0.50)	767. Active (0.52)	768. Active (0.73)	769. Inactive (0.65)
770. PS-11	771. 3500	772. 5	773. Inactive (0.67)	774. Active (0.54)	775. Inactive (0.54)	776. Active (0.71)	777. Inactive (0.58)
778. PS-12	779. 3500	780. 5	781. Inactive (0.84)	782. Active (0.61)	783. Active (0.56)	784. Active (0.8)	785. Inactive (0.57)
786. PS-13	787. 4500	788. 5	789. Inactive (0.74)	790. Active (0.53)	791. Inactive (0.52)	792. Active (0.76)	793. Inactive (0.62)
794. PS-14	795. 3500	796. 5	797. Inactive (0.60)	798. Active (0.63)	799. Inactive (0.52)	800. Active (0.77)	801. Inactive (0.58)
802. PS-15	803. 3500	804. 5	805. Inactive (0.82)	806. Active (0.66)	807. Active (0.67)	808. Active (0.70)	809. Inactive (0.74)
810. PS-16	811. 3500	812. 5	813. Inactive (0.76)	814. Active (0.55)	815. Active (0.62)	816. Active (0.76)	817. Inactive (0.62)
818. PS-17	819. 3500	820. 5	821. Inactive (0.70)	822. Inactive (0.50)	823. Active (0.55)	824. Active (0.74)	825. Inactive (0.69)
826. PS-18	827. 1646	828. 4	829. Inactive (0.64)	830. Active (0.72)	831. Active (0.55)	832. Active (0.79)	833. Inactive (0.64)
834. PS-19	835. 3500	836. 5	837. Inactive (0.62)	838. Active (0.61)	839. Inactive (0.54)	840. Active (0.75)	841. Inactive (0.73)
842. PS-20	843. 3500	844. 5	845. Inactive (0.67)	846. Active (0.52)	847. Inactive (0.53)	848. Active (0.75)	849. Inactive (0.67)

Table 6 Toxicity End Points:

850. NAME	851. TOXICITY END POINTS							
852.	853. CARCINOGENICITY	854. IMMUNOTOXICITY	855. MUTAGENICITY	856. CYTOTOXICITY	857. BB-BARRIER	858. EOTOXICITY	859. CLINICAL TOXICITY	860. NUTRITIONAL TOXICITY
861. Original	862. Inactive (0.66)	863. Inactive (0.98)	864. Inactive (0.94)	865. Inactive (0.75)	866. Active (0.89)	867. Active (0.53)	868. Inactive (0.71)	869. Inactive (0.56)
870. PS-1	871. Inactive (0.69)	872. Inactive (0.99)	873. Inactive (0.82)	874. Inactive (0.69)	875. Active (0.63)	876. Inactive (0.79)	877. Inactive (0.61)	878. Inactive (0.56)
879. PS-2	880. Inactive (0.57)	881. Inactive (0.99)	882. Inactive (0.64)	883. Inactive (0.76)	884. Active (0.55)	885. Inactive (0.68)	886. Inactive (0.66)	887. Inactive (0.56)
888. PS-3	889. Inactive (0.75)	890. Inactive (0.99)	891. Inactive (0.81)	892. Inactive (0.70)	893. Inactive (0.52)	894. Inactive (0.76)	895. Inactive (0.57)	896. Inactive (0.58)
897. PS-4	898. Inactive (0.72)	899. Inactive (0.99)	900. Inactive (0.83)	901. Inactive (0.70)	902. Inactive (0.51)	903. Inactive (0.75)	904. Inactive (0.56)	905. Inactive (0.59)
906. PS-5	907. Inactive (0.69)	908. Inactive (0.99)	909. Inactive (0.70)	910. Inactive (0.73)	911. Active (0.58)	912. Inactive (0.73)	913. Inactive (0.64)	914. Inactive (0.62)

915. PS-6	916. Inactive (0.71)	917. Inactive (0.99)	918. Inactive (0.83)	919. Inactive (0.73)	920. nactive (0.51)	921. Inactive (0.73)	922. Inactive (0.56)	923. Inactive (0.56)
924. PS-7	925. Inactive (0.74)	926. Inactive (0.99)	927. Inactive (0.82)	928. Inactive (0.72)	929. nactive (0.52)	930. Inactive (0.73)	931. Inactive (0.58)	932. Inactive (0.55)
933. PS-8	934. Inactive (0.68)	935. Inactive (0.99)	936. Inactive (0.80)	937. Inactive (0.73)	938. ctive (0.59)	939. Inactive (0.81)	940. Inactive (0.61)	941. Inactive (0.61)
942. PS-9	943. Inactive (0.72)	944. Inactive (0.99)	945. Inactive (0.73)	946. Inactive (0.81)	947. ctive (0.57)	948. Inactive (0.74)	949. Inactive (0.54)	950. Inactive (0.58)
951. PS-10	952. Inactive (0.67)	953. Inactive (0.99)	954. Inactive (0.80)	955. Inactive (0.70)	956. ctive (0.58)	957. Inactive (0.74)	958. Inactive (0.65)	959. Inactive (0.55)
960. PS-11	961. Inactive (0.72)	962. Inactive (0.97)	963. Inactive (0.84)	964. Inactive (0.68)	965. ctive (0.56)	966. Inactive (0.75)	967. Inactive (0.64)	968. Inactive (0.56)
969. PS-12	970. Inactive (0.68)	971. Inactive (0.99)	972. Inactive (0.73)	973. Inactive (0.78)	974. ctive (0.50)	975. Inactive (0.71)	976. Inactive (0.67)	977. Inactive (0.60)
978. PS-13	979. Inactive (0.70)	980. Inactive (0.99)	981. Inactive (0.81)	982. Inactive (0.73)	983. ctive (0.53)	984. Inactive (0.67)	985. Inactive (0.67)	986. Inactive (0.59)
987. PS-14	988. Inactive (0.69)	989. Inactive (0.99)	990. Inactive (0.76)	991. Inactive (0.72)	992. ctive (0.61)	993. Inactive (0.76)	994. Inactive (0.52)	995. Inactive (0.58)
996. PS-15	997. Inactive (0.65)	998. Inactive (0.99)	999. Inactive (0.76)	1000. Inactive (0.80)	1001. ctive (0.52)	1002. Inactive (0.70)	1003. Inactive (0.6)	1004. Inactive (0.56)
1005. PS-16	1006. Inactive (0.68)	1007. Inactive (0.99)	1008. Inactive (0.75)	1009. Inactive (0.73)	1010. nactive (0.52)	1011. Inactive (0.74)	1012. Inactive (0.63)	1013. Inactive (0.65)
1014. PS-17	1015. Inactive (0.68)	1016. Inactive (0.96)	1017. Inactive (0.83)	1018. Inactive (0.68)	1019. nactive (0.53)	1020. Inactive (0.74)	1021. Inactive (0.62)	1022. Inactive (0.56)
1023. PS-18	1024. Inactive (0.69)	1025. Inactive (0.98)	1026. Inactive (0.70)	1027. Inactive (0.78)	1028. ctive (0.56)	1029. Inactive (0.7)	1030. Inactive (0.52)	1031. Inactive (0.58)
1032. PS-19	1033. Inactive (0.64)	1034. Inactive (0.99)	1035. Inactive (0.75)	1036. Inactive (0.66)	1037. nactive (0.60)	1038. Inactive (0.76)	1039. Inactive (0.50)	1040. Inactive (0.59)
1041. PS-20	1042. Inactive (0.73)	1043. Inactive (0.99)	1044. Inactive (0.83)	1045. Inactive (0.68)	1046. ctive (0.60)	1047. Inactive (0.77)	1048. Inactive (0.63)	1049. Inactive (0.57)

Adverse Drug Reaction. Adverse drug reactions caused by the hybrids were predicted by using ADVER-Pred which are presented in table – 7

Table 7 (Adverse Drug Reactions):

1050.	MOLECULE	1051.	PA	1052.	PI	1053.	SIDE EFFECT
1054.	PPS1	1055.	0.953	1056.	0.005	1057.	Nephrotoxicity
		1058.	0.779	1059.	0.067	1060.	Hepatotoxicity
		1061.	0.426	1062.	0.093	1063.	Cardiac failure
		1064.	0.315	1065.	0.17	1066.	Myocardial infarction
1067.	PPS2	1068.	0.547	1069.	0.171	1070.	Hepatotoxicity
		1071.	0.535	1072.	0.039	1073.	Nephrotoxicity
1074.	PPS3	1075.	0.793	1076.	0.012	1077.	Nephrotoxicity
		1078.	0.51	1079.	0.19	1080.	Hepatotoxicity
		1081.	0.375	1082.	0.206	1083.	Arrhythmia
		1084.	0.268	1085.	0.204	1086.	Cardiac failure
1087.	PPS4	1088.	0.858	1089.	0.044	1090.	Hepatotoxicity
		1091.	0.857	1092.	0.007	1093.	Nephrotoxicity
		1094.	0.395	1095.	0.107	1096.	Cardiac failure
1097.	PPS5	1098.	0.838	1099.	0.008	1100.	Nephrotoxicity
		1101.	0.517	1102.	0.186	1103.	Hepatotoxicity
1104.	PPS6	1105.	0.865	1106.	0.007	1107.	Nephrotoxicity
		1108.	0.827	1109.	0.053	1110.	Hepatotoxicity

		1111.	0.366	1112.	0.121	1113.	Cardiac failure
1114.	PPS7	1115.	0.815	1116.	0.01	1117.	Nephrotoxicity
		1118.	0.383	1119.	0.272	1120.	Hepatotoxicity
		1121.	0.341	1122.	0.242	1123.	Arrhythmia
1124.	PPS8	1125.	0.929	1126.	0.005	1127.	Nephrotoxicity
1128.		1129.	0.796	1130.	0.062	1131.	Hepatotoxicity
1132.	PPS9	1133.	0.791	1134.	0.063	1135.	Hepatotoxicity
		1136.	0.517	1137.	0.044	1138.	Nephrotoxicity
		1139.	0.329	1140.	0.259	1141.	Arrhythmia
1142.	PPS10	1143.	0.912	1144.	0.005	1145.	Nephrotoxicity
		1146.	0.716	1147.	0.094	1148.	Hepatotoxicity
		1149.	0.313	1150.	0.173	1151.	Myocardial infarction
		1152.	0.266	1153.	0.206	1154.	Cardiac failure
1155.	PPS11	1156.	0.905	1157.	0.005	1158.	Nephrotoxicity
		1159.	0.807	1160.	0.058	1161.	Hepatotoxicity
		1162.	0.471	1163.	0.049	1164.	Myocardial infarction
		1165.	0.349	1166.	0.131	1167.	Cardiac failure
1168.	PPS12	1169.	0.896	1170.	0.006	1171.	Nephrotoxicity
		1172.	0.683	1173.	0.107	1174.	Hepatotoxicity
		1175.	0.346	1176.	0.121	1177.	Myocardial infarction
1178.	PPS13	1179.	0.77	1180.	0.071	1181.	Hepatotoxicity
		1182.	0.766	1183.	0.014	1184.	Nephrotoxicity
1185.	PPS14	1186.	0.799	1187.	0.011	1188.	Nephrotoxicity
		1189.	0.632	1190.	0.128	1191.	Hepatotoxicity
		1192.	0.353	1193.	0.229	1194.	Arrhythmia
		1195.	0.34	1196.	0.129	1197.	Myocardial infarction
		1198.	0.253	1199.	0.218	1200.	Cardiac failure
1201.	PPS15	1202.	0.453	1203.	0.065	1204.	Nephrotoxicity
		1205.	0.407	1206.	0.067	1207.	Myocardial infarction
1208.	PPS16	1209.	0.93	1210.	0.005	1211.	Nephrotoxicity
		1212.	0.681	1213.	0.108	1214.	Hepatotoxicity
		1215.	0.366	1216.	0.094	1217.	Myocardial infarction
		1218.	0.325	1219.	0.148	1220.	Cardiac failure
1221.	PPS17	1222.	0.919	1223.	0.005	1224.	Nephrotoxicity
		1225.	0.677	1226.	0.109	1227.	Hepatotoxicity
		1228.	0.427	1229.	0.092	1230.	Cardiac failure
1231.	PPS19	1232.	0.321	1233.	0.160	1234.	Myocardial infarction
		1235.	0.279	1236.	0.194	1237.	Cardiac failure
1238.	PPS20	1239.	0.951	1240.	0.005	1241.	Nephrotoxicity
		1242.	0.717	1243.	0.093	1244.	Hepatotoxicity
		1245.	0.313	1246.	0.173	1247.	Myocardial infarction
		1248.	0.294	1249.	0.178	1250.	Cardiac failure
1251.	PPS0	1252.	0.522	1253.	0.184	1254.	Hepatotoxicity

Auto Dock Vina Molecular Docking Score:

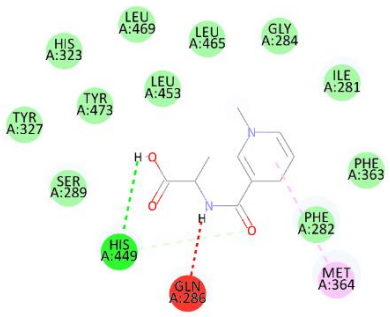
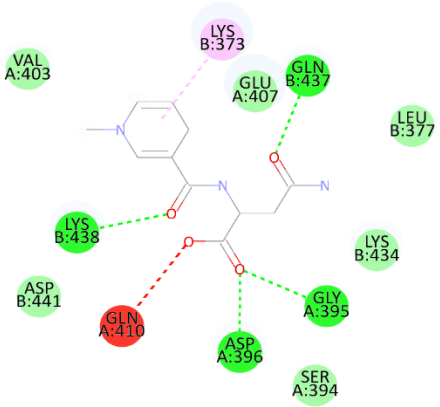
A total of 20 hybrid compounds listed in Table 1 were docked using PyRx (Auto Dock Vina) software. The binding affinity scores of their best models are presented in table 8.

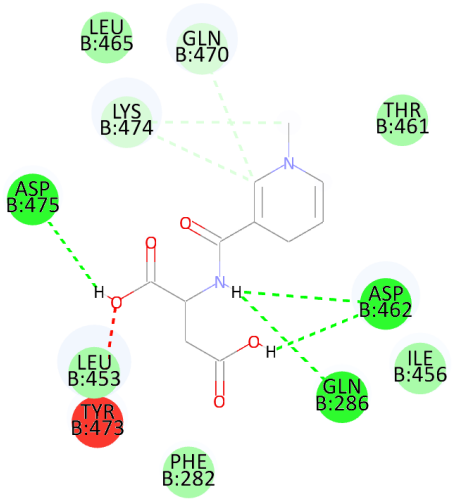
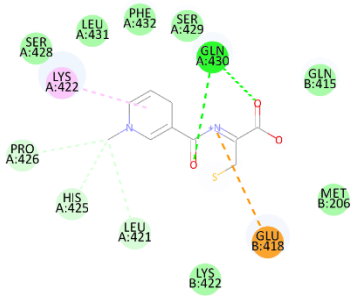
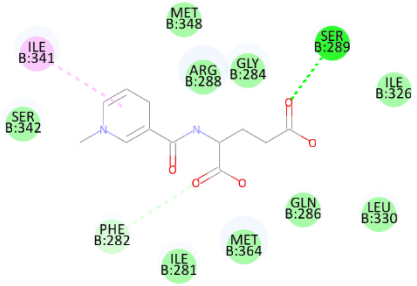
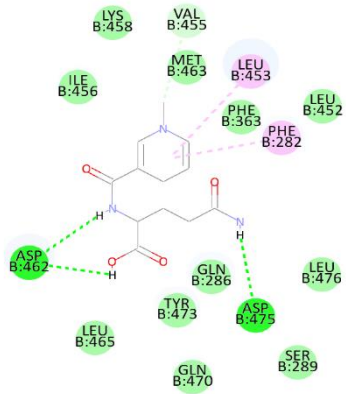
Table 8 AutoDock Vina docking Score of ligand with Protein DPP-4 (PDB ID: 3et0):

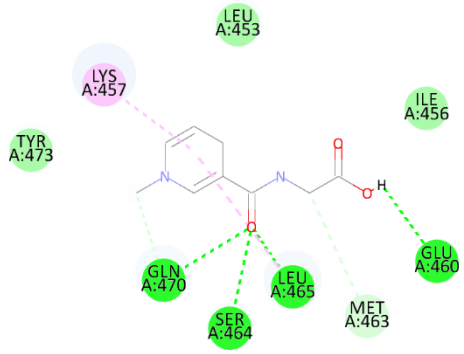
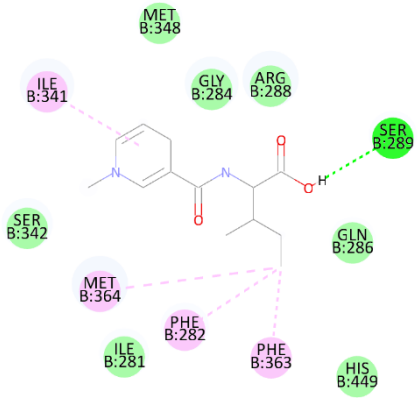
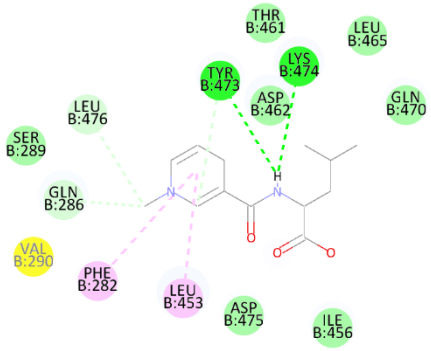
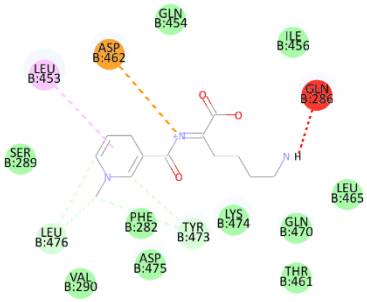
1255. MOLECULE	1256. BINDINGAFFINITY (KCAL/MOL)
1257. PPS1	1258. -6.2
1259. PPS2	1260. -5.6
1261. PPS3	1262. -6.2
1263. PPS 4	1264. -6.2
1265. PPS 5	1266. -5.6
1267. PPS 6	1268. -6.3
1269. PPS 7	1270. -6.6
1271. PPS 8	1272. -6.2
1273. PPS 9	1274. -6
1275. PPS 10	1276. -6.1
1277. PPS 11	1278. -6.3
1279. PPS 12	1280. -5.7
1281. PPS 13	1282. -5.9
1283. PPS 14	1284. -6.7
1285. PPS 15	1286. -6.6
1287. PPS 16	1288. -6.4
1289. PPS 17	1290. -5.9
1291. PPS 18	1292. -7.7
1293. PPS 19	1294. -7.9
1295. PPS 20	1296. -5.6

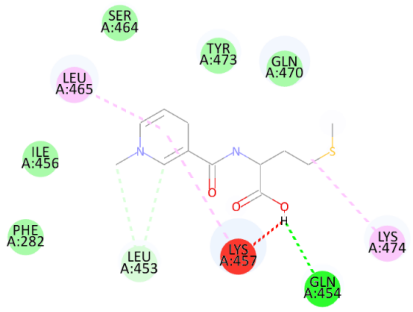
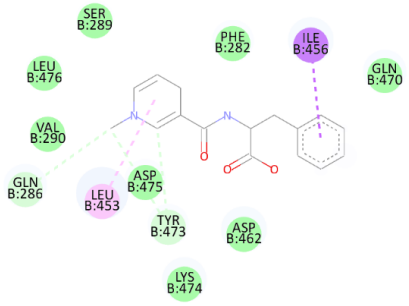
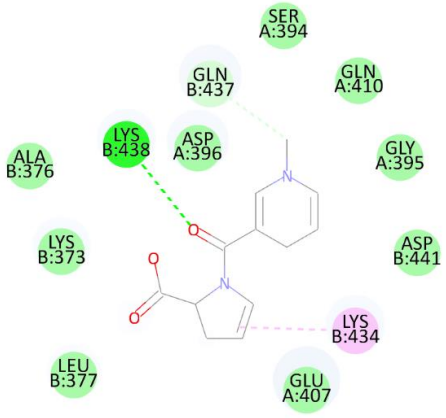
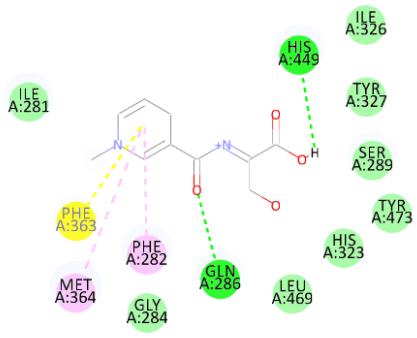
Visualization. 2-D images of the docked models were generated by visualization through Biovia Discovery studio software as shown in table -9

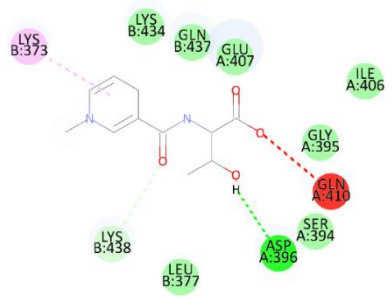
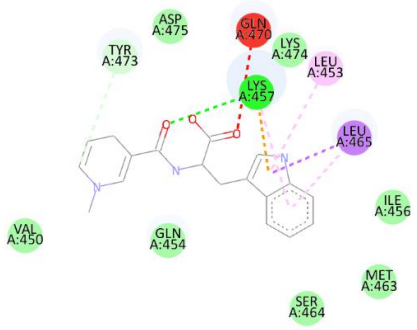
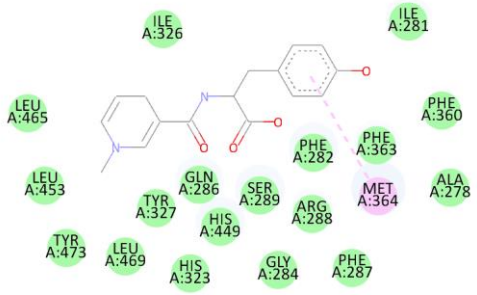
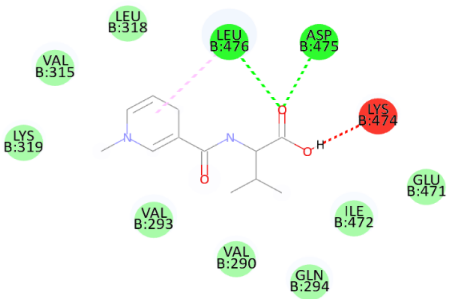
Table 9 Ligand-Protein Interaction Visualization:

1297. MOLECULE	1298. VISUALISATION IMAGES
1299. PPS 1	 1300.
1301. PPS 3	 1302.

1303. PPS 4	 1304.
1305. PPS 5	 1306.
1307. PPS 6	 1308.
1309. PPS 7	 1310.

1311. PPS 8	 1312.
1313. PPS 10	 1314.
1315. PPS 11	 1316.
1317. PPS 12	 1318.

1319. PPS 13	 1320.
1321. PPS 14	 1322.
1323. PPS 15	 1324.
1325. PPS 16	 1326.

1327. PPS 17	 1328.
1329. PPS 18	 1330.
1331. PPS 19	 1332.
1333. PPS 20	 1334.

Biological Activity Prediction. PASS online tool was used to predict the biological activities of the hybrids as shown in table 10'

Table 10 (Biological Activity):

MOLECULE	PA	PI	BIOLOGICAL ACTIVITY
PPS 1	0,531	0,005	Antidiabetic symptomatic
	0,173	0,030	Antidiabetic (type 1)
	0,314	0,183	Diabetic neuropathy treatment
PPS 2	0,236	0,088	Antidiabetic symptomatic
	0,328	0,153	Diabetic neuropathy treatment
PPS 3	0,336	0,024	Antidiabetic symptomatic
	0,027	0,014	Diabetes insipidus treatment
	0,325	0,160	Diabetic neuropathy treatment
PPS 4	0,444	0,010	Antidiabetic symptomatic
	0,152	0,050	Antidiabetic (type 1)
	0,320	0,171	Diabetic neuropathy treatment
PPS 5	0,345	0,021	Antidiabetic symptomatic
	0,374	0,072	Diabetic neuropathy treatment
PPS 6	0,152	0,050	Antidiabetic (type 1)
	0,466	0,009	Antidiabetic symptomatic
	0,325	0,159	Diabetic neuropathy treatment
PPS 7	0,129	0,098	Antidiabetic (type 1)
	0,356	0,019	Antidiabetic symptomatic
	0,028	0,013	Diabetes insipidus treatment
	0,384	0,059	Diabetic neuropathy treatment
PPS 8	0,191	0,176	Antidiabetic
	0,177	0,028	Antidiabetic (type 1)
	0,612	0,005	Antidiabetic symptomatic
	0,412	0,032	Diabetic neuropathy treatment
PPS 9	0,223	0,100	Antidiabetic symptomatic
PPS 10	0,359	0,018	Antidiabetic symptomatic
	0,303	0,210	Diabetic neuropathy treatment
PPS 11	0,125	0,108	Antidiabetic (type 1)
	0,418	0,011	Antidiabetic symptomatic
	0,320	0,170	Diabetic neuropathy treatment
PPS 12	0,418	0,011	Antidiabetic symptomatic
PPS 13	0,522	0,006	Antidiabetic symptomatic
	0,428	0,022	Diabetic neuropathy treatment
	0,170	0,032	Diabetic retinopathy treatment
PPS 14	0,408	0,012	Antidiabetic symptomatic
	0,333	0,144	Diabetic neuropathy treatment
PPS 15	0,170	0,157	Diabetic nephropathy treatment
	0,343	0,123	Diabetic neuropathy treatment
PPS 16	0,158	0,043	Antidiabetic (type 1)
	0,559	0,005	Antidiabetic symptomatic
	0,170	0,158	Diabetic nephropathy treatment
	0,323	0,164	Diabetic neuropathy treatment
	0,153	0,052	Diabetic retinopathy treatment
PPS 17	0,226	0,135	Antidiabetic
	0,147	0,057	Antidiabetic (type 1)
	0,478	0,008	Antidiabetic symptomatic
	0,185	0,117	Diabetic nephropathy treatment
PPS 19	0,124	0,111	Antidiabetic (type 1)
PPS 20	0,133	0,086	Antidiabetic (type 1)
	0,418	0,011	Antidiabetic symptomatic
	0,349	0,113	Diabetic neuropathy treatment

Conclusion:

This study shows how molecular docking and computer-aided drug design (CADD) can be used to design and assess trigonelline hybrids as possible antidiabetic medications. As a lead molecule, trigonelline was employed and its derivatives were methodically designed and studied. The safety and drug-likeness of the derivatives were further confirmed by the pharmacokinetic and toxicity profiles that were determined using tools like SwissADME, ProTox 3.0 and ADVERPred. Furthermore, their antidiabetic potential was confirmed by biological activity estimates made with PASS Online. Strong interactions between the ligands and target proteins were validated by docking and visualization investigations carried out with PyRx and BIOVIA Discovery Studio, which shed light on binding mechanisms. The molecules demonstrated good binding affinities with the important diabetes-related target DPP-4 using molecular docking, underscoring its potential to alter glucose metabolism and enhance insulin sensitivity.

In conclusion, this study not only underscores the therapeutic potential of trigonelline derivatives in diabetes management but also highlights the importance of computational approaches in accelerating early-stage drug discovery. Future studies involving in vitro and in vivo experiments are required to validate these findings and further explore the clinical potential of the designed compounds.

Declaration of conflict of interests:

The authors affirm that they have no conflicts of interest related to the research, authorship, or publication of this article.

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