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# A Review on Alpha-Amylase Inhibitors For The Treatment of Diabetes Mellitus

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## Abstract:

Diabetes mellitus (DM) is the metabolic disorder by which a lot of people are suffering all around the world. In which 94% of the diabetes cases are of Noninsulin-dependent diabetes mellitus (NIDDM). In case of NIDDM,(T2DM), irregular release of insulin formed in the β-cells of pancreatic glands or either the amount produced is not sufficient for the cellular components in the body become resistant to it (insulin resistance).In such conditions, trapping of glucose by the individual cell get reduced as it level gets increased in the systemic circulation. As insulin is produced in body were not get utilized due to insulin resistance, we are using oral hypoglycaemic agents to lower the blood glucose level. Alpha amylase enzyme (AAE)is used for the metabolism of carbohydrate and other oligosaccharides to convert monosaccharide like glucose (thus increases blood glucose level). This enzyme is produced by the salivary and pancreatic glands. Thus, we utilize the target inhibitor like as α-amylase inhibitors (AAIs) which prevent glucose formation from complex carbohydrate, as the result no absorption of glucose take place in systemic circulation. The wide ranges of organic compounds were engaged in $AAI_S$activity as we gone to report some synthesized scheme, novel moiety of alpha amylase inhibitor (in-vitro)and also the dry lab studies (*in silico*).

**Introduction:**

Drugcreation isahecticandmore costlyprocess.Thedevelopmentofanewdrugtakesalmost 12-15 years with a cost of $800 to $1000 million. From approximately 10,000 compounds in preclinicaltrailsandstudiesonanimals,amaximumof10compoundsmayreachclinicalt

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rialson human's stage in order to find the potential compound that can be released into the market. The drug discovery process is generally known as identification of a lead molecule. To find the lead molecule the drug should have some desirable properties such as good pharmacological activity, optimum pharmacokinetic properties with very low toxiceffects [1]. Now a day's dry lab (*in silico)* techniques are playing vital role in the drugdiscovery process from hit identification to lead optimization [2]. To reach the targets in drug discovery many computational techniques are widely using. The active structures can be filter tested by using computationalmodels. Thedry lab techniques canalsocontributetothestudy the drugmetabolismwith using the metabolic enzymes such as CYP450 isoform [3]. Lipinski's rule of five is used as a decision gate to enable the discovery of orally bioavailable drug molecules [4]. To reduce the failures in the drug discovery scientists have introduced some computer-based techniques known as computer aided drug design (CADD). The study of pharmaceutical drug molecule properties based on the computational techniques is called as pharmacoinformaticstudies

DM is a disease(non-infectious) in which the body ability to produce or respond to the hormone insulin is loses,as the result leads to abnormal metabolism of carbohydrate food in the body. Thus, the levels of glucoseareincrease in the blood as it is not treated for longer duration of time. Recent studies indicate the occurrence of disease is budding, from a worldwide occurrencedata of 423 million people in 2019 to 845 million people in 2050 [5].In which 94% of the DM cases are of Non-insulin-dependent diabetes mellitus (NIDDM). In case of NIDDM, (also called type 2 diabetes mellitus, T2DM) the irregular release of insulin produced by the β-cells of pancreas or either the amount produced is not sufficient for the cellular components in the body leads to its cell resistant (insulin resistance)[6].There are multiple factors which cause DM, the main menace cause of NIDDM is obesity, extra weight (insulin resistance) and physical inactivity [7].

Concentrating on the biological preparation and its downsides, the various chemical oral hypoglycaemics were identified an antidiabetic agent includes α-amylase inhibitors ($AAI_S$) [8]. salivary and pancreatic Glands are the main spot for the production and Release of α-amylase enzyme(AAE). AAE plays a vital

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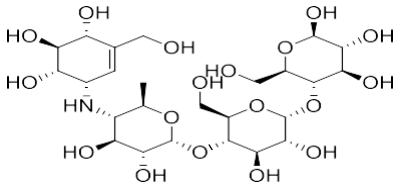
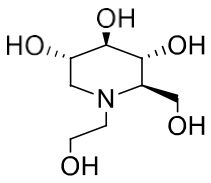
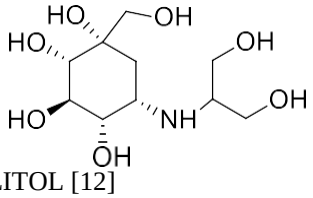
role in the digestion of carbohydrate in the human body. (conversion of oligosaccharides to Monosaccharides)Inhibitors of AAE may lower the blood glucose concentration that can take place after the meal consumption, by reducing the speed of conversion of oligosaccharides to simple sugars(like glucose) [9].So, by usingalpha amylaseinhibitors ($AAI_S$) Inhibit the actionofAAE andreducestheglucoseformation may leads to reduce absorption of glucose in to systemic circulation, whichultimatelydeclinein blood glucose levels in the body [10]. The standard reported $AAI_S$ are showed in the following table (**table:1**)Recently some new novel alpha amylase inhibitors were identified, and this new reported moiety are exposed in this report according to synthesized scheme, activity and its potency (in-vitro) and also the dry lab studies (*in silico*) [11].

**Table:1** list of standard α-amylase inhibitors

| Activity | Mode of Action | Standard reported drugs in the Market |
|---|---|---|
| Alpha amylase inhibitors | Inhibit the actionofAAE andreducestheglucoseformation may leads to reduce absorption of glucose in to systemic circulation, whichultimatelydeclinein blood glucose levels in the body |  ACARBOSE  VOGLIBOSE  MIGLITOL [12] |

F.Rahim*et al*. prepared 19 novel derivatives of aryl hydrazide bearing Schiff bases/thiazolidinone and evaluated them for α- amylase, urease activity in

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comparison with standard drug acarbose and also performed their molecular docking study to determine binding efficacy with receptor.[12]

**Scheme 2**. Synthesis of aryl hydrazide derivatives

All the compounds were active and shows $IC_{50}$tends starts form 0.8±0.05to 12.50±0.5μMascomparedstandard acarbosehaving $IC_{50}$ =1.70± 0.10 μM.

Among the synthesizedcompounds, the compound**1j (**0.8±0.05μM**),1r(**0.9±0.05μM**),1k(**1.00±0.05μM**),1e(**1.10 ± 0.10μM**),1b(**1.20 ± 0.10μM**)** and **1f(**1.30 ± 0.10μM**)** having best inhibitory activity againt the protein.

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**Fig :1** Indicates the in vitro data of the most potent compounds

Dry lab studies report

The compounds **1j,1r,1k** and **1e** shown *In-silico* docking studies as follows

| Compounds | Amino acid involved in the hydrogen bonding formation |
|---|---|
| 1j | GLU233 (Benzene OH group) and GLN63 (methylidene group) |
| 1r | GLN63 (methylidene group) |
| 1k | GLU233 and NH group, HIS305 (Nitrile group) |
| 1e | GLU233 (Phenol OH group), ASP197 (Benzene ring), HIS305 (Nitrile group) |

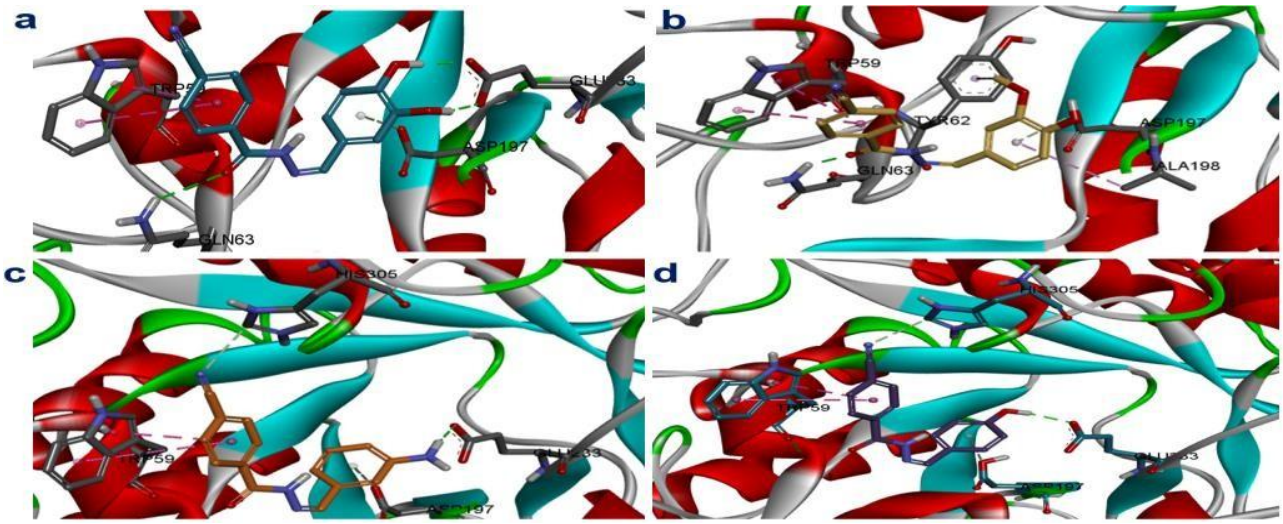


**Fig.1**: Binding pattern of the active derivatives of arylhydrazide-**1j (a), 1r (b), 1k** (c) and 1e (d)to the binding site of *α*-amylaseenzyme.

R. Basharyet *al*. synthesized 1,3-diaryl-3(aryl amino)propan-1-one derivatives in 2019 employing aza-Michael addition and performed its evaluation for α-amylase inhibitory and anti-oxidant activity.[5]They had prepared 116 new novel derivatives in which molecule **3e** as foremost potent α-amylase inhibitor molecule having $IC_{50}$23.17µg/ml value. And the compound 3a was to be next potent derivative having $IC_{50}$=25.7µg/ml[13].

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**Fig :2**working plan of developing novel of alpha-amylase inhibitor by using Trans-chalcone

**Scheme 2**. Synthesis of planed 1,3diaryl-3(aryl amino) propanone derivatives

Acarbose(standard drug)

$IC_{50}$ =891.25µg/mL.

In molecule 3a having aniline group at beta Carbon is linked with heterocyclic indole part amino acid of TRP59 through π-π interaction. TYR62 (aryl ring) had connected to two aryl rings of 3a by π-π bonds.Compound 3e which is most potent having binding affinity on 4gqr is -8.2kcal/mole.

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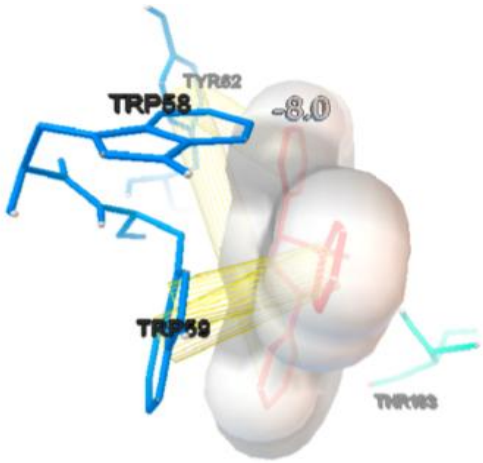


**Fig :3** The binding of 3acompound withα-amylase inhibitor (PDB No :4gqr).

A.A. Adegboye*et al.* were prepared the 45 derivatives of new heterocyclic 2-aryl benzimidazoles in 2018,Identified α-amylase inhibitory activity.The most active compound was identified and characterized its binding interaction with active binding potent site of α- amylase enzyme using dry labtechniques were done.[14]

**scheme:3**working plan designed for the synthesis of benzimidazole derivatives (**1-45**).

Among the synthesized derivatives, compound **3,10 23** and **34** were good inhibitorsand their $IC_{50}$ values having 1.51±1.82,1.48±0.38,1.57±1.07, and 1.51 ± 0.38 respectively comparing with the standard inhibitor for alpha-amylase enzyme (Acarbose $IC_{50}$ = 1.46 ± 0.26 μM).

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**Fig :4** Indicates the in vitro data of the most potent compounds

*In silico* docking study

Docking score of 2-aryl benzimidazole derivatives like **3,10,23** and **34** which shows the best activity against the alpha-amylase.

| Compound | Docking Score | Amino acid involved in the hydrogen bonding formation |
|---|---|---|
| 3 | -5.468 | ASP-300 (Nitrogen 13) LEU-162 (6-ring) |
| 10 | -5.993 | GLU-233 (Carbon 16) ASP-197 (Bromine 29) LEU-162 (Nitrogen 10) |
| 23 | -5.564 | GLU-233 (Carbon1) ASP-197 (Nitrogen 12) |
| 34 | -5.403 | TRP-59 (Carbon 30) ILEU-235(Chlorine 4) PHE-256 (Chlorine 4) |

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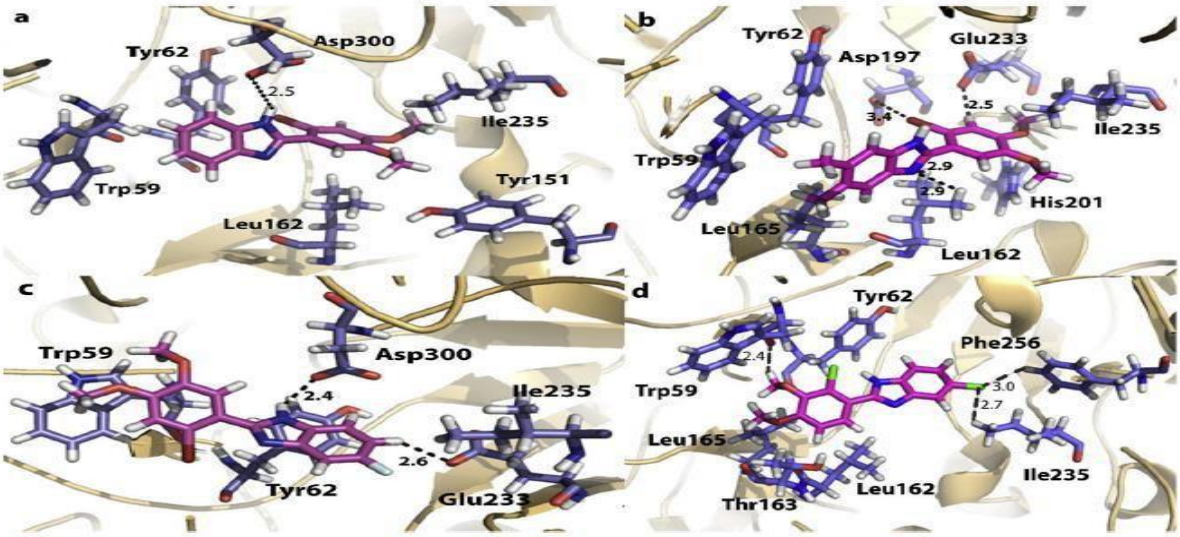


**Fig:5** Binding pattern of best derivatives 3, 10, 23, and 34 (a, b, c, and d) (ligand is indicated by pink) inside the active site of α-amylase (blue), dark dotted line is showing H-bond.

S. Yousuf *et.al* prepared 18 derivatives of 2′-Aryl and 4′-Arylidene derived Pyrazolonesin 2018 and checked for α-amylase inhibitory action [15]. IC50 value for all compounds determined was in range from 1.61±0.16 $\mu$Mup to 2.38 ± 0.09 $\mu$M, which shows excellent inhibitory activity as compare to acarbose (IC50 = 1.46 ± 0.26 $\mu$M).

They synthsised (**1-18**) by the refluxed the equal quantity of 4-chlorophenylpyrazolone and aryl aldehydes in the presence catalyst (MgO). The reaction is taking place by the presence of acetonitrile with continues stirring(**scheme:4**).

**Scheme:4** Synthesis of (Z)-2-(4-chlorophenyl)-4-ethyldene-5-methyl-2,4-dihydro-3H-pyrazol-one derivatives (**1-18**)

The compound **1** and **4** showing the inhibition activity towards the alpha-amylase

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enzyme.

*In silico* docking study

Table: docking score of 2′-Arylpyrazolones and 4′-arylidene pyrazolones against Alpha-amylase.

| Compound | Docking Score | Amino acid involved in the hydrogen bond formation |
|---|---|---|
| 1 | -11.2608 | Trp59, Leu162, and Ala198 |
| 4 | -11.5395 | Trp59, Thr163, and His201 |
| 8 | -12.2303 | Trp59, Glu240, and Ile235 |
| 12 | -10.1284 | Thr163, Lys200 and Ile235 |
| 14 | -12.0078 | Asp300, and His201 |
| 17 | -9.9760 | Arg195 and Lys200 |

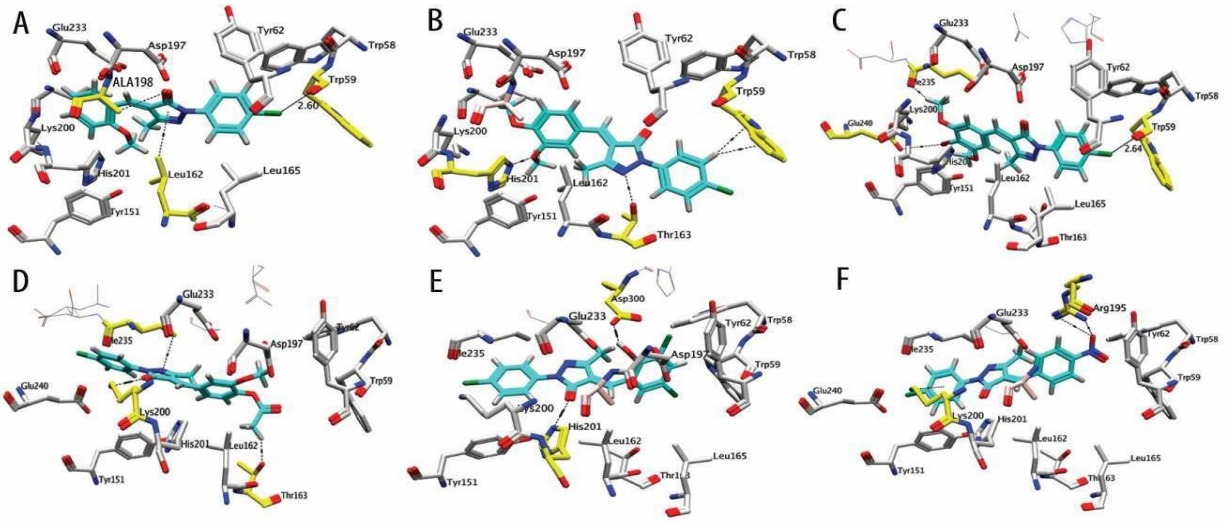


**Fig:6** Binding pattern of compound-1 (A), compound-4 (B), compound-8 (C), compound-12 (D), comound 14 (E)and compound 17 (F) to the active potent binding site of α-amylase.

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A.T. Bale *et.al.* synthesized chalcones and bis-chalcones in 2018, and all derivatives were screened for their potential as an α-amylase inhibitor. [16] Acetophenones and acetone is reacted with different types of benzaldehydes to form chalcone and bis-chalcone derivatives respectively at room temperature (60% NaOH) .

**Scheme:** synthesis of **(A)** chalcones **1-13** and **(B)** bis-chalcones **14-18**

The above derivatives show (**1-13,14-18**) exhibitgood in-*vitro* α-amylase inhibitory activity as to that of standard acarbose ($IC_{50}$=1.04 ± 0.3 μM). The compound **4**of chalcones and compound **16** in case bis-chalcones were found to be best inhibitory activity compare to remaining compounds, there $IC_{50}$ values are 1.27 ± 0.7 and 1.63 ± 0.18 μM.

*In silico* docking study

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| Compound | Docking Score | Amino acid involved in the hydrogen bond formation |
|---|---|---|
| 4 | −9.0231 | GLU233(Sulphur 18), ASP300(Sulphur 18) and GLU233(Carbone 19) |
| 10 | −9.3467 | GLU356 (Carbone 3), ASP197(Oxygen) and TRP59(Sulphur 19) |
| 14 | −8.9887 | ASP356(Carbone 4), ASP197(Carbone 8), TRP58(Carbone12), TRP357(Carbone 18) and PRO54(Chlorine 19) |
| 16 | −8.4512 | ASP356(Carbone 4), ASP300(Carbone 8) and HIS305(Carbone 12) |

T. Noreen *et.al.* synthesized 25 derivatives of indole carbohydrazide in 2017 and examined them for their α-amylase inhibitory activity [17].

**chemistry**

First methyl-1-indole-5-carboxylate is prepared with reacting indole-5-carbohydrazide and hydrazine in the presence of methanol refluxing it about 6 hours. Finally, it is reacted with various aromatic aldehydes to give 5-indole hydrazones. The crude solid product is recrystallized with methanol to get good yield (74-86%).

They had prepared (**1-25**) indole carbohydrazide derivatives and evaluated against alpha-amylase activity. All the derivatives are having alpha-amylase inhibitory activity starting 9.28 ± 0.153 µM up to 599.0 ± 0.21 µM as compared Acarbose whose $IC_{50}$ value 8.78 ± 0.16µM.

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**Fig :7** Indicates the in vitro data of the most potent compounds

The 6 derivatives, the compound **25**shows ($IC_{50}$ = 9.28 ± 0.15 µM), compound **22**shows ($IC_{50}$ = 9.79 ± 0.43 µM), compound **4**shows ($IC_{50}$ = 11.08 ± 0.35 µM), compound **1**shows ($IC_{50}$ = 12.65 ± 0.169 µM), compound **8**shows ($IC_{50}$ = 21.37 ± 0.07 µM) and compound **14**having ($IC_{50}$ = 43.21 ± 0.14 µM) having potent as compared to standard acarbose. The compound **25** is most potent comparing among the all the compound which is having chloro substituent at *4th*position on the benzyl group.The binding patterns prepared indole carbohydrazide (**1-25**), dry lab simulation was done targeting the crystal structure of alpha-amylase enzyme (PDB ID: 4W93) The highly potent compounds like **25** and **22,** both shows the hydrogen bond between the indole Nitrogen of the compound with the Y62.

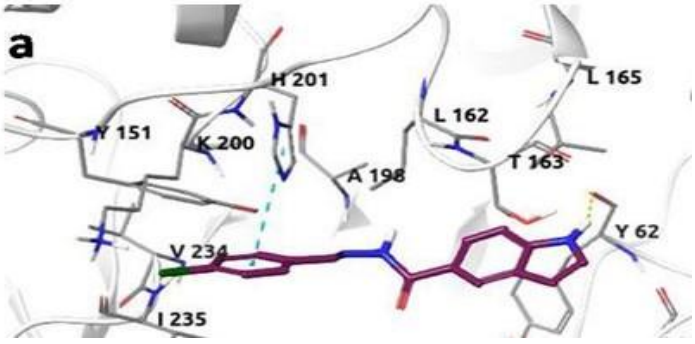

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**Fig:8** Predicted binding patterns of active indole carbohydrazide (a) compound **25** (pink). Doted yellow and blue lines indicates the hydrogen bond.

M. Taha *et.al.* prepared (**1-25**) derivatives of benzofuran carbohydrazide in 2017 and evaluated for Alpha-amylaseinhibitoryactivity [18]. (wet lab and dry lab techniques)

**Chemistry**

The equal amount of methyl 3-methylbenzofuran-2-carboxylate is treated with hydrazine to give 3-methylbenzofuran-2-carbonydrazide in the presence of methanol refluxed for 4 hours. And at last further treated with different aldehyde derivatives to give the final product called 3-N-arylidene-3-methylbenzofuran-2-carbonydrazide derivatives (methanol refluxed for 3 hours)

Thederivativesshowsignificantinhibitory potentialhaving$IC_{50}$valuerangingfrom1.078±0.19to2.926±0.05µMascomparetostandard drug acarbose ($IC_{50}$ = 0.62 ± 0.22 µM). In all synthesis compounds the compound **5** shows the good active potential towards the alpha-amylase enzyme inhibition having $IC_{50}$ = 1.078 ± 0.25 µM compares to the standard acarbose shows $IC_{50}$ = 0.62 ± 0.22 µM.

The compound **5** is having highly potent compare remaining compound in which the two hydroxyl groups are present at ortho and para position on the phenyl group. Which indicates the position of substituents also plays the vital role in the activity of the compounds.

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*In silico* docking study of the highly potent compounds like **5,10.21.22** is shown in **table.7**

| **compounds** | **Amino acid involved in H-bond formation** |
|---|---|
| 5 | TRP59 (4 hydroxyl group of rings) and GLN63 (4 hydroxyl group of rings) |
| 10 | GLN63 (Oxygen and 2-hyroxyl groups) |
| 21 | HIS201 (Nitro group oxygen) |
| 23 | HIS201 (pi-pi interaction seen) |

Table.7: *In silico* docking study of benzofuran carbohydrazide derivatives

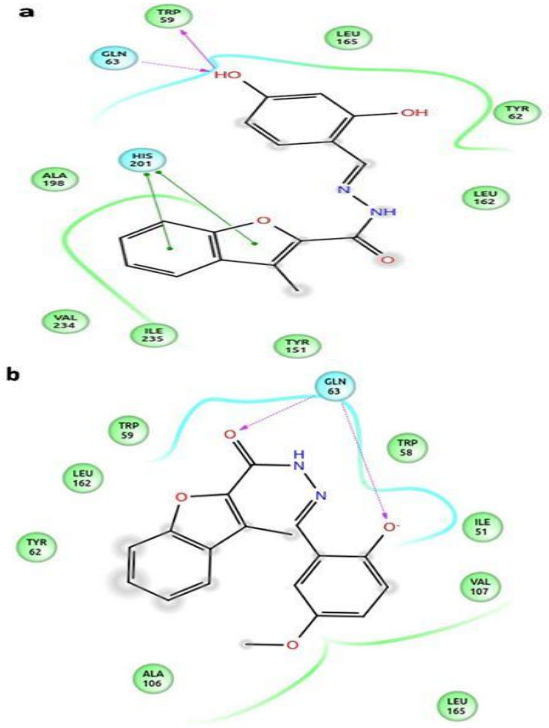


Fig.6: Predicted binding patterns of active benzofuran hydrazone derivatives (a) compound **5** and (b) compound **10** showing stick form.

M. Taha *et.al.* synthesized (**1-23)** derivatives of 2-(2-methyl-5-nitro-1H-imidazol-1-yl) ethyl aryl ether. They also performed there *in vitro* and *in silico* study to determine their α-amylase inhibitory potential. [19]

**Chemistry**

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The 2-(2-methyl-5-nitro-1H-imidazol-1-yl) ethanol is reacted with sodium hydride in dried THF followed by the addition of 1.1 equivalent benzyl halide to give the 2-(2-methyl-5-nitro-1H-imidazol-1-yl) ethyl aryl ether.

All the derivativesshowsignificantinhibitory potentialhaving$IC_{50}$valuerangingfrom0.38±0.82to3.16±0.31µMascomparetostand ard drug acarbose. In all synthesis compounds the compound **19** shows the good active potential towards the alpha-amylase enzyme inhibition having $IC_{50}$ = 0.38 ± 0.82 µM to that of marketed drug called acarbose having $IC_{50}$ = 0.62 ± 0.22 µM.

In order to show the binding patterns of synthesized indole carbohydrazide derivatives (**1-23**), dry lab simulation was done targeting the crystal structure of alpha-amylase enzyme (PDB ID: 4W93).

Dry lab studies reveal the Binding pattern of compound **19**, with enzyme alpha-amylase showed that the imidazole nitrogen forms a hydrogen bond with side chain $NH_2$of amino acid GLN63 .

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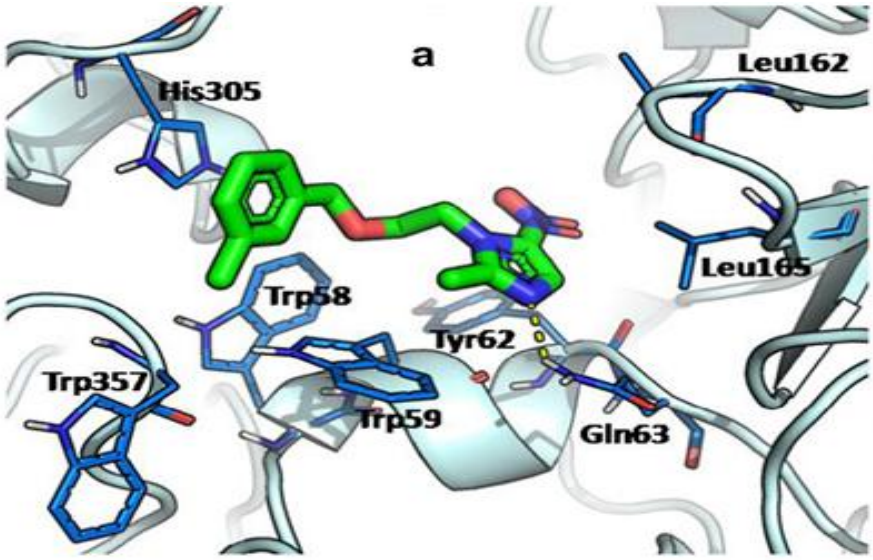


**Fig:9** Predicted binding patterns of active 2-(2-methyl-5-nitro-1H-imidazol-1-yl) ethyl aryl ether derivatives (a) compound **19** (green). Doted yellow lines indicates the hydrogen bond.

U.Salar*et.al.* synthesized (**5-27**) derivatives of HydrazinylThiazoleChromones as a α-amylase inhibitor and performed *in vitro* and dry labstudy.[20]

Chemistry

The new HydrazinylThiazoleform of Chromones (**5-27**) were prepared by multiple steps

First the 6-methylchromone (2) is prepared by treating 5-methyl-2-acetophenone (1) in the presence of $POCl_3$ and DMF.The product formed in the step-1 is condensed (2 hrs.) with thiosemicarbazide in ethanol leads to corresponding 5-methyl-thiosemicarbazone (3) is formed.

The compound (3) formed in step-2 undergoreaction withverity of phenacyl bromides, which undergoes cyclic reaction in the by the help of triethylamine (4) under reflux for 3 hours leads to formation of HydrazinylThiazole substituted Chromones (4).

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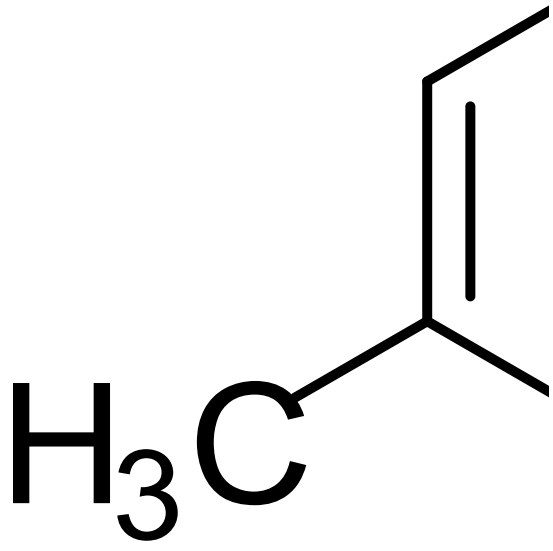


All the compound (**5-27**)showsignificantinhibitory activity having$IC_{50}$valuerangingfrom2.186±0.03to3.405±0.21µM.In all synthesis compounds the compound **19** shows the good active potential towards the alpha-amylase enzyme inhibition having $IC_{50}$ = 2.186 ± 0.03 µM compared with the acarbose having $IC_{50}$ = 1.90 ± 0.07 µM.

Dry lab studies reveal the Binding pattern of compound **19**, with enzyme alpha-amylase having dock score -9.7919.

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It forms a hydrogen bond ASP197 with first Carbone of the compound and nitrogen (19) form with amino acid ASP300 also. A hydrogen acceptor force of attraction is present between oxygen (15) of compound with amino acid HIS305 in the crystal structure of alpha-amylase enzyme.

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| Compounds | Docking Score | Amino acid involved in H-bond formation |
|---|---|---|
| 19 | −9.7919 | ASP197, ASP356, HIS305 |
| 20 | −8.9694 | ASP197, ASP300, HIS101 |
| 21 | −8.5183 | ASP300,ASP356, TRP59, TRP59 |
| 22 | −8.2417 | ASP356, ASP197, TYR62, GLU233 and ALA198 |

Table.8: *In silico* docking study (docking score of hydrazinylthiazole derivatives)

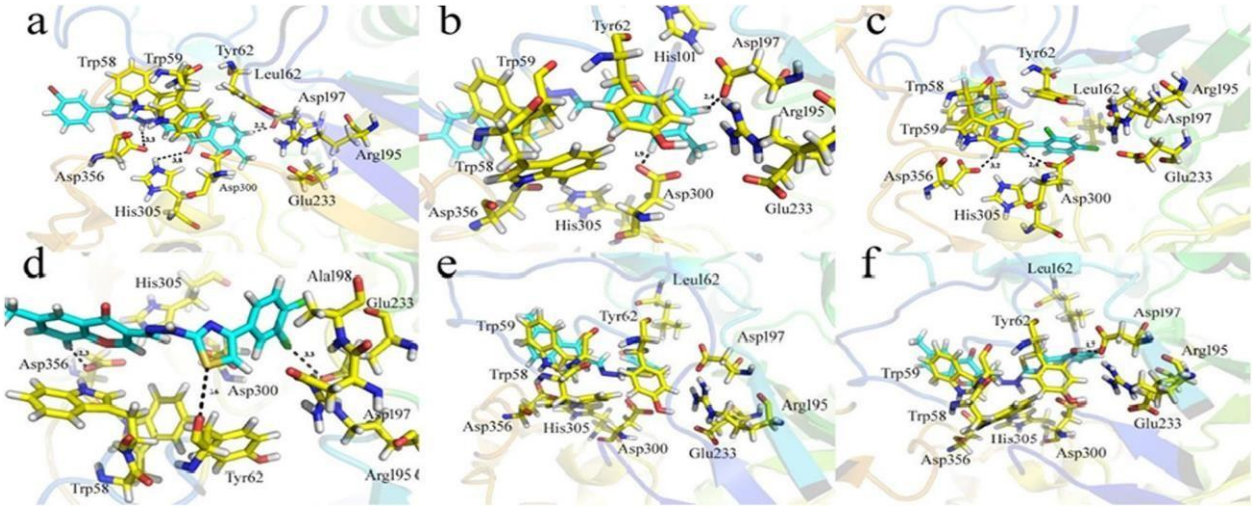


**Fig:10**Binding pattern of compounds- 19 (a), 20 (b), 21 (**c**), 22 (**d**), 17 (**e**), 18 (**f**) on active site of *α*-amylase enzyme.

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## Conclusion

Diabetes mellitus (DM) is one of the present leading metabolic disorder leads to several complicative parameter develops in the human body as directly or indirectly. As the timely the condition is not treated lead to severe ill-health condition in the body, even the death condition took place. However, there is more need of new novel moiety to be developed on the urgent bases to reduce the sever complication developed by the DM in the human body. Hence my review tends to simply and effectively gives the information of new novel moiety at one place.

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