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# Heterocyclic compounds as a magic bullet for diabetes mellitus: a review

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Diabetes mellitus (DM) is a major metabolic disorder due to hyperglycemia, which is increasing all over the world. From the last two decades, the use of synthetic agents has risen due to their major involvement in curing of chronic diseases including DM. The core skeleton of drugs has been studied such as thiazolidinone, azole, chalcone, pyrrole and pyrimidine along with their derivatives. Diabetics assays have been performed in consideration of different enzymes such as  $\alpha$ -glycosidase,  $\alpha$ -amylase, and  $\alpha$ -galactosidase against acarbose standard drug. The studied moieties were depicted in both models: *in vivo* as well as *in vitro*. Molecular docking of the studied compounds as antidiabetic molecules was performed with the help of Auto Dock and molecular operating environment (MOE) software. Amino acid residues Asp349, Arg312, Arg439, Asn241, Val303, Glu304, Phe158, His103, Lys422 and Thr207 that are present on the active sites of diabetic related enzymes showed interactions with ligand molecules. In this review data were organized for the synthesis of heterocyclic compounds through various routes along with their antidiabetic potential, and further studies such as pharmacokinetic and toxicology studies should be executed before going for clinical trials.

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## 1 Diabetes mellitus

Diabetes mellitus<sup>1</sup> is an ordinary, chronic,<sup>2</sup> persistent,<sup>3</sup> and metabolic disease.<sup>4</sup> It is a disorder that arises due to the increase of glucose<sup>5,6</sup> in blood, which leads to hyperglycemia.<sup>7</sup> DM is linked with dysfunction of the eyes,<sup>8</sup> kidneys,<sup>9</sup> and heart.<sup>10</sup> In broad terms,<sup>11</sup> DM is classified into type-I DM, which is due to the impairment of pancreatic  $\beta$  cells,<sup>11</sup> and type-II DM,<sup>12</sup> due to insulin resistance<sup>13</sup> or by destruction of secreted insulin.<sup>14</sup> Type-II, also known as non-insulin-dependent diabetes mellitus<sup>15</sup> is the most commonly occurring diabetes in 80% of the total affected patients around the world.<sup>16</sup> It is a complex disease<sup>17</sup> distinguished by resistance of insulin and lower insulin secretion.<sup>18</sup> The effect of this disease on social health is closely related to the co-occurrence of both disorders, metabolic and cardiovascular.<sup>19</sup> About 0.5 billion patients are affected world wide by these metabolic disorders. It is accountable for nearly 5 million deaths every year.<sup>20</sup> DM generally impairs the body's potential to use the energy in food.<sup>21</sup> The World Health Organization (WHO) reported that the global spreading number of diabetes has been 108 million people in 1980 which raised to 422 million people in 2014.<sup>22</sup> It is presumed that it will rise by 5.4% in 2025.<sup>23</sup> Similarly, report from the WHO narrated that about 250 million people are right now living with diabetes and this number is expected to be more than 366 million by 2030. This increase has been linked with

lifespan expansion, higher cases of obesity, and stress. Recent trends in medicinal chemistry research have showed that there is a higher acceptance of molecular hybridization for drug synthesis, which is based on the mixture of two or more pharmacophoric moieties of various biologically active substances to prepare a new influential hybrid molecule with greater effectiveness and affinity in comparison with standard one.<sup>24</sup> In 2016, it was the seventh most death-causing disease in the world.<sup>25</sup> Another report of WHO narrated that more than 400 million cases of diabetes, and this figure may increase to 592 million by 2035, owing to an increased rate of adult-onset diabetes (T2DM).<sup>26</sup>

### 1.1 Diabetes mellitus and other diseases

Diabetics carrier person faces various complications<sup>27</sup> regarding health<sup>28</sup> including endothelial defectiveness,<sup>29</sup> a key source for chief macro-vascular complications<sup>30</sup> such as hypertension,<sup>31</sup> myocardial ischemia,<sup>32</sup> and peripheral vasculopathy.<sup>33</sup> In the past few days, heart problems, stroke<sup>34</sup> are the major reasons for death<sup>35</sup> and dysfunction among people with type-II diabetes.<sup>36</sup> Lower levels of glucose tolerance<sup>37</sup> and higher blood pressure are nearly associated. Hypertension<sup>38</sup> and high blood pressure rate<sup>39</sup> are mostly common in all types of diabetes and also effects nephrons of kidneys.<sup>40</sup> Long-term insulin affects the weight of the patient,<sup>41</sup> which is indirectly associated with blood pressure issues. Diabetic patients also have non-specific arteriolar hyalinosis,<sup>42</sup> interstitial fibrosis,<sup>43</sup> and mild glomerulopathy.<sup>44</sup> Although synthetic drugs have so many complications even in the form of their side effects and they are still being sold

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in the market as therapeutic agents. The chronic DM consequence is higher blood sugar levels, causing the metabolic disturbance of protein,<sup>45</sup> fat,<sup>46</sup> and carbohydrate.<sup>47,48</sup> It is currently the third foremost cause of mortality worldwide.<sup>49</sup> It is also associated with numerous postprandial effects<sup>50</sup> *i.e.* atrial fibrillation<sup>51</sup> dying, obesity,<sup>52</sup> blindness,<sup>53</sup> lower limb amputation,<sup>54</sup> and fatty liver disease.<sup>55</sup> All through the current Covid-19 pandemic, it was seen that the likelihoods of diabetic patients<sup>56,57</sup> to be sick by the virus are 5–18% higher than the others. However, in the SARS-CoV-1 epidemic in 2002–2003, diabetes was the single sovereign factor to surge the complications.<sup>58</sup>

## 1.2 Natural resources for treatment of diabetes mellitus

Aloe,<sup>59</sup> mint,<sup>60</sup> banana,<sup>61</sup> bitter melon,<sup>62</sup> caper bush,<sup>63</sup> cinnamon,<sup>64</sup> cocoa,<sup>65</sup> coffee,<sup>66</sup> fenugreek,<sup>67</sup> garlic,<sup>68</sup> guava,<sup>69</sup> turmeric,<sup>70</sup> tea,<sup>71</sup> walnuts,<sup>72</sup> Shaggy bindweed,<sup>73</sup> *Yerba mates*,<sup>74</sup> *Bambusa tulda*,<sup>75</sup> *Ficus bengalensis*,<sup>76</sup> *Ferula orientalis*,<sup>77</sup> *Gymnema sylvestre*,<sup>78</sup> *Dioscorea japonica*,<sup>79</sup> *Artemisia abyssinica*,<sup>80</sup> *Phaseolus vulgaris*,<sup>81</sup> *Datura quercifolia*,<sup>82</sup> *Cassia fistula*,<sup>83</sup> *Citrus aurantium*,<sup>84</sup> *Ficus benghalensis*,<sup>85</sup> *Polygonum aviculare*,<sup>86</sup> *Allium tuncelianum*,<sup>87</sup> *Astragalus brachycalyx*,<sup>88</sup> *Ferulago stelletta*,<sup>89</sup> and *Rhizophora mucronate*<sup>90</sup> are natural sources that contain chemical moieties which are effective against diabetes.<sup>91</sup> However, recent research-based studies showed more aim to develop new drugs that can be provided orally for the therapeutics uses of diabetes disease.<sup>92–95</sup>

## 2 Diabetes therapy

The main curative way used for diabetes Type-I is the injection of insulin in the subcutaneous layer of the body, which is an invasive process. However, for diabetes type-II, diet adjustment, exercise, and usage of several antidiabetic medicines.<sup>96</sup> These treatments have few sorts of side effects which are given as pain in the area of injection, obesity, low sugar level, and less control of blood glucose levels (BGL). Therefore, novel antidiabetic agents that can be administered using a less-invasive approach are needed.<sup>97</sup> At present available oral anti-hyperglycemic agents have contrary reactions such as gastrointestinal disorders, hypersensitivity reactions, weight gain, and harm to main organs.<sup>98</sup> If the number of DM patient reaches 366 million in 2030 from 171 million in 2000, novel medications will be needed to cure it.<sup>98</sup> Treatments of type-II DM include improvement of insulin sensitivity<sup>99</sup> or falling the proportion of carbohydrate absorption from the gastrointestinal tract. Although, the medicines used to treat DM have liver and renal dysfunction.<sup>100</sup>

### 2.1 $\alpha$ -Glycosidase and diabetes

$\alpha$ -Glycosidase is an enzyme<sup>101</sup> of upper part of small intestine<sup>102</sup> which is used for hydrolyzation of polysaccharides.<sup>103</sup> Its competitive restraint is a helping tool for the administration of blood sugar regulation.<sup>104</sup> Therefore,  $\alpha$ -glycosidase inhibiting agents either synthetic or natural are considered as a drug that can lower type 2 diabetes. Till now, mainly three naturally

occurring  $\alpha$ -glycosidase inhibitors; voglibose, miglitol, and acarbose are remotely using for the control of diabetes.<sup>105–109</sup> Insulin controls glucose of blood by phosphatidylinositol 3-kinase<sup>110</sup> *via* signaling pathway. The major issue in type II diabetes is that the insulin-producing cells become resistant, which disrupts the insulin signaling pathway and impairs the ability of target tissues like lipids and muscles to absorb glucose.<sup>111</sup> Correspondingly, any irregularity that occurs in the PI3K pathway influences the insulin signal transduction.<sup>112</sup> Metabolic enzymes play essential roles in biological systems, and their activation and suppression is associated with a variety of health problems.<sup>113</sup>  $\alpha$ -Glycosidase inhibition leads to the reduction of increased postprandial blood glucose levels.<sup>114</sup>

Polysaccharide of sugars are digested by the enzyme  $\alpha$ -amylase to produce sub units of disaccharides and oligosaccharides which are subsequently degraded by the enzyme  $\alpha$ -glycosidase to produce monosaccharide units.<sup>115</sup> The inhibition of  $\alpha$ -amylase and  $\alpha$ -glycosidase hampers blood glucose levels rises afterward consumption of carbohydrates and can be a central approach in the administration of non-insulin-dependent diabetes.<sup>7</sup> The two complex enzymes as maltase-glucoamylase and sucrose-isomaltase play role in the breakdown of alimentary sugars and starch to glucose.<sup>25</sup> Few other auspicious targets that are considered for DM are dipeptidyl peptidase-4, insulin secretagogues, peroxisome proliferator-activated receptor (PPAR- $\gamma$ ), *etc.*,<sup>116</sup>  $\alpha$  and  $\beta$ -Glycosidases are identified to catalyze the cleavage of glycosidic bonds.<sup>58</sup> Different types of medicines were used to inhibit  $\alpha$ -glycosidase, including acarbose, voglibose, and miglitol in the actual treatment of type-II diabetes mellitus.  $\alpha$ -Glycosidase<sup>117</sup> acetylcholinesterase (AChE), and butyrylcholinesterase (BChE) enzymes have all been positively inhibited by sedative medications such as hipnodex, ketamine midazolam, pentil sodium and propofol.<sup>118</sup> But, such inhibitors, which have a structural range, need tedious multi-steps in preparation.<sup>119</sup> Recently, numerous synthetic agents have been stated to inhibit  $\alpha$ -glycosidase.<sup>120</sup> Appropriate care and early diabetes diagnosis should be prioritized in order to lessen the impact of diabetes on a person and society.<sup>121</sup> Insulin is a vital hormone<sup>122</sup> that plays a key role in the development of human tissues<sup>123</sup> and leads to glucose homeostasis.<sup>124</sup> The active molecule of insulin is a small protein that contains two chains  $\alpha$  and  $\beta$  which have two disulfide bonds.<sup>125</sup> An anabolic hormone insulin<sup>126</sup> plays an imperious part in glucose metabolism, synthesis of protein,<sup>127</sup> and translocation of important substances *i.e.*, fatty acids, amino acids, and glucose along the biological membrane.<sup>128,129</sup> The source of insulin secretion is pancreatic  $\beta$ -cells<sup>130</sup> as a single-chain precursor, preproinsulin, along a signal sequence that allows its way to move into secretory vesicles.<sup>131</sup> The proteolytic signal is removed by proteolytic manners then resultantly proinsulin is formed. In response, an increase in blood sugar, secreted proinsulin transformed into active insulin by certain proteases.

The major purpose of this review is to reveal new findings of heterocyclic synthetic agents for diabetes, along objective focused on novel synthesis approaches and antidiabetic potentials.



### 3 Synthetic agents as antidiabetics

A number of synthetic drugs are available in market that had their great potential in order to cure diabetes as metformin,<sup>132</sup> gliquidone,<sup>133</sup> nateglinide,<sup>134</sup> phenformin,<sup>135</sup> rosiglitazone,<sup>136</sup> glimepiride,<sup>137</sup> pioglitazone,<sup>138</sup> glibenclamide, exenatide,<sup>139</sup> mitiglinide,<sup>140</sup> gliclazide,<sup>141</sup> chlorpropamide,<sup>142</sup> glipizide,<sup>143</sup> acetohexamide,<sup>144</sup> tolbutamide,<sup>145</sup> dapagliflozin,<sup>146</sup> dulaglutide,<sup>147</sup> liraglutide,<sup>148</sup> glyburide,<sup>149</sup> canagliflozin,<sup>150</sup> and repaglinide.<sup>151</sup> Some therapeutic agents are used to cure DM, classified as  $\alpha$ -glycosidase inhibitors, thiazolidinediones,<sup>5,152</sup> biguanides,<sup>153</sup> sulfonyleureas,<sup>154</sup> and gliptins.<sup>155</sup> Deazaxanthine<sup>156</sup> and also various heterocyclic synthetic based pyrrole,<sup>157</sup> pyrazole,<sup>158</sup> pyrrolidine,<sup>159</sup> oxindole,<sup>160</sup> isatin,<sup>161</sup> imidazole,<sup>162</sup> benzimidazole,<sup>163</sup> triazole,<sup>164</sup> oxadiazole,<sup>165</sup> thiazole,<sup>166</sup> pyridine,<sup>167</sup> piperazine,<sup>168</sup> thiazolidinone, thiadiazole,<sup>169</sup> benzofuran,<sup>170</sup> benzoxazole,<sup>171</sup> coumarin,<sup>172</sup> flavone,<sup>173</sup> piperidine,<sup>174</sup>

xanthone<sup>175</sup> and pyrimidine.<sup>176</sup> The core structures of antidiabetic moieties are given in Fig. 1. There are many synthetic agents used for diabetes that control glucose levels of plasma and to gain insulin-mimetic effects. Every class of drug has various mechanisms to control the blood glucose. Drugs are also connected with numerous negative effects; it is good to search for more and new drugs that can combat this disease more effectively with lower side effects.<sup>177</sup>

#### 3.1 Synthesis of thiazolidinone

Ottana and co-authors reported the synthesis of thiazolidinone by multistep reaction using phenyl isothiocyanate and amino acetic acid as reactants. The reaction was carried out in acidic pH under reflux conditions. The resulting intermediate was further condensed undergoes Knoevenagel condensation with appropriate aromatic aldehydes on refluxing in ethanolic medium using piperidine as a base.<sup>178</sup> The formulation of fused

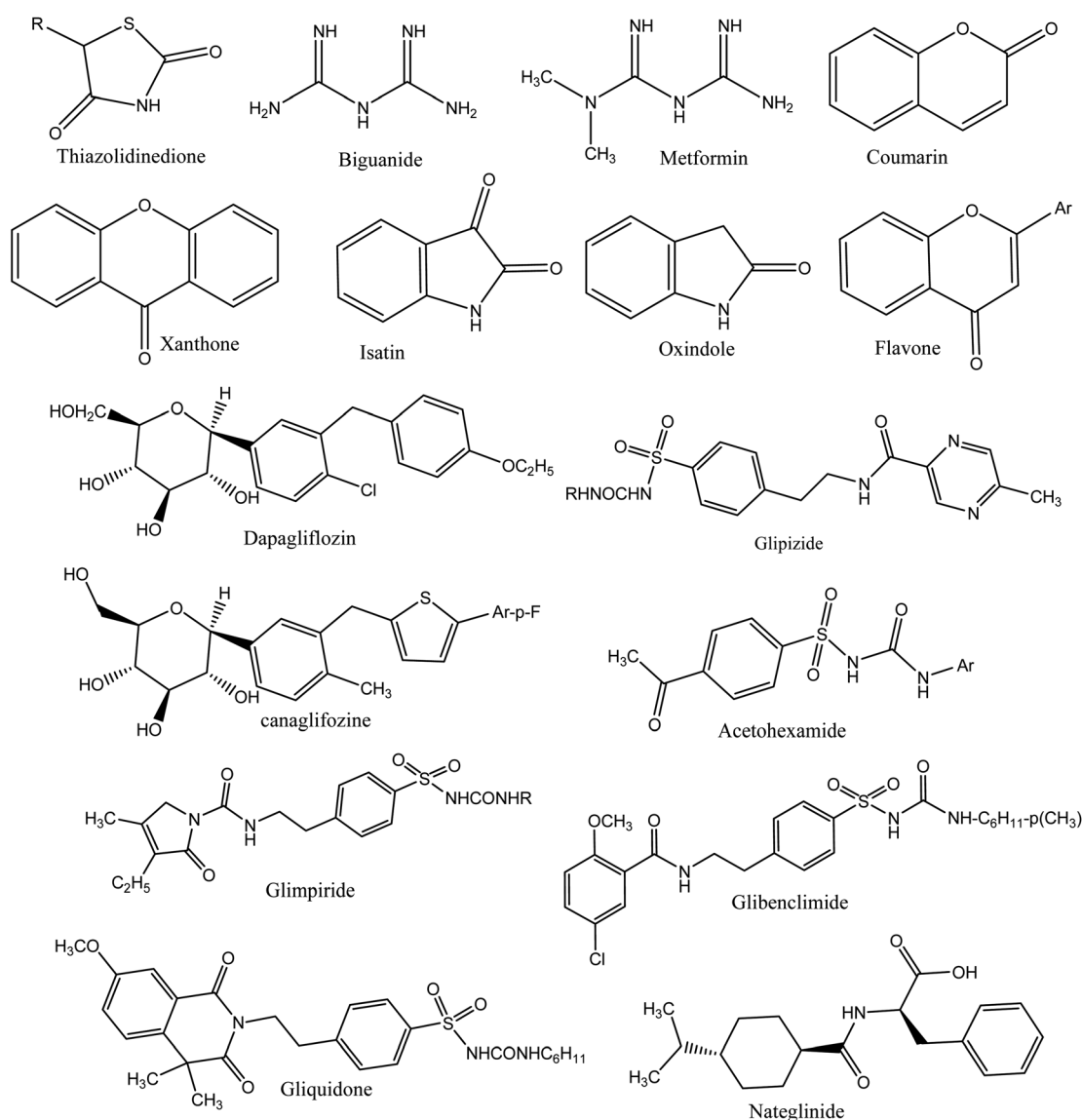


Fig. 1 The core structures of antidiabetic moieties.

substituted thiazolidinone was reported from chloroacetic acid and thiourea under reflux in concentrated HCl. The thiazolidine-2,4-dione was further reacted with anhydrous sodium acetate in glacial acetic acid at 110–120 °C followed by Knoevenagel condensation with thiophene carboxaldehyde.<sup>179</sup> Naim along colleagues reported the synthesis of thiazolidine-dione derivatives. In the first step sulphanilamide in concentrated HCl, sodium nitrite and cold SnCl<sub>2</sub> were stirred to form hydrazinyl benzene sulphonamide which was further converted into substituted pyrazole carbaldehydes and thiazolidinedione using different aldehydes and other reagents on reflux for 2–3 h.<sup>22</sup> Thiazolidinone also synthesized from 3-acetyl coumarins as starting material which was reacted with Br<sub>2</sub> in acetic acid at 25 °C to form 3-bromoacetyl coumarin which was allowed to reflux with substituted benzaldehyde resulting thiosemicarbazones up to 8 h to form intermediate in good yields. The last product was treated with thiolactic acid under reflux in ZnCl<sub>2</sub> and dioxane to form end product. The structures of the compounds were characterized by IR, H-NMR.<sup>180</sup> Knoevenagel condensation reaction was done between terephthalaldehyde and 1,3-thiazolidine-2,4-dione (prepared by refluxing chloroacetic acid and thiourea in water). Furthermore, base-catalyzed condensation with appropriate aromatic ketones and potassium hydroxide in the presence of ethanol to form a targeted product in good yield.<sup>181</sup> A series of amino-derived thiazolidinone were prepared by the reaction of ethylenediamine with CS<sub>2</sub> in the presence of triethylamine and ethanol, followed by a reaction with chloroacetic acid. The five-membered ring was obtained after stirring the former suspension in hot HCl for 5 min. The final products were synthesized by refluxing of basic skeleton with respective aldehyde in acidic medium.<sup>182</sup> The pyrazolyl-based thiazolidinones were prepared by reacting *p*-toluidine, acetic acid, sodium acetate, and chloroacetyl chloride. The starting material was refluxed in a microwave synthesizer in the presence of thiourea. Schiff bases were formed using different aldehyde, upon thioglycolic addition and reflux under microwave synthesizer effective product was formed.<sup>183</sup> The substituted oxo-thiazolidinones were prepared through electrophilic substitutions reaction by ethyl chloroacetate on hydroxy pyrazine on refluxing. The synthesized intermediate was further, aminated with alkyl isocyanate and chloroacetic acid yielded the end product.<sup>184</sup>

Imines were initially synthesized by reacting piperonylamine with substituted aromatic aldehydes. The imine was created quite practically at this point by just shaking the reactants, and was employed in the cyclization reaction. The most widely used technique for attaining 4-thiazolidinones, was employed as cyclization process by Refluxing in EtOH, and end product of piperonyl based 4-thiazolidinones (**2a–i**) derivatives were obtained.<sup>185</sup>

### 3.2 Antidiabetic activities of thiazolidinone

The inhibition of aldose reductase (bovine lens) was done *via in vitro* model using sorbinil and epalrestat as standard drugs. The more satisfactory inhibitors of aldose reductase (ALR2) were **5c** and **5e** compounds with IC<sub>50</sub> values 0.25 mM and 1.32 mM

respectively, owing to the presence of an acetic acid group that more actively interacted with the enzyme. A molecular modeling study was done with **5c** and **5h** compounds. ARL2 binding site can be divided into two different regions. The docking outcomes were anticipated that **5c** compound forms very stable IDD594 conformation ( $\Delta GAD4 = -9.14 \text{ kcal mol}^{-1}$ ) along with more occupied cluster (size 60/100). However, standards sorbinil ( $\Delta GAD4 = -7.27 \text{ kcal mol}^{-1}$ ) and tolrestat ( $\Delta GAD4 = -7.61 \text{ kcal mol}^{-1}$ ) were not found with such a populated cluster.<sup>178</sup>

Insulin has a negative regulator known as protein tyrosine phosphatase 1B (PTP1B) dephosphorylates. *In vitro* model, compounds **13** and **16** showed inhibition of PTP1B with IC<sub>50</sub> 7.31  $\mu\text{M}$  and 8.73  $\mu\text{M}$  respectively using *in vitro* model. The consequences directed those compounds with phenyl and methyl sulphonate substituted profoundly inhibited PTP1B. *In silico* inhibition of PTP1B by more active compounds **13** and **16** were performed. Hydrogen bonding was observed between the oxygen of C-4 carbonyl and Ser216, Ala217, and Arg221 amino acids of the active site in docking studies. Thiazolidinone nitrogen group has H-bonding contact with Arg221, along other interactions. Anti-hyperglycemic action of compounds checked by *in vivo* model after 7 days of administration. Almost 15.71 to 32.13% lowering of sugar level was seen in contrast to pioglitazone (31%). Compounds **13** and **16** decreased the blood sugar level by 32.13% and 30.22% respectively. Comparable results of SAR inferred that compounds having alkyl substitutions ( $-\text{RSO}_3$ ) at benzene ring improved anti-hyperglycemic activity with methyl and phenyl than bulky groups (Ar-NO<sub>2</sub>, 2,4,6-trimethylphenyl, 2-naphthyl, etc.).<sup>179</sup>

*In vivo* hypoglycemic activity was seen in STZ induced diabetic rats and almost all compounds exhibited PPAR- $\gamma$  trans-activation. Blood glucose level was checked after 1, 7, 15 days of drug administration. The decreasing order of lowering of glucose level for **7b**, **7d** and **7p** was  $138.7 \pm 4.4 \text{ mg dL}^{-1} > 137.4 \pm 5.3 \text{ mg dL}^{-1} > 134.1 \pm 4.2 \text{ mg dL}^{-1}$  respectively. The anti-hyperglycemic activity for standard pioglitazone was  $132.2 \pm 5.0 \text{ mg dL}^{-1}$  although **7c**, and **7f** compounds exposed modest results in contrast to standard drugs. The SAR assay of compounds was focused on an aryl ring (substitution) that connected with the pyrazole core. Though, those compounds like **7d** having halogen substitution at *meta* and *para* position were considered as more inhibitory compounds than others. Those compounds that had electron decreasing groups also reduced activity.<sup>22</sup>

Antihyperglycemic effect of compounds was determined by orally administering of Albino rats by synthesized coumarino thiazolo-thiazolidinones (**4a–4j**) and reference drug rosiglitazone (200 mcg kg<sup>-1</sup>) solution in Tween-80 while diabetes was induced by streptozocin. The blood sugar level was assessed by semi auto analyzer using a glucose estimation kit. Average glucose concentrations (mg day<sup>-1</sup>  $\pm$  SEM) for **4a**, **4g**, and **4h** were  $74.33 \pm 1.156$ ,  $75.58 \pm 1.375$  and  $75.63 \pm 1.197$  respectively, although the values of mean percentage change in anti-hyperglycemic activity were found to be  $23.845 \pm 2.134\%$ ,  $27.567 \pm 1.708\%$  and  $27.394 \pm 2.564\%$ , respectively.<sup>180</sup>





$\alpha$ -Glycosidase inhibitory activity of compounds was studied using phosphate buffer (50 mM) and PNP glycoside (1 mM) by incubation. The outcomes of the test were also compared with acarbose and type of inhibition was also assessed by plotting Lineweaver Burk plots using various concentrations of compounds. Minimum inhibitory concentration (MIC) of highly active compounds **5p** and **5o** was  $6.56 \pm 0.81$  and  $8.92 \pm 0.21 \mu\text{g mL}^{-1}$  respectively. This inhibitory activity was substantially varied owing to different groups on  $\alpha$ ,  $\beta$  unsaturated ketone. Compounds showed a decreasing order of compounds **5p** > **5n** > **5m** regarding to  $\text{IC}_{50}$  values ( $2,4\text{-di-F-C}_6\text{H}_3$ ,  $\text{IC}_{50}$ :  $6.56 \pm 0.81 \mu\text{g mL}^{-1}$ ) > ( $2,4\text{-di-Cl-C}_6\text{H}_3$ ,  $\text{IC}_{50}$ :  $29.47 \pm 0.32 \mu\text{g mL}^{-1}$ ) > ( $2\text{-Cl-C}_6\text{H}_4$ ,  $\text{IC}_{50}$ :  $32.11 \pm 0.33 \mu\text{g mL}^{-1}$ ) respectively.<sup>181</sup>

$\alpha$ -Glycosidase inhibition was done through *in vitro* assay. All derivatives showed inhibition (%) in a good range, however, **3a** ( $77.7 \pm 1.3\%$ ), **b** ( $88.1 \pm 0.8\%$ ) whereas, **4c** ( $74.8 \pm 1.4\%$ ) compared to acarbose ( $89.3 \pm 1.0\%$ ). The molecular modeling study was accomplished by the MOE program against PDB file of 3WEO ( $\alpha$ -glycosidase). The values of *E*-score range between  $-0.7121$  to  $-5.2428$ , while, **3b**, **4a** and **4b** docking score values are  $-4.9815$ ,  $-5.2428$  and  $-5.1597$ , respectively.<sup>182</sup>

The antidiabetic action of reported compounds was checked by tail tipping method for streptozocin-induced higher glucose levels in male Wistar rats. The promising antidiabetic activity of **TZN-4** and **TZN-8** was higher than the reference drug. Glibenclamide was a standard drug while streptozocin was used to induce diabetes. Streptozotocin solution was made by mixing with citrate buffer (0.05 M) maintained at a pH of 4.5 up to 24 h. After 72 h of administration, hyperglycemia condition was observed. A dose of just  $100 \text{ mg kg}^{-1}$  (b.w. of rat) of each compound was given and a reduction in sugar level was observed near to 50%. Compound **TZN-2**, **TZN-4**, and **TZN-8** were reported with a certain decrease in mean  $\pm$  SEM values from  $300.5 \pm 0.12$  to  $116.5 \pm 5.90 \text{ mg dL}^{-1}$ ,  $213.5 \pm 8.78$  to  $95.75 \pm 6.06 \text{ mg dL}^{-1}$ , and  $203.7 \pm 13.79$  to  $101.5 \pm 4.5 \text{ mg dL}^{-1}$ , respectively.<sup>183</sup>

The particular dosage (200 mg per kg of body weight) of oxothiazolidinone was administered and dexamethasone was used to induce hyperglycemic activity. The level of percentage of blood glucose reduction was maximum; 155.44% and 124.93% in case of compounds **1** and **2** respectively compared to control. However, intermediate reduction of 103.14%, 100.46% and 70.52% for compounds **3**, **4**, and **5** possessed activity respectively. Although, compounds **6**, **7**, and **8** were confirmed with the lowest antidiabetic potential of 33.88%, 50.00%, and 43.09% respectively against rosiglitazone (145.01%) as a standard drug. Compounds **1** and **2** also showed reduced insulinemia by the effect of dexamethasone and values mainly fall in a good range ( $3.000 \pm 0.033$  to  $3.100 \pm 0.057 \text{ milM}^{-1}$ ).<sup>184</sup> Scheme 1 depicted various synthesis protocols for thiazolidinone.

### 3.3 Synthesis of azole

The azole moiety was prepared according to Mitsunobu reaction by reacting 4-bromo-2-methoxy phenol and (*S*)-ethyl lactate in

THF yielding ester that was converted into alcohol first, later on into azide after reacting with tosyl. The azide was converted into azole by 1,3-dipolar cycloaddition between azide and alkyne in presence of CuI.<sup>186</sup> Ferreira and his colleague synthesized glycolated triazoles *viz* 1,3-dipolar cycloaddition reaction. The structure elucidation was done with modern techniques.<sup>187</sup> The substituted azoles were also synthesized by reacting *p*-halo acetophenones with aldehyde to form chalcones which on reaction with 2-hydrazinobenzothiazole-6-sulfonic acid amide.<sup>188</sup> The substituted oxazole was synthesized from a cheaper source by the reaction of 2-aminophenol and carbon disulfide ( $\text{CS}_2$ ) in alkaline ethanol<sup>189</sup> while, the synthesis of imidazopyridine was done by the reaction of different aldehydes and 5-chloropyridine-2,3-diamine.<sup>190</sup> Similarly, azole-type compounds from a heterocyclic carboxylic acid; carboxylic acid was firstly converted into ester then into amide by reaction with hydrazine. The hydrazine was further treated with  $\text{CS}_2$  in a basic medium to yield azoles.<sup>191</sup> The amino acid-coupled triazole derivatives were prepared using a green approach *via* multicomponent reaction. Salicylaldehyde was reacted with amino acids and thiosemicarbazide using lemon juice as a catalyst at  $100^\circ\text{C}$  for 2 to 3 h which further reflux with *p*-toluenesulfonyl chloride in chloroform using piperidine catalyst and obtained end product.<sup>164</sup> Mamatha and his colleagues reported the synthesis of mercapto oxadiazole using fluoro-benzoic acid as starting agent, other chemical agents used were ethanol, conc.  $\text{H}_2\text{SO}_4$ , hydrazine hydrate, carbon disulfide, potassium hydroxide, and hydrochloric acid, DMF, and anhydrous  $\text{K}_2\text{CO}_3$ .<sup>192</sup> A series of new thiazole derivatives was formulated by “one-pot” multicomponent reaction, by a variety of phenyl hydrazine treatment with aryl isothiocyanate in ethanol to get thiosemicarbazide intermediate which were further treated with phenacyl bromide to get the desired product.<sup>193</sup>

### 3.4 Antidiabetic activities of azoles

Compounds were given well inhibition (*in vitro*) of about 50% of  $\alpha$ -glycosidase ( $14.2\text{--}218.1 \mu\text{M}$ ) as contrasted to acarbose ( $\text{IC}_{50} = 942.0 \mu\text{M}$ ). Enzyme Inhibition  $\text{IC}_{50} = 14.2 \mu\text{M}$  was possessed by **10b** having methoxy substitution on phenyl, which is 67 times more active than acarbose while **10a** with methyl group exhibited lower activity ( $\text{IC}_{50} = 83.8 \mu\text{M}$ ) and had 5 times least inhibitory activities. Compound **10e** with nitro, **10c** with trifluoro phenyl, and **10d** with fluorophenyl having  $\text{IC}_{50}$  values  $21.6 \mu\text{M}$ ,  $28.7 \mu\text{M}$  and  $56.2 \mu\text{M}$ , respectively. Molecular docking score of **10b**, **10c** and **10e** was  $-13.6171$ ,  $-12.0273$  and  $-12.9459$ . Different substitutions had different effects on the interaction of the molecule with receptors as **10b** exhibited with Arg312, Glu304, and Phe158 their bond lengths were 2.93, 3.25, 3.63 Å, respectively, whereas, bond energies were ranged between  $-0.8$ , to  $-0.3$ .<sup>186</sup>

The inhibition of  $\alpha$ -glycosidase was examined using the maltase enzyme (yeast) in comparison to acarbose as reference drug. All three types of  $\beta$ -D-ribosyl,  $\alpha$ -D-galactosyl, and  $\alpha$ -D-xylosyl triazoles were given maximum inhibition values by  $500 \mu\text{M}$  while  $\text{IC}_{50}$  values are also in effective range (4 to  $25 \mu\text{M}$ ) against



acarbose  $108.8 \pm 12.3 \mu\text{mol L}^{-1}$ . The extreme percentage of inhibition seen in the case of **4f** which was  $99.5 \pm 0.1\%$  and lowest one for **7b**  $33.3 \pm 46.1\%$ . Others compounds with different substitutions at C-4 of triazole ring *i.e.*, **4b** (1-cyclohexenyl), **4e** (phenoxyethyl), and **4g** (1-cyclohexanol) were also depicted good inhibition. The glycolated triazole interatomic contacts with MAL12 were inspected using the Ligplot program and CSU/LPC server. A comparison of interactions was done between maltase (MAL12) and **4b**, **4m** (stereoisomers: **4mR** and **4mS**), and standard drug acarbose. The shortest contact distance and potent bonding were seen in the case of **4b**, among nitrogen of triazole ring, Thr207, and OGI atom ( $2.6 \text{ \AA}$ ) with contact area  $39.8 \text{ \AA}^2$ , for **4mR**, H-bonding among pyran (C-14), His103, and CEI atom ( $3.4 \text{ \AA}$ ) with contact area  $20.6 \text{ \AA}^2$  and in **4mS** hydrophobic interactions among pyran (C-13), Phe169 and CEI atom ( $2.4 \text{ \AA}$ ) along contact area of  $34.8 \text{ \AA}^2$ .<sup>187</sup>

Compounds were docked over PPAR agonist and compared with the standard drug, rosiglitazone. Molecular docking studies of synthesized compounds against the PPAR target. Almost eighteen compounds possessed good docking score value than rosiglitazone ( $-5.72$ ). Compound **7k** ( $-10.06$ ) was observed pi-pi contacts and hydrogen bonding with Arg280 and Lys261 while, compound **8g** ( $-10.03$ ) had various hydrogen bonding interactions with Lys261 residue. Synthesized compounds **7c**, **7d**, **7i-l**, **8c**, **8d**, **8g**, and **8h** in transactivation test were found with intermediate alleviation of PPAR. Compounds **7k**, **7j** and **8h** evaluated with elevation in PPAR transactivation  $54.93\%$ ,  $54.01$  and  $54.29\%$ , respectively than rosiglitazone ( $81.68\%$ ). In STZ-induced diabetic rats, it was found that compounds **7i-l**, **8g**, and **8h** caused lowering of blood plasma sugar level up to normal range on 15<sup>th</sup> day of the administration while, **7c**, **7d**, **8c**, and **8d** lowered glucose level nearly as rosiglitazone and glibenclamide. Compounds with *p*-chloroacetophenone are found more active than *p*-bromoacetophenone. Fluoro group on aryl ring increase activity than chloro, however, presence of alkyl and alkoxy on phenyl ring dropped biological activity.<sup>188</sup>

Substituted oxazole's **4a-4m** were assessed for *in vitro*  $\alpha$ -glycosidase (baker's yeast) inhibitory activity using acarbose as a positive control. The more effective inhibition was shown by **4f-4i**, **4k** and **4m** ( $32.49 \pm 0.17$ – $120.24 \pm 0.51 \mu\text{M}$ ) as contrasted to acarbose ( $\text{IC}_{50} = 817.38 \pm 6.27 \mu\text{M}$ ). Different substitution at phenyl ring was found to play an imperative role in inhibition like for **4g** with 4-phenoxy ( $\text{IC}_{50} = 32.49 \pm 0.17$ ). Electron-donors *i.e.*, alkyl and alkoxy groups were decreased the rate of inhibition of enzymes in **4b**, **4c**, **4d**, **4e**, **4l**, and **4j** compared to electron-withdrawing groups 3- $\text{CF}_3$ , 4-F, 4-Cl and 2,4- $\text{Cl}_2$  in respective compounds **4f**, **4h**, **4i**, and **4k** ( $\text{IC}_{50}$ :  $120.24 \pm 0.51$  to  $44.4 \pm 0.17 \mu\text{M}$ ). A molecular simulations study was done using *Saccharomyces cerevisiae* extracted  $\alpha$ -glycosidase over Autodock vina 1.1.2. and contacts illustrated visually by PyMOL 1.7.6. Dichlorophenyl substituted exhibited arene-cation contacts with Arg439 and  $\pi$ - $\pi$  stacking interaction with Phe157 in both **4k** and **4g**, while benzoxazole rings with Phe157, Phe300, and Val303. Hydrogen bonding was observed with Asp349 by **4k** and **4g** ( $3.2$ – $3.3 \text{ \AA}$ ). Contrary to all, the terminal phenyl group of **4g**

also formed alkyl- $\pi$  respective interactions with Tyr71 and Phe177 and made **4g** more active compound.<sup>189</sup>

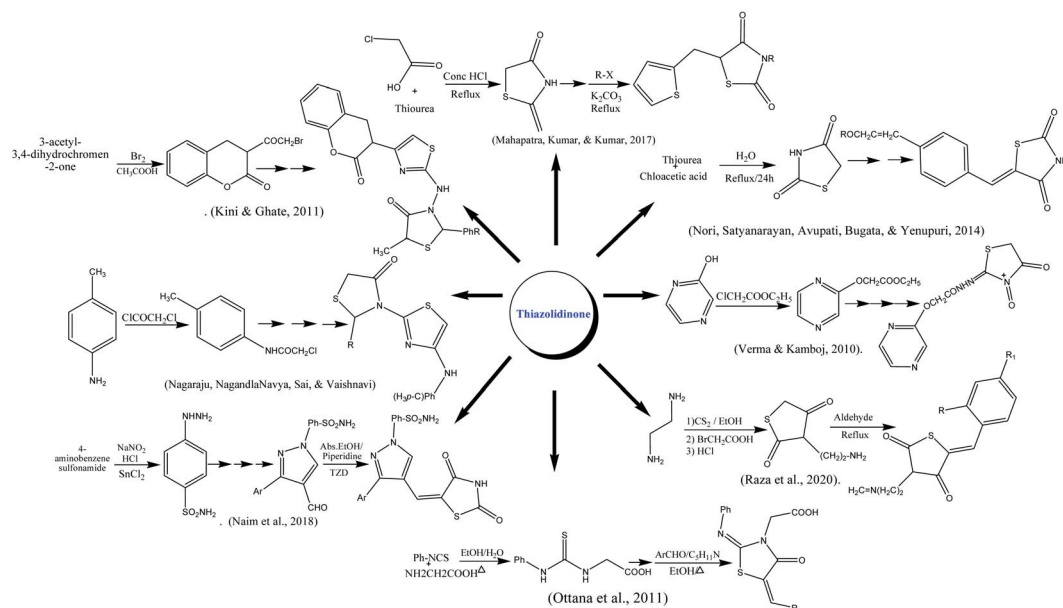
Antiglycation activities of all compounds (**1-26**) were estimated against rutin ( $\text{IC}_{50} = 294.46 \pm 1.50 \mu\text{M}$ ). The assay had revealed that hydroxyl group bearing compound depicted as best antiglycation agents *i.e.*, **2**, **3**, **4**, **6**, **13** and **26** exhibited  $\text{IC}_{50} = 240.10 \pm 2.40 \mu\text{M}$ – $292.10 \pm 3.20 \mu\text{M}$ . However, mono -OH compounds were found less active than di-OH compounds. Compounds with one hydroxyl group at *ortho* position even more inhibition potential than rutin except for **26** contained *p*-hydroxyl groups.<sup>190</sup> Oxadiazole substituted compounds (**8a-l**) were showed inhibition of the  $\alpha$ -glycosidase enzyme and  $\text{IC}_{50}$  values for compounds **8l**, **8h**, **8c**, **8e**, **8d**, and **8f** were  $9.37 \pm 0.03$ ,  $9.46 \pm 0.03$ ,  $12.68 \pm 0.04$ ,  $14.35 \pm 0.02$ ,  $21.49 \pm 0.04$ , and  $21.64 \pm 0.04 \mu\text{M}$  respectively that were more effective than acarbose ( $\text{IC}_{50}$  of  $37.38 \pm 0.12 \mu\text{M}$ ). Compound **8i** revealed percentage of inhibition  $94.74 \pm 0.11$  at concentration of  $0.5 \text{ mM}$ . MOE dock program was used to accomplish modeling over  $\alpha$ -glycosidase (baker's yeast) with PDB ID code: 3N04. In **8h** indolic-NH proton and the carbonyl oxygen of acetamide form effective polar and acidic contacts with Asp73 and Arg404 with  $1.80$  and  $2.01$  angstroms, respectively. Although, these interactions were also in **8i** with Lys422 and Asp420 at a distance of  $2.25 \text{ \AA}$  and  $2.15 \text{ \AA}$ , respectively which bind the compounds at active sites.<sup>191</sup>

Amino acid coupled triazoles were inhibited the  $\alpha$ -amylase enzyme through *in vitro* assay using starch solution ( $0.1\%$ ) with sodium acetate buffer ( $\text{pH} = 4.8$ ,  $16 \text{ mM}$ ). The percentage of inhibition was ranged ( $80.0$ – $75.43\%$ ). *In vivo* inhibition was seen male Wistar by orally administered triazoles compared to gliclazide as a standard drug. Afterward, 4 weeks of compound **3c** ( $100 \text{ mg Kg}^{-1}$ ), dropped the glucose level up to  $49.2\%$ , however, reference drug lowered sugar level about  $54.4\%$ .<sup>164</sup>

The *in vitro* inhibitory potential of compounds was also checked and GOD-POD method was employed to check the glucose liberation. For sucrose inhibition, compound benzothiazole **5** was found with  $14\%$  inhibition ( $5 \text{ mg mL}^{-1}$ ), and **5a**, **5b**, **5f**, and **5h** showed moderate inhibition substituted with benzoyl, *p*-methyl benzoyl, heptyl, and *p*-chloro benzoyl substituents, while compound **5i** (hexyl substituted) and **5j** (acetate group) given lesser activity. The inhibition of  $\alpha$ -glycosidase, **5e** was detected with  $48\%$  inhibition while again  $1\%$  inhibition was shown by **5i** and **5j**. The compound **5e** with coumarin was depicted  $62\%$  inhibition of  $\alpha$ -amylase.<sup>192</sup>

$\alpha$ -Glycosidase inhibition potential of compounds was checked ( $\text{IC}_{50} = 9.06 \pm 0.10$ – $82.50 \pm 1.70 \mu\text{M}$ ) and compared to standard acarbose ( $\text{IC}_{50} = 38.25 \pm 0.12 \mu\text{M}$ ). Compound **12** with the presence of *p*-chloro aniline gives the greatest inhibition than others ( $\text{IC}_{50} = 9.06 \pm 0.10 \mu\text{M}$ ) and effective docking score ( $-11.8617$ ). In benzamide-based azole **1** and **2** with *p*-Cl, *p*-CN at phenyl ring was given inhibitory values ( $\text{IC}_{50}$ ) from  $22.40 \pm 0.32$  to  $23.60 \pm 0.39 \mu\text{M}$  due to electron-withdrawing groups, found that activity increased. While in diphenyl methanimine based azoles showed lesser activity than the other two substituted groups. Docking study of the compounds was exhibited for all three categories compounds. The compound showed **12** pi-interaction on the pocket *via* arene-arene moieties of chloro benzene and aniline with residues which depicted a good



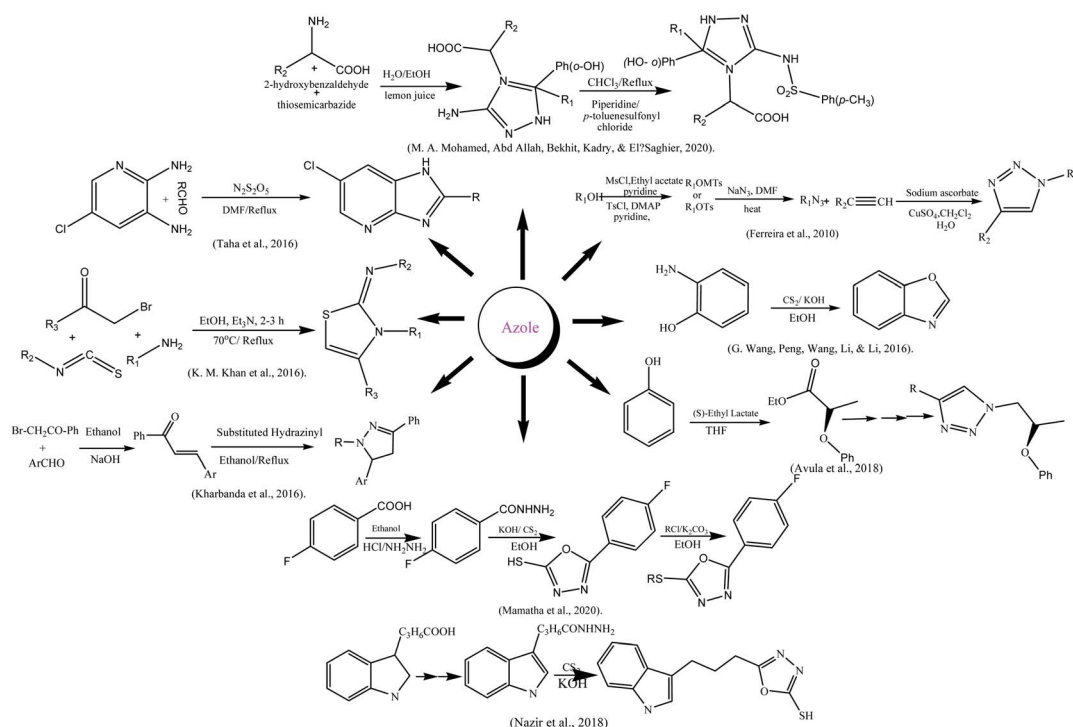


Scheme 1 Protocols for synthesis of thiazolidinone.

docking score  $-11.8617$ . In compound 17 *m*-Cl on phenyl substitution lowered docking score ( $-9.9130$ ). In methyl-substituted benzamide *i.e.*, compound 1 imperative interaction was found with His279, Asn241, and Phe157 along with docking score ( $-12.5054$ ). In diphenyl methenamine based azoles (19–24), compound 20 was most active with a docking score  $-13.6348$ .<sup>193</sup> Scheme 2 depicted various synthesis protocols for azole.

### 3.5 Synthesis of chalcones

The synthesis of chalcone was reported in a multistep reaction; firstly, 2,4-dihydroxy acetophenone and isoprene reacted to give chroman. Secondly, propargyl bromide was reacted with 4-hydroxy benzaldehyde in potassium carbonate by refluxing the mixture. The chalcone moiety was prepared by treating products of steps 1 and 2 *via* aldol condensation. The final product having triazole chalcone moiety was prepared by reacting



Scheme 2 Protocols for synthesis of azole.

chalcone with aromatic azide.<sup>194</sup> Chen along coworkers reported that chalcone derivatives were synthesized using furoic acid as preparatory material. The desired products were prepared by the Claisen–Schmidt condensation.<sup>195</sup> Kaur and Kaushal reported the synthesis of vanadyl chalcone complexes according to the method along with certain modifications. The ethanolic solution of both  $\text{VOSO}_4 \cdot x\text{H}_2\text{O}$  and chalcone ligands in a 1 : 2 molar ratio was mixed with constant stirring followed by dropwise addition of NaOH solution. The reaction mixture was further refluxed up to 10 h and green-colored precipitate of the complex was formed, which was filtered, and washed with ethanol.<sup>196</sup> The synthesis of amino chalcones was accomplished by microwave-assisted synthesis.<sup>22</sup> 4-Aminoacetophenone and aromatic aldehyde in the equimolar ratio were dissolved in ethanol and basified with NaOH. The reaction mixture was irradiated under 180 microwave radiations for 15 min and the reaction completion was confirmed with TLC.<sup>197</sup> Konidala and his colleagues reported the synthesis of coumarin–chalcone derivatives. Salicylaldehyde, acetylacetone, urea, thiourea, and citric acid were used as starting materials for their synthesis.<sup>198</sup> The one-step synthesis of chalcone derivatives with high purity and yield was reported.<sup>199</sup> Cai and co-authors narrated the synthesis of chalcones and bis-chalcones. The reaction starts from aromatic aldehyde, diacetyl benzene, and 50% KOH/ $\text{CH}_3\text{OH}$ . The desired product was obtained by the demethylation of reaction intermediates in the presence of  $\text{BBr}_3/\text{CH}_2\text{Cl}_2$ , respectively.<sup>200</sup> The trihydroxy chalcone derivatives were prepared by reaction of acetophenone and benzaldehyde in ethanol (basic pH) in a round-bottomed flask under nitrogen atmosphere and stirred for 72 h at 25 °C. The end product was purified and recrystallized from ethanol to yield the chalcones.<sup>201</sup> Tetrabromo-chalcones derivatives were obtained from previously reported methanoisindole-substituted chalcones by adding 2 mol of molecular bromine in chloroform at 25 °C for 2 h, yielding the tetrabromo chalcone derivatives (**2a–i**). The recrystallization of compounds in  $\text{CH}_2\text{Cl}_2$  was done in order to purify the end products. The structural analysis of compounds (**2a–i**) were also done using spectroscopic approaches.<sup>202</sup> Chalcone-imide derivatives were synthesized starting from amino chalcone derivatives were synthesized using the well-known Claisen–Schmidt condensation method and on reaction with the benzaldehyde derivatives (**2a–g**) in base catalyzed medium about 3 h gave the amino chalcone derivatives (**3a–g**) in excellent yields. The reaction with maleic anhydride (**4**) in the presence of a few drops of  $\text{NEt}_3$  target crude solid product were obtained and was refined by recrystallisation using an ethanol and *n*-hexane solvent combination.<sup>203</sup> When phloroglucinol and aqueous solution of acetic anhydride at 80 °C with methanesulfonic acid (MSA), compound **2** was synthesized. Following the successful synthesis of compound **2**, compound **2** with dimethyl sulfate given compound **3** and in similar manner on reaction with benzaldehydes in a basic medium fluoro-substituted trischalcones in good yields were obtained.<sup>204</sup> Chalcones derivatives were synthesized by bromination of 2,4,6-trimethoxyacetophenone to the 3-bromo-2,4,6-trimethoxyacetophenone (**14**) and an effective yield (95%) were obtained utilizing a general bromination method. The

compound (**14**) in a base catalyzed mechanism with different reported benzaldehydes new chalcone derivatives were obtained.<sup>205</sup>

New halogenated chalcones (**2a–n**) were synthesized from starting from 6-acetyl-2(3*H*)-benzoxazolone that already synthesized from mixing of DMF and aluminum chloride solution that warmed at 45 °C for 5–10 min then acetyl chloride and 2-(3*H*)-benzoxazolone were added 80 °C for 3 h and after it poured out in cold water with HCl. The combination of 6-acetyl-2(3*H*) benzoxazolone and a suitable aldehyde in ethanol then an addition of an aqueous solution of KOH obtained end product.<sup>206</sup>

### 3.6 Antidiabetic activities of chalcones

$\alpha$ -Glycosidase inhibitory activity of rat intestine was measured using phosphate buffer and by maintaining pH up to 6.8. The sample solution was made in DMSO (5 mg  $\text{mL}^{-1}$ ) and incubated with crude  $\alpha$ -glycosidase. The inhibition of the enzyme was measured by comparing the value of absorbance in control with the test sample solution. Regression analysis was applied to get  $\text{IC}_{50}$  values from average values of inhibition. The best inhibition activity was shown by compounds **4m**, **4p**, and **4s** having  $\text{IC}_{50}$  values in the range of 67.77–102.10  $\mu\text{M}$ . Structural features of these compounds exhibited that maximum inhibitory activity is correlated to a straight 5-C chain of triazole.<sup>194</sup>

The inhibition of PTP1B by synthesized chalcones was done using positive control; ursolic acid ( $\text{IC}_{50} = 3.40 \pm 0.21 \mu\text{M}$ ). Compounds **4e–4m** had greater inhibitory potential, although, **4l** given the  $\text{IC}_{50}$  value ( $3.12 \pm 0.18 \mu\text{M}$ ) and outstanding inhibition of 99.17% with 20  $\mu\text{g mL}^{-1}$ . The moderate inhibition of PTP1B was achieved by compound **4** ( $\text{IC}_{50} = 13.72 \pm 1.53 \mu\text{M}$ ). Few compounds (**4a**, **4b**, **4d**, and **4h**) were also possessed lower inhibitory activity than lead compounds while, both **4c** and **4n** displayed no inhibition.<sup>195</sup>

The inhibition assays of amylase by iodine starch process and  $\alpha$ -glycosidase using the reported *p*-NPG method were accomplished by chalcone complexes. All complexes shown a very active inhibition of  $\alpha$ -glycosidase having  $\text{IC}_{50}$  value (7.35  $\mu\text{g mL}^{-1}$ ) for complex-1, complex-2 (9.15  $\mu\text{g mL}^{-1}$ ), complex-3 (3.26  $\mu\text{g mL}^{-1}$ ) and complex-4 (8.51  $\mu\text{g mL}^{-1}$ ) against standard acarbose. However, complex-3 confirmed good positive activity owing to the presence of *m*- $\text{NO}_2$  derivative on the ligand. In amylase, complex-2 ( $\text{IC}_{50} = 302 \mu\text{g mL}^{-1}$ ) seen with very high activity that is also better than standard ( $\text{IC}_{50} = 388 \mu\text{g mL}^{-1}$ ). Modeling studies of all complexes showed that complex-3 against  $\alpha$ -glycosidase showed maximum inhibition with effective binding energy ( $-10.02 \text{ kcal mol}^{-1}$ ) due to hydrogen bonding (bond length = 2.92 Å) between the oxygen atom of the nitro group with Asp630 residue while complexes-1, 2 and 4 also showed moderate inhibition. *In silico* study of complexes with acarbose also supported the *in vitro* studies of compounds as complex-2 given best binding energy ( $-11.33 \text{ kcal mol}^{-1}$ ) along with inhibition constant  $K_i$  (4.99 nM).<sup>196</sup>

Rats were treated with normal control, positive control with alloxan monohydrate, alloxan monohydrate followed by 0.025 units of insulin, and also with chalcones of **3a–3j**. A glucose





*In vitro* anti diabetic activity was performed in adipocytes 3T3-L1 culture medium. Both pioglitazone and rosiglitazone

Antihyperglycemic effect was observed in mice after administration of 4 weeks of chalcones. A blood glucose tolerance test revealed that chalcone **13** was found to be active in blood glucose maintenance. Serum-free fatty acid levels and fat deposition were also notably reduced. Skeletal muscles of mice were also subjected to a TEM study that also disclosed that no fat accretion was detected. Chalcone **13** was also inhibited the



activity of PTP1b by interacting strongly with it and giving a value of  $IC_{50} = 0.92 \text{ mM L}^{-1}$ .<sup>201</sup> Scheme 3 depicted various synthesis protocols for chalcones.

In this work, the  $IC_{50}$  values for hCA I were determined to be between 13.58 and 18.72 nM, whereas those for hCA II were in between 9.62 and 12.60 nM. All of the tested compounds' (2a–i) were extremely effective hCA I inhibitors, with  $K_i$  values ranging between  $11.30 \pm 2.01$  and  $21.22 \pm 5.63$  nM, and hCA II inhibitors, with  $K_i$  values ranging between  $8.20 \pm 1.62$  and  $12.86 \pm 1.98$  nM. The standard drug AZA found with  $IC_{50}$  values for hCA I and II were 40.45 and 24.16 nM, respectively.<sup>202</sup>

Chalcone-imide derivatives (5a, 5c–g) effectively inhibited the cytosolic hCA I with  $K_i$  values found to be from  $426.47 \pm 72.10$  and  $699.58 \pm 115.8$  nM. This isoform's best inhibition was identified with 5d, having a  $K_i$  value of  $426.47 \pm 72.10$  nM. Acetazolamide (AZA) was designated broadly for CA inhibitor due to its more inhibitory action against CAs and its  $K_i$  value of  $977.77 \pm 227.4$  nM against hCA I. Chalcone-imide derivatives (5a, 5c–g) showed  $K_i$  values for hCA II that ranged from  $214.92 \pm 2.172$  to  $532.21 \pm 81.52$  nM. The standard drug AZA normally prescribed to cure following ailments as epilepsy, idiopathic intracranial hypertension, altitude sickness, glaucoma, glaucoma, central sleep apnea and cystinuria had also intermediate potency for CA II inhibition.<sup>203</sup>

Novel fluoro-substituted tris-chalcones and their derivatives (5a–5i) revealed  $IC_{50}$  and  $K_i$  values between  $8.30 \pm 3.80$ – $32.30 \pm 4.02$  nM for  $\alpha$ -glycosidase, which is found on cells lining of gut and hydrolyzes monosaccharides to be absorbed *via* the intestine. The  $\alpha$ -glycosidase assay findings revealed that all new fluoro-substituted tris-chalcones derivatives (5a–5i) exhibited more efficient  $\alpha$ -glycosidase inhibitory characteristics than acarbose ( $IC_{50}$ : 22.8 mM). Also obtained were very effective  $K_i$  values for chalcone 5c, with a  $K_i$  value of  $8.30 \pm 3.80$  nM.<sup>204</sup>

$\alpha$ -Glycosidase inhibitory action of new chalcone derivatives (5–12) was demonstrated with  $K_i$  values ranging from  $12.54 \pm 4.16$  to  $35.22 \pm 2.10$  nM. The findings also concluded that all chalcone derivatives were more efficient at inhibiting  $\alpha$ -glycosidase than acarbose ( $IC_{50}$ : 22.800 mM), a commonly used  $\alpha$ -glycosidase inhibitor. The  $K_i$  values ranging from  $16.24 \pm 5.10$  to  $40.96 \pm 8.95$  nM for novel chalcone derivatives demonstrated low nanomolar inhibition levels against hCA I. Acetazolamide (AZA), a sulfonamide-based reference inhibitor, had a  $K_i$  value of  $141.02 \pm 50.84$ . The hCA II isoenzyme is inhibited by new chalcones (5–12), in a same manner as to CA I and  $K_i$  values were shown in the range of  $29.61 \pm 5.65$ – $67.15 \pm 16.21$  nM.<sup>205</sup> Derivates of chalcones (2a–n) actively inhibited the human carbonic anhydrase with  $IC_{50}$  ( $\mu$ M) values of 27.2–73.7 for hCA I and 29.1–72.6 for hCA II, despite typical AZA values of 16.6 for hCA I and 8.4 for hCA II. The values of  $K_i$  ( $\mu$ M) *versus* hCA I and hCA II vary from  $30.5 \pm 11.3$ – $65.5 \pm 25.6$  and  $7.3 \pm 1.8$ – $58.8 \pm 12.3$ , respectively. The lowest value is 2g 27.2 and the highest is 2d 29.1.<sup>206</sup>

### 3.7 Synthesis of pyrroles

The derivatives of pyrrole were synthesized by reaction of amine, 1,3-dicarbonyl and nitro styrene in ethanol by refluxing

for 4 h in the presence of diacetoxyiodo benzene.<sup>207</sup> Similarly, Lohray and coworkers reported the synthesis of novel pyrrole-containing compounds by the reaction of 4-disubstituted compounds with amino ethanol. They have further evaluated their hypoglycemic and hypotriglyceridemic potential.<sup>208</sup> The zinc complexes of pyrrole-3-carboxamide were reported by complexing *N*-trialkylated acrylamide with  $ZnSO_4$  in the presence of LiOH.<sup>209</sup> The pyrrole-2-carbaldehydes were synthesized *via* Malliard reaction in which glucose in presence of oxalic acid was treated with diverse amines at 90 °C for 30 min. The final product was obtained by reacting furopyridine-dione with piperidine.<sup>210</sup> Pyrrole was also synthesized *via* a series of reactions; 2,3-dicarbonyl was reacted with phenylamine in benzene at 80 °C for 9 h. After cooling the reaction mixture, malononitrile was added, followed by a catalytic amount of pyridine portion-wise and left to reflux till solid formed. Pyrrole derivatization was done by triethyl orthoformate and acetic anhydride.<sup>211</sup> Goel and fellows reported the preparation of methyl triphenyl pyrroles by refluxing benzoin, benzyl methyl ketone, and ammonium acetate mixture in acetic acid. A minor tetraphenyl pyrazine as a byproduct was also probably formed by self-condensation of benzoin with ammonium acetate.<sup>212</sup> Pyrrole moiety was also prepared from amine, nitro styrene, and 1,3-dicarbonyl compound in the ethanolic medium by stirring at 25 °C up to 10 min. The reaction mixture, was refluxed in DIB for 4 h. However, nitro styrene's were synthesized from corresponding aromatic aldehydes and nitromethane by considering the reported method.<sup>207</sup> Tafesse and co-workers narrated the synthesis of pyrrole started from substituted aldehyde and methyl vinyl ketone. The other chemical reagents that used were NaCN, dimethylformamide, *p*-toluene sulfonic acid and ethanol. Pyrrole derivatives prepared by reaction of pyrrole with oxalyl chloride, dichloromethane, triethylamine and *N,N*-dimethyl aminopyridine at 0 °C.<sup>213</sup> A class of advantageous heterocyclic of new pyrrole and enamine and their derivatives easily synthesized employing two-component condensation, that actually comprise of glycolic acid and the ethyl ether, these substances with various functional groups successfully used in medicine. First, under the catalytic action of ytterbium(III) trifluoromethanesulfonate, (*Z*)-ethyl 2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate (1) was synthesized as reaction of glycine ethyl ester hydrochloride and dibenzoylmethane occurred. The subject of investigation was then chosen to be enamine that then was mixed with *tert*-BuOK after being dissolved in butyl alcohol and crystals of ethyl-3,5-diphenyl-1*H*-pyrrole-2-carboxylate are the end product (2) that easily attained.<sup>214</sup> 1,3-Dicarbonyl compounds were employed as the starting reactant in the synthesis process. These chemicals were reacted with oxalyl chloride to produce furan-2,3-diones employing the Wittig reaction. The final step was the optimally controlled synthesis of the end product as novel pyrrole-sulfonamide derivatives, from sulfa medicines and furan-3-one. The target compounds (5a–i) were synthesized in the last stage by refluxing using 1-propanol solvent for 6 h. The process of product formation consists of only two steps. The amino group attacks at C-5 of the furan ring in the first step, which causes ring opening and the cyclization process synthesized the pyrrole ring in the second



step. The novel compounds (**5a–5i**) have recrystallization yields that vary from 76 to 88%.<sup>215</sup>

### 3.8 Antidiabetic activities of pyrrole

The  $\alpha$ -amylase inhibitory assay of pyrrole was accomplished, aliphatic amines-based pyrroles and branched amino acids-based pyrroles; **3**, **7**, **12**, and **18** exhibited effective  $IC_{50}$  values. Compounds **7** and **12** were found to be the best inhibitors of  $\alpha$ -amylase and  $\alpha$ -glycosidase. The  $\alpha$ -amylase and  $\alpha$ -glycosidase  $IC_{50}$  ( $\mu\text{mol mL}^{-1}$ ) for **3**;  $0.430 \pm 0.82$  and  $0.861 \pm 0.35$ , **7**;  $0.365 \pm 0.58$  and  $0.804 \pm 0.18$ , **12**;  $0.408 \pm 0.11$  and  $0.779 \pm 0.259$ , **18**;  $0.456 \pm 0.42$  and  $0.840 \pm 0.17$  respectively. Molecular docking study of **3** on  $\alpha$ -amylase (PDB ID-10SE) cleared that oxygen of carboxylic group showed H-bonding with Hip305, pyrrole ring interacted with Trp58, Trp59, Glu63, Leu165, and Val163 though, phenyl ring showed contacts with cavity residues Leu162, Hie101, Glu233, Ala198, Ash197, and Arg195. Molecular modeling of **3** with  $\alpha$ -glycosidase displayed a very strong interaction of the oxygen atom of the carboxylic group also with Lys348. However, **3** had docking scores  $-7.995$  and  $-8.236$  while **7** had  $-7.65$  and  $-7.896$  against  $\alpha$ -amylase and glycosidase respectively.<sup>207</sup>

The antihyperglycemic effect of compounds was shown by compounds **29**, **31**, and **34** in mice ( $\text{mg kg}^{-1}$ ) after 6 days of continuous administration. Blood glucose reduction percentage was found for respective compounds as  $61.9 \pm 1.7\%$ ,  $58.2 \pm 1.5\%$ , and  $65 \pm 2\%$ . The highest percentage of triglyceride reduction was seen in the case of **34** that was about  $54.9 \pm 3.2\%$ .<sup>208</sup>

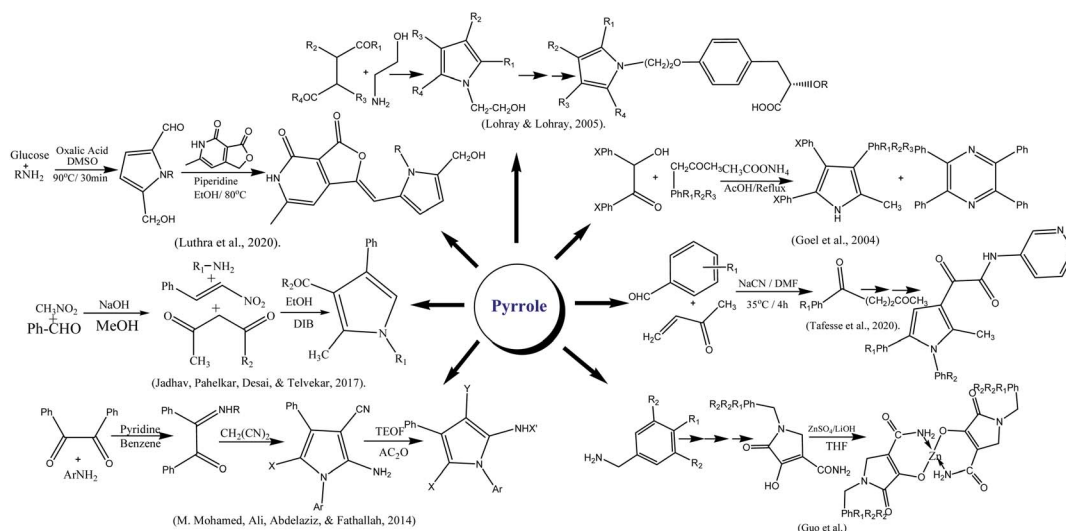
The insulin-mimetic activity over adipose tissues of male Wistar rats was performed. To check activity, pyrrole–zinc(II) complexes (**10a–d**) inhibited adipose cells free fatty acid release that was stimulated with epinephrine except **10e** due to non-solubility in the assay medium. Complexes acted as potent hypoglycemic agents and  $IC_{50}$  values of Zn complex **10a**, **10b**, **10c**, **10d** and  $\text{ZnSO}_4$  were  $0.37 \text{ mM}$ ,  $0.36 \text{ mM}$ ,  $0.39 \text{ mM}$ ,  $0.41 \text{ mM}$  and  $0.44 \text{ mM}$  as respective.<sup>216</sup>

*In vitro* ( $\alpha$ -glycosidase) inhibitory activity revealed that compound **3k** was found to be four times more potent with  $IC_{50}$  of  $0.56 \mu\text{M}$  against acarbose ( $IC_{50} = 2.1 \mu\text{M}$ ) while, **3d** shown value  $4.4 \mu\text{M}$ . Compounds **3a** and **3f–i** had value ranged  $20–33 \mu\text{M}$  although, other compounds showed no activity. The presence of pyridine dione, pyrrolidine increased activity and indolyl ring at C-3 to the pyrrolidiny nitrogen (**3d**) also had higher activity values than **3e** with phenyl. It was also seen that aromatic moiety at the pyrrolidiny nitrogen **3f–i** compared to aliphatic **3b** and **c** had higher inhibitory potential. Functional group  $p\text{-CO}_2\text{Et}$  on the aromatic ring in **3k** effect activity,  $p\text{-halo}$  and  $p\text{-hydroxy}$  at the *para* **3g–i** and  $o\text{-CH}_3$  in **3j** almost did not affect the activity of compounds. The Gold program was used to dock **3k** over the  $\alpha$ -glycosidase and value of binding ( $\Delta G$ ) was  $-15.53 \text{ kcal mol}^{-1}$ . Four hydrogen bonding interactions are seen between protein and compound **3k**.<sup>210</sup>

Pyrroles-based compounds were assessed by STZ and SLM using glimepiride as a reference drug. In comparison to untreated normal control compound **1a**, **1c**, and **1e** were lowered  $17.4\%$ ,  $18\%$ , and  $16.7\%$ , respectively in SLM, although in STZ compared to diabetic group reduced induced glucose level  $33.3\%$ ,  $35.3\%$ , and  $29.5\%$ , respectively. In contrast to glimepiride **1a**, **1c**, and **1e** showed a significantly decline in the blood sugar level  $109.4\%$ ,  $116.2\%$ , and  $97\%$ , respectively.<sup>211</sup>

*In vivo* antihyperglycemic activity in male Sprague Dawley rats was determined using a sucrose loaded model (SLM) and a streptozotocin loaded model (STZ). In SLM and STZ compound **3d** having F group at phenyl ring exhibited blood sugar levels up to  $50\%$  and  $34.7\%$  respectively, while **3c** with  $\text{CF}_3$  substitution at phenyl ring given  $40.8\%$  and  $25.1\%$ . In **3h** and **3i** with methoxy group also on phenyl ring given respective  $27.8\%$  and  $20.3\%$  inhibitory activity in SLM.<sup>212</sup>

$\alpha$ -Glycosidase inhibition was done by incubation of compounds **5a–i** in potassium phosphate buffer. Compound **5e** ( $111 \pm 2 \mu\text{M}$ ) showed higher activity due electron withdrawing substitution as 2,4-dichloro **5f** substitution and 3,4-dichloro **5g**



Scheme 4 Protocols for synthesis of pyrrole.

on phenyl ring connected to pyrrole moiety and  $IC_{50}$  values were  $573 \pm 12 \mu\text{M}$  and  $639 \pm 13 \mu\text{M}$  respectively than standard acarbose  $750 \pm 9 \mu\text{M}$ . The presence of 2,4-dichloro **5a** ( $IC_{50} = 196 \pm 10 \mu\text{M}$ ) compared to 2,5-dichloro **5b** ( $IC_{50} = 663 \pm 11 \mu\text{M}$ ) decreased the activity of compound up to three folds. Prior to this, presence of phenyl substitution on pyrrole ring **5h** ( $IC_{50} = 494 \pm 10 \mu\text{M}$ ) and methyl in **5i** ( $IC_{50} = 673 \pm 12 \mu\text{M}$ ) decreased the activity. Molecular docking was accomplished using auto dock Tools version 1.5.6. In compound **5e** (binding energy  $-4.27 \text{ kcal mol}^{-1}$ ) and **5a** (binding free energy  $-3.17 \text{ kcal mol}^{-1}$ ) carbonyl oxygen of acetamide formed hydrogen bonding with His280 and Arg442 respectively. 5-Phenyl ring also showed pi-pi contacts with Tyr158 in **5e**, while, Phe303, and Phe178 interact with the **5a**.  $\pi$ -anion interactions were observed between pyridine and Asp307 in **5e** and Glu411 in **5a**. Standard acarbose exhibited binding free energy of  $2.47 \text{ kcal mol}^{-1}$ .<sup>213</sup> Scheme 4 depicted various synthesis protocols for pyrrole.

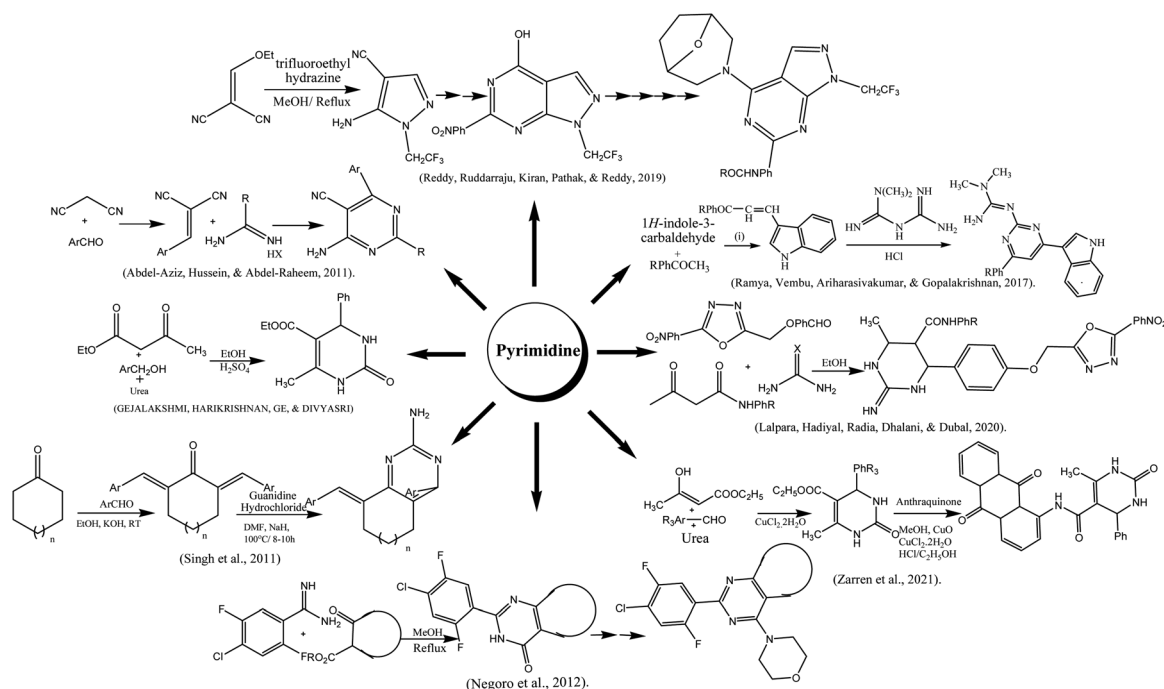
The hCA I inhibitory constant  $K_i$  value for compound **1** is  $85.07 \pm 10.04 \mu\text{M}$  and for **2** is  $47.21 \pm 5.06 \mu\text{M}$ . Although, the results against CA II, and the inhibitory constant of **1** found at  $66.01 \pm 8.47 \mu\text{M}$  and of **2** was  $35.77 \pm 3.53 \mu\text{M}$ , compounds **1** and **2** exhibited less than inhibitory activity in contrast with the standard medication AZA ( $27.04 \pm 2.43 \mu\text{M}$ ). Compound **1** demonstrated less inhibitory action than AZA, according to the  $K_i$  values:  $35.51 \pm 3.32 \mu\text{M}$ . Additionally, compound **2** produced findings that were very similar to those of AZA, a drug used to treat a number of common diseases, including glaucoma. The goal of the current investigation was to examine substances that inhibit  $\alpha$ -glycosidase activity, synthetic compounds have  $K_i$  values of **1**  $63.76 \pm 7.12 \mu\text{M}$  and for **2**  $93.54 \pm 11.20 \mu\text{M}$ . Both

substances demonstrated weaker inhibitory effects than acarbose based on the  $IC_{50}$  and  $K_i$  values  $45.21 \pm 5.34 \mu\text{M}$ .<sup>214</sup>

The cytosolic hCA I and hCA II isoforms as well as AChE were evaluated against their inhibition by newly pyrrole-3-one derivatives (**5a-i**). The inhibitor concentrations ( $IC_{50}$ ) were 10.66 to 30.13 nM and their inhibitory constant values in between  $1.20 \pm 0.19$  to  $44.21 \pm 1.09 \text{ nM}$ , all pyrrole-3-one derivative medicines containing sulfur groups efficiently inhibited hCA I. These pyrrole derivatives effectively inhibited hCA II, with  $IC_{50}$  values 8.15–22.35 nM and  $K_i$  in between the  $8.93 \pm 1.58$  to  $46.86 \pm 8.41 \text{ nM}$ . In addition, the studied compounds demonstrated the best inhibition when compared to AZA ( $K_i$ :  $47.32 \pm 3.21 \text{ nM}$ ).<sup>215</sup>

### 3.9 Pyrimidine

The indole-based pyrimidine derivatives were synthesized by condensing of indole-3-carboxaldehyde with *p*-substituted acetophenones followed by treating with metformin hydrochloride to form the final product.<sup>217</sup> A simple method for the preparation of amino pyrimidine derivatives from malononitrile and benzaldehyde was reported. The precipitates formed in water were acidified with hydrochloric acid, filtered, and recrystallized in ethanol.<sup>218</sup> Reddy and co-authors reported the synthesis of the pyrimidine-containing pyrazole group. Trifluoro ethyl hydrazine and malononitrile were reacted in methanol at reflux condition for 3 h to obtain intermediate that was used for final product with good yield after a series of steps such as amide formation, cyclization, chlorinated, nucleophilic substitution, reduction, and coupling.<sup>219</sup> The synthesis of tetrahydropyrimidine was done *viz* Bignelli condensation followed by microwave irradiation. To a mixture of benzaldehyde, urea, and



Scheme 5 Protocols for synthesis of pyrimidine.





ethyl acetoacetate in a round bottom flask, concentrated hydrochloric acid was added and poured into a china dish for microwave 180 watts irradiation for one minute.<sup>220</sup> Zarren and his colleagues reported the anthraquinone-derived pyrimidine derivative by one-pot relay method using a catalytic amount of copper chloride and cupric oxide in methanolic medium. The reaction mixture of both compounds was allowed to stir up to 30 min at ambient temperature.<sup>221</sup> Biginelli condensation was also used for the preparation of hydroxy pyrimidine (HPM) derivatives. The reaction of oxadiazole contains aldehyde moiety with substituted acetoacetanilide and urea derivatives in acidic ethanol under microwave irradiation (200 W) up to 25 min.<sup>222</sup> The reaction of various bis-benzylidene cycloheptanones and bis-benzylidene cyclohexanones with guanidine hydrochloride was conducted in the presence of NaH and DMF as a solvent to obtain the amino pyrimidine in moderate to good yields.<sup>223</sup> Negoro and coworkers reported the synthesis of morpholino pyrimidine derivatives. The reaction was started by condensation of substituted benzamidine with cyclic  $\beta$ -keto ester followed by chlorination using phosphorous oxychloride resulting in the formation of 4-chloro-fused-pyrimidines. These compounds were subjected to substitution with morpholine to acquire the final product.<sup>224</sup> To start with thiourea and using trifluoroacetic acid as a catalyst, it was simple to synthesize derivatives of pyrimidine thiones. As the reaction was complete, white crystals of the final product were attained.<sup>225</sup> Tetrahydropyrimidine carboxylates and their derivatives were synthesized by Sujayev and colleagues using benzaldehyde, urea, 2-(methacryloyloxy)ethyl acetoacetate in ethanol and acetyl acetone as solvents (3 : 1). Desired products were then got through a reaction with epichlorohydrin and 1,2-epoxobutane. Utilizing a sulfol UV 254 plate to monitor the reaction, and compound's structural details were clarified by an X-ray diffractogram analysis.<sup>226</sup> Similar methods were used to synthesize cyclic thioureas (**1–8**) by reacting substituted *p*-tolualdehyde, *p*-anisaldehyde, *o*-tolualdehyde, salicylaldehyde, and benzaldehyde with methylene active substances such  $\beta$ -diketones and thiourea. At 60–75 °C, the three-component condensation processes took place in 2.5–3.0 hours. The synthesized compounds were crystalline in nature, and <sup>1</sup>H, and <sup>13</sup>C-NMR spectroscopic methods as well as elemental analyses were used to determine their structural details. In the region of 3370–3040 cm<sup>−1</sup> areas of the IR spectra of the produced compounds (**1–8**), NH bond valence vibrations were detected.<sup>227</sup> In acetylacetone and ethyl alcohol, pyrimidine-thiones are dissolved, and then drop by drop 1,2-epoxypropane (1,2-epoxobutane) is added, AlCl<sub>3</sub> catalyst is used and heated at 60–65 °C. 4-Chlorobutanol (**G–K**) is added to the pyrimidine-thione solution and mixed for 10–15 minutes. The mixture is shaken for 1–3 hours at 70–78 °C.<sup>228</sup> For synthesis of *N*-heterocyclic salts, firstly, 1,2-diaminoethane, 1,3-diaminopropane, and 1,4-diaminobutane were condensed with two molar equivalents of the aromatic aldehydes in ethanol to create the Schiff bases that later on converted to equivalent benzylic diamines by the reduction of sodium borohydride in methanol. Finally, by cyclizing triethyl orthoformate in the presence of ammonium chloride, *N,N'*-

dialkylalkanediamines were transformed into 1,3-dialkylazolium salts. Following, purification, pure products were recovered as colorless solids with effective yields (60 to 87%).<sup>229</sup>

### 3.10 Antidiabetic activities of pyrimidines

Docking outputs of compounds (**11a–g**) were achieved using CDocker against glucokinase (LV4S). From results, the synthesized compound showed good docker energy; **11a** (−11.36) and **11b** (−8.77 kcal mol<sup>−1</sup>) and **11g** (−9.13 kcal mol<sup>−1</sup>) respectively while, metformin had 21.60 kcal mol<sup>−1</sup>. Compound **11a** had strong contacts with residues Pro66, Arg63, Ile211, Val452, Thr65, Gln98, Tyr215, Met235, and Met210. Compounds 4-indolylphenyl-6-arylpyrimidine-2-imines (**11a–g**) have been assessed for inhibition of  $\alpha$ -amylase and  $\alpha$ -glycosidase by *in vitro* methods. The maximum inhibition of  $\alpha$ -glycosidase was depicted by **11a** and **11g** with IC<sub>50</sub> values 55.98  $\mu$ g mL<sup>−1</sup> and 56.27  $\mu$ g mL<sup>−1</sup> while against  $\alpha$ -amylase values were 49.50  $\mu$ g mL<sup>−1</sup>, and 49.90  $\mu$ g mL<sup>−1</sup> respectively. STZ induced diabetic albino Wistar rats were used and evaluated through *in vivo* anti diabetic models. The synthesized compounds (**11a–g**) were administrated till 28 days. However, glucose level was observed 152.23 mg dL<sup>−1</sup> with **11a**, 170.21 mg dL<sup>−1</sup> for **11e**, 167.45 mg dL<sup>−1</sup> for **11f** and 173.44 mg dL<sup>−1</sup> for **11g** compared to metformin (154.23 mg dL<sup>−1</sup>). Compounds **11b**, **11c** and **11d** showed less inhibition as 182.5  $\pm$  11 mg dL<sup>−1</sup>, 180.232  $\pm$  12 mg dL<sup>−1</sup>, 181.32  $\pm$  12 mg dL<sup>−1</sup>, respectively.<sup>217</sup>

Compound **5d–l**, and **6d–l** were assessed for antidiabetic effect, induced by alloxan monohydrate in rats *via* determined the percentage reduction in average glucose after seven days of administration in contrast to standard metformin. Compounds **5d–f**, exhibited no decrease in blood glucose, **6d–f** reduced up to 15–21% and **5g–i** showed about 6–15% decrease. Compound **6g–l** with 2-cyclohexylamino-4-oxopyrimidines fasting blood glucose up to 34% excluding **6g** due to absence of substituents on phenyl ring at position 6 decrease glucose just 2%. In compounds **5j–l**, particularly **5k** having *p*-chlorophenyl at position 6 decrease in glucose by about 45%. In **6j–l** especially in **6l** with *p*-methylphenyl substitution, about 46% decreased. Hence, **5k** and **6l** are normally considered as lead compounds against metformin.<sup>218</sup>

Novel pyrimidine compounds **8a–l** were analyzed for *in vitro*  $\alpha$ -amylase inhibition and IC<sub>50</sub> values in between 1.60  $\pm$  0.48 to 2.04  $\pm$  1.20  $\mu$ M in contrast to reference acarbose (1.73  $\pm$  0.05  $\mu$ M). Compound **8i** was found to be more active due to *o*-nitro and *m*-fluoro-substitution on the phenyl ring. Comparison studies have been carried out among the analogues (**8f–k**) by substituting the nitro group at the *ortho*, *meta*, and *para* on the phenyl ring. The presence of *p*-nitro on aryl ring in **8k** activity increased 1/3-fold than **8a**. Most active compounds were **8d**, **8f**, **8g**, **8h**, **8i**, **8j**, and **8k** had IC<sub>50</sub> values of 1.77  $\pm$  2.84, 1.65  $\pm$  0.45, 1.66  $\pm$  2.24, 1.73  $\pm$  0.37, 1.60  $\pm$  0.48, 1.75  $\pm$  0.36, and 1.64  $\pm$  0.03  $\mu$ M, respectively. The effective antidiabetic activity was accompanied by compound **8d** and **8k** in alloxan-induced diabetic Wistar rats having glucose higher than 270 mg dL<sup>−1</sup>. Compound **8d** with 25 mg kg<sup>−1</sup> and 50 mg kg<sup>−1</sup> dose after 2 h of

administration on 5<sup>th</sup> hrs  $198.6 \pm 18.6$  and  $182.2 \pm 13.7$  respectively, while for **8k** values were  $204.2 \pm 18.6$  and  $193.2 \pm 18.7$  against standard glibenclamide ( $174.1 \pm 13.9$ ). *In silico* modeling studies were exhibited (**8a-l**) on  $\alpha$ -amylase (PDB : 1HNY) against standard acarbose. The **8d** with *m*-nitro and *o*-methyl group had 59.46 gold score. It formed H-bonding with Gly351 and also hydrophobic contacts with His305, Tyr62, Gly304, Asp356, and Trp59. However, compound **8k** had also a score 48.12, which showed hydrophobic contacts with Thr163, Tyr62, Trp59, Ile51, Leu165, along H-bonding with Glu233, Arg195 and Asp197.<sup>219</sup>

In molecular docking study, substituted pyrimidine showed interactions with insulin receptor. The amino acid residues for binding were Asp1150, Asp1083, His1081, Met1079, Ser1006, Glu1108, Glu1077 with respective ligand pose energy (kcal mol<sup>-1</sup>); -8.03805, -7.58741, -7.51747, -9.13544, -7.62575, -5.44869, -5.00426 respectively. The ligand and receptor pose energy values were obtained and Pymol viewer was used to view every single binding site interaction.<sup>220</sup> Antidiabetic activity of **G1-G4** was determined for *in vitro*  $\alpha$ -amylase inhibition and acarbose showed 61.70% inhibition. Compound **G2** was found with the highest 57.80% inhibition along IC<sub>50</sub>  $24.23 \mu\text{g mL}^{-1}$  although **G1**, **G4**, and **G3** exhibited 40.96%, 39.36%, and 37.94%, respectively. Docking studies were accomplished for **G1-G4** against human pancreatic  $\alpha$ -amylase and docking score found in effective ranges (-119.48 to -131.536 Kcal mol<sup>-1</sup>) although, the acarbose docking score was -111.57 kcal mol<sup>-1</sup>. **G2** (-184.273 kcal mol<sup>-1</sup>) showed contacts with Thr163 and His305 while bond length values were 2.602 Å and 2.44 Å respectively. In compound **G4** oxygen atom of aldehyde showed contacts with Ile235 (2.89 Å). Compound **G2** showed the best inhibition of  $\alpha$ -amylase than others.<sup>221</sup>

Synthesized compounds **4a-j** and **5a-j** were assessed using various concentrations (50–125 lg mL<sup>-1</sup>) for *in vitro*  $\alpha$ -amylase inhibition and acarbose considered as reference drug. Compounds **4d**, **4g**, **4i**, **4j**, **5b** and **5f** that exhibited IC<sub>50</sub> values (lg mL<sup>-1</sup>) in good ranges; 71.46, 72.41, 72.27, 70.62, 72.79, and 72.10 respectively that nearer to 69.71 for acarbose.<sup>222</sup> Aminopyrimidines (**21-40**) were showed a good percentage of inhibition for  $\alpha$ -glycosidase (13–72%) and glycogen phosphorylase (10–40%) and by excluding **31**, **34**, **35**, and **37** had moderate to good inhibitory potential. SAR study of the compounds revealed that phenyl ring substitution in arylidene showed good inhibition of glycosidase enzyme, *i.e.*, compounds **24**, **25**, **29** and **36** with *p*-bromo (71.8%), *p*-chloro (72.8%), *p*-benzyloxy (53.1%), and *p*-methoxy (63.2%), respectively, against  $\alpha$ -glycosidase but also found more effective against glycogen phosphorylase. A 2-naphthyl substituent compound **40**, showed also inhibition of both glycogen phosphorylase and  $\alpha$ -glycosidase and 2-aminopyrimidine analogs with fused cyclohexyl compared to cycloheptyl more active against  $\alpha$ -glycosidase.<sup>223</sup>

Pyrimidine derivatives were acted as GPR119 agonist, compound **12a** with cyclopentane fused-pyrimidine ring and 4-chloro-2,5-difluorophenyl moiety behaved as a strong GPR119

agonist while **14a** due to structural modification having 5,7-dihydrothieno[3,4-*d*]pyrimidine 6,6-dioxide found to be about 10-fold enhanced activity as a GPR119 agonistic. However, substitution at 4-position in pyrimidine (**16b**), enhanced not only activity but also improved glucose tolerance. Compound **16b** along its derivatives considered potential therapeutic agents for type-II diabetes mellitus.<sup>224</sup> Scheme 5 depicted various synthesis protocols for pyrimidine.

Pyrimidine thiones were assayed for the inhibition of both cytosolic human CA (I and II) and acetazolamide AZA used as a standard drug. Compound **3** CA exhibited maximum inhibition constant *K<sub>i</sub>* (pM) against hCA I and hCA II as  $312.6 \pm 61.1$  and  $273.6 \pm 41.4$  respectively, although reference drug showed values at  $369.4 \pm 68.5$  and  $271.8 \pm 54.5$ .<sup>225</sup>

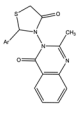
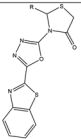
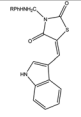
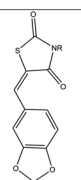

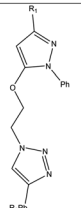
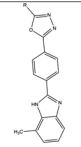
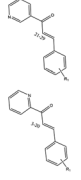

Tetrahydropyrimidine-5-carboxylates derivatives (**1-3**) were given effective inhibition of cytosolic hCA I and *K<sub>i</sub>* (nM) values in a range between of  $429.24 \pm 87.89$ – $539.30 \pm 106.70$ . In all derivatives compound **2** possesses good effective inhibitory activity due to following functional as: -C=O, -C=S, -NH, -OH, Cl, -CH<sub>2</sub>, and -CH<sub>3</sub> have highest value of *K<sub>i</sub>*  $429.24 \pm 87.89$  nM and standard AZA given  $281.33 \pm 55.33$ . However, against hCA II synthesized compounds showed *K<sub>i</sub>* value in a limit of  $391.86 \pm 40.16$ – $530.80 \pm 103.60$  nM. Hand, AZA values found at  $202.70 \pm 162.5$  nM.<sup>226</sup>

Cyclic thioureas (**1-8**) is generally inhibited the hCA I isoenzyme and their lower *K<sub>i</sub>* values found between  $47.40 \pm 4.43$ – $77.68 \pm 3.69$  nM in contrast to standard acetazolamide (AZA),  $289.22 \pm 2.60$  nM. The inhibition hCA II that naturally present in red blood cells, compounds depicted with *K<sub>i</sub>* values  $30.63 \pm 7.62$  to  $76.06 \pm 3.15$  nM and among which the cyclic thiourea **2** was found to be best inhibitor of hCA II with *K<sub>i</sub>*:  $30.63 \pm 7.62$  nM value.<sup>227</sup>

The new pyrimidine-thiones (**A-K**) compounds under investigation suppressed release of hCA I, with *K<sub>i</sub>* values ranging from  $4.3$  to  $9.1 \pm 2.8$  nM, a *K<sub>i</sub>* value of  $4.3 \pm 1.0$  nM compound (**K**) also proved to have the strongest hCA I inhibitory potential. Acetazolamide (AZA), a commonly prescribed medication, with a *K<sub>i</sub>* value of  $13.9 \pm 5.1$  nM. The new pyrimidine-thiones (**A-K**) compounds examined here effectively suppressed the hCA II as well these substances had *K<sub>i</sub>* values that ranged from  $4.2 \pm 1.1$  to  $14.1 \pm 4.4$  nM, suggesting that they substantially inhibited hCA II. These numbers surpass those of the therapeutically utilized medication AZA, which has a *K<sub>i</sub>* of  $18.1 \pm 8.5$  nM.<sup>228</sup>

The newly synthesized tetrahydropyrimidinium, tetrahydrodiazepinium salt and imidazolinium, and derivatives (**5a-l**) inhibited the hCA I with *K<sub>i</sub>* value found between  $1.88 \pm 0.83$  and  $50.66 \pm 12.35$  nM, however, **5f** and **5e** recorded the most potent hCA I inhibition abilities with a *K<sub>i</sub>* value of  $1.88 \pm 0.83$  and  $2.16 \pm 0.47$  nM, respectively. Although *K<sub>i</sub>* values ranging from  $20.18 \pm 6.78$  nM to  $124.04 \pm 46.23$  nM found for synthesized compounds to inhibit hCA II. The *K<sub>i</sub>* values of freshly created molecules are superior to those of the AZA standard compound *K<sub>i</sub>* with  $187.07 \pm 16.55$  nM. The CA isoenzyme was significantly inhibited by compounds **5g** and **5h**, with *K<sub>i</sub>* values of  $20.18 \pm 6.78$  and  $24.23 \pm 5.55$  nM, respectively.<sup>229</sup>



Core Structure	<i>In silico</i> analysis				<i>In vitro / In vivo</i> analysis				
	Docking Tool	Enzyme (PDB)	E-Score/ Binding Energy (Kcal/mol)	Interacted Residues	Type of Analysis	Conditions	standard	IC <sub>50</sub> value / Percentage of Inhibition	Reference
	Auto Dock 1.5.6 while Discovery Studio 3.5 visualizer	PPAR $\gamma$ (4PRG)	-8.95 to -11.46	Lys263, Lys265, Ser342, Glu342 and Leu228	<i>In vivo</i>	Blood glucose 200-300mg/dL.raised by STZ (mg/kg weight)	Pioglitazone	BGL (121.49 $\pm$ 0.47 to 130.78 $\pm$ 0.43) against standard 117.63 $\pm$ 0.29	[230]
	Maestro 9.0 Schrodinger suite	Gamma-PPAR (1FM9) & $\alpha$ -glycosidase (2QMJ)	-47.80 to -59.80	Leu340, Ser342, Glu343, His323 and Tyr473 and Ile326	<i>In vivo</i>	Albino Wistar rats weighing 180-240 gm, STZ in 0.1M citrate buffer, pH at 4.5	Pioglitazone	BGL (134.32 $\pm$ 2.67 to 175.50 $\pm$ 2.16) against pioglitazone 178.32 $\pm$ 1.88.	[231]
	AutoDock 4.2.6 software	g-PPAR receptor (2PRG)	-6.48 to -9.65	Arg288, Ser289, Gln286, Lys296, Leu268, Met348, Tyr473, Tyr396	<i>In vivo</i>	Blood glucose levels 150 mg/dL, glibenclamide (500 mg/kg) body weight, sample 35 mg/kg, glucose level at intervals 0, 1,2,4,6 and 8 hrs, respectively.	Glibenclamide	BGL was found between (90.58 $\pm$ 4.73 to 301.82 $\pm$ 4.56) against glibenclamide 85.42 $\pm$ 2.53	[232]
	MOE.2019	PPAR- $\gamma$ (2PRG) and $\alpha$ -amylase, (2QV4)	For PPAR- $\gamma$ : -11.85 to -6.48 for amylase -7.66	For PPAR- $\gamma$ : CYS 285, Glu233, His 449, Ser299, His323, Cys285, Asp 300, Arg195 while for $\alpha$ -amylase Asp300, Glu233 and Asp197	<i>In vitro</i>	Phosphate buffer pH 6.8, 50-250 $\mu$ L/kg of compound, 10 $\mu$ L enzyme and incubation at 25°C	Acarbose	IC <sub>50</sub> (9.06 to 13.98 $\mu$ g/mL) compared to Acarbose IC <sub>50</sub> = 24.1 $\mu$ g/mL	[233]
	HEX 8.0.0	$\alpha$ -Glycosidase (1R47)	For $\alpha$ -glycosidase -532.15 to -475.42	-	<i>In vitro</i>	<i>p</i> -NPG and phosphate buffer (PB) 75 $\mu$ L.	Acarbose	For $\alpha$ -glycosidase IC <sub>50</sub> (11.65 to 42.14 mM) while for <i>K<sub>i</sub></i> (16.11 $\pm$ 3.13 to 48.08 $\pm$ 6.40 mM)	[234]
	Molegro Virtual Docker Ver 6.0.	DPP-4, DPP-8 & DPP9 (2OLE, 7A31 & 6QZV, respectively)	-1.00 kcal/mol to -6.77 and dock score -64.27 to -142.64	Tyr631, Tyr662, Phe357, Val711, Ser630, Tyr547 and Asn710	<i>In vitro</i> & <i>in vivo</i>	For <i>In vitro</i> : HEPES IV 50 mM, GP- AMC 15 $\mu$ M, pH 7.5	Sitagliptin	IC <sub>50</sub> (4.54 to 114.28 nM) against sitagliptin 7.69 BGL was found to be 117.2 for 7f and 8h 95.8	[235]
	Gold version 5.5.	$\alpha$ -Glycosidase (3TOP)	-	Asp1526, Phe1559, Trp1418, Met1421, Phe1427 and Phe1560	<i>In vitro</i>	Phosphate buffer (50 mM), pH 6.8, 0.5 mM test compound, 10 $\mu$ L enzyme	acarbose	IC <sub>50</sub> $\pm$ SEM (2.6 $\pm$ 0.1 - 72.0 $\pm$ 1.3 $\mu$ M) as compared to 38.45 $\pm$ 0.80 acarbose	[236]
	MOE 2018.	$\alpha$ -Amylase (3BAJ) $\alpha$ -glycosidase	For amylase -5.6919 to -6.1235 and for $\alpha$ -glycosidase -6.1701 to -6.4424	For $\alpha$ -amyl Arg439, His111, Phe158 and Phe177 while $\alpha$ -gly Arg439, His111, Phe158 and Phe177	<i>In vitro</i>	$\alpha$ -glycosidase, phosphate buffer (pH 6.8), 10 $\mu$ L of the sample, spectrophotometrically at 400 nm.	Acarbose	IC <sub>50</sub> $\pm$ SEM ( $\mu$ M) values of 3-20 compounds 23.08 $\pm$ 0.03 to 88.15 $\pm$ 0.12 against $\alpha$ -amyl 26.08 $\pm$ 0.43 to 87.13 $\pm$ 0.12 against $\alpha$ -gly 18.08 $\pm$ 0.07, 18.67 $\pm$ 0.09	[237]
	MOE 2010.11)	$\alpha$ -Glycosidase (3AJ7)	-	Asp349, Arg212, and Arg439	<i>In vitro</i>	$\alpha$ -Glycosidase (20 mL) from <i>Saccharomyces cerevisiae</i> , 70% DMSO, phosphate buffer (135 $\mu$ L)	Acarbose	Compound 3 showed a IC <sub>50</sub> (305 $\pm$ 3.8 mM), and against acarbose (IC <sub>50</sub> ¼ 840 $\pm$ 1.73 mM).	[238]



## 4. Future perspectives of synthetic compounds

As a health concern, one of the utmost fatal diseases known as diabetes, prevailing around worldwide and natural resources are not enough for the complete eradication of this disease. In light of this review, positive diabetic actions of synthetic analogs are summarized in a well-organized way. Although, the search for novel antidiabetic compounds along their wanted pharmacological profiles is an endless job regarding to drug discovery. Emergent heterocyclic equivalents with prior physicochemical, and pharmacodynamic characteristics might be valuable moieties for future studies. The accessible literature survey on thiazolidinone, azole, pyrrole, chalcone, and pyrimidine analogues is comparatively at ease for pharmaceutical chemists to pursue with coherent synthesis and advance treatment. The general addition, substitution, and elimination (functional groups) reaction process are also operative approaches for scheming new drug molecules. The aforementioned antihyperglycemic activities either by *in vitro* and *in vivo* mechanism and drug-receptor or enzyme interaction depicted that just how can ligand adjustment improved mechanistic studies of researchers. In near days, toxicological investigations and reversibility parameters with selectivity effect of novel heterocyclic compounds are likely to predict their opposing and therapeutic effects towards diabetics.

## Conflicts of interest

All authors declared that they have no conflict of interest.

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