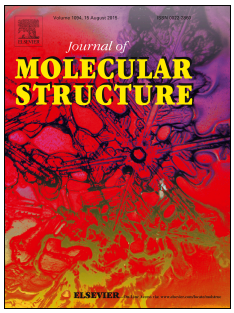

Synthesis, characterization, α-glucosidase inhibiton and molecular modeling studies of some pyrazoline-1*H*-1,2,3-triazole hybrids

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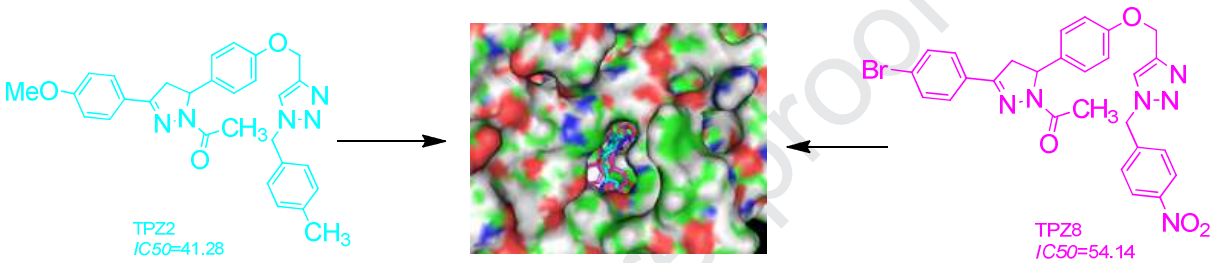
Credit author statement

Lokesh Kumar: Validation, Formal analysis, Investigation Writing - original draft, Writing review; **Kashmiri Lal**: Conceptualization, Methodology, Resources, Data curation, Supervision; **Pinki Yadav**: Methodology, Data curation, Visualization; **Ashwani Kumar**: Software, Data curation. **Avijit K. Paul**: Single crystal analysis, Investigation.

Synthesis, Characterization, α-Glucosidase inhibiton and Molecular Modeling studies of some pyrazoline-1*H*-1,2,3-Triazole hybrids

Graphical Abstract



Synthesis, Characterization, *α*-Glucosidase inhibition and Molecular Modeling studies of some pyrazoline-1*H*-1,2,3-Triazole hybrids

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ABSTRACT

A series of molecular hybrids based on pyrazoline and 1,2,3-triazole pharmacophore were designed and synthesized as antidiabetic agents. The structures of all the derivatives were confirmed using ^{1}H NMR, ^{13}C NMR and HRMS. Moreover, the structure of one of the intermediate precursor was confirmed using single crystal X-ray diffraction. The anti-diabetic potential of all the synthesized compounds and their precursors was explored in terms of *α*-glucosidase inhibition studies. All the compounds exhibited remarkable inhibition of *α*-glucosidase. The inhibition of enzyme by compound **TPZ2** (IC_{50}= 41.29±0.123) and **TPZ8** (IC_{50}=47.94±0.246) was found to be more promising as compared to the reference drug *i.e.*, Acarbose (IC_{50}=60.68±0.123). The inhibition of *α*-glucosidase was further supported by *in silico* docking studies. In order to explore the most favorable binding interactions the binding pose of lowest energy was then subjected to molecular dynamics studies. Both the ligands have reasonable interactions with the protein active site with average interaction energy of -270.88 Kcal/mol and -273.90 Kcal/mol for **TPZ8** and **TPZ2**, respectively.

Keywords: 1,2,3-Triazole, Pyrazoline, *α*-glucosidase, Docking, Molecular dynamics

1 Introduction

Diabetes mellitus is one of the most common and serious diseases caused by high blood glucose level worldwide [1]. As per W.H.O reports, occurrence of diabetes in adult has increased 4.7% in 1980 to 8.5% in 2014 [2, 3]. Diabetes caused 1.6 million deaths in 2016 worldwide and would be

largest cause of death by 2040 [4, 5]. Most of the people with diabetes are diagnosed with type 2 diabetes which is non-insulin dependent**.** Type 2 diabetes is typically a polygenic disease that results from a complex interplay between genetic predisposition and environmental factors such as diet, degree of physical activity, and age.

α-Glucosidase is a key enzyme responsible for digestion of carbohydrates and biosynthesis of glycoproteins and plays a significant role in the treatment of degenerative diseases including type 2 diabetes. *α*-Glucosidase inhibitors can reduce the complications of diabetes by decreasing the liberation of glucose in the bloodstream *via* interfering with the enzymatic action of intestinal *α*-glucosidase [3]. Currently used drugs are associated with some disadvantages including flatulence, diarrhea and low efficacy. To combat this problem, there is an urgent need to develop novel alternative, safe and potent drugs with a broader spectrum of anti-diabetic activity.

Pyrazolines represents a privileged structural class containing five membered rings with two nitrogen atoms and a double bond. Pyrazolines are even more special due to their marked physiological and pharmacological activity. This class is associated with numerous pharmacological activities such as antidiabetic [6], antimicrobial [7, 8], antimalarial [9], antitumor [10], antitubercular [11], anticancer [12, 13], Monoamine oxidase inhibitors [12], anti-inflammatory [14-16], antidepressant [17] and anticonvulsant [18]. Similarly, 1,2,3-triazole also represents a well-established five membered heterocyclic scaffold which has gained significant attention in the drug-discovery field since the introduction of the "click" chemistry concept by Sharpless [19]. Due to active participation in hydrogen bonding and dipole-dipole interactions 1,2,3-triazoles are extremely stable to hydrolysis and oxidative/reductive conditions. Moreover, contrary to other aza-heterocycles, 1,2,3-triazole are less basic owing to which their protonation at physiological *p*H is not feasible. 1,2,3-Triazoles are associated with diverse biological activities including sensing [20], anticancer [21], antiHIV [22], antimicrobial [23-27], antiviral [28], antiproliferative [29] and insecticides [30]. Moreover, 1,2,3-triazole namely benzotriazole is also used as one of the reagent to synthesize peptide and peptide conjugates [31, 32].

Recently, molecular hybridization approach has been explored in medicinal chemistry [33]. This approach enables the synthesis of molecular hybrids by joining two or more biologically active compounds. These hybrid molecules are supposed to have high efficacy and novel mechanism of action in comparison to their parent pharmacophoric units. There are very

few reports on hybrid containing 1,2,3-triazole showing α-glucosidase inhibition. For instance, Mina Saeedia *et al.* synthesized quinazolinone-1,2,3-triazole hybrids compounds and reported their alpha-glucosidase inhibitory activity [34]. All the synthesized compounds exhibited good inhibitory activity against yeast α-glucosidase (IC_{50} = 181.0-474.5 μM) and were found to be more potent than standard drug acarbose (IC_{50} = 750.0 μM). Among them, quinazolinone-1,2,3-triazoles possessing 4-bromobenzyl moiety connected to 1,2,3-triazole ring demonstrated the most potent inhibitory activity towards α-glucosidase. Likewise, Avula *et al.* also synthesized (*R*)-4-fluorophenyl-1*H*-1,2,3-triazole derivatives with remarkable contribution in the overall activity (Figure 1) [35].

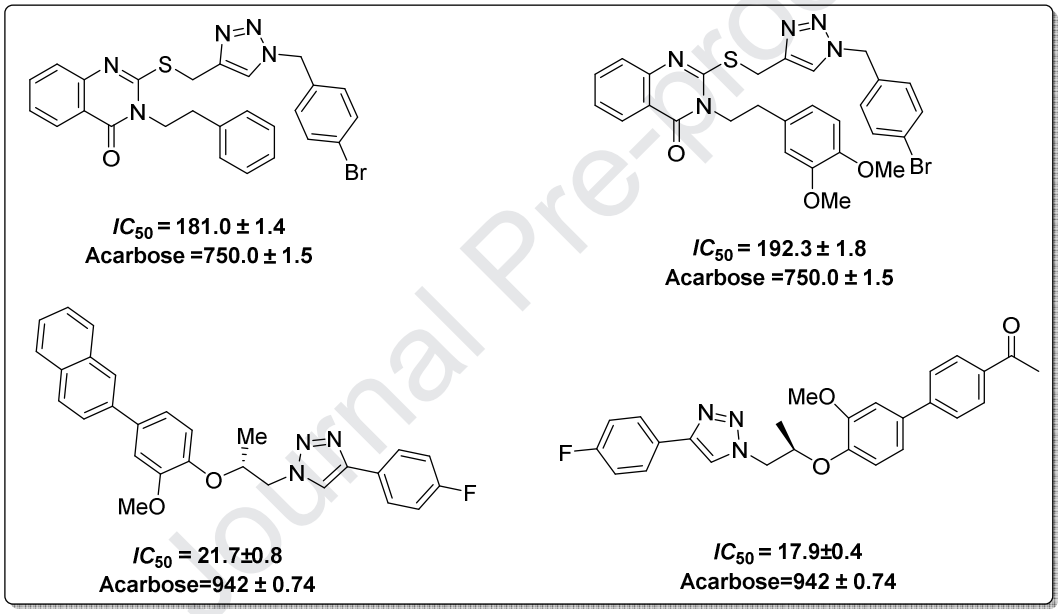


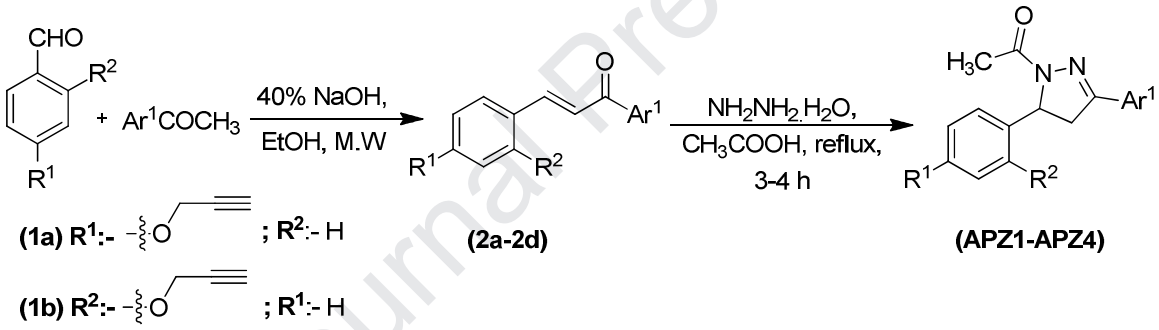
Figure 1: Structures of some hybrids triazoles showing α-glucosidase inhibition

Based on above observations, we planned that molecular hybrids containing 1,2,3-triazole and a pyrazoline moiety may act as good inhibitors of glucosidase enzyme. Therefore, on the basis of above cited and our efforts towards the development of novel 1,2,3-triazole based hybrid molecules [36-42], herein, we have designed and synthesized some 1,2,3-triazole-pyrazoline hybrids as α-glucosidase inhibitors.

2 Results and Discussion

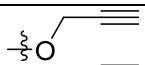
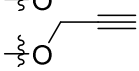
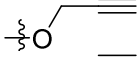
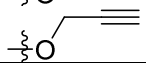
2.1 Chemistry

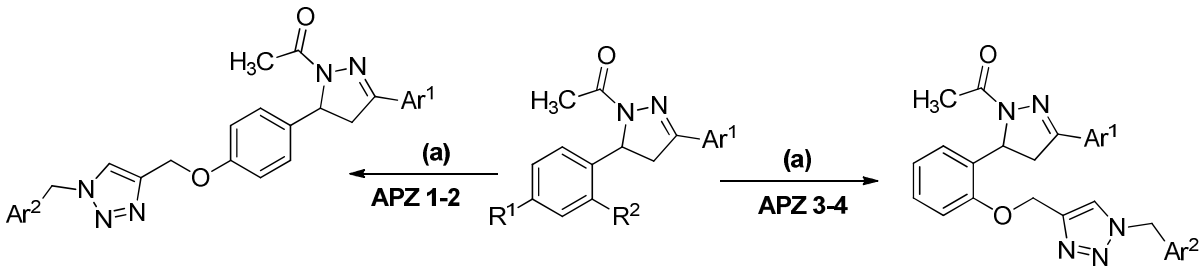
Synthesis of target hybrid compounds was carried out in various steps as presented in scheme **1** and **2**. Firstly, propargylated aldehydes (**1a-1b**) prepared using reported procedure [43] were subjected to Claisen-Schmidt reaction under microwave with 4-methoxy and 4-bromoacetophenone in presence of NaOH to furnish propargylated chalcones **(2a-2d)** in high yield. In next step, propargylated chalcones (**2a-2d**) were refluxed with hydrazine hydrate in acetic acid to yield pyrazoline containing a terminal alkyne (**APZ1-APZ4**) in very good yield (Scheme 1, Table 1). In the final step, pyrazolines with a terminal alkyne were then subjected to copper (I)-catalyzed azide-alkyne cycloaddition with organic bromides (**TPZ1-TPZ16**) in the presence of copper sulphate pentahydrate and sodium ascorbate using DMF: Water (8:2, (*v/v*)) as solvent to yield pyrazoline-1,2,3-triazole hybrids in very good yield (Scheme 2, Table 2).



Scheme 1: Synthesis of 1-(3-aryl-5-(2/4-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-ones (**APZ1-APZ4**)**.**

Table 1: Synthesis of 1-(3-aryl-5-(2/4-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-ones (**APZ1-APZ4**)**.**

S.No	Compound	Ar^1	R^1	R^2	Yield, %	M. Pt (°C)
1	**APZ1**	4-$OMeC_6H_4$		H	70	110-112
2	**APZ2**	4-BrC_6H_4		H	64	114-117
3	**APZ3**	4-$OMeC_6H_4$	H		60	94-98
4	**APZ4**	4-BrC_6H_4	H		62	103-105



Reaction conditions: (a) $ArCH_2Br$, NaN_3, $CuSO_4.5H_2O$, Sodium ascorbate, DMF:H_2O (8:2, *v/v*).

Scheme 2: Synthesis of 1,2,3-triazole linked pyrazoline based molecular hybrids **(TPZ1-TPZ16)**

Table 2: Synthesis of 1,2,3-triazole linked pyrazoline based molecular hybrids **(TPZ1-TPZ16)**

S. No.	Compound	Ar^1	Ar^2	Yield, %	M. Pt (°C)
1	**TPZ1**	4-$OMeC_6H_4$	-C_6H_5	87	120-122
2	**TPZ2**	4-$OMeC_6H_4$	4-MeC_6H_4	86	70-72
3	**TPZ3**	4-$OMeC_6H_4$	4-BrC_6H_4	84	90-93
4	**TPZ4**	4-$OMeC_6H_4$	4-$NO_2C_6H_4$	90	130-132
5	**TPZ5**	4-BrC_6H_4	-C_6H_5	82	140-143
6	**TPZ6**	4-BrC_6H_4	4-MeC_6H_4	80	119-112
7	**TPZ7**	4-BrC_6H_4	4-BrC_6H_4	78	125-127
8	**TPZ8**	4-BrC_6H_4	4-$NO_2C_6H_4$	86	120-123
9	**TPZ9**	4-$OMeC_6H_4$	-C_6H_5	82	65-67
10	**TPZ10**	4-$OMeC_6H_4$	4-MeC_6H_4	78	70-74
11	**TPZ11**	4-$OMeC_6H_4$	4-BrC_6H_4	84	128-130
12	**TPZ12**	4-$OMeC_6H_4$	4-$NO_2C_6H_4$	86	120-122
13	**TPZ13**	4-BrC_6H_4	-C_6H_5	82	95-97
14	**TPZ14**	4-BrC_6H_4	4-MeC_6H_4	79	168-170
15	**TPZ15**	4-BrC_6H_4	4-BrC_6H_4	81	180-183
16	**TPZ16**	4-BrC_6H_4	4-$NO_2C_6H_4$	85	130-132

All the synthesized pyrazolines and triazole derivatives were fully characterized by various analytical and spectral techniques including FTIR, ^{1}H NMR, ^{13}C NMR, MS techniques.

2.1.1 IR Analysis

The IR spectrum of propargylated pyrazoline **(APZ1)** showed two absorption bands at 1683 cm^{-1} and 1651 cm^{-1} due to -C=O stretching of amide and C=N stretching of pyrazoline ring. Two bands due to alkyne ≡C-H stretching and C≡C stretching were also observed at 3197 cm^{-1} and 2123 cm^{-1} which were absent in the IR spectra of all triazole hybrids **(TPZ1-TPZ16)**. The presence of characteristic bands in the region 3128 cm^{-1} in the IR spectra of the triazole **(TPZ1)** evidenced the formation of triazole ring.

2.1.2 ^{1}H NMR analysis

The ^{1}H NMR spectra of the synthesized propargylated pyrazolines **(APZ1)** exhibited doublet at δ 4.67 (J = 2.3 Hz) and triplet at δ 2.52 (J = 2.3 Hz), which confirms the formation of terminal alkyne. An ABX system was found in the structure of pyraozline due to three doublets attributed for H_a, H_b and H_x. H_a appeared at δ 3.16 (J=17.6 & 4.3 Hz), H_b at δ 3.72 (J=17.6,11.7Hz) and H_x resonated at δ 5.56 (J =11.6, 4.3 Hz) with characteristic coupling constants. Aromatic protons appeared in the region at δ 6.95-7.71. In the ^{1}H NMR of triazole **(TPZ1)** peaks at δ 4.67 and δ 2.52 were disappeared and a sharp peak at δ 7.52 has been appeared due to the proton present in triazole ring.

2.1.3 ^{13}C NMR analysis

In the ^{13}C NMR of pyrazoline **(APZ1)** due to ABX system C-H_a and C-H_b signal appears at δ 42.4 and C-H_x signal arises at δ 55.4. While carbonyl carbon appears at δ 168.68 confirms the acetylation during the reaction and C=N appears at δ 156.7. In the ^{13}C NMR of final compound **(TPZ1)** a peak at δ 144.0 confirms the formation of triazole ring. Peaks at δ 168.7 and δ 157.6 appeared due to carbonyl group and C=N of pyrazoline ring.

2.1.4 HRMS analysis

The HRMS data of all the synthesized products were in good agreement with their calculated values

2.2 X-Ray Crystallographic study

The X-ray single crystal data revealed that the compound **APZ2** crystallized in monoclinic cell with space group *C2/c* (

Table 3). The crystal structure for **APZ2** is shown in Figure 2. It is clearly revealed that **APZ2** is a bromo derivative. The resultant crystal structure of **APZ2** shows that the pyrazoline substituted five membered ring is perpendicular to benzene ring which has attached to propargyl units *via* oxygen atom. The propargyl unit is parallel or trans to pyrazole ring. Different intermolecular interactions present in case of **APZ2** are shown in Figure 3. The packing diagram for **APZ2** along c-axis has shown in Fig S45.

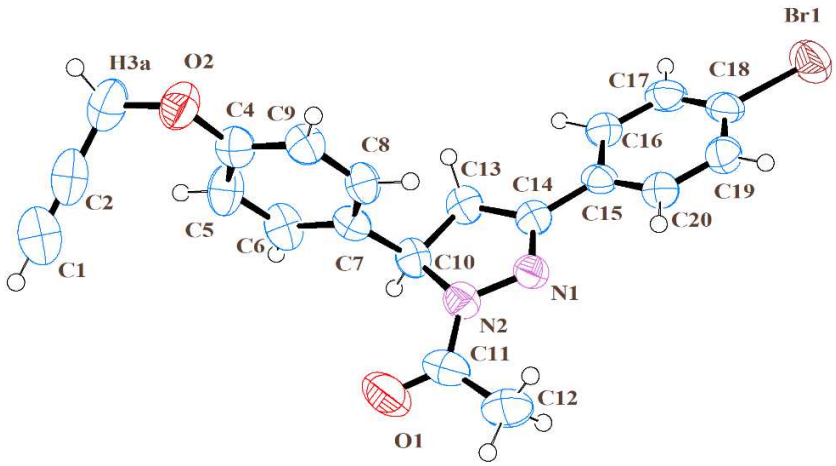


Figure 2: Ortep diagram of the compound **APZ2**.

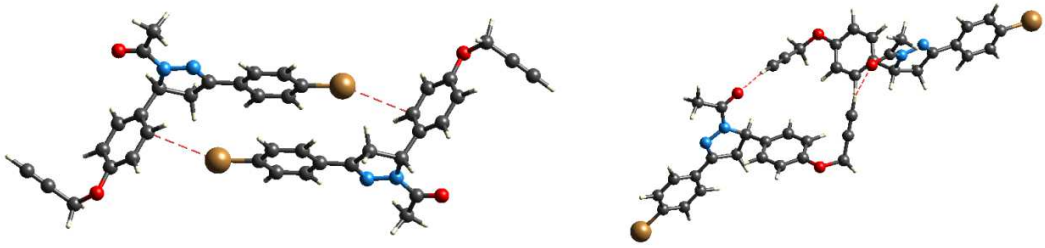


Figure 3: Different intermolecular interactions present in case of **APZ2.**

Table 3: Crystal data and structure refinement parameters for **APZ2.**

Compound	**APZ2**
Empirical formula	$C_{20}H_{17}BrN_2O_2$
Formula weight	397.27
Crystal system	Monoclinic
Space group	*C2/c*
a (Å)	16.267(5)
b (Å)	13.859(5)
c (Å)	16.767(6)
α (°)	90.00
β (°)	103.698(8)
γ (°)	90.00
V (Å^3)	3672(2)
Z	8
D (calc/gcm^{-3})	1.437
μ (mm^{-1})	2.254
λ (Mo K*α*/Å)	0.71073
θ range (°)	1.95-25.00
Total data collected	14730
Unique data	3242
Rint	0.0991
R indexes [$I > 2\sigma(I)$]	R_1 = 0.0605; wR_2 = 0.1588
R indexes (all data)	R_1 = 0.1146; wR_2 = 0.1882

2.3 *α*-Glucosidase inhibitory activity

All the synthesized pyrazoline alkynes (**APZ1-APZ4**), and 1*H*-1,2,3-triazole hybrid derivatives (**TPZ1-TPZ16**) were evaluated for their *α*-glucosidase inhibitory activity and the results are presented in Table 4. It has been revealed that most of the compounds exhibited very good *α*-glucosidase inhibition potential with IC_{50} values ranging from 41.281 to 106.71 μM. Moreover, some of the compounds displayed even better inhibitory profile than acarbose. Some of the

compounds *i.e.*, **TPZ2** (IC_{50} = 41.29 μM), **TPZ4** (IC_{50} = 60.03 μM), **TPZ4** (IC_{50}= 50.73 μM), and **TPZ8** (IC_{50}= 47.94 μM) displayed better inhibitory potencies against α-glucosidase than acarbose (IC_{50} = 60.68μM). The activity of triazole hybrids (**TPZ1-TPZ16**) was found to be more promising when compared with their precursors (pyrazoline-alkynes; **APZ1-APZ4**) thereby it can be concluded that the attachment of triazole ring to pyrazoline has led to increased activity. From structure activity relationship studies, it was observed that all the pyrazoline-triazoles hybrids derived from para propargylated chalcones exhibited better activity those derived from ortho isomers. Apparently, the activity of the potent compounds is likely due to the presence of central pyrazoline ring which interacts with the active site of the enzyme. The Ar^1 substitutions in the pyrazoline influence the activities too. Compound containing methoxy group at pyrazoline are more active than bromo, methyl and nitro.

Table 4: α-Glucosidase inhibition (IC_{50}) activity of synthesized pyrazoline-alkynes (**3a-3d**) and triazole hybrids **(4a-4p)**

Entry	Compound	IC_{50} value*	Docking score
1	**APZ1**	84.90±0.060	-8.4
2	**APZ2**	94.00±0.061	-7.6
3	**APZ3**	101.67±0.123	-7.4
4	**APZ1**	106.71±0.246	-7.0
5	**TPZ1**	64.19±0.185	-9.7
6	**TPZ2**	41.29±0.123	-10.7
7	**TPZ3**	63.84±0.370	-10
8	**TPZ4**	60.03±0.061	-9.8
9	**TPZ5**	50.73±0.246	-10.4
10	**TPZ6**	65.65±0.123	-9.8
11	**TPZ7**	63.89±0.863	-9.6
12	**TPZ8**	47.94±0.246	-10.3
13	**TPZ9**	74.66±0.185	-8.8
14	**TPZ10**	87.87±0.061	-8.3
15	**TPZ11**	79.13±0.185	-8.8
16	**TPZ12**	76.22±0.246	-9.4

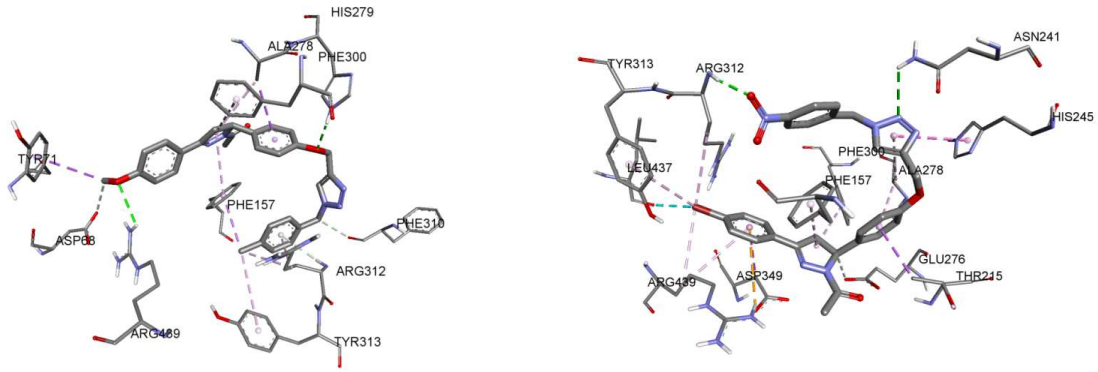
17	**TPZ13**	78.22±0.061	-9.8
18	**TPZ14**	80.51±0.678	-9.9
19	**TPZ15**	87.7± 0.123	-8.4
20	**TPZ16**	74.03± 0.493	-8.4
21	**Acarbose**	60.68± 0.123	-7.4

*Values are means ± SD (n: 3); $p < 0.05$

2.4 Molecular modeling studies

2.4.1 Docking simulations

The 3D structure of *Saccharomyces cerevisiae* α-glucosidase was predicted by homology modeling technique as till now no crystal structure for this enzyme has been reported. The primary structure was assessed in FASTA form from Uniprot database (accession ID: P53341) and SWISS-MODEL Homology Modelling web server was used for homology modeling [44]. The services of BLAST and HHBlits were utilized for template search which resulted in Oligo-1,6-glucosidase (3axh.1.A) structure as best template for protein alignment [45-48]. The latter function was performed with ProMod3 while quality of structure was judged using QMEAN scoring function (QMEAN value = 0.04) [49-51]. More than 96 % of the residues were in favored region and 100 % residues were in permitted area in the Mol Probity Ramachandran plot [52]. Most preferred 3D conformations of compounds **TPZ2** and **TPZ8** in the binding site of the enzyme are shown in Figure 4.



(a) (b)

Figure 4: Binding interactions of compounds **(a) TPZ2**; **(b) TPZ8** (green: hydrogen bond; purple: pi sigma; yellow: electrostatic; blue: halogen bond; dark pink: pi-pi interaction; light pink: hydrophobic)

Methoxy oxygen of the compound **TPZ2** created a hydrogen bond with Arg439 while phenoxy oxygen atom made a hydrogen bond with His279. Two carbon hydrogen bonds were observed with Asp68 and Phe310. Phenyl group attached with triazole ring displayed one Pi-Donor hydrogen bond with Arg312. Pyrazoline ring showed sigma-pi interactions with Phe157 and Phe300. In molecule TPZ8, oxygen atom of nitro group and nitrogen atom of triazole displayed hydrogen bond interactions with Arg312 and Asn421 respectively. Bromine atom made halogen bond with Leu437. Pi orbitals of bromophenyl ring exhibited pi-anion electrostatic interactions with Asp349 while pi electrons of triazole were involved in T-shaped pi-pi interactions with pi orbitals of His245. Pyrazoline ring, again, put on view sigma-pi interactions with Phe157 and Phe300.Surface diagram of protein along with docked molecules is shown in Figure 5. It can be seen that the molecules went deep in the binding pocket.

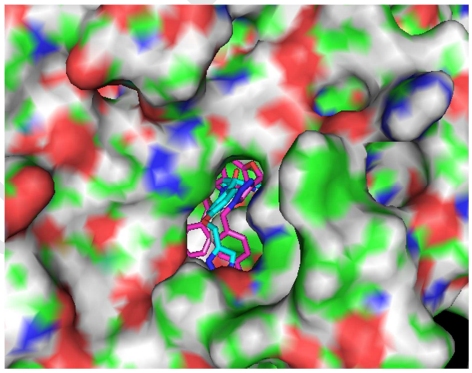


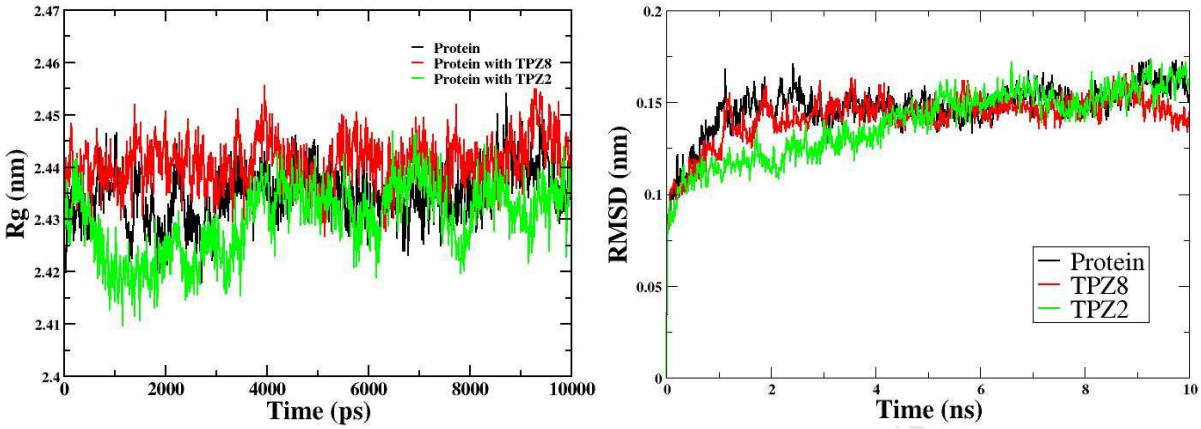
Figure 5: Surface diagram of alpha glucosidase containing docked molecules TPZ2 (cyan) and TPZ8 (magenta)

2.4.2 Molecular dynamics studies

Further, to ascertain the stability of the docked complexes of the molecules with protein in the physiological conditions, molecular dynamics studies were carried out (Fig 6 and Fig 7). Three systems were investigated by using Newtonian mechanics-based molecular dynamic simulations. The first system contains protein while the other two consists of one of each ligand along with the protein. For each system Cartesian coordinates were placed in the center of the cubic box, the remaining volume of the box was filled by water molecules. Solvation is followed by the

neutralization where a respective number of ions were added to each system to mimic physiological conditions. Both solvation and neutralization steps were processed by using GROMACS 5.4 [53]. To remove unusual contacts between atoms energy minimization was performed using the steepest descendant method followed by 10 ns equilibration. The potential energy of the system is calculated by using OPLS force fields integrated into GROMACS 5.4 package [54]. Whereas, Extended Simple Point Charge (SPCe) potential is used to describe the molecular mechanics of the water molecules [55].

Classical simulations consider each atom as a hard-sphere with a user-defined charge. Whereas, the motion of each atom is governed by the newton`s equation of motion through estimation of the force on each atom from potential energy function. Before making any conclusion out of the simulated system especially protein one needs to assure that the system must be equilibrated. Therefore, we check the protein backbone RMSD for all the three systems which shows a stable behavior after an initial surge. Both the ligands have reasonable interaction with the protein active site with average interaction energy of -270.88 Kcal/mol and -273.90 Kcal/mol for **TPZ8** and **TPZ2**, respectively. We also calculated the diffusion coefficient for both the ligands to compare their displacement from the initial docked positions. The calculated diffusion coefficient shows that throughout the MD run both the ligands are tightly restrained within the active site with a diffusion coefficient of $0.14e^{-5}$ cm^2/sec and $0.15e^{-5}$ cm^2/sec for **TPZ8** and **TPZ2**, respectively.



(a) (b)

Figure 6: Qualitative analysis of the Molecular dynamics trajectory. (a) Radius of gyration; RMSD plot of protein and ligand.

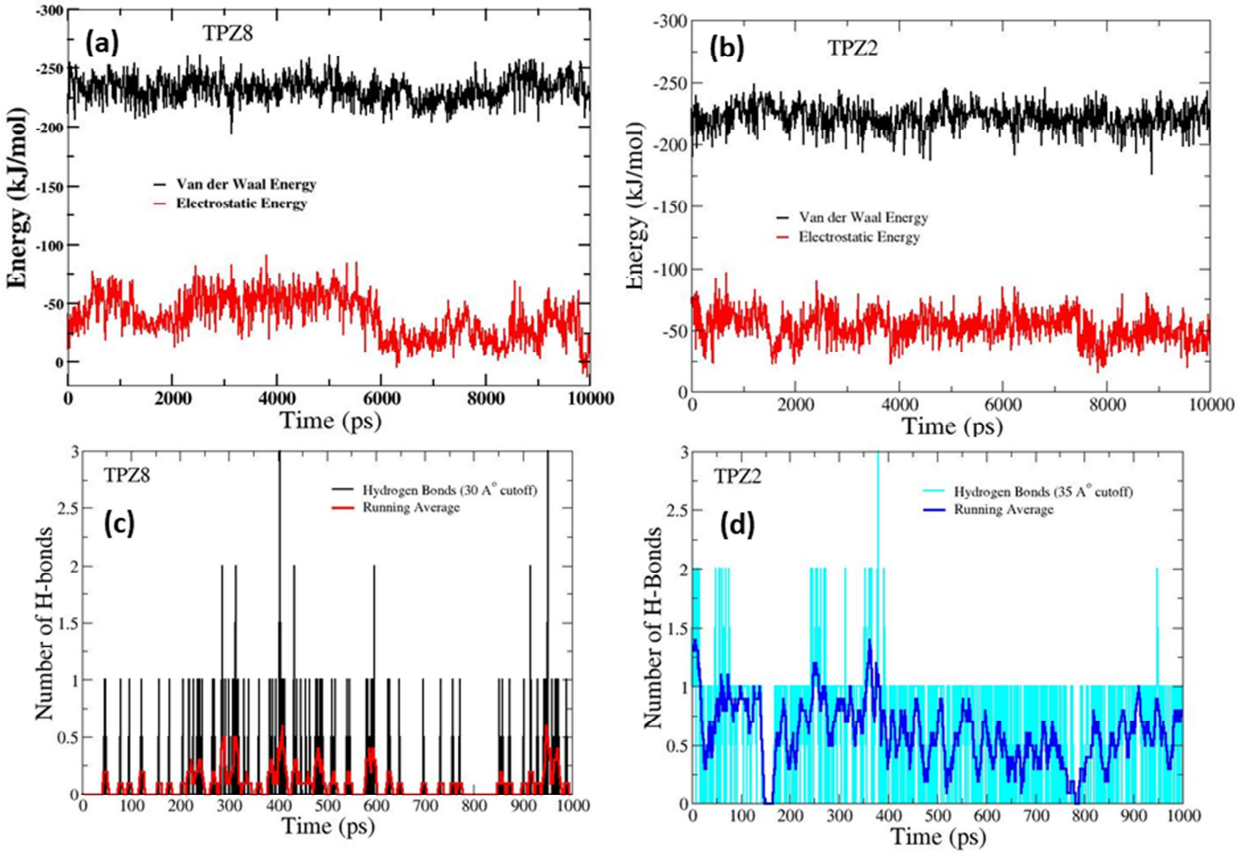


Figure 7: (a) Energy plot of ligand **TPZ8**; (b) Energy plot of ligand **TPZ2**; (c) The plot of hydrogen bonds formed between protein and ligand **TPZ8**; (d) The plot of hydrogen bonds formed between protein and ligand **TPZ2**.

2.5 Conclusion

In summary, we have successfully designed, synthesized and evaluated the *α*-glucosidase inhibition potential of some pyrazoline-1,2,3-triazole hybrids. All the synthesized compounds were fully characterized with the help of various spectral techniques. The *α*-glucosidase inhibition studies showed that most of the compounds exhibited better or comparable activity to that of standard drug Acarbose. It was also observed that the attachment of triazole ring to pyrazoline has increased the activity as suggested by molecular hybridization approach. Further, the docking results also showed that the two most potent compounds bind more strongly than the Acarbose with *α*-glucosidase enzyme. Moreover, the molecular dynamics studies also supported

the wet experiment results. Therefore, it can be said that these kind of pyrazoline-triazole hybrids can be useful for the development of lead molecules for diabetes.

3 Experimental

3.1 Chemistry

All chemicals and solvents used in the present work were purchased from Sigma Aldrich, Alfa-Aesar and Hi-media and used without further purification. Melting point of the synthesized compounds was recorded in open capillaries and is uncorrected. The ^{1}H and ^{13}C were recorded on Bruker Avance II 400 MHz at 400 MHz and 100 MHz respectively, using deuterated chloroform as solvent ($CDCl_3$) and tetramethylsilane (TMS) as an internal standard (chemical shift in del, ppm). The IR spectra were recorded on Shimazdu IR Affinity-I FT-IR spectrophotometer using potassium bromide (KBr) and the values are given in cm^{-1}. High resolution mass spectra (HRMS) were recorded on SCIEX-QTOF spectrometer spectrophotometer. The completion of the reaction and the purity of the compounds were monitored by thin layer chromatography (TLC) using silica gel plates (SIL G/UV254, ALUGRAM) and visualized under ultraviolet lamp.

3.1.1 Synthesis of pyrazolines from chalcones with terminal alkyne. (3a-3d)

The synthesis of pyrazolines from chalcones with terminal alkyne were achieved *via* sequential synthesis. For this, firstly 2-(prop-2-yn-1-yloxy) benzaldehyde (**1a**)/ 4-(prop-2-yn-1-yloxy) benzaldehyde (**1b**) were synthesized using reported procedure. After synthesis of propargylated aldehyde they were subjected to Claisen Schmidt reaction with differently substituted acetophenones (**2**) under microwave. The chalcones (**2a-2d**) (1.0 mml), thus formed were reacted with hydrazine hydrate (3.0 mml) in acetic acid (20 mL) and the mixture was refluxed under stirring for 6 h. The progress of the reaction was monitored using TLC. After completion of the reaction as indicated by TLC the reaction was quenched using ice cold water and precipitate thus formed was filtered under suction. The solid so obtained was recrystallized using ethanol.

4.1.1. 1-(3-(4-methoxyphenyl)-5-(4-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (APZ1): Appearance: solid; Brown solid; FT-IR (KBr, υ_{max} cm^{-1}): 3197 (≡C-H str.), 3020 (C-H str., aromatic ring), 2935, 2123 (C≡C str) 1683 (C=O str, Amide), 1608 (C=N str); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.95 (t, *J*

= 9.2 Hz, 4H), 5.56 (dd, *J* = 11.6, 4.3 Hz, 1H), 5.56 (dd, *J* = 11.6, 4.3 Hz, 1H), 4.67 (d, *J* = 2.3 Hz, 2H), 4.67 (d, *J* = 2.3 Hz, 2H), 3.87 (s, 3H), 3.72 (dd, *J* = 17.6, 11.7 Hz, 1H), 3.23-3.08 (m, 1H), 2.52 (t, *J* = 2.4 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (s), 161.3 (s), 156.9 (s), 153.7 (s), 135.1 (s), 128.1 (s), 126.9 (s), 124.1 (s), 115.1 (s), 114.1 (s), 78.5 (s), 75.5 (s), 59.2 (s), 55.8 (s), 55.4 (s), 42.3 (s), 21.9 (s); HRMS (m/z) $[M+H]^+$calculated for $C_{21}H_{20}N_2O_3$ 349.1552 found: 349.1582

3.2.3 1-(3-(4-bromophenyl)-5-(4-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (APZ2): Appearance: solid; Brown solid; FT-IR (KBr υ_{max}, cm^{-1}): 3219 (≡C-H str.), 3049 (=C-H str., aromatic ring), 2951, 2113 (C≡C str), 1658 (C=O str), 1608(C=N str); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.6 Hz, 3H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.07 (d, *J* = 9.1 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 5.86 (dd, *J* = 11.9, 4.8 Hz, 1H), 4.75 (dd, *J* = 4.3, 2.4 Hz, 2H), 3.74 (dd, *J* = 17.7, 11.9 Hz, 1H), 3.08 (dd, *J* = 17.7, 4.8 Hz, 1H), 2.49 (t, *J* = 2.4 Hz, 1H), 2.48 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (s), 154.1 (s), 153.6 (s), 131.8 (s), 130.6 (s), 129.6 (s), 128.6 (s), 128.0 (s), 126.2 (s), 124.4 (s), 121.7 (s), 112.5 (s), 78.5 (s), 75.6 (s), 56.1 (s), 41.3 (s), 21.9 (s); HRMS (m/z) $[M+H]^+$ calculated for $C_{20}H_{17}BrN_2O_2$: 397.0552 found: 397.0587

3.2.2 1-(3-(4-methoxyphenyl)-5-(2-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (APZ3)

Appearance: Brown solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3213 (≡C-H str., triazole ring), 3041 (C-H str., aromatic ring), 2941, 2115 (-C≡C str), 1651 (C=O str), 1593 (C=N str); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.9 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 9.1 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 5.86 (dd, *J* = 11.7, 4.6 Hz, 1H), 4.76 (dd, *J* = 4.7, 2.4 Hz, 1H), 3.86 (s, 2H), 3.74 (dd, *J* = 17.6, 11.7 Hz, 1H), 3.08 (dd, *J* = 17.6, 4.6 Hz, 1H), 2.51 (t, *J* = 2.3 Hz, 1H), 2.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7 (s), 161.2 (s), 154.6 (s), 154.2 (s), 130.0 (s), 128.4 (s), 128.2 (s), 126.0 (s), 124.3 (s), 121.7 (s), 114.0 (s), 112.5 (s), 78.6 (s), 75.5 (s), 56.2 (s), 55.6(s), 55.4(s), 41.6(s), 21.9 (s); HRMS (m/z) $[M+H]^+$:calculated for $C_{21}H_{20}N_2O_3$ 349.1552 found: 349.1582

3.2.4 1-(3-(4-bromophenyl)-5-(2-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (APZ4)

Appearance: Brown solid ; FT-IR (KBr, υ $_{max}$, cm^{-1}): 3250 (≡C-H str.), 3211 (C-H str., aromatic ring), 2943, 2113 (C≡C str), 1681 (C=O str), 1599 (C=N str); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 20.7, 8.6 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 5.58 (dd, *J* = 11.8, 4.5 Hz, 1H), 4.67 (d, *J* = 2.3 Hz, 1H), 3.72 (dd, *J* = 17.7, 11.8 Hz, 1H), 3.14 (dd, *J* = 17.7, 4.6 Hz, 1H), 2.52 (t, *J* = 2.4 Hz, 1H), 2.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (s), 157.0 (s), 152.7 (s), 134.8 (s), 131.9 (s), 130.1 (d, *J* = 54.7 Hz), 128.0 (s), 126.9 (s), 124.6 (s), 115.2 (s), 78.5 (s), 75.6 (s), 59.5 (s), 55.8 (s), 42.1 (s), 21.9 (s); HRMS (m/z) $[M+H]^+$calculated for $C_{20}H_{17}BrN_2O_2$: 397.0552 found: 397.0587

3.3 General procedure for the synthesis pyrazoline-1,2,3-triazol hybrids (TPZ1-TPZ16):

To a stirred solution of benzyl bromide (1.0 mmol) in dimethylformamide, aqueous solution of sodium azide (3.0 mmol) was added. Then, after 1-2 h, pyrazoline alkyne **(APZ1-APZ4)**, (1.0 mmol), copper sulphate pentahydrate (0.1mmol) and sodium ascorbate (0.4 mmol) were added successively [10]. Stirring of the reaction content was continued at 40-45°C for 3-5 h (Scheme 2). The progress of reaction was monitored by thin layer chromatography. On completion of the reaction, aqueous cold ammonia solution was added to the reaction mixture and filtered the precipitated solid. The solid product was washed with water. The crude products obtained above were purified by washing with ethyl acetate and dried under vacuum to get the target compounds **(TPZ1-TPZ16)**

3.3.1 1-(5-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ1): Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3126 (C-H str., triazole ring), 3078 (C-H str., aromatic ring), 2941, 1664 (C=O str), 1606 (C=N str pyrazoline); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.52 (s, 1H), 7.38 (s, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.93 (dd, *J* = 18.6, 8.5 Hz, 4H), 5.54 (s, 2H), 5.16 (s, 2H), 3.87 (s, 3H), 3.71 (dd, *J* = 17.4, 11.9 Hz, 1H), 3.13 (d, *J* = 22.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7 (s), 161.3 (s), 157.6 (s), 153.7 (s), 144.6 (s), 134.8 (s), 134.4 (s), 129.1 (s), 128.8 (s), 128.2 (s), 128.1 (s), 126.9 (s), 124.1 (s), 122.6 (s), 115.1 (s), 114.2 (s), 62.1 (s), 59.2 (s), 55.4 (s), 54.3 (s), 42.4 (s), 22.0 (s). HRMS (m/z) $[M+H]^+$calculated for $C_{28}H_{27}N_5O_3$: 482.2194 found: 482.1875

3.3.2 1-(3-(4-methoxyphenyl)-5-(4-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ2)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3134 (C-H str., triazole ring), 3007 (C-H str., aromatic ring), 2939, 1664 (C=O str), 1606 (C=N str, pyrazoline); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.50 (s, 1H), 7.20 (s, 4H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.95 (t, *J* = 6.9 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.54 (dd, *J* = 11.6, 4.0 Hz, 1H), 5.49 (s, 2H), 5.15 (s, 2H), 3.87 (s, 3H), 3.70 (dd, *J* = 17.4, 11.8 Hz, 1H), 3.12 (dd, *J* = 17.5, 4.1 Hz, 1H), 2.41 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7 (s), 161.4 (s), 157.5 (s), 153.6 (s), 144.6 (s), 134.7 (s), 134.4 (s), 129.1 (s), 128.7 (s), 128.2 (s), 128.2 (s), 126.8 (s), 124.2 (s), 122.5 (s), 115.1 (s), 114.1 (s), 62.1 (s), 59.3 (s), 55.4 (s), 54.3 (s), 42.4 (s), 22.0 (s) 21.3 (s). HRMS (m/z) $[M+H]^+$calculated for $C_{29}H_{29}N_5O_3$: 496.2349 found: 496.1265

3.3.3 1-(5-(4-((1-(4-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-methoxy phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ3)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3122 (C-H str., triazole ring), 3080 (C-H str, aromatic ring), 2935, 1666 (C=O str), 1606 (C=N str Pyrazoline); ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.77–7.65 (d, 2H), 7.55-7.52 (m, 2H), 7.52 (s, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 3H), 6.96 (d, 2H), 6.91 (d, 2H), 5.53 (dd, *J* = 10.1, 5.0 Hz, 1H), 5.49 (s, 2H), 5.17 (s, 2H), 3.87 (s, 3H), 3.71 (dd, 1H), 3.13 (dd, *J* = 17.5, 5.6 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (s), 161.3 (s), 157.5 (s), 153.7 (s), 144.8 (s), 134.9 (s), 133.4 (s), 132.3 (s), 131.9 (s), 129.8 (s), 129.7 (s), 128.1 (s), 126.9 (s), 124.0 (s), 122.9 (s), 122.5 (s), 115.1 (s), 114.1 (s), 62.1 (s), 59.2 (s), 55.4 (s), 53.5 (s), 42.4 (s), 21.9 (s); HRMS (m/z) $[M+H]^+$ calculated for $C_{28}H_{26}BrN_5O_3$: 560.1297 found: 560.1477

3.3.4 1-(3-(4-methoxyphenyl)-5-(4-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ4)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3124 (C-H str., triazole ring), 3086 (C-H str, aromatic ring), 2939, 1635 (C=O str), 1606 (C=N str pyrazoline),1517 (N=O str), 1342 (N=O str); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.60 (s, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.65 (s, 1H), 5.54 (dd, *J* = 11.6, 4.3 Hz, 1H), 5.20 (s, 2H), 3.87 (s, 3H), 3.72 (dd, *J* = 17.5, 11.7 Hz, 1H), 3.12 (dd, *J* = 17.5, 4.4 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (s), 161.3 (s), 157.6 (s), 153.7 (s), 144.7 (s), 134.9 (s), 133.5 (s), 132.4 (s), 132.0 (s), 129.7

(s), 129.7 (s), 128.2 (s), 126.8 (s), 124.2 (s), 122.0 (s), 122.4 (s), 115.1 (s), 114.1 (s), 62.2 (s), 59.3 (s), 55.4 (s), 53.4 (s), 42.4 (s), 21.9 (s). HRMS (m/z) $[M+H]^+$ calculated for $C_{28}H_{26}N_6O_5$: 527.2043 found: 527.2082

3.3.5 1-(5-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ5)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3122 (C-H str., triazole ring), 3066 (C-H str, aromatic ring), 2992, 1670 (C=O str), 1585 (C=N str, pyrazoline).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (q, *J* = 8.7 Hz, 4H), 7.52 (s, 1H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.32-7.28 (m, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.61-5.55 (dd, 1H), 5.55 (s, *J* = 5.1 Hz, 2H), 5.17 (s, 2H), 3.72 (dd, *J* = 17.7, 11.8 Hz, 1H), 3.12 (dd, *J* = 17.7, 4.6 Hz, 1H), 2.41 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (s), 157.7 (s), 152.7 (s), 144.5 (s), 134.5 (s), 134.4 (s), 131.9 (s), 130.4 (s), 129.1 (s), 128.8 (s), 128.1 (s), 128.0 (s), 126.9 (s), 124.6 (s), 122.5 (s), 115.1 (s), 62.1 (s), 59.5 (s), 54.2 (s), 42.1 (s), 30.3(s), 21.9 (s); HRMS (m/z) calculated for $C_{27}H_{24}BrN_5O_2$ $[M+H]^+$: 530.1192 found: 530.1352.

3.3.6 1-(3-(4-bromophenyl)-5-(4-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone(TPZ6)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3120 (C-H str., triazole ring), 3072 (C-H str, aromatic ring), 2995, 1672 (C=O str), 1595 (C=N str., pyrazoline).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.64-7.59 (d, 2H), 7.56 (d, 2H), 7.50 (s, 1H), 7.20 (d, 3H), 7.18-7.13 (m, 1H), 6.93 (t, *J* = 8.9 Hz, 1H), 5.62-5.53 (dd, 1H), 5.49 (s, 2H), 5.15 (s, 2H), 3.76-3.65 (dd, 1H), 3.13 (dd, *J* = 17.7, 5.7 Hz, 1H), 2.98 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9 (s), 162.5 (s), 158.1 (s), 152.8 (s), 144.4 (s), 138.8 (s), 134.4 (s), 131.9 (s), 129.8 (s), 128.2 (s), 128.0 (s), 126.9 (s), 124.6 (s), 122.4 (s), 115.2 (s), 115.1 (s), 62.1 (s), 59.5 (s), 54.6 (s), 42.1 (s), 36.5 (s), 31.4 (s), 25.3 (s), 21.9 (s), 21.1 (s); HRMS: (m/z) $[M+H]^+$ calculated for $C_{28}H_{26}BrN_5O_2$: 544.1348 found: 544.1515

3.3.7 1-(5-(4-((1-(4-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ7)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}):3122 (C-H str., triazole ring), 3078 (C-H str, aromatic ring), 2943, 1664 (C=O str), 1591 (C=N str, pyrazoline); ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.62 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.55-7.51 (m, 2H), 7.16 (m, *J* = 8.5, 4.8 Hz, 4H), 6.92 (d, *J* = 8.7 Hz, 1H), 5.56 (dd, *J* = 11.8, 4.5 Hz, 1H), 5.49 (s, 2H), 5.17 (s, 2H), 3.72 (dd, *J* = 17.7, 11.8 Hz, 1H), 3.12 (dd, *J* = 17.6, 4.6 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9 (s), 157.6 (s), 152.8 (s), 144.7 (s), 134.5 (s), 133.4 (s), 132.3 (s), 131.9 (s), 130.3 (s), 129.7 (s), 128.0 (s), 126.9 (s), 124.6 (s), 123.0 (s), 122.5 (s), 115.1 (s), 62.1 (s), 59.7 (s), 53.6 (s), 42.5 (s), 22.0 (s). HRMS (m/z) $[M+H]^+$ calculated for $C_{27}H_{23}Br_2N_5O_2$: 608.0297 found: 608.0483

3.3.8 1-(3-(4-bromophenyl)-5-(4-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ8)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}):3118 (C-H str., triazole ring), 3080 (C-H str., aromatic ring), 2943, 1651 (C=O str), 1597 (C=N str, pyrazoline), 1523 (N=O str), 1350 (N=O str); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.8 Hz, 2H), 7.60 (s, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 1H), 5.65 (s, 2H), 5.54 (dd, *J* = 11.6, 4.3 Hz, 1H), 5.20 (s, 2H), 3.87 (s, 3H), 3.72 (dd, *J* = 17.5, 11.7 Hz, 1H), 3.12 (dd, *J* = 17.5, 4.4 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ168.9 (s), 158.5 (s), 152.9 (s), 144.9 (s), 135.5 (s), 134.4 (s), 133.3 (s), 132.8 (s), 131.3 (s), 129.7 (s), 129.0 (s), 127.8 (s), 125.6 (s), 124.0 (s), 123.5 (s), 115.1 (s), 62.1 (s), 60.3 (s), 53.5 (s), 43.2 (s), 22.4 (s); HRMS (m/z) $[M+H]^+$ calculated for $C_{27}H_{23}BrN_6O_4$:575.1042 found: 575.1219

3.3.9 1-(5-(2-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ9)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3134 (C-H str., triazole ring), 3068 (C-H str., aromatic ring), 2941, 1666 (C=O str), 1604 (C=N str); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.6 Hz, 2H),), 7.65 (s, 1H), 7.22 (m, *J* = 7.7 Hz, 5H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.97-6.90 (m, 2H), 5.79 (dd, *J* = 11.8, 4.8 Hz, 1H), 5.49 (s, 2H), 5.26 (s, *J* = 5.6 Hz, 2H), 3.86 (s,3H), 3.61 (dd, *J* = 17.7, 11.8 Hz, 1H), 3.05 (dd, *J* = 28.4, 15.7 Hz, 1H), 2.43 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (s), 161.2 (s), 154.6 (s), 154.5 (s), 144.4 (s), 134.6 (s), 129.8 (s), 129.1 (s), 128.2 (s), 128.1 (s), 128.0 (s), 126.2 (s), 124.1 (s), 122.9 (s), 121.4 (s), 114.1 (s), 112.4 (s), 62.4 (s), 55.7 (s), 55.4 (s), 54.1 (s), 41.6 (s), 21.9 (s); HRMS (m/z)calculated for $C_{28}H_{27}N_5O_3$ $[M+H]^+$: 482.2114 found: 482.1876

3.3.10 1-(3-(4-methoxyphenyl)-5-(2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ10)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3136 (C-H str., triazole ring), 3068 (C-H str, aromatic ring), 2941, 1662 (C=O str), 1589 (C=N str, pyrazoline); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.7 Hz, 2H), 7.58 (s, 1H), 7.18 (m, 5H), 7.07 (d, *J* = 7.0 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 3H), 5.78 (dd, *J* = 11.7, 4.7 Hz, 1H), 5.45 (s, 2H), 5.25 (d, *J* = 5.8 Hz, 2H), 3.86 (s, 3H), 3.61 (dd, *J* = 17.6, 11.8 Hz, 1H), 3.03 (dd, *J* = 17.6, 4.8 Hz, 1H), 2.43 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (s), 161.2 (s), 154.6 (s), 154.4 (s), 144.3 (s), 138.6 (s), 131.5 (s), 129.7 (s), 129.7 (s), 128.6 (s), 128.1 (s), 126.2 (s), 124.2 (s), 122.7 (s), 121.4 (s), 114.0 (s), 112.5 (s), 62.4 (s), 62.4 (s), 55.7 (s), 55.4 (s), 54.0 (s), 54.0 (s), 41.5 (s), 21.9 (s), 21.1 (s); HRMS m/z calculated for $C_{29}H_{29}N_5O_3$ $[M+H]^+$: 496.2270 found: 496.1567

3.3.11 1-(5-(2-((1-(4-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone TPZ11

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}):3136 (C-H str., triazole ring), 3009 (C-H str, aromatic ring), 2939, 1662 (C=O str), 1591 (C=N str, pyrazoline); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 9.1 Hz, 3H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.22 (t, *J* = 7.0 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.94 (t, *J* = 7.9 Hz, 3H), 5.80 (dd, *J* = 11.7, 4.8 Hz, 1H), 5.43 (s, 2H), 5.30 (s, 2H), 3.86 (s, 3H), 3.63 (dd, *J* = 17.6, 11.8 Hz, 1H), 3.04 (dd, *J* = 17.6, 4.9 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 168.6 (s), 161.2 (s), 154.4 (s), 154.4 (s), 144.6 (s), 133.6 (s), 132.2 (s), 130.1 (s), 129.6 (s), 128.6 (s), 128.1 (s), 126.2 (s), 124.1 (s), 122.9 (s), 122.8 (s), 121.5 (s), 114.0 (s), 112.6 (s), 62.5 (s), 60.4 (s), 55.5 (s), 55.4 (s), 53.4 (s), 41.5 (s), 21.9 (s); HRMS (m/z) $[M+H]^+$calculated for $C_{28}H_{26}BrN_5O_3$: 560.1297 found: 560.1477

3.3.12 1-(3-(4-methoxyphenyl)-5-(2-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ12)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}):3134 (C-H str., triazole ring), 3076 (C-H str., aromatic ring), 2941, 1641 (C=O str), 1606 (C=N str., pyrazoline), 1517 (N=O str), 1346

(N=O str); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.2 Hz, 2H), 7.81 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.28 (s, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.83 (dd, *J* = 11.4, 4.2 Hz, 1H), 5.58 (s, 2H), 5.36 (s, 2H), 3.86 (s, 3H), 3.65 (dd, *J* = 17.5, 11.9 Hz, 1H), 3.05 (dd, *J* = 17.6, 4.5 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$):δ 168.6 (s), 161.3 (s), 154.4 (s), 154.2 (s), 145.0 (s), 141.7 (s), 130.3 (s), 128.6 (s), 128.6 (s), 128.1 (s), 126.2 (s), 124.2 (s), 124.1 (s), 123.4 (s), 121.7 (s), 114.1 (s), 112.8 (s), 62.5 (s), 55.4 (s), 55.2 (s), 53.0 (s), 41.6 (s), 31.5 (s), 22.6 (s), 21.9 (s); HRMS (m/z) $[M+H]^+$ calculated for $C_{28}H_{26}N_6O_5$: 527.2043 found: 527.2082

3.3.13 1-(5-(2-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ13)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3136 (C-H str., triazole ring), 3064 (C-H str, aromatic ring), 2941, 1666 (C=O str), 1593 (C=N str, pyrazoline); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.54 (s, 4H), 7.38 (d, *J* = 6.9 Hz, 3H), 7.28 (s,2H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 5.79 (dd, *J* = 11.9, 5.0 Hz, 1H), 5.48 (s, 2H), 5.25 (d, *J* = 3.7 Hz, 2H), 3.61 (dd, *J* = 17.7, 11.9 Hz, 1H), 3.04 (dd, *J* = 17.7, 5.0 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 168.8 (s), 154.7 (s), 153.5 (s), 144.2 (s), 134.5 (s), 131.8 (s), 130.5 (s), 129.5 (s), 129.1 (s), 128.8 (s), 128.7 (s), 128.0 (s), 127.9 (s), 126.4 (s), 124.4 (s), 122.8 (s), 121.4 (s), 112.5 (s), 62.3 (s), 56.2 (s), 54.2 (s), 41.2 (s), 31.58 (s), 22.65 (s), 21.94 (s); HRMS (m/z) $[M+H]^+$ calculated for $C_{27}H_{24}BrN_5O_2$: 530.1192 found: 530.1352

3.3.14 1-(3-(4-bromophenyl)-5-(2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ14)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3130 (C-H str., triazole ring), 3013 (C-H str, aromatic ring), 2931, 1660 (C=O str), 1595 (C=N str, pyrazoline); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 5H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.18 (s, 4H), 7.06 (d, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 5.79 (dd, *J* = 11.9, 5.0 Hz, 1H), 5.44 (s, 2H), 5.23 (d, *J* = 4.5 Hz, 2H), 3.60 (dd, *J* = 17.7, 11.9 Hz, 1H), 3.05 (s, 3H), 2.42 (s, 3H), 2.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 168.8 (s), 154.7 (s), 153.6 (s), 144.1 (s), 138.7 (s), 131.8 (s), 131.5 (s), 130.5 (s), 129.7 (s), 129.4 (s), 128.8 (s), 128.1 (s), 127.9 (s), 126.3 (s), 124.4 (s), 122.7 (s), 121.4

(s), 112.5 (s), 62.3 (s), 56.2 (s), 54.0 (s), 41.2 (s), 21.9 (s), 21.1 (s); HRMS (m/z) $[M+H]^+$ calculated for $C_{27}H_{26}BrN_5O_2$: 544.1348 found: 544.1515

3.3.15 1-(5-(2-((1-(4-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ15)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}):3136 (C-H str., triazole ring), 3064 (C-H str, aromatic ring), 2943, 1664 (C=O str), 1593 (C=N str, pyrazoline); ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (t, *J* = 8.7 Hz, 2H), 7.59 (t, *J* = 6.7 Hz, 3H), 7.56 (s, 1H), 7.49 (s, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.64 (s, 2H), 5.54 (dd, *J* = 11.7, 4.2 Hz, 1H), 5.18 (s, 2H), 3.70 (dd, *J* = 24.5, 12.3 Hz, 1H), 3.10 (dd, *J* = 17.7, 4.3 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (s), 157.5 (s), 152.7 (s), 148.1 (s), 145.1 (s), 141.5 (s), 134.6 (s), 131.9 (s), 130.3 (s), 128.6 (s), 128.1 (s), 126.9 (s), 124.6 (s), 124.3 (s), 124.0 (s), 122.9 (s), 115.1 (s), 62.0 (s), 59.5 (s), 53.1 (s), 42.1 (s), 21.9 (s); HRMS (m/z) $[M+H]^+$ calculated for $C_{27}H_{23}Br_2N_5O_2$: 608.0292 found: 608.0483

3.3.16 1-(3-(4-bromophenyl)-5-(2-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (TPZ16)

Appearance: Light yellow solid; FT-IR (KBr, υ_{max}, cm^{-1}): 3180 (C-H str., triazole ring), 3076 (C-H str, aromatic ring), 2945, 1662 (C=O str), 1593 (C=N str, pyrazoline), 1521 (N=O str), 1346 (N=O str); ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.6 Hz, 2H), 7.55 (s, 1H), 7.54-7.46 (m, 2H), 7.19 (d, *J* = 8.3 Hz, 3H), 7.16-7.10 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 1H), 5.53 (dd, *J* = 11.8, 4.4 Hz, 1H), 5.47 (s, 2H), 5.14 (s, 2H), 3.70 (dd, *J* = 17.7, 11.8 Hz, 1H), 3.09 (dd, *J* = 17.7, 4.5 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 168.90 (s), 154.21 (d, *J* = 12.0 Hz), 153.62 (d, *J* = 11.7 Hz), 148.02 (s), 144.8 (s), 141.6 (s), 131.9 (s), 130.6 (s), 129.9 (s), 128.8 (s), 128.6 (s), 128.0 (s), 127.9 (s), 126.2 (s), 124.2 (s), 123.3 (s), 121.7 (s), 78.5 (s), 75.6 (s), 62.4 (s), 56.1 (s), 56.8 (s), 53.0 (s), 41.3 (s), 31.5 (s), 22.6 (s), 21.9 (s); HRMS (m/z) $[M+H]^+$calculated for $C_{27}H_{23}BrN_6O_4$: 575.1042 found: 575.1219.

2.2 *α*-Glucosidase inhibitory activity

α-Glucosidase enzyme ((EC3.2.1.20, *Saccharomyces cerevisiae*, 20 U/mg) and substrate (pnitrophenylglucopyranoside) were purchased from Sigma-Aldrich. All solutions were prepared in potassium phosphate buffer (*p*H 6.9, 50 mM), and all samples **(APZ1-APZ4)**, **(TPZ1-TPZ16)**

were dissolved in DMSO. The various concentrations of compounds **(APZ1-APZ4)** (10 µL), enzyme solution (10 µL) and potassium phosphate buffer (120 µL), were added in the 96-well plate and incubated at 37 °C for 15 min. Then, the substrate (20 µL) was added to the mentioned mixture and allowed to incubate at 37 °C for 20 min. Finally, the change in absorbance was measured at 405 nm by using spectrophotometer (Gen5, Power wave xs2, BioTek, America). DMSO and Acarbose were used respectively as control and standard drug. The percentage of enzyme inhibition was calculated and IC_{50} values were obtained from non-linear regression. Statistical analysis was performed using MS Excel. The data were analyzed by one way analysis of variance (ANOVA). All the results were expressed as mean ± SD for triplicate determinations.

3.2 Computational details

Compounds **TPZ2** and **TPZ8** were placed in this binding pocket by using AutoDockVina program. The center of the search box were x = -20.0948507758, y = -14.1248385256, z = -24.3380527589 and size of the box was x = 34.8708465392, y = 36.1942925778, z = 31.0074280237. The binding interactions and conformations were visualized with discovery studio visualizer and PyMOL.

3.3 Single crystal X-ray crystallography

Yellow colour single crystals were carefully picked under a polarizing microscope and pasted to very fine glass fibers with the help of cyanoacrylate (superglue) adhesive. The single-crystal X-ray diffraction data were collected with Bruker D8 Quest PHOTON II diffractometer with monochromatic Mo $K\alpha$ radiation (λ = 0.71073 Å) at 296 (2) K by using ω and ϕ scan. The X-ray generator was operated at 50 KV and 20 mA. The data were reduced by using APEX3 and SAINTPLUS program was used for diffraction profiles integration and absorption correction (multi-scan) has been done by SADABS program [56]. The structure was solved and refined by full matrix least square method on F^2 using SHELXL1997 program [57] present in the WinGx package of programs (version 1.63.04a) [58]. All the hydrogen positions were initially located in the difference Fourier maps and for the final refinement, the hydrogen atoms were placed in geometrically ideal positions and refined in the riding mode. Final refinement comprised the atomic positions of all the atoms, isotropic thermal parameters for all the hydrogen atoms and anisotropic thermal parameters for all the non-hydrogen atoms. The crystallographic data for the

compound **APZ2** can be found in CCDC No: 1953241 by free of charge from The Cambridge Crystallographic Data Centre (CCDC) *via* www.ccdc.cam.ac.uk/data_request/cif.

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Highlights

- A series of molecular hybrids based on pyrazoline-1,2,3-triazole is reported.
- All products and precursors were explored for *α*-glucosidase inhibition.
- Compound **TPZ2** and **TPZ8** exhibited significant activity.
- Molecular docking and dynamics studies supported the activity results.

Synthesis, Characterization, α-Glucosidase inhibiton and Molecular Modeling studies of some pyrazoline-1*H*-1,2,3-Triazole hybrids

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No conflict of interest.