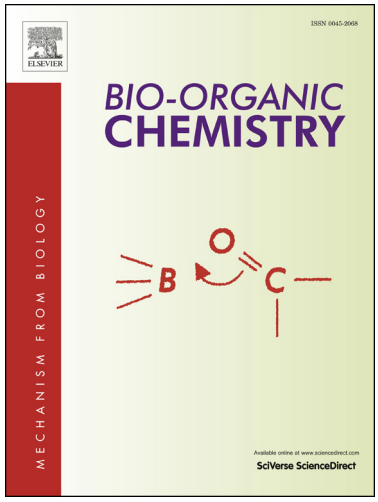

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Evaluation of 2-Indolcarbohydrazones as Potent α-Glucosidase inhibitors, *In Silico* Studies and DFT based Stereochemical Predictions

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Abstract:

2-Indolcarbohydrazones **1-28** were synthesized and evaluated for their α-glucosidase inhibitory potential. A varying degree of inhibitory potential with IC_{50} values in the range of 2.3 ± 0.11 - 226.4 ± 6.8 μM was observed while comparing these outcomes with the standard acarbose (IC_{50} = 906.0 ± 6.3 μM). The stereochemistry of ten (**10**) randomly selected compounds (**1**, **3**, **6**, **8**, **12**, **18**, **19**, **23**, **25** and **28**) was predicted by Density Functional Theory (DFT). The stability of *E* isomer was deduced by comparing the calculated and experimental vibration modes of $\nu_{C=O}$, $\nu_{N=C}$ and ν_{CH} (CH in –N=**CH**-R). It was observed that except compound **18**, all other compounds were deduced to have *E* configuration while molecular modelling studies revealed the key interactions between enzyme and synthesized compounds.

Keywords: 2-Indolcarbohydrazones, α-Glucosidase Inhibition, Structure-Activity Relationship**,** Density Functional Theory (DFT), *In Silico* studies

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1. Introduction

Indole derivatives have found numerous pharmaceutical applications such as anticancer [1], antioxidant [2], antibacterial [3], antidepressant [4], anxiolytic [5] as well as anti-HIV [6] properties. Many drugs are available in the markets which contain indole moiety as their pharmacophore such as delavirdine, a non-nucleotide reverse-transcriptase inhibitor, used for the treatment of HIV type 1 [7], yohimbine for the treatment of male impotency [8], oxypertine for the treatment of schizophrenia [9], arbidol for the treatment of influenza infection [10], sumatriptan for migraine treatment [11], ondansetron for the suppression of nausea [12], alosetron for the treatment of irritable bowel syndrome [13] and perindopril for the treatment of hypertension [14] *etc*.

Schiff base is an important pharmacophore in pharmaceutical chemistry. They exhibit various biological activities such as antidiabetic [15-18], antioxidant [19-21], antileishmanial [22] and analgesic [23-27] potentials *etc*.

α-Glucosidases (EC 3.2.1.20) are hydrolase enzymes which exist in the brush border surface of the human intestinal cells. These enzymes are essential for the hydrolysis of carbohydrate into glucose monomers which are absorbed into the blood stream [28]. During hydrolysis process, hydrolytic reaction takes place by splitting the bond between the glucosidic oxygen and anomeric carbon of glucosyl residues. Glucosyl residue is then replaced by a proton from water or an acceptor, namely an exchange reaction between the glucosyl residue and the proton in both hydrolysis and transglucosylation. Since α-glucosidase plays a crucial biological role in the digestion of carbohydrates and for the processing of glycoproteins in viruses, its inhibitors are suitable to be employed against diseases like cancers, diabetes, and HIV [29-31]. During the last two decades, various α-glucosidase inhibitors have been reported [32, 33a-i]. These inhibitors have the potential to be used for the treatment of diabetes mellitus (DM) [34]. Indoles [35] as well as Schiff base derivatives are reported to have excellent α-glucosidase inhibitory potentials [36].

Based on reported *α*-glucosidase inhibitory potentials of indole and Schiff bases, we hypothesized that Schiff bases of indole might act as *α*-glucosidase inhibitors with the efficacies better than indole and Schiff bases themselves independently. Therefore, we have synthesized Schiff base derivatives of indole in order to evaluate them for their *α*-glucosidase inhibitory activity *in vitro*.

2. Results and Discussion

2.1. Chemistry

Intermediate 1*H*-indole-2-carbohydrazide was obtained from methyl-1*H*-indole-2-carboxylate after refluxing it with hydrazine hydrate. Corresponding hydrazide was recrystallized from methanol and employed in second step for the preparation of 2-indole hydrazones after condensation with various aromatic aldehydes (**Scheme-1**). The crude solid products obtained so were recrystallized from methanol with excellent yields, *i.e.* 78-92%. Structures of synthesized compounds (**1-28)** were confirmed by various spectroscopic techniques and CHN analysis. Compounds **8** [37], **9** [38], **10** [39], **16**, [40], **17** [41], **18**, **22**, **23**, **24**, **27** [42], **20**, **25** [43] and **21** [44] are known, however, rest of the compounds are new. Elemental analyses were found to be in good agreement with the calculated values for all the compounds.

Insert scheme 1 here

2.2. DFT Predictions on *E/Z* Configurations

The –N=CH-R bond in 2-indolcarbohydrazone derivatives **1-28** (Scheme-1) may exist as *Z* or *E* isomers. To determine which configuration (*Z* or *E*) exist in the current series of compounds, the electronic energies and vibration modes $\nu_{C=O}$, $\nu_{N=C}$ and ν_{CH} (CH in –N=**CH**-R) were calculated for ten randomly selected compounds (**1**, **3**, **6**, **8**, **12**, **18**, **19**, **23**, **25**, and **28**) at the B3LYP/6-311++G(d,p) level of theory. The electronic and relative energies of *E* and *Z* configurations are presented in Table-1. Results showed that *E* configuration is relatively more stable than *Z* by 8-10 kcal/mol for compounds **1**, **3**, **6**, **8**, **12,** and **19** and by 2-4 kcal/mol for compounds **23**, **25** and **28**. Inversely, the *Z* configuration of compound **18** was found more stable than *E* by 2 kcal/mol. The stability of the *Z* configuration of **18** with respect to *E* is explained by

the formation of hydrogen bonding (2.37 Å) between the oxygen atom of the furan and NH of amide (Figure 1S).

The stability of *E* configuration was confirmed by comparing the calculated and experimental vibration modes of $\nu_{C=O}$, $\nu_{N=C}$ and ν_{CH} (CH in –N=**CH**-R) (Table-1). Except compound **18**, the variations of vibrational modes $\Delta\nu_{C=O}$ ($\Delta\nu_{N=C}$) between the calculated and experimental values vary from 1 to 11 cm^{-1} (1 to 13 cm^{-1}) and 12 to 29 cm^{-1} (0 to 27 cm^{-1}) for *E* and *Z* configurations, respectively. The variation modes obtained with *E* configuration are closer to the experimental values than *Z* configuration. Instead, for compound **18** the vibrational modes of *Z* configuration are closer to the experimental value. These variations are not sufficient to distinguish between *Z* and *E* configurations (small variation). However, the large variations between the *E* and *Z* configurations were obtained for ν_{CH} (CH in –N=**CH**-R) vibration modes. Except for compound **18**, a variation of 1-21 cm^{-1} was observed for *E* configuration for the selected compounds, while for Z configuration the variation varies 99 to 125 cm^{-1}. These results are in good agreement with electronic energies obtained above. Therefore, for all selected compounds (except **18**), the stereochemistry of –N=CH- is *E* configuration. Based on these results, we compared the νCH (CH in –N=CH-R) of all other compounds (**2**, **4**, **5**, **7**, **9-11**, **13-17**, **20-22**, **24**, **26**, and **27**) and they were found to be in the range of 2905-2942. Hence, they are predicted to have *E* configuration.

Insert Table 1 here

2.3. *α*-Glucosidase Inhibition and SAR Analysis

α-Glucosidase inhibitory activity of indole hydrazones **1-28** were evaluated by using *α*-glucosidase enzyme isolated from *Saccharomyces cerevisiae* (yeast) and *p*-nitrophenyl-*α*-D-glucopyranoside as standard substrate [33i]; the IC_{50} values of all screened compounds **1-28** are shown in Table 2.

Insert Table 2 here

Out of twenty-eight (28) synthesized compounds **1**-**28**, fourteen (14) compounds displayed potent inhibitory potentials against α-glucosidase with the IC_{50} values in the range of 2.3 to 226.4 μM, in comparison to the standard, acarbose (IC_{50} = 906 ± 6.3 μM). Compound **1** was found to be the most potent inhibitor of α-glucosidase enzyme with the IC_{50} value of 2.3 ± 0.11 μM. Compounds **19, 27, 4, 2, 13, 14** and **6** demonstrated commanding potential of inhibition (10-34 folds) than the standard inhibitor, while compounds **3, 8, 11, 9,** and **7** showed five to eight (5-8) folds better activity than the standard acarbose. However, compounds **5**, **12**, **15**-**18**, **20**-**26**, and **28** did not show any activity (Table-2).

Structure-activity relationship (SAR) analysis indicated that α-glucosidase inhibitory activity of this class of compounds is mainly dependent upon the variation of substituents on the aromatic side chains, derived from aldehydes, of the 1*H*-indole-2-carbohydrazones.Compound **1** (IC_{50} = 2.3 ± 0.11 μM) showed highest α-glucosidase inhibition among the synthesized library of compounds. It was found to be 400 times more potent than the standard acarbose. This suggests that the presence of three hydroxyl groups at 3′,4′,5′-position has made this compound such a potent *lead* molecule that could be employed for further investigations leading to *in vivo* and toxicity analysis. On the other hand compound **2** having 2′,4′,6′ trihydroxy showed almost twenty-two (22) folds lesser activity than compound **1**. This depicts that any alteration in the position of substituents on aromatic ring influences greatly the inhibition.

This finding was further endorsed when dihydroxy analogues **4** (IC_{50} = 41.0 ± 4.96 μM), a 3,4-dihydroxy and **6** (IC_{50} = 86.5 ± 0.98 μM μM), a 2,3-dihydroxy, were compared. Furthermore, when analogues, **4** and **6,** were compared with those of **3** and **7** as well as **5;** it clearly showed that position of substituents have greatly shaped the inhibitions. Activity potentials were improved broadly when one of the hydroxyl groups in dihydroxy analogues (**3**-**7**) was substituted with methoxy group. For example, in **3** where a hydroxyl group at position 5 was replaced with a methoxy group (**13**), the activity of compound **13** was seen to be improved almost three folds. However, compounds **8** (3-methoxy analogue) and **11** (4-methoxy analogue) were found less active when compared with compound **4** (3,4-dihydroxy analogue), this finding was contrary to what was explained *vide supra*. This might be due to the fact

that the position of hydroxyl group that contributes significant interactions with enzyme active site is lost. On the other hand, when both 3,4-dihydroxyls are replaced with 3,4-dimethoxy groups (compound **16**), the activity is completely vanished. Similarly compound **15** was found to be inactive when 3,5-dihydroxyl substitutions (compound **7**) were converted into 3,5-dimethoxy substitutions such as in **15**.

Among the mono-hydroxy analogues, compound **10** having 2-hydroxyl substitution showed very potent activity, as compared to its analogue **9** having 4-hydroxl substituent, which indicates that 2-hydroxyl group better interacts with enzyme active site. Compound **13**, a 2-hydroxy-5-methoxy analogue, was found to be the second most active inhibitor amongst the mono-hydroxyl analogues. This finding corroborated our assumption that 2-hydroxy position is important for potent inhibitory potentials in mono hydroxyl analogues. More interestingly, compound **12** with 3-bromo-4-hydroxy substituents showed no activity which may be due to the bulk of bromine atom that it has introduced in the molecular structure which possibly hindered the H-bond interaction of this compound with the enzyme.

Compound **14**, 3-hydroxy-2-iodo-4-methoxy analogue, showed 50 times more activity than the standard drug. When we compared compound **11** with compound **14**, we found that iodine substitution at position 2 improves the activity almost 3 folds.

Compounds **19,** a 3-fluoro-4-bromo analogue, (IC_{50} = 26.6 ± 0.80 μM) and **27**, a 4-chloro analogue, (IC_{50} = 32.1 ± 3.05 μM) also showed very potent activities when compared with standard.

Molecular Docking Calculations

MOE docking program was used to analyze the binding modes of the ligands with the protein molecule. To find the correct conformations of the ligands and to obtain minimum energy structures, ligands were allowed to be flexible. The default parameters of MOE-Dock program were used for the molecular docking of the ligands. The top ranked pose of each compound was selected on the basis of docking score (S) for further analysis. At the end of docking, the best conformations on the

basis of score were analyzed for hydrogen bonding/π-π interactions. It was observed in the docking studies that the substituent groups of the compounds are involved in bonding especially as compared to the rest of the body of compounds. Analysis of the predicted binding conformations showed that the compounds in which the electron rich substituents have such positions where the delocalization of their electronic density is restricted are more active than others. For example the most active compound **1** (IC_{50} = 2.3 ± 0.11 μM) showed better interactions through the three adjacent OH groups located on aromatic ring as shown in **Figure 1a**. In this compound the three OH groups are located over the three adjacent C atoms of the aromatic ring and thus the delocalization of their electronic density over the ring is highly restricted. Due the concentrated electronic density over these groups they interact with various important residues of target protein, *i.e.* Arg 439, Asp 214 and Glu 276. The imidazole moiety of this compound also interacts with Phe 157. In compound **2** the three OH groups occupy alternate C atoms of the ring and their electronic density have some space to delocalize over the ring. Due to slightly dispersed electronic density of these groups compound **2** showed poor interactions with the residues of protein i.e. Asp 349, His 279 as shown in **Figure 1b.**

Figure 1 insert here

The docking study revealed that the interaction mode of these compounds may depend on the electron rich nature of the substituted groups, their number and positions. As the number of OH groups goes on decreasing from three to two in compounds **3**, **4**, **5**, **6**, **7** and to one in compounds **9**, **10**, their interactions also go on decreasing. However, the compounds in which the OH groups are at adjacent position such as compound **4** competes with compound **2** having three OH but at alternate

positions. The interaction mode of compound **4** is shown in **Figure 2a.** In our series of compounds, the other compounds giving good results are the compounds having halogen groups over the substituted aromatic ring. Compound **19** having Br and F showed three interactions with the residues Arg 212, Asp 349 and Phe 298 as shown in **Figure 2b.** The binding mode analysis of inactive compounds clearly verified the reason of inactivity. These compounds do not make any remarkable interactions with the surrounding amino acid residues.

Figure 2 insert here

Conclusion

In this study, we identified new class of highly potent α-glucosidase inhibitors. Further to this, we found that only those hydroxyl derivatives (*di*- and *tri*-) such as **1**, **4**, and **6** showed potent activities which had vicinal hydroxyl positions. In monohydroxy derivatives, activity depends on the position of hydroxyl group such as 2-OH > 4-OH. The halogenated compounds showed a good activity. We also determined the configuration of stereoisomers (*E/Z*). It was found that only compound **18** has *Z* configuration due to hydrogen bonding.

Experimental

4.1. Material and methods

NMR experiments were performed on Bruker FT NMR 500 MHz. IR experiments were performed on Perkin Elmer FT-IR and UV on the Perkin Elmer Lamda 35 UV-VIS Spectrometer. CHN analysis was performed on a Carlo Erba Strumentazion-Mod-1106, Italy. Electron impact mass spectra (EI MS) were recorded on a Finnigan MAT-311A, Germany. Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by UV at 254 and 365 nm. Chemicals are Substrate: *p*-Nitrophenyl-*α*- D-glucopyranoside. Lot # (BCBD7865V) CAS #3767-28-0 Sigma Aldrich and Enzyme: *α*-Glucosidase from Saccharomyces cerevisiae recombinant, G0660-750UN CAS9001-42-7 Sigma Aldrich.

4.2. Assay for *α*-Glucosidase Inhibitory Activity

Assay Protocol of *α*-Glucosidase

The 135 μL of 50 mM phosphate saline buffer pH (6.8) was added in the 96-well plate and 20 μl of test sample with 70% DMSO added into the wells. The solution of Enzyme 20 μL was added into the wells, and incubated the plate for 15 minutes. After incubation pre- read of the plate was taken by the spectra max. Afterward 25 μL of the substrate (*p*NPG) was added and a reading was taken on spectra max at 400 NM for 30 minutes. The normal reading is taken and the percent inhibition was calculated.

4.2.1 Synthesis of 1*H*-indole-2-carbohydrazide

The methyl 1*H*-indole-2-carboxylate (10 g, 57.14 mmol) was refluxed with the mixture of hydrazine hydrate (10 mL) and methanol (25 mL) for 6 hours. The excess hydrazine hydrate and methanol was evaporated to afford crude product which was recrystallized by methanol to produce pure 1*H*-indole-2-carbohydrazide with 92% (9.2g, 52.57mmol) yield.

4.2.2. The optimization and frequency calculations of the ground states of *Z* and *E* configurations of compounds **1**, **3**, **6**, **8**, **12**, **18**, **19**, **23**, **25**, and **28** of 2-

indolcarbohydrazone derivatives have been performed at the B3LYP/6-311++G(d,p) level of theory [45]. The minima were confirmed by the absence of imaginary frequencies. The vibrational modes were calculated at the same level of theory and scaled by 0.9679 [46]. All calculations were carried out using Gaussian09 package [47].

4.2.3 General procedure for the synthesis 1*H*-Indole-2-carbohydrazones

1*H*-Indole-2-carbohydrazones were synthesized by refluxing in methanol a mixture of 1 mmol each 1*H*-indole-2-carbohydrazide with different arylaldehydes catalyzed by acetic acid for 3 h. The progress of reaction was monitored by TLC. After completion of reaction, the solvent was evaporated by vacuum to afford crude products which were further recrystallized in methanol and got pure product in good to excellent yields.

4.3.1. *(E)-N′*-(3,4,5-Trihydroxybenzylidene)-1*H*-indole-2-carbohydrazide (1)

Yield: 82%. m.p. 254-256 $^{\circ}$C; Gray crystals; UV (MeOH) λ_{max}(nm) 339.43; IR (KBr): 3304 cm^{-1} (OH-str), 3270 cm^{-1} (2^{o}amine N-H Str), 3072 cm^{-1} (Ar CH str), 1674 cm^{-1} (C=N), 1630 cm^{-1} (C=O), 1600 cm^{-1} (Ar C=C), 1533 cm^{-1} (N-H Bend), 1321 cm^{-1} (C-N str), 1125 cm^{-1} (C-O str). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.74 (*s*, 2H, 2xNH), 11.10 (s, 2H, 2xOH), 10.50 (s,1H, OH), 8.16 (*s*, 1H, ArCH=N), 7.67 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.47 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.26 (*s*, 1H, H-3), 7.23 (*t*, 1H, *J* = 7.5 Hz, H-5), 7.09 (*t*, 1H, *J* = 8.5 Hz, H-6), 6.72 (*s*, 2H, H-6′, H-2′);^{13}C NMR (125 MHz, DMSO-d_6): δ 157.40, 146.60, 146.10, 146.10, 139.70, 138.30, 138.10, 131.10, 129.20, 121.60, 120.40, 119.60, 114.80, 111.10, 108.60, 108.60; Anal. Calcd for $C_{16}H_{13}N_3O_4$, C = 61.72, H = 4.20, N = 13.51, Found C = 61.73, H = 4.21, N = 13.50; EI MS *m/z* (% rel. abund.): 311 (M^+,40), 10 (293) 144 (100), 116 (20), 75 (10).

4.3.2. *(E)-N′*-(2,4,6-Trihydroxybenzylidene)-1*H*-indole-2-carbohydrazide (2)

Yield: 85%. m.p. 256-258 $^{\circ}$C; Brown crystals; UV (MeOH) λ_{max}(nm) 346.62; IR (KBr): 3380 cm^{-1} (OH-str), 3326 cm^{-1} (2^{o}amine N-H Str), 1642 cm^{-1} (C=O), 1615 cm^{-1} (Ar C=C), 1581 cm^{-1} (N-H Bend), 1259 cm^{-1} (C-N str), 1160 cm^{-1} (C-O str). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.97 (*s*, 1H, NH), 11.77 (*s*, 1H, NH), 11.14 (*s*, 1H, OH), 9.92 (*s*, 2H, 2xOH), 8.80 (*s*, 1H, ArCH=N), 7.68 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.48 (*d*,

1H, *J* = 8.0 Hz, H-7), 7.27 (*s*, 1H, H-3), 7.24 (*t*, 1H, *J* = 7.0 Hz, H-5), 7.09 (*t*, 1H, *J* = 7.5 Hz, H-6), 5.86 (*s*, 2H, H-3′, H-5′); ^{13}C NMR (125 MHz, DMSO-d6): δ163.80, 163.80, 163.20, 157.40, 143.60, 139.60, 138.70, 131.20, 121.60, 120.60, 119.50, 114.60, 111.10, 106.50, 96.20, 96.20; Anal. Calcd for $C_{16}H_{13}N_3O_4$, C = 61.72, H = 4.20, N = 13.51, Found C = 61.71, H = 4.20, N = 13.49; EI MS *m/z* (% rel. abund.): 311. (M^+,30), 293 (12) 144 (100), 116 (15), 75 (12).

4.3.3. *(E)-N′*-(2,5-Dihydroxybenzylidene)-1H-indole-2-carbohydrazide (3)

Yield: 78%. m.p. 278-279 °C; Beige powder; UV (MeOH) λ_{max}(nm) 321; IR(KBr): 3507 cm^{-1} (OH-str), 3346 cm^{-1} (2°amine N-H Str), 3050 cm^{-1} (Ar CH str), 1663 cm^{-1} (C=N), 1617 cm^{-1}(Ar C=C), 1546 cm^{-1} (N-H Bend), 1307-1274 cm^{-1} (C-N str), 1147 cm^{-1} (C-O str). ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.05 (*s*, 1H, NH), 11.81 (*s*, 1H, NH), 10.33 (*s*, 1H, OH), 9.06 (*s*, 1H, OH), 8.58 (*s*, 1H, ArCH=N), 7.69 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.48 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.32 (*s*, 1H, H-3), 7.25 (*t*, 1H, *J* = 7.5 Hz, H-5), 7.10 (*t*, 1H, *J* = 7.0 Hz, H-6), 7.03 (*s*, 1H, H-6′), 6.78-6.72 (*m*, 2H, H-4′,H-3′); ^{13}C NMR (125 MHz, DMSO-d_6): δ157.30, 153.20, 151.40, 146.10, 139.70, 138.40, 131.20, 121.60, 120.30, 120.10, 119.70, 119.60, 119.40, 116.20, 114.80, 111.10; Anal. Calcd for $C_{16}H_{13}N_3O_3$, C = 65.08, H = 4.44, N = 14.23, Found C = 65.06, H = 4.43, N = 14.24; EI MS *m/z* (% rel. abund.): 295. (M^+,27), 277 (12), 144 (100), 116 (20), 75(10).

4.3.4. *(E)-N′*-(3,4-Dihydroxybenzylidene)-1H-indole-2-carbohydrazide (4)

Yield: 84%. m.p. 234-237 °C; Dark brown crystals; UV (MeOH) λ_{max}(nm) 339; IR (KBr): 3412cm^{-1} (OH-str), 3253 cm^{-1} (2° amine N-H Str), 3043 cm^{-1} (Ar CH str), 1630 cm^{-1} (C=O), 1557cm^{-1} (N-H Bend), 1250cm^{-1} (C-N str), 1111cm^{-1} (C-O str).^{1}H NMR (500 MHz, DMSO-d_6): δ 11.74 (*s*, 1H, NH), 11.69 (*s*, 1H, NH), 9.41 (*s*, 2H, 2xOH), 8.26 (*s*, 1H, ArCH=N), 7.67 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.48 (*d*, 1H, *J* = 8.5 Hz, H-7), 7.27 (*s*, 2H, H-3,H-2′), 7.23 (*t*, 1H, *J* = 7.5 Hz, H-5), 7.08 (*t*, 1H, *J* = 7.5 Hz, H-6), 6.98 (*d*, 1H, *J* = 8.0 Hz, H-5′), 6.82 (*d*, 1H, *J* = 8.0 Hz, H-6′); ^{13}C NMR (125 MHz, DMSO-d_6): δ157.50, 149.40, 146.70, 146.30, 139.40, 138.20, 131.20, 131.20, 123.40, 121.60, 120.40, 119.40, 117.20, 116.10, 114.80, 111.20; Anal. Calcd for $C_{16}H_{13}N_3O_3$, C = 65.08, H = 4.44, N = 14.23, Found C = 65.07, H = 4.44, N = 14.23; EI MS *m/z* (% rel. abund.): 295 (M^+,50), 277 (14), 144 (100), 116 (24), 75(6).

4.3.5. *(E)-N′*-(2,4-Dihydroxybenzylidene)-1H-indole-2-carbohydrazide (5)

Yield: 85%. m.p. 280-282 °C; Orange micro crystals; UV (MeOH) λ_{max}(nm) 342; IR (KBr): 3416 cm^{-1} (OH-str), 3268 cm^{-1} (2° amine N-H Str), 1630 cm^{-1} (C=O), 1602 cm^{-1} (Ar C=C), 1555 cm^{-1} (N-H Bend), 1233 cm^{-1} (C-N str), 1078 cm^{-1} (C-O str). ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.00 (*s*, 1H, NH), 11.78 (*s*, 2H, 2×OH), 11.40 (*s*, 1H, NH), 8.51 (*s*, 1H, ArCH=N), 7.68 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.48 (*d*, 1H, *J* = 8.5 Hz, H-7), 7.36 (*d*, 1H, *J* = 8.5 Hz, H-6′), 7.28 (*s*, 1H, H-3), 7.24 (*t*, 1H, *J* = 7.0 Hz, H-5), 7.10 (*t*, 1H, *J* = 7.5 Hz, H-6), 6.39 (*d*, 1H, *J* = 8.5 Hz, H-5′), 6.34 (*d*, 1H, *J* = 1.5 Hz, H-3′); ^{13}C NMR (125 MHz, DMSO-d_6): δ162.20, 162.10, 157.40, 146.30, 139.60, 138.40, 133.50, 131.10, 121.40, 120.30, 119.60, 114.80, 111.30, 111.10, 108.40, 103.60; Anal. Calcd for $C_{16}H_{13}N_3O_3$, C = 65.08, H = 4.44, N = 14.23, Found C = 65.08, H = 4.45, N = 14.26, EI MS *m/z* (% rel. abund.): 295 (M^+ ,30), 277 (18) 144 (100), 116 (30), 75 (16).

4.3.6. *(E)-N′*-(2,3-Dihydroxybenzylidene)-1H-indole-2-carbohydrazide (6)

Yield: 86%. m.p. 224-227 °C; Gray crystals; UV (MeOH) λ_{max}(nm) 326; IR (KBr): 3420 cm^{-1} (OH-str), 3268 cm^{-1} (2° amine N-H Str), 1609 cm^{-1} (Ar C=C), 1555 cm^{-1} (N-H Bend), 1237 cm^{-1} (C-N str). ^{1}H NMR (500 MHz, DMSO-d_6): δ11.85 (br. *s*, 2H, 2×NH), 10.60 (s, 2H, 2xOH), 8.61 (*s*, 1H, ArCH=N), 7.70 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.49 (*d*, 1H, *J* = 8.5 Hz, H-7), 7.33 (*s*, 1H, H-3), 7.26 (*t*, 1H, *J* = 7.0 Hz, H-5), 7.10 (*t*, 1H, *J* = 7.5 Hz, H-6), 7.02 (*d*, 1H, *J* = 8.0 Hz, H-6′), 6.88 (*d*, 1H, *J* = 8.0 Hz, H-4′), 6.78 (*t*, 1H, *J* = 7.0 Hz, H-5′); ^{13}C NMR (125 MHz, DMSO-d_6): δ157.40, 151.60, 145.80, 145.70, 139.20, 138.10, 131.80, 124.60, 122.60, 121.60, 120.20, 119.60, 119.50, 19.20, 114.50, 111.00; Anal. Calcd for $C_{16}H_{13}N_3O_3$, C = 65.08, H = 4.44, N = 14.23, Found C = 65.05, H = 4.42, N = 14.24; EI MS *m/z* (% rel. abund.): 295 (M^+ , 30), 277 (25), 144 (100), 116 (22), 75 (20).

4.3.7. *(E)-N′*-(3,5-Dihydroxybenzylidene)-1H-indole-2-carbohydrazide (7)

Yield: 81%. m.p. 200-202 °C; Light brown crystals; UV (MeOH) λ_{max}(nm) 325; IR (KBr): 3346 cm^{-1} (OH-str), 3290 cm^{-1} (2° amine N-H Str), 3072 cm^{-1} (Ar CH str), 1624 cm^{-1} (C=O), 1588 cm^{-1} (N-H Bend),1159 cm^{-1} (C-O str).^{1}H NMR (500 MHz, DMSO-d_6): δ 11.82 (*s*, 1H, NH), 11.78 (*s*, 1H, NH), 9.56 (*s*, 2H, 2×OH), 8.24 (*s*, 1H,

ArCH=N), 7.68 (*d*, 1H, *J* = 7.5 Hz, H-7), 7.48 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.29 (*s*, 1H, H-3), 7.24 (*t*, 1H, *J* = 7.5 Hz, H-5), 7.10 (*t*, 1H, *J* = 7.5 Hz, H-6), 6.64 (*s*, 2H, H-6′, H-2′), 6.28 (*s*, 1H, H-4′); ^{13}C NMR (125 MHz, DMSO-d_6): δ161.20, 161.20, 157.20, 146.10, 139.10, 138.70, 136.40, 131.20, 121.10, 120.60, 119.90, 114.80, 111.30, 108.20, 108.20, 105.40; Anal. Calcd for $C_{16}H_{13}N_3O_3$, C = 65.08, H = 4.44, N = 14.23, Found C = 65.06, H = 4.45, N = 14.25; EI MS *m/z* (% rel. abund.): 295 (M^+ ,50), 277 (18) ,144 (100), 116 (24), 75(6).

4.3.8. *(E)-N′*-(4-Hydroxy-3-methoxybenzylidene)-1H-indole-2-carbohydrazide (8)

Yield: 83%. m.p. 146-149 °C; Beige crystals; UV (MeOH) λ_{max}(nm) 338; IR (KBr): 3355 cm^{-1} (OH-str), 3260 cm^{-1} (2° amine N-H Str), 1635 cm^{-1} (C=O), 1591 cm^{-1} (Ar C=C), 1282 cm^{-1} (C-N str), 1031 cm^{-1} (C-O str). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.76 (*s*, 1H, NH), 11.74 (*s*, 1H, NH), 9.60 (*s*, 1H, OH), 8.35 (*s*, 1H, ArCH=N), 7.68 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.48 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.35 (*s*, 1H, *J* = 1.0 Hz, H-2′), 7.30 (*s*, 1H, H-3), 7.24 (*t*, 1H, *J* = 7.0 Hz, H-5), 7.13 (*d*, 1H, *J* = 7.5 Hz, H-5′), 7.08 (*t*, 1H, *J* = 7.5 Hz, H-6), 6.87 (*d*, 1H, *J* = 8.0 Hz, H-6′), 3.85 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ157.50, 151.10, 149.20, 146.70, 139.70, 138.40, 131.20, 130.80, 122.80, 121.60, 120.60, 119.60, 117.00, 114.80, 112.20, 111.10, 56.20; Anal. Calcd for $C_{17}H_{15}N_3O_3$, C = 66.01, H = 4.89, N = 13.58, Found C = 66.02, H = 4.88, N = 13.57; EI MS *m/z* (% rel. abund.): 309 (M^+ ,70), 291(14), 276 (8) 144 (100), 116 (19).

4.3.9. *(E)-N′*-(4-Hydroxybenzylidene)-1H-indole-2-carbohydrazide (9)

Yield: 92%. m.p. 270-271 °C. Gold crystals, UV (MeOH) λ_{max}(nm) 332; IR (KBr): 3449 cm^{-1} (OH-str), 3213 cm^{-1} (2° amine N-H Str), 3050 cm^{-1} (Ar CH str), 1607 cm^{-1} (Ar C=C), 1512 cm^{-1} (N-H Bend), 1229 cm^{-1} (C-N str), 1164 cm^{-1} (C-O str). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.76 (br. *s*, 3 H, 2×NH, OH), 8.35 (*s*, 1H, ArCH=N), 7.68 (*d*, 1H, *J* = 7.5 Hz, H-4), 7.60 (*d*, 2H, *J* = 8.0 Hz, H-6′, H-2′), 7.48 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.28 (*s*, 1H, H-3), 7.23 (*t*, 1H, *J* = 7.5 Hz, H-5), 7.08 (*t*, 1H, *J* = 8.0 Hz, H-6), 6.87 (*d*, 2H, *J* = 7.5 Hz, H-5′, H-3′); ^{13}C NMR (125 MHz, DMSO-d_6): δ160.70, 157.50, 146.70, 139.70, 138.40, 131.20, 130.40, 130.40, 126.20, 121.60, 120.60, 119.70, 116.10, 116.10, 114.80, 111.10; Anal. Calcd for $C_{16}H_{13}N_3O_2$, C = 68.81, H =

4.69, N = 15.05, Found C = 68.82, H = 4.68, N = 15.06; EI MS *m/z* (% rel. abund.): 279 (M^+,38), 261 (10), 144 (100), 116 (12).

4.3.10. *(E)-N′*-(2-Hydroxybenzylidene)-1H-indole-2-carbohydrazide (10)

Yield: 88%. m.p. 270-272 °C; White milky powder; UV (MeOH) λ_{max}(nm) 334; IR (KBr): 3324 cm^{-1} (OH-str), 3213 cm^{-1} (2° amine N-H Str), 3050 cm^{-1} (ArCH str), 1650 cm^{-1} (C=O), 1613 cm^{1} (Ar C=C), 1537 cm^{-1} (N-H Bend), 1203 cm^{-1} (C-N), 1147 cm^{-1} (C-O str), 753 cm^{-1} (ortho-subst.opp). 1H NMR (500 MHz, DMSO-d_6): δ 12.18 (*s*, 1H, NH), 11.83 (*s*, 1H, NH), 11.27 (*s*, 1H, broad OH), 8.65 (*s*, 1H, ArCH=N), 7.70 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.60 (*d*, 1H, *J* = 7.0 Hz, H-6′), 7.49 (*d*, 1H, *J* = 8.5 Hz, H-7), 7.31-7.30 (*m*, 2H, H-3, H-3′), 7.26 (*t*, 1H, *J* = 7.0 Hz, H-5), 7.10 (*t*, 1H, *J* = 7.5 Hz, H-6), 6.93 (*s*, 2H, H-4′,H-5′); ^{13}C NMR (125 MHz, DMSO-d_6): δ157.20, 157.10, 146.10, 139.60, 138.80, 132.40, 131.10, 127.40, 121.60, 121.20, 120.60, 119.60, 118.40, 117.60, 114.80, 111.00; Anal. Calcd for $C_{16}H_{13}N_3O_2$, C = 68.81, H = 4.69, N = 15.05, Found C = 68.81, H = 4.67, N = 15.05; EI MS *m/z* (% rel. abund.): 279 (M^+,58), 261 (20), 144 (100), 116 (18), 75 (19).

4.3.11. *(E)-N′*-(3-Hydroxy-4-methoxybenzylidene)-1H-indole-2-carbohydrazide (11)

Yield: 90%. m.p 150-152 °C; Orange needles; UV (MeOH) λ_{max}(nm) 333; IR (KBr): 3335 cm^{-1} (OH-str), 3260 cm^{-1} (2° amine N-H Str), 3043 cm^{-1} (Ar C-H str), 1617 cm^{-1} (Ar C=C), 1560 cm^{-1}(N-H Bend), 1275 cm^{-1} (C-N str), 1125 cm^{-1} (C-O str). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.77 (*s*, 1H,NH), 11.76 (*s*, 1H, NH), 9.38 (*s*, 1H, OH), 8.30 (*s*, 1H, ArCH=N), 7.67 (*d*, 1H, *J* = 7.5 Hz, H-4), 7.48 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.30-7.29 (*m*, 2H, H-3, H-2′), 7.24 (*t*, 1H, *J* = 7.5 Hz, H-5), 7.10-7.06 (*m*, 2H, H-6, H-5′), 7.00 (*d*, 1H, *J* = 8.5 Hz, H-6′), 3.82 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ157.50, 152.30, 147.20, 146.90, 139.70, 138.40, 131.20, 131.10, 122.70, 121.60, 120.60, 119.70, 115.70, 114.60, 112.10, 111.00, 56.30; Anal. Calcd for $C_{17}H_{15}N_3O_3$, C = 66.01, H = 4.89, N = 13.58, Found C = 66.00, H = 4.90, N = 13.56; EI MS *m/z* (% rel. abund.): 309 (M^+ , 64), 291(18), 276 (11), 144 (100), 116 (20).

4.3.12. *(E)-N′*-(3-Bromo-4-hydroxybenzylidene)-1H-indole-2-carbohydrazide (12)

Yield: 87%. m.p. 274-276 °C; Light yellow powder; UV (MeOH) λ_{max}(nm) 317; IR (KBr): 3440 cm^{-1} (OH-str), 3260 cm^{-1} (2° amine N-H Str), 1656 cm^{-1} (C=N str), 1617 cm^{-1}(Ar C=C), 1545 cm^{-1} (N-H Bend), 1270 cm^{-1} (C-N str), 1143 cm^{-1} (C-O str), 1038 cm^{-1} (C-Br str). ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.12 (*s*, 1H, NH), 11.81 (*s*, 1H, NH), 10.61 (*s*, 1H, OH), 8.64 (*s*, 1H, ArCH=N), 7.70 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.49 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.33 (*s*, 1H, H-3), 7.25 (*t*, 1H, *J* = 8.0 Hz, H-5), 7.18 (*d*, 1H, *J* = 2.0 Hz, H-5′), 7.10 (*t*, 1H, *J* = 7.5 Hz, H-6), 6.94 (*dd*, 1H, *J* = 9.0 Hz, H-2′), 6.89 (*d*, 1H, *J* = 9.0 Hz, H-6′); ^{13}C NMR (125 MHz, DMSO-d_6): δ 158.80, 157.50, 146.70, 139.60, 138.40, 131.20, 130.20, 128.40, 129.40, 121.60, 120.50, 119.60, 118.10, 114.80, 113.60, 111.10; Anal. Calcd for C $C_{16}H_{12}BrN_3O_2$, C = 53.65, H = 3.38, N = 11.73, Found C = 53.64, H = 3.38, N = 11.75; EI MS *m/z* (% rel. abund.): 359 (M^+, 41), 357 (M^+ -2, 40), 279 (14), 144 (100), 116 (15).

4.3.13. *(E)-N′*-(2-Hydroxy-5-methoxybenzylidene)-1H-indole-2-carbohydrazide (13)

Yield: 90%. m.p. 256-257 °C. Gray crystals; UV (MeOH) λ_{max}(nm) 333; IR (KBr): 3543 cm^{-1} (OH-str), 3420 cm^{-1} (2° amine N-H Str), 1627 cm^{-1} (C=O str), 1596 cm^{-1} (Ar C=C), 1561 cm^{-1} (N-H Bend), 1248 cm^{-1} (C-N str), 1129 cm^{-1} (C-O str). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.84 (*s*, 1H, NH), 11.79 (*s*, 1H, NH), 10.81 (*s*, 1H, OH), 8.32 (*s*, 1H, ArCH=N), 7.89 (*s*, 1H, H-6′), 7.68 (*d*, 1H, *J* = 7.5 Hz, H-4), 7.60 (*d*, 1H, *J* = 8.5 Hz, H-7), 7.48 (*d*, 1H, *J* = 8.5 Hz, H-3′), 7.30 (*s*, 1H, H-3), 7.24 (*t*, 1H, *J* = 7.5 Hz, H-5), 7.09 (*t*, 1H, *J* = 8.0 Hz, H-6), 6.97 (*d*,1H, *J* = 8.5 Hz,H-5′), 3.82 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 157.50, 153.20, 153.10, 146.00, 139.70, 138.40, 131.20, 121.60, 120.60, 119.70, 119.40, 118.20, 117.10, 114.60, 113.20, 111.00, 55.60; Anal. Calcd for $C_{17}H_{15}N_3O_3$, C = 66.01, H = 4.89, N = 13.58, Found C = 66.01, H = 4.89, N = 13.59; EI MS *m/z* (% rel. abund.): 309 (M^+ ,44), 291(16), 276 (15) 144 (100), 116 (14).

4.3.14. (*E*)-*N′*-(3-Hydroxy-2-iodo-4-methoxybenzylidene)-1H-indole-2-carbohydrazide (14)

Yield: 87%. m.p. 256-258 °C; Cream crystals; UV (MeOH) λ_{max}(nm) 340; IR (KBr): 3405 cm^{-1} (OH-str), 3292 cm^{-1} (2° amine N-H Str), 3057 cm^{-1} (Ar CH str), 1660 cm^{-1} (C=N str), 1620 cm^{-1} (C=O str), 1589 cm^{-1} (N-H Bend), 1274 cm^{-1} (C-N str), 1136

cm^{-1} (C-O str), 645 cm^{-1} (C-I str); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.04 (*s*, 1H, NH), 11.79 (*s*, 1H, NH), 8.70 (*s*, 1H, ArCH=N), 7.69 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.50 (*d*, 1H, *J* = 8.5 Hz, H-7), 7.48 (*d*, 1H, *J* = 8.5 Hz, H-5′), 7.34 (*s*, 1H, H-3) ,7.25 (*t*, 1H, *J* = 7.5 Hz, H-5), 7.11-7.06 (*m*, 2H, *J* = 7.5 Hz, H-5, H-6′), 3.84 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ157.40, 155.10, 151.80, 143.20, 139.60, 138.40, 133.60, 131.20, 124.30, 121.60, 120.60, 119.60, 114.80, 111.10, 111.00, 84.20, 56.20; Anal. Calcd for $C_{17}H_{14}IN_3O_3$, C = 46.92, H = 3.25, N = 9.66, Found C = 46.93, H = 3.24, N = 9.67, EI MS *m/z* (% rel. abund.): 435 (M^+ ,24), 307(26), 144 (100), 116 (14).

4.3.15. *(E)-N′*-(3,5-Dimethoxybenzylidene)-1*H*-indole-2-carbohydrazide (15)

Yield: 82%. m.p. 204-207 °C; White powder; UV (MeOH) λ_{max}(nm) 327; IR υ cm^{-1} (KBr disk): 3299 cm^{-1} (NH stretch), 3072 cm^{-1} (Ar.C-H stretch), 1636 cm^{-1} (C=O), 1591 cm^{-1} (C=N), 1555 cm^{-1} (C-N), 1452 cm^{-1} (C=C), 677 (1,3,5-Ar); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.94 (*s*, 1H, NH), 11.79 (*s*, 1H, NH), 8.37 (*s*, 1H, ArCH=N), 7.69 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.49 (*d*, 1H, *J* = 8.5 Hz, H-4), 7.32 (*s*, 1H, H-3), 7.25 (*t*, 1H, *J* = 6.0 Hz, H-5), 7.09 (*t*, 1H, *J* = 7.0 Hz, H-6), 6.92 (*d*, 2H, *J* = 2.0 Hz, H-2 ′/H-6′), 6.58 (*d*, 1H, *J* = 2.0 Hz, H-4′), 3.81 (*s*, 6H,2×OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ161.60, 161.60, 157.50, 146.70, 139.60, 138.40, 135.60, 131.20, 121.50, 120.60, 119.70, 114.80, 111.00, 103.40, 103.40, 102.60, 55.60, 55.60; Anal. Calcd for $C_{18}H_{17}N_3O_3$, C = 66.86, H = 5.30, N = 13.00, Found C = 66.87, H = 5.31, N = 13.01; EI MS *m/z* (% rel. abund.): 323 (M^+ ,65), 294 (18), 144 (100), 116 (19).

4.3.16. *(E)-N′*-(3,4-Dimethoxybenzylidene)-1*H*-indole-2-carbohydrazide (16)

Yield: 84%. m.p. 249-251 °C; White powder; UV (MeOH) λ_{max}(nm) 336; IR υ cm^{-1} (KBr disk): 3325 cm^{-1} (NH stretch), 3043 cm^{-1} (Ar.C-H stretch), 1631 cm^{-1} (C=O), 1568 cm^{-1} (C=N), 1510 cm^{-1} (C-N), 1421 cm^{-1} (C=C), 828 (1,3,4-Ar); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.81 (*s*, 1H, NH), 11.77 (*s*, 1H, NH), 8.37 (*s*, 1H, ArCH=N), 7.68 (*d*, 1H, *J* = 7.5 Hz, H-7), 7.48 (*d*, 1H, *J* = 8.5 Hz, H-4), 7.39 (*s*, 1H, H-2 ′), 7.30 (*s*, 1H, H-3) 7.24 (*m*, 2H, H-5'/6'), 7.09 (*t*, 2H, *J* = 7.5 Hz, H-5/H-6) 3.84 (*s*, 3H, OCH_3), 3.82 (*s*, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ157.50, 152.00, 149.60, 146.70, 139.60, 138.40, 131.20, 130.40, 122.30, 120.60, 121.60, 119.70,

114.80, 111.60, 111.00, 109.10, 56.10, 56.10; Anal. Calcd for $C_{18}H_{17}N_3O_3$, C = 66.86, H = 5.30, N = 13.00, Found C = 66.88, H = 5.29, N = 13.02; EI MS *m/z* (% rel. abund.): 323 (M^+,74), 294 (24), 144 (100), 116 (24).

4.3.17. *(E)-N′*-(3-Methoxybenzylidene)-1*H*-indole-2-carbohydrazide (17)

Yield: 83%. m.p. 130-132 °C; Milky white powder; UV (MeOH) λ_{max}(nm) 328; IR υ cm^{-1} (KBr disk): 3234 cm^{-1} (NH stretch), 3058 cm^{-1} (Ar.C-H stretch), 1657 cm^{-1} (C=O), 1598.09 cm^{-1} (C=N), 1575 cm^{-1} (C-N), 1273 cm^{-1} (C-O), 740 (3- Ar); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.94 (*s*, 1H, NH), 11.80 (*s*, 1H, NH), 8.42 (*s*, 1H, ArCH=N), 7.69 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.49 (*d*, 1H, *J* = 8.5 Hz, H-4), 7.41 (*t*, 1H, *J* = 7.5 Hz, H-5), 7.33-31 (*m*, 3H, H-3/ H-2′/H-5′), 7.25, (t, 1H, *J* = 7.5 Hz, H-6), 7.10, (t, 1H, *J* = 7.5 Hz, H-6′), 7.04 (dd, 1H, *J* = 2.0, 7.0 Hz, H-4′), 3.84 (*s*, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 160.50, 157.40, 146.70, 139.60, 138.40, 138.20, 131.20, 129.70, 121.60, 121.40, 120.50, 119.60, 116.40, 114.80, 111.10, 111.00, 55.70; Anal. Calcd for $C_{17}H_{15}N_3O_2$, C = 69.61, H = 5.15, N = 14.33, Found C = 69.62, H = 5.16, N = 14.32; EI MS *m/z* (% rel. abund.): 293. (M^+ ,80), 264 (13), 144 (100), 116 (12).

4.3.18. *(Z)-N′*-((Furan-2-yl)methylene)-1*H*-indole-2-carbohydrazide (18)

Yield: 85%. m.p. 241-242 °C; Yellowish powder; UV (MeOH) λ_{max}(nm) 333; IR υ cm^{-1} (KBr disk): 3368 cm^{-1} (NH stretch), 3056 cm^{-1} (Ar.C-H stretch), 1646 cm^{-1} (C=O), 1550 cm^{-1} (C=N), 1579 cm^{-1} (C-N), 1480 cm^{-1} (C=C), 1066 (C-O-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.88 (*s*, 2H, 2×NH), 8.33 (*s*, 1H, ArCH=N), 7.86 (*s*, 1H, H-4′), 7.68 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.47 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.27 (*s*, 1H, H-3), 7.25 (*t*, 1H, *J* = 7.0 Hz, H-5), 7.09 (*t*, 1H, *J* = 7.5 Hz, H-6), 6.96 (*d*, 1H, *J* = 3.5 Hz, H-2′), 6.66 (*dd*, 1H, *J* = 1.5 Hz, *J* = 3.0 Hz, 3′); ^{13}C NMR (125 MHz, DMSO-d_6): δ 157.30, 149.00, 144.20, 139.70, 138.20, 134.40, 131.20, 122.40, 121.50, 120.40, 119.70, 118.60, 114.80, 111.20; Anal. Calcd for $C_{14}H_{11}N_3O_2$, C = 66.40, H = 4.38, N = 16.59, Found C = 66.42, H = 4.39, N = 16.60; EI MS *m/z* (% rel. abund.): 253 (M^+ ,85), 185 (12), 144 (100), 116 (14).

4.3.19. *(E)-N′*-(3-Bromo-4-fluorobenzylidene)-1*H*-indole-2-carbohydrazide (19)

Yield: 87%. m.p. 223-225 °C; Milky white powder; UV (MeOH) λ_{max}(nm) 326; IR υ cm^{-1} (KBr disk): 3297 cm^{-1} (NH stretch), 3043 cm^{-1} (Ar.C-H stretch), 1639 cm^{-1} (C=O), 1566 cm^{-1} (C=N), 1538 cm^{-1} (C-N), 1496 cm^{-1} (C=C), 1255 cm^{-1} (C-F), 578 cm^{-1} (C-Br); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.07 (*s*, 1H, NH), 11.82 (*s*, 1H, NH), 8.41 (*s*, 1H, ArCH=N), 8.10 (*d*, 1H, *J* = 6.5 Hz, H-7), 7.83 (*s*, 1H, H-1′), 7.69 (*d*, 1H, *J* = 8.0 Hz, H-4), 7.51-7.470 (*m*, 2H, H-5′/H-6′), 7.33 (*s*, 1H, H-3), 7.25 (*t*, 1H, *J*

= 8.0 Hz, H-5), 7.10 (*t*, 1H, *J* = 7.0 Hz, H-6); ^{13}C NMR (125 MHz, DMSO-d_6): δ167.50, 157.60, 146.70, 139.60, 138.40, 134.20, 131.40, 131.20, 129.70, 121.40, 120.60, 119.60, 117.60, 114.80, 111.30, 110.10; Anal. Calcd for $C_{16}H_{11}BrFN_3O$, C = 53.35, H = 3.08, N = 11.67, Found C = 53.36, H = 3.07, N = 11.67; EI MS *m/z* (% rel. abund.): 361 (M^+, 41), 359 (M^+−2, 40), 341 (18), 339 (16), 279 (25), 144 (100), 116 (17).

4.3.20. *(E)-N′*-(4-Methoxybenzylidene)-1*H*-indole-2-carbohydrazide (20)

Yield: 88%. m.p. 122-125 °C; White powder; UV (MeOH) λ_{max}(nm) 331; IR υ cm^{-1} (KBr disk): 3287 cm^{-1} (NH stretch), 3053 cm^{-1} (Ar.C-H stretch), 1634 cm^{-1} (C=O), 1604 cm^{-1} (C=N), 1511 cm^{-1} (C-N), 1422 cm^{-1} (C=C), 829 (4-Ar); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.80 (*s*, 2H, 2×NH), 8.39 (*s*, 1H, ArCH=N), 7.72 (*d*, 2H, *J* = 8.0 Hz, H-3′/H-5′), 7.68 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.48 (*d*, 1H, *J* = 8.5 Hz, H-4), 7.29 (*s*, 1H, H-3), 7.24 (*t*, 1H, *J* = 7.0 Hz, H-5), 7.09 (*d*, 1H, *J* = 7.0 Hz, H-6), 7.05 (*d*, 2H, *J* = 8.0 Hz, H-2′/H-6′), 3.82 (*s*, 3H,OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ162.80, 157.50, 146.60, 139.70, 138.40, 131.20, 130.10, 130.10, 126.20, 121.40, 120.60, 119.70, 114.80, 114.20, 114.20, 111.10, 55.70; Anal. Calcd for $C_{17}H_{15}N_3O_2$, C = 69.61, H = 5.15, N = 14.33, Found C = 69.62, H = 5.16, N = 14.32; EI MS *m/z* (% rel. abund.): 293. (M^+ ,70), 264 (18), 144 (100), 116 (16).

4.3.21. *(E)-N′*-Benzylidene-1*H*-indole-2-carbohydrazide (21)

Yield: 90%. m.p. 197-199 °C; White powder; UV (MeOH) λ_{max}(nm) 325; IR υ cm^{-1} (KBr disk): 3258 cm^{-1} (NH stretch), 3055 cm^{-1} (Ar.C-H stretch), 1656 cm^{-1} (C=O), 1528.18 cm^{-1} (C=N), 1374 cm^{-1} (C-N); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.92 (*s*, 1H, NH), 11.82 (*s*, 1H, NH), 8.46 (*s*, 1H, ArCH=N), 7.77 (*d*, 2H, *J* = 8.0 Hz, H-2′/H-6′), 7.69 (*d*, 1H, *J* = 7.5 Hz, H-4), 7.49-7.46 (*m*, 4H, H-7, H-3′/H-4′/H-5′), 7.33 (*s*, 1H, H-3), 7.25 (*t*, 1H, *J* = 7.0 Hz, H-6), 7.09 (*d*, 1H, *J* = 8.0 Hz, H-5); ^{13}C NMR (125 MHz, DMSO-d_6): δ157.50, 146.60, 139.60, 138.30, 133.50, 131.20, 131.20, 129.10, 129.10, 128.50, 128.50, 121.40, 120.50, 119.60, 114.80, 111.20; Anal. Calcd for $C_{16}H_{13}N_3O$, C = 72.99, H = 4.98, N = 15.96, Found C = 72.98, H = 5.00, N = 15.95; EI MS *m/z* (% rel. abund.): 263.(M^+ ,82), 186 (13), 144 (100), 116 (12), 25 (77).

4.3.22. *(E)-N′*-((Pyridin-3-yl)methylene)-1*H*-indole-2-carbohydrazide (22)

Yield: 92%. m.p. 250-252 °C; Milky white powder; UV (MeOH) λ_{max}(nm) 328; IR υ cm^{-1} (KBr disk): 3489 cm^{-1} (C-N-C), 3281 cm^{-1} (NH stretch), 3050 cm^{-1} (Ar.C-H stretch), 1635 cm^{-1} (C=O), 1550 cm^{-1} (C=N), 1473 cm^{-1} (C-N); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.08 (*s*, 1H, NH), 11.84 (*s*, 1H, NH), 8.90 (*s*, 1H, ArCH=N), 8.63 (*d*, 1H, *J* = 4.5 Hz, H-6′), 8.51 (*s*, 1H, H-2′), 8.19 (*d*, 1H, *J* = 7.5 Hz, H-4'), 7.70 (*d*, 1H, *J* = 7.5 Hz, H-7), 7.53-7.49 (*m*, 2H, H-4/H-5′), 7.35 (*s*, 1H, H-3), 7.25 (*t*, 1H, *J* = 7.0 Hz, H-5), 7.10 (*t*, 1H, *J* = 7.5 Hz, H-6); ^{13}C NMR (125 MHz, DMSO-d_6): δ 157.40, 151.80, 149.10, 143.20, 139.40, 138.20, 133.60, 131.20, 130.30, 123.80, 121.50, 120.60, 119.60, 114.80, 111.30; Anal. Calcd for $C_{15}H_{12}N_4O$, C = 68.17, H = 4.58, N = 21.20; Found C = 68.19, H = 4.59, N = 21.21; EI MS *m/z* (% rel. abund.): 264. (M^+ ,74), 185 (16), 144 (100), 116 (11), 78 (18).

4.3.23. *(E)-N′*-((Pyridin-4-yl)methylene)-1*H*-indole-2-carbohydrazide (23)

Yield: 90%. m.p. 273-275 °C; Milky white powder; UV (MeOH) λ_{max}(nm) 329; IR υ cm^{-1} (KBr disk): 3437 cm^{-1} (C-N-C), 3173 cm^{-1} (NH stretch), 3068 cm^{-1} (Ar.C-H stretch), 1643.87 cm^{-1} (C=O), 1594.96 cm^{-1} (C=N), 1519.70 cm^{-1} (C-N); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.18 (*s*, 1H, NH), 11.87 (*s*, 1H, NH), 8.68 (*d*, 2H, *J* = 5.5 Hz, H-3′/H-5′), 8.45 (*s*, 1H, ArCH=N), 7.71 (*d*, 3H, *J* = 5.5 Hz, H-2′/H-6′/H-4), 7.50 (*d*, 1H, *J* = 8.5 Hz, H-7), 7.37 (*s*, 1H, H-3), 7.26 (*t*, 1H, *J* = 7.5 Hz, H-5), 7.10 (*t*, 1H, *J* = 7.5 Hz, H-6); ^{13}C NMR (125 MHz, DMSO-d_6): δ 157.50, 149.10, 149.10, 146.50, 144.20, 139.70, 138.40, 131.10, 121.40, 120.60, 120.30, 120.30, 119.70, 114.80, 111.20; Anal. Calcd for $C_{15}H_{12}N_4O$, C = 68.17, H = 4.58, N = 21.21, Found C = 68.19, H = 4.57, N = 21.23; EI MS *m/z* (% rel. abund.): 264. (M^+ ,70), 185 (12), 144 (100), 116 (16), 78 (25).

4.3.24. *(E)-N′*-(Pyridin-2-ylmethylene)-1H-indole-2-carbohydrazide (24)

Yield: 82%. m.p. 253-254 °C; Yellowish green powder; UV (MeOH) λ_{max}(nm) 328; IR υ cm^{-1} (KBr disk): 3274 cm^{-1} (NH stretch), 3058 cm^{-1} (Ar.C-H stretch), 1646 cm^{-1} (C=O), 1587 cm^{-1} (C=N), 1530 cm^{-1} (C-N); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.12 (*s*, 1H, NH), 11.88 (*s*, 1H, NH), 8.64 (*d*, 1H, *J* = 4.5 Hz, H-3′), 8.50 (*s*, 1H, ArCH=N), 8.03 (*d*, 1H, *J* = 7.5 Hz, H-7), 7.92 (*t*, 1H, *J* = 7.5 Hz, H-5′), 7.71 (*d*, 1H, *J* = 7.5 Hz,

H-4) , 7.50 (*d*, 1H, *J* = 8.5 Hz, H-6′), 7.44 (*t*, 1H, *J* = 6.5 Hz, H-4′), 7.37 (*s*, 1H, H-3), 7.26 (*t*, 1H, *J* = 7.5 Hz, H-5), 7.10 (*t*, 1H, *J* = 7.5 Hz, H-6); ^{13}C NMR (125 MHz, DMSO-d_6): δ 157.40, 153.40, 149.30, 144.80, 139.70, 138.40, 136.20, 131.20, 126.10, 121.60, 120.10, 120.40, 119.60, 114.80, 111.20; Anal. Calcd for $C_{15}H_{12}N_4O$, C = 68.17, H = 4.58, N = 21.20, Found C = 68.16, H = 4.59, N = 21.19, EI MS *m/z* (% rel. abund.): 264. (M^+,68), 185 (18), 144 (100), 116 (9), 78 (12).

4.3.25. *(E)-N′*-(Thiophen-2-ylmethylene)-1H-indole-2-carbohydrazide (25)

Yield: 88%. m.p. 250-251 °C; Yellowish powder; UV (MeOH) λ_{max}(nm) 337; IR υ cm^{-1} (KBr disk): 3394 cm^{-1} (NH stretch), 3283 cm^{-1} (Ar.C-H stretch), 1643 cm^{-1} (C=O), 1588 cm^{-1} (C=N), 1555 cm^{-1} (C-N), 1229 (C-S-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.87 (*s*, 1H, NH), 11.79 (*s*, 1H, NH), 8.67 (*s*, 1H, ArCH=N), 7.70 (*d*, 1H, *J* = 5.0 Hz, H-7), 7.67 (*s*, 1H, H-5′), 7.50 (*d*, 1H, *J* = 3.5 Hz, H-3′), 7.48 (*d*, 1H, *J* = 8.5 Hz, H-4) , 7.29 (*s*, 1H, H-3), 7.24 (*t*, 1H, *J* = 8.0 Hz, H-5), 7.17 (*dd*, 1H, *J* = 3.5 Hz, *J* = 5.0 Hz, H-4'), 7.09 (*t*, 1H, *J* = 7.0 Hz, H-6); ^{13}C NMR (125 MHz, DMSO-d_6): δ 157.40, 144.6, 139.60, 138.40, 131.40, 130.10, 128.10, 127.10, 125.30, 121.60, 120.40, 119.70, 114.80, 111.20; Anal. Calcd for $C_{14}H_{11}N_3OS$, C = 62.43, H = 4.12, N = 15.60, Found C = 62.41, H = 4.13, N = 15.61; EI MS *m/z* (% rel. abund.): 269 (M^+,48), 185 (13), 144 (100), 116 (11), 83 (11).

4.3.26. (*E*)-Methyl 4-((2-(1H-indole-2-carbonyl)hydrazono)methyl)benzoate (26)

Yield: 90%. m.p. 249-251 °C; White powder; UV (MeOH) λ_{max}(nm) 335; IR υ cm^{-1} (KBr disk): 3351 cm^{-1} (NH stretch), 3148 cm^{-1} (Ar.C-H stretch), 1698 cm^{-1} (O-C=O), 1633 cm^{-1} (C=O), 1547 cm^{-1} (C=N), 1436 cm^{-1} (C-N), 828 (4- Ar); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.09 (*s*, 1H, NH), 11.83 (*s*, 1H, NH), 8.51 (*s*, 1H, ArCH=N), 8.07 (*d*, 2H, *J* = 8.5 Hz, H-3′/ H-5′), 7.91 (*d*, 2H, *J* = 8.5 Hz, H-2′/ H-6′), 7.70 (*d*, 1H, *J* = 7.5 Hz, H-7), 7.48 (*d*, 1H, *J* = 8.0 Hz, H-4) , 7.35 (*s*, 1H, H-3), 7.26 (*t*, 1H, *J* = 7.0 Hz, H-5), 7.10 (*t*, 1H, *J* = 7.0 Hz, H-6), 3.89 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.50, 157.40, 146.50, 139.40, 138.40, 138.20, 132.20, 131.20, 130.20, 130.20, 129.30, 129.30, 129.00, 121.50, 120.40, 119.70, 114.60, 51.10, Anal. Calcd for $C_{18}H_{15}N_3O_3$, C = 67.28, H = 4.71, N = 13.08, Found C = 67.27, H = 4.70, N = 13.06; EI MS *m/z* (% rel. abund.): 321 (M^+, 54), 289 (19), 261 (10), 144 (100), 135 (18), 116 (11),

4.3.27. *(E)-N′*-(4-Chlorobenzylidene)-1H-indole-2-carbohydrazide (27)

Yield: 92%. m.p. 247-249 °C; Milky white powder; UV (MeOH) λ_{max}(nm) 329; IR υ cm^{-1} (KBr disk): 3304 cm^{-1} (NH stretch), 3080 cm^{-1} (Ar.C-H stretch), 1637 cm^{-1} (C=O), 1551 cm^{-1} (C=N), 1492 cm^{-1} (C-N), 1315 cm^{-1} (C=C), 748 cm^{-1} (C-Cl); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.98 (*s*, 2H, 2xNH), 8.45 (*s*, 1H, ArCH=N), 7.8 (*d*, 2H, *J* = 8.5 Hz, H-3′/H-5′), 7.70 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.56 (*d*, 2H, *J* = 8.0 Hz, H-2′/H-6′), 7.48(*d*, 1H, *J* = 8.5 Hz, H-4), 7.33 (*s*, 1H, H-3), 7.25 (*t*, 1H, *J* = 6.0 Hz, H-5), 7.09 (*t*, 1H, *J* = 7.0 Hz, H-6); ^{13}C NMR (125 MHz, DMSO-d_6): δ 157.30, 146.40, 139.60, 138.30, 138.20, 132.00, 131.10, 130.40, 130.40, 128.70, 128.70, 121.40, 120.60, 119.50, 114.30, 111.4; Anal. Calcd for $C_{16}H_{12}ClN_3O$, C = 64.54, H = 4.06, N = 14.11, Found C = 64.56, H = 4.05, N = 14.13; EI MS *m/z* (% rel. abund.): 299 (M^+, 30), 297 (M^+ -2, 60), 341 (18), 261 (12), 144 (100), 116 (17).

4.3.28. (*E*)-Methyl2-((2-(1H-indole-2-carbonyl)hydrazono)methyl)-3,5-dimethoxy -benzoate (28)

Yield: 91%. m.p. 202-203 °C; Milky white powder; UV (MeOH) λ_{max}(nm) 335; IR υ cm^{-1} (KBr disk): 3313cm^{-1} (NH stretch), 3062 cm^{-1} (Ar.C-H stretch), 1740 cm^{-1} (CO_2), 1645 cm^{-1} (C=O), 1602 cm^{-1} (C=N), 1568 cm^{-1} (C-N); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.83 (*s*, 1H, NH), 11.7 (*s*, 1H, NH), 8.64 (*s*, 1H, ArCH=N), 7.67 (*d*, 1H, *J* = 8.0 Hz, H-7), 7.46 (*t*, 1H, *J* = 8.5 Hz, H-4), 7.30 (*s*, 1H, H-3), 7.23 (*t*, 1H, *J* = 7.0 Hz, H-5), 7.08 (*t*, 1H, *J* = 7.5 Hz, H-6), 6.78 (*s*, 1H, H-5′), 6.63 (*s*, 1H, H-3′), 3.91 (*s*, 3H,OCH_3), 3.87 (*s*, 3H,OCH_3), 3.85 (*s*, 3H,OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.20, 163.20, 161.10, 157.40, 143.40, 139.70, 138.60, 133.50, 131.20, 121.50, 120.4, 119.6, 114.7, 111.10, 110.10, 108.6, 105.7, 55.4, 55.4, 51.6; Anal. Calcd for $C_{20}H_{19}N_3O_5$, C = 62.99, H = 5.02, N = 11.02, Found C = 62.98, H = 5.00, N = 11.01; EI MS *m/z* (% rel. abund.): 381 (M^+,34), 321 (19), 306 (10), 144 (100), 116 (11).

4.4 Molecular Docking Calculations

The study was designed to dock 2-indolcarbohydrazones derivatives against α-glucosidase enzyme with the following communications; Intel$^{(R)}$ xenon$^{(R)}$ CPU E5620@2.40GHz system having 3.8GB RAM with the open 11.4 (X 86_64) operating platform. Protein-Ligand docking was carried out using the Molecular

Operating Environment (MOE 2010.11) software package. The three dimensional structure for *α*-glucosidase of *Saccharomyces cerevisiae* has not been solved up-to yet. Only few homology models have been reported [48-50]. In the current study we predict 3D structure for *α*-glucosidase of *Saccharomyces cerevisiae* by using same protocol as described by (Burke et al) of homology modeling [51]. The primary sequence of *α*-glucosidase for *Saccharomyces cerevisiae* was retrieved from UniProt (Access code P53341). Template search was performed using MOE-Search tools against the PDB implemented in MOE v2010.11. The crystallographic structure of *Saccharomyces cerevisiae* isomaltase (PDB code 3AJ7; Resolution 1.30 Å) with 72.4% of sequence identity with the target was selected as a template. The 3D structure of α-glucosidase for *Saccharomyces cerevisiae* was predicted using MOE homology modeling tools. The developed model was then subjected to energy minimization up to 0.05 gradients.

The quality of the modeled structure was assessed by Ramachandran and ProSA plot. The evaluation of backbone Psi and Phi dihedral angles for *α*-glucosidase model revealed that 94.8% residues lie in favored region, 4.8% residues lie in allowed region and only 0.3% residues lies in outlier region. Analysis of ProSA shows the Z-value of -10.76 indicating no significant deviation from the score determined for the protein of similar size. The results of both Ramachandran and ProSA plots reflect the accuracy of our modeled structure to be used in docking protocol.

Before docking, ligands and protein were prepared using MOE v2010.11. 3D structure of compound 3 was built by using Molecular Builder Module program implemented in MOE and save as a (.mdb) file for molecular docking. Subsequently, the energy of compound 3 was minimized up to 0.05 Gradient using MMFF 94x force field. *Energy minimization* of the compound 3 was followed by the preparation of protein for docking purposes. Most macromolecular crystal structures contain little or no hydrogen coordinate data due to limited resolution and thus protonation was done prior to docking using Protonate 3D tools. *Protonation* was followed by energy minimization up to 0.05 Gradient using Amber 99 force field. The compound 3 was docked into the active site of protein using the Triangular Matching docking method and 30 conformations of compound 3 and protein complex were generated with docking score (S). The complex was analyzed for interactions and their 3D images were taken by using visualizing tool PyMol.

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Caption of Figure

Scheme-1: Synthesis of 1H-Indole-2-carbohydrazones

Figure 1 Binding mode of compound 1(a) and compound 2 (b) in the active site of a-glucosidase. Each dotted line indicates a hydrogen bond; the ligand is shown in Yellow stick (Molecular color).

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Figure 2 Molecular interactions of the 2-indolcarbohydrazones derivatives in the active site of α-glucosidase enzyme: compound 4 (a) and compound 19 (b), the ligand is shown in Yellow stick (Molecular color).

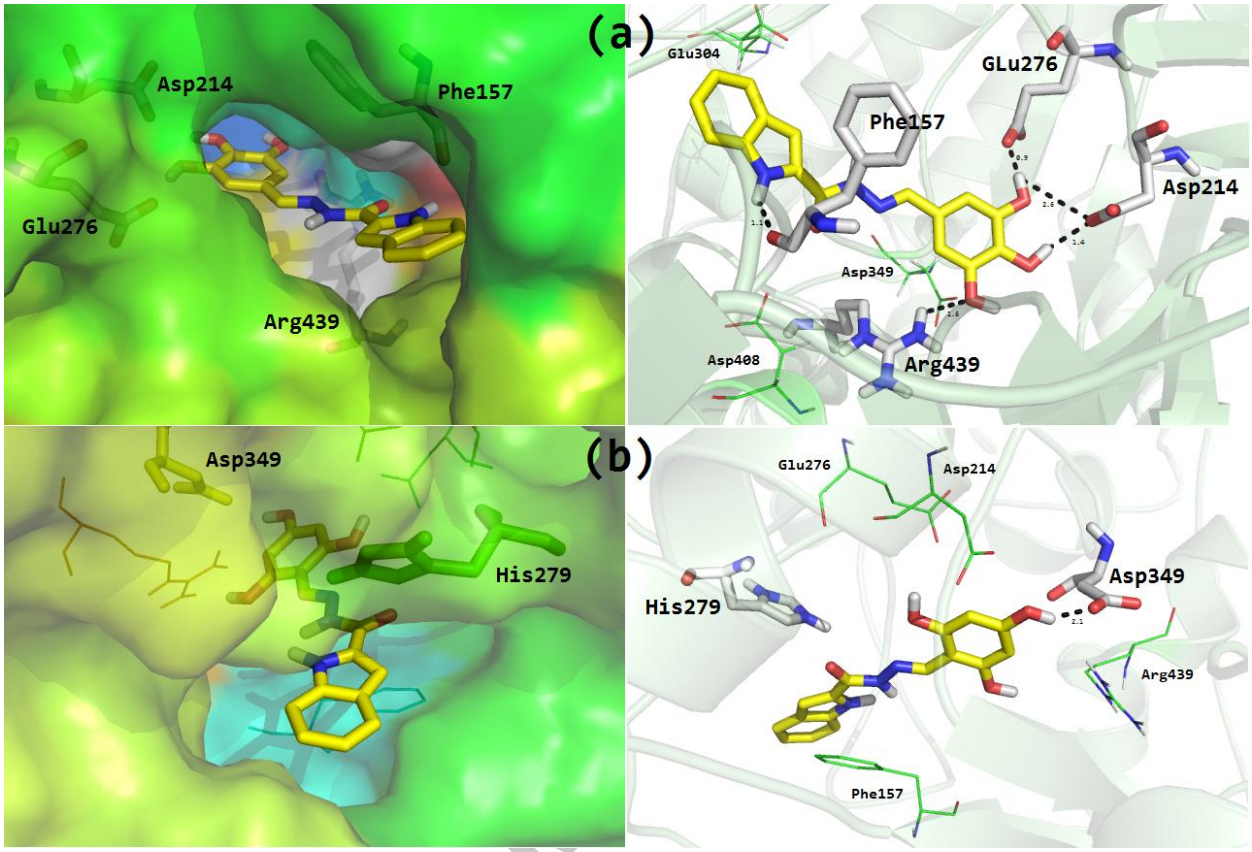


Figure-1:

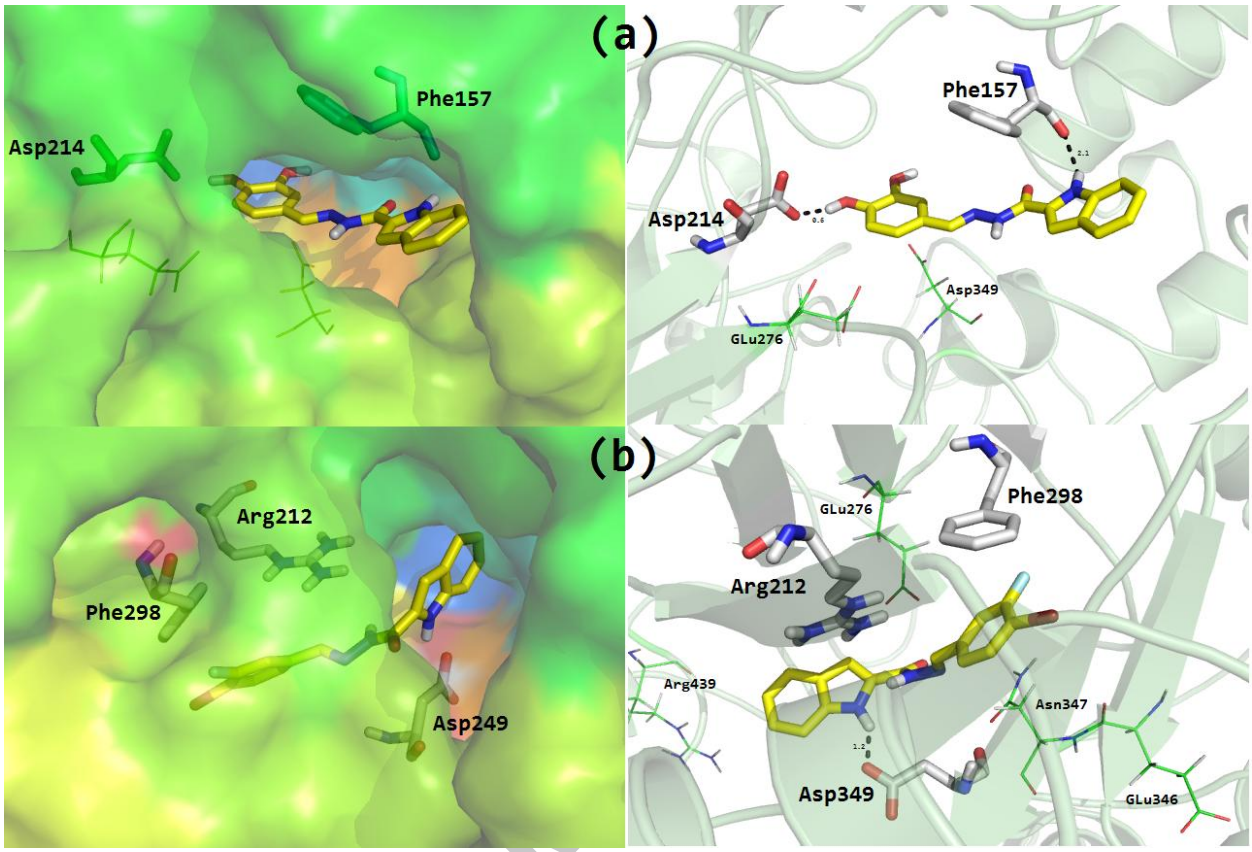
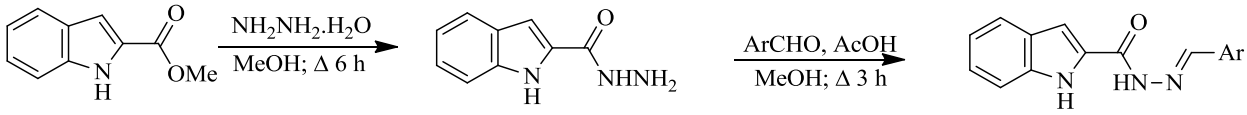


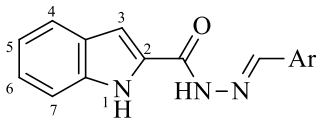
Figure-2:



Scheme-1: Synthesis of 1H-Indole-2-carbohydrazones

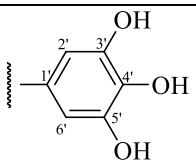
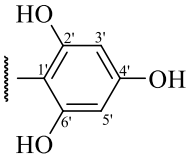
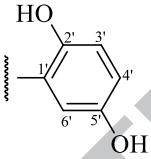
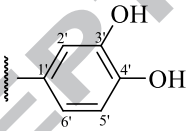
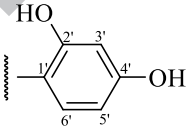
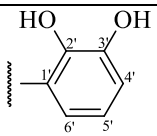
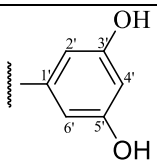
Table 1. Calculated and experimental vibrational modes (cm^{-1}) and energydifference (kcal/mol) for selected compounds.

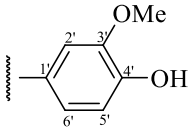
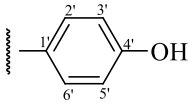
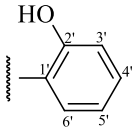
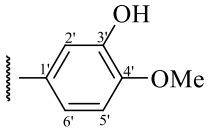
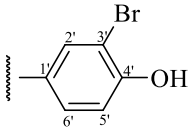
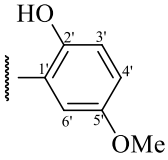
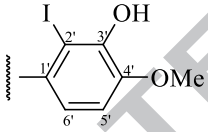
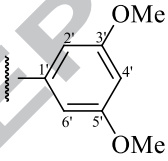
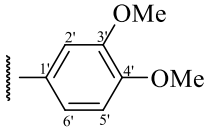
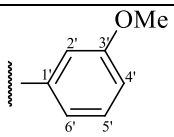
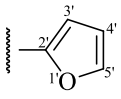
N°	$\nu_{C=O}$			$\nu_{N=C}$			ν_{CH}			Energy (kcal/mol)		ΔE (kcal/mol)
	Calculated		Exp	Calculated		Exp	Calculated		Exp	Calculated		
	E	*Z*		*E*	*Z*		*E*	*Z*		*E*	*Z*	
1	1689	1703	1684	1623	1673	1619	2910	3032	2918	-679570	-679560	10
3	1687	1710	1681	1616	1667	1617	2929	3027	2926	-632354	-632344	9
6	1685	1709	1684	1616	1666	1620	2936	3027	2928	-632358	-632347	10
8	1688	1700	1678	1619	1669	1624	2904	3027	2910	-657018	-657009	10
12	1693	1703	1689	1620	1665	1622	2906	3029	2914	-2200054	-2200046	8
18	1695	1700	1718	1627	1660	1652	2924	3056	3042	-536517	-536519	-2
19	1697	1706	1691	1618	1660	1625	2915	3034	2909	-2215123	-2215115	8
23	1699	1709	1688	1618	1658	1627	2915	3041	2920	-547976	-547973	4
25	1695	1713	1691	1612	1651	1625	2913	3037	2924	-739193	-739192	2
28	1697	1702	1690	1616	1672	1624	2966	3049	2945	-824714	-824712	2

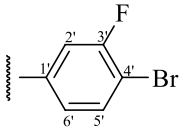
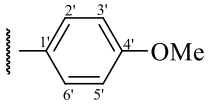
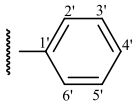
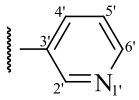
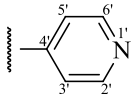
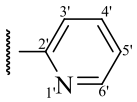
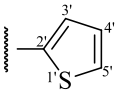
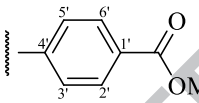
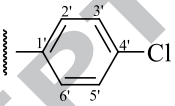
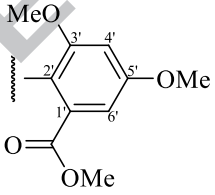


1*H*-Indole-2-carbohydrazones

Table-2: *In vitro* α-glucosidase inhibition activity of compounds **1-28**

Compound No.	Ar	Yield; %	IC_{50} ± SEM[a] [μM]
1		82	2.3 ± 0.11
2		85	49.2 ± 0.86
3		78	143.5 ± 1.5
4		84	41.0 ± 4.96
5		85	NA[b]
6		86	86.5 ± 0.98
7		81	226.4 + 6.8

8		83	155.1 ± 8.27
9		92	205.7 ± 9.6
10		88	42.6 ± 0.75
11		90	191 ± 9.9
12		87	NA[b]
13		90	49.2 ± 7.7
14		87	54.6 ± 4.96
15		82	NA[b]
16		84	NA[b]
17		83	NA[b]
18		85	NA[b]

19		87	26.6 ± 0.80
20		88	NA[b]
21		90	NA[b]
22		92	NA[b]
23		90	NA[b]
24		82	NA[b]
25		88	NA[b]
26		90	NA[b]
27		92	32.1 ± 3.05
28		91	NA[b]

[a]SEM standard error of the mean.
[b]NA Not Active
Standard: Acarbose, IC_{50} ± SEM = 906 ± 6.3 μM

Graphical Abstract

Synthesis of 2-indolehydrazone derivatives as potent α-glucosidase inhibitors

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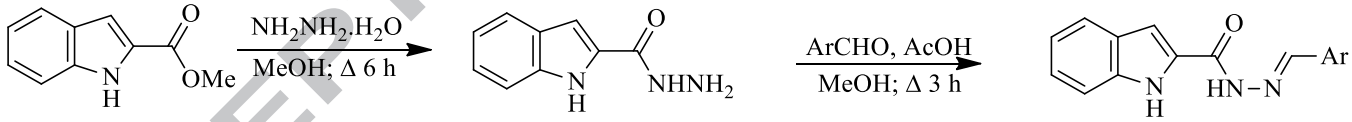

Twenty-eight (28) indole Schiff bases were synthesized and they showed potent α-glucosidase inhibitory activities.

Highlights

- Synthesis of 2-indolehydrazone **1**-**28**
- *In vitro* α-glucosidase inhibitory activity.
- Some of compounds are more active than standard drug
- Structure-activity relationship has been established.
- Stereochemistry determination
- Docking study