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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 modeling studies revealed the key interactions between enzyme and synthesized compounds.

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].

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.

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

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last two decades, various α-glucosidase inhibitors have been reported [32–34a–34i]. 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.

2.2. DFT predictions on E/Z configurations

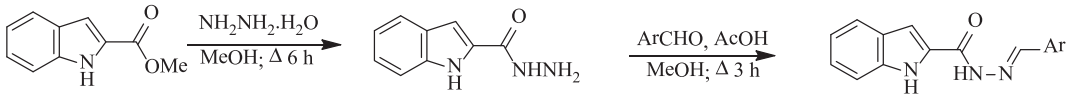
The —N=**CH**-R bond in 2-indolcarbohydrazone derivatives **1–28** (Scheme 1) may exist as *Z* or *E* isomers. To determine which configuration (*Z* or *E*) exist in the current series of compounds, the electronic energies and vibration modes $\nu_{C=O}$, $\nu_{N=C}$ and ν_{CH} (CH in —N=**CH**-R) were 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 (Fig. 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} (1–13 cm^{-1}) and 12 to 29 cm^{-1} (0–27 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 99–125 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.

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 [34i]; the IC_{50} values of all screened compounds **1–28** are shown in Table 2.

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 2.3–226.4 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



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)		Δ*E* (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	−679,570	−679,560	10
3	1687	1710	1681	1616	1667	1617	2929	3027	2926	−632,354	−632,344	9
6	1685	1709	1684	1616	1666	1620	2936	3027	2928	−632,358	−632,347	10
8	1688	1700	1678	1619	1669	1624	2904	3027	2910	−657,018	−657,009	10
12	1693	1703	1689	1620	1665	1622	2906	3029	2914	−2,200,054	−2,200,046	8
18	1695	1700	1718	1627	1660	1652	2924	3056	3042	−536,517	−536,519	−2
19	1697	1706	1691	1618	1660	1625	2915	3034	2909	−2,215,123	−2,215,115	8
23	1699	1709	1688	1618	1658	1627	2915	3041	2920	−547,976	−547,973	4
25	1695	1713	1691	1612	1651	1625	2913	3037	2924	−739,193	−739,192	2
28	1697	1702	1690	1616	1672	1624	2966	3049	2945	−824,714	−824,712	2