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SYNTHESIS, α-GLUCOSIDASE AND β-GLUCURONIDASE INHIBITORY ACTIVITIES OF BISINDOLYLMETHANE BEARING HYDRAZIDE-HYDRAZONE, SULFONOHYDRAZIDE AND CARBOTHIOAMIDE MOIETIES

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ABSTRACT

Extensive research has been carried out on bisindole compounds due to their potent activities. Modifying the structures of bisindoles has been proven to be useful in the search for new therapeutic agents. Since varying substituents is a common method for drug design in medicinal chemistry, 66 derivatives of bisindolylmethane bearing hydrazide-hydrazone, sulfonylhydrazide, and carbothioamide moieties were synthesized and evaluated for their β-glucuronidase and α-glucosidase inhibition potential. As the first step, acid-catalyzed reaction of 5-bromo and 5-cyano, substituted indole with methyl 4-formylbenzoate was carried out. The products were reacted with hydrazine hydrate forming two key-intermediates which were further derivatized into three series of target compounds (**37**-**102**). Synthesized compounds were characterized using ^{1}H-NMR, ^{13}C-NMR, FT-IR, and EI-MS spectroscopic techniques. Bisindolylmethanehydrazide-hydrazone derivatives **37**-**66** were evaluated for their *in-vitro* β-glucuronidase inhibition potential while the sulfonohydrazides **67**-**83** and carbothioamide analogs **84**-**102** were tested for α-glucosidase inhibitory activity. The results are stated as IC_{50} values and the structure-activity relationships were established based on the presence and location of different substituents, i.e., hydroxyl, methyl, methoxy, nitro, cyano, bromine, chlorine, and fluorine. Among the bisindolylmethanehydrazide-hydrazone derivatives, trihydroxylated compounds such as **6** (0.60 μM), **20** (1.50 μM), and **25** (0.50 μM) were found to be the most active. Comparing the IC_{50} values, compound **25** was approximately 100 times more active than the standard *D*-saccharic acid 1,4-lactone (IC_{50} = 48.40 μM). The results from SAR reveal that the presence of hydroxyl, fluorine, and chlorine groups significantly contributes to the activity, while methyl and methoxy substituents, or replacing the benzene ring with pyridine diminishes the activity. Bisindolylmethane-sulfonohydrazide analogs **67**-**83**, except for compounds **73** and **77**, inhibited Baker's yeast α-glucosidase with the IC_{50} values in the range between 2.80 μM and 37.20 μM. The 2,5-dichlorinated compound **72** was the most active among the bisindolylmethane-sulfonohydrazide having an IC_{50} value of 2.80 μM, a fifteen-fold enhancement compared to the standard acarbose (IC_{50} = 39.40 μM). Compounds **68** (5.30 μM) and **82** (5.30 μM), with fluorine substituent showed the second highest activity. The halogenated compounds showed relatively high activity within the series. Moreover, methyl group and halogen atoms at *ortho* position were significant in enhancing the activity. Bisindolylmethane-carbothioamide hybrids **84**-**102** also exhibited significant activity (IC_{50} = 5.18-35.60 μM) to inhibit α-glucosidase. From the activity comparison, the bromo substituent, as in compounds **93**-**102** (IC_{50} = 5.18 ± 0.07-12.41 μM), led to enhancement in activity. Besides that, cyano substituted compounds **84**-**92** (IC_{50} = 5.60-35.60 μM) were also better than the standard. In summary, it was observed that most of the synthesized compounds were active for the selected activities. The results suggest that modification of the bisindolylmethane plays a significant role in the activity of these compounds, which may lead to further improvement in designing selective, potent, inhibitors of α-glucosidase and β-glucuronidase in the future.

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Thank you

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