

Research Article

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“Synthesis and in-vitro Glucosidase Inhibitory Activity of Some Novel Indole Derivatives”

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ABSTRACT

The objective of this paper is to focus on developing new entities of the heterocyclic molecule for its in-vitro inhibitory activities of glucosidase enzyme and the preparation and separation of new entities of the indole derivatives.

Most of the indole derivatives are synthesized from the Phenyl Hydrazine and Ketone as a precursor. The prepared molecules were thoroughly tested for qualitative and quantitative analysis such as preliminary test, melting points, boiling points, Thin Layer Chromatography, Infra-Red spectroscopy, proton NMR spectroscopy, and element are determined by confirmation of final structure. The Indole ring compounds were analyzed and evaluated for glucosidase inhibitory activity by the In-vitro studies through the glucosidase inhibitory activity assay. Acarbose was used as a standard drug. The present data of in-vitro studies have led to the probable conclusion that the new Indole analogs would be taken as efficient glucosidase inhibitory activity.

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Introduction

Diabetes mellitus is considered as a metabolic disorder of disturbances of protein, fat, and prominently carbohydrate metabolism with various causes characterized by chronic hyperglycemic conditions resulting from the imperfection in the secretion of insulin and insulin action or both. As it results in the increasing the sugar level in blood and consequences of that shows uncontrolled diabetes with serious complications to many of the body's organs or system to function normally, especially blood vessels and nerves. Diabetes mellitus type-II accounts for 80-90% of all cases of diabetes in the world and it is one potential threat to the health of people suffering from it. In the digestive process, the α -glucosidase enzyme is useful for catalyzing the final step in the digestion of carbohydrates, which is mainly present on the surface of the intestinal membrane. Meanwhile, the absorption of carbohydrates from the gastrointestinal tract can be inhibited by using α -glucosidase enzyme inhibitors, which can potentially retard the absorption of carbohydrates by inhibiting the digestion of polysaccharides and disaccharides, thus it helps to reduce the post absorption blood glucose level. Various glucosidase inhibitors drugs based on the sugar moieties including acarbose,

voglibose, and miglitol are been used clinically used in the effective treatment of type-II diabetes mellitus. The Food and Drug Administration-approved acarbose (Precose®) and miglitol (Glyset®) are α -glucosidase inhibitors as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The α -glucosidase inhibitors reduce the blood glucose level in a dose-dependent way by altering the gastrointestinal absorption of carbohydrates and fat. α -glucosidases enzyme inhibitors, specifically responsible for converting complex polysaccharide carbohydrates into monosaccharides that slow down the absorption of glucose, and the resulting slower rise in postprandial blood glucose level in blood is potentially beneficial in patients with diabetes [1,2]. Because these α -glucosidase inhibitors work in the gastrointestinal tract, gastrointestinal-related events such as diarrhea and flatulence, are the primary adverse events associated with treatment and may confine the acceptance of the α -glucosidase inhibitors by patients. Acarbose and miglitol these dosages form available in tablet forms and are to be administered three times each day with each main meal. At present, acarbose is the only α -glucosidase enzyme inhibitor that is available in the generic dosage form. These are sugar-based agents effective in reducing the glycosylated hemoglobin and postprandial glucose levels in type 2 diabetes patients when they are administered as monotherapy or in combination with other antidiabetic agents. The

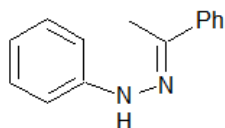
indole moiety is present in widely nitrogen-containing heterocyclic compounds. Indole is the most essential part of some amino acids like tryptophan and the neurotransmitter serotonin. It is found in naturally occurring plant-based alkaloids. The biological activities of indol-containing compounds cover a wide range of activities such as antimicrobial, anticancer, anti-inflammatory, anti-malarial, and antitubercular. The structure of indole containing a nitrogen hetero atom, non-basic in which a benzene ring and pyrrole nucleus have fused in 2, 3 positions of the pyrrole ring. Indole is aromatic, heterocyclic organic compound and it is crystalline solid, melts at 52°C, indol is soluble in alcohol, benzene, and ether. It may be recrystallized from water. Goes through all types of electrophilic substitution reactions such as protonation, nitration, sulfonation, acylation, halogenations reactions, etc. it also gives nucleophilic reactions. Indole is basic functional units in plants as well as animal and bacteria also produces indole as a degradation product of the amino acid tryptophan. It is a planar molecule which has 10 electrons having resonance energy 47-49 K cal/mole. The electrophilic attack on indol prefers at 3rd position because of presence of high electron density at 3rd position [4].

Materials and Method

The scheme summarises a synthetic technique for the manufacture of indole derivatives. The molecule was made by combining phenylhydrazine with aldehydes or ketones in the presence of an acid catalyst. E. Merck and LOBA Co. provided the substances utilised in this experiment. TLC with silica gel G was used to monitor all of the responses. The melting points were determined in an open glass capillary using a liquid paraffin Kjeldahl flask. Using KBr pellets, IR spectra were collected on the (JASCO) FTIR-Spectrophotometer. In DMSO, ¹H NMR spectra were acquired using a BRUKER AVANCE II 400 NMR spectrometer using TMS as an internal reference.

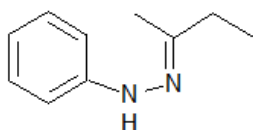
General procedure for preparation of hydrazine: SYNTHESIS OF HYDRAZONES

Acetophenonephenylhydrazone (3aa) ¹



A boiling tube was filled with a solution of phenylhydrazine (5.495 g, 50.8 mmol) in glacial acetic acid (10 ml) and water (10 ml) and a solution of acetophenone (4.12 g, 34.3 mmol) in glacial acetic acid (20 ml). Colourless hydrazone crystals formed when the mixture was chilled in ice and agitated for 5 minutes. The hydrazone was obtained as white crystals (3.45 g, 48 percent) after filtering and washing with weak acetic acid and water. ¹H (250 MHz; CDCl₃) 2.4 (3 H, s) 7.1 (1 H, m) 7.4-7.7 (7 H, m) 8.0 (1 H, m).

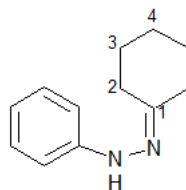
Butanone phenylhydrazone (3ab) ²



In a 50 ml rounded bottom flask, phenylhydrazine (1.08 g, 0.01 mol) was added to a solution of methyl ethyl ketone (0.78 g, 0.01

mol) in toluene (10 ml) and glacial acetic acid (5 ml). At 95°C, the mixture was refluxed for 3 hours. The toluene and acetic acid were then removed under pressure, resulting in hydrazone 3 ab (1.68 g, 80%) as a brown solid (1.68 g, 80%).

Cyclohexanone-phenylhydrazone (3ac) ³

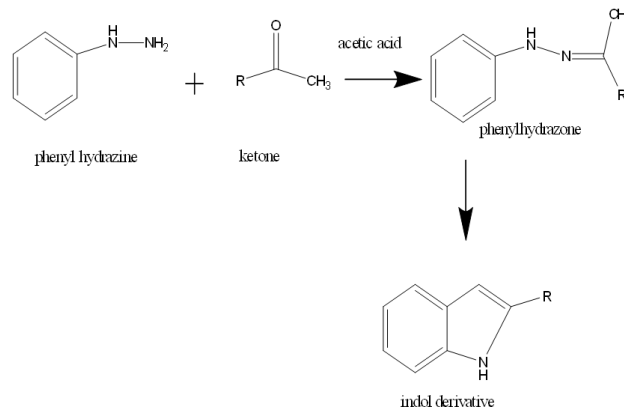


In the same way phenylhydrazine (1.08 g, 0.01 mol) and cyclohexanone (0.98 g, 0.01 mol) gave hydrazone 3ac (1.12 g, 6 mmol) as a brown solid. ¹H (250 MHz; CDCl₃) 1.9-2.0 (6 H, m, 3-H and 4-H) 2.5-2.7 (4 H, m, 2-H) 7.01 (1 H, m, Ph) 7.3 (2 H, m, Ph) 7.5 (2 H, m, Ph); ¹³C (250 MHz; CDCl₃) 25.75 (CH₂, 4-C) 27.4 (CH₂, 3-C) 35.7 (CH₂, 2-C) 113.3 (2 CH, 6-C) 119.9 (CH, 5-C) 129.5 (2 CH, 7-C) 146.4 (C, 8-C) 151.5 (C, 1-C); *m/z* (ES⁺) 189 (M⁺, 50%), 102 (100).

Synthesis of Benzophenone:

A solution of phenylhydrazine (5.495 g, 50.8 mmol) in glacial acetic acid (10 ml) and water (10 ml) was added to a solution of benzophenone (4.12 g, 34.3 mmol) in glacial acetic acid (20 ml) contained in a boiling tube. The mixture was cooled in ice and shaken for 5 minutes, colourless crystals of hydrazone precipitated. The product was filtered, washed with dilute acetic acid and water to yield the hydrazones as colourless crystals

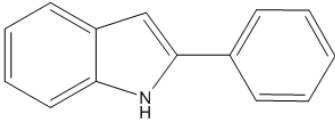
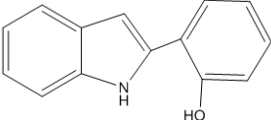
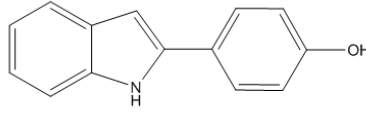
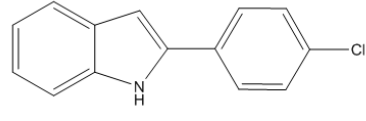
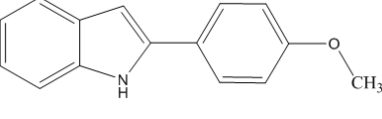
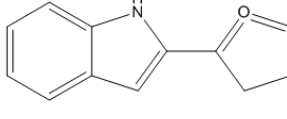
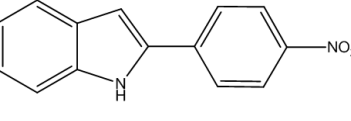
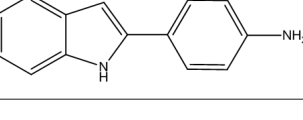
SCHEME



For Compounds: A1-A8

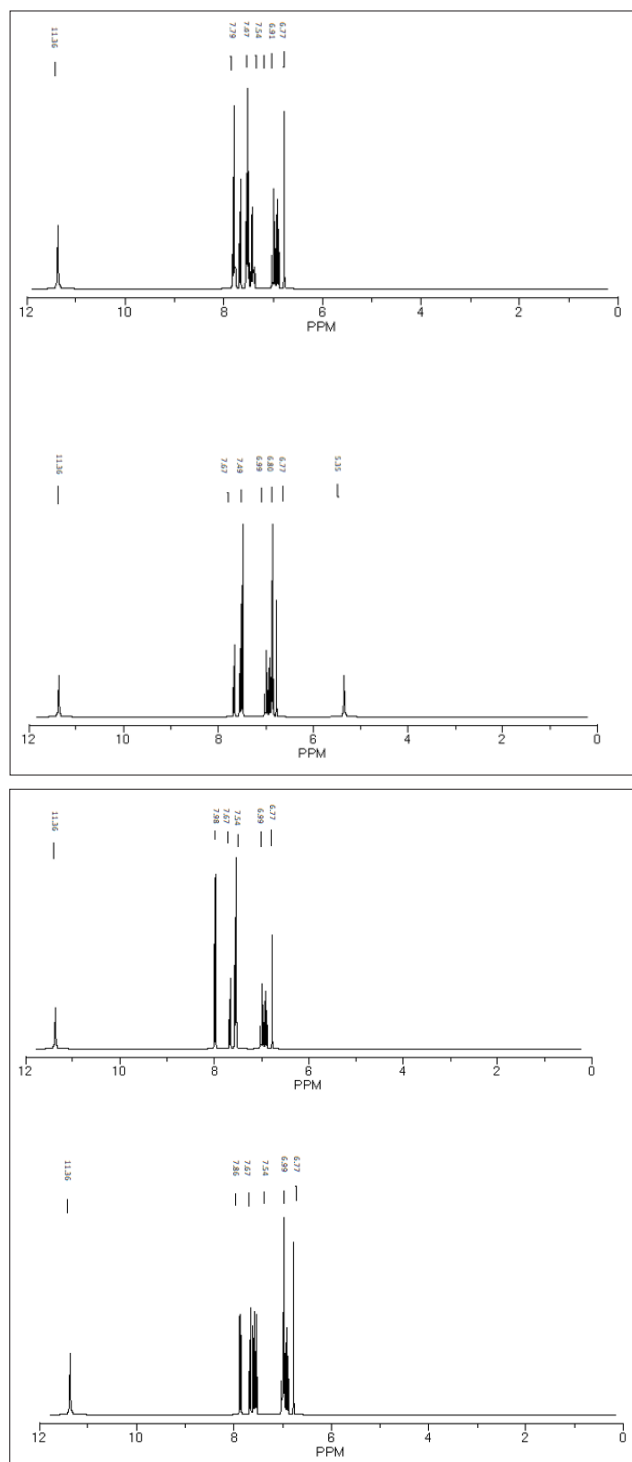
Comp.code	R	Comp. code	R
A1		A5	
A2		A6	
A3		A7	
A4		A8	

Analytical & physicochemical data of the synthesized compound.	Mol. Formula	Mol. Wt.	M.P.°C	Yield %	Elemental Analyses calculated			
					C	H	N	O
A1	C ₁₄ H ₁₃ N	195.259	140-150°C	81	87.01	5.74	7.25	
A2	C ₁₄ H ₁₁ NO	209.243		83	5.74			
A3	C ₁₄ H ₁₁ NO	209.243		83				
A4	C ₁₄ H ₁₄ CLN	231.720		85				
A5	C ₁₅ H ₁₃ NO	223.275		87				
A6	C ₁₂ H ₉ NO	183.21		89				
A7	C ₁₄ H ₁₀ N ₂ O ₂	238.241		70				
A8	C ₁₄ H ₁₂ N ₂	208.258		72				

Sr. No	Comp. Name	Structure	I R	N M R
1	A1		3245.23(-CH Str.), 1080(-C-N str.), 2283(C=C str.), 3540(N-H str.), 3110(C-C str.)	11.36(NH), 7.79-6.77(9H-CH), 7.51(8H-indole),
2	A2		3240(CH str.), 2273(C=C str.), 3583(NH str.), 3650(C-O str.), 1245(CN str.)	
3	A3		3241(CH str.), 2240(C=C str.), 1360(CN str.), 3641(C-O str.), 3548(NH str.), 3655(OH str.)	5.00(Ar-OH), 11.36(NH), 7.26-7.40(5H-Indole), 6.86-7.49(3H-Benzene)
4	A4		3255(CH str.), 2281(C=C str.), 745.20(C-Cl str.), 3550(NH str.), 1160(CN str.)	11.36(NH), 7.55-7.98(3CH-Benzene), 6.45-7.55(3H-Indole)
5	A5		3243(CH str.), 2215(C=C str.), 1300(CO str.), 3588(NH str.), 1122(CN str.)	
6	A6		3245(CH str.), 2210(C=C str.), 1120(CN str.), 1000(C=C str.), 3060(C-C str.), 3573(NH str.)	7.30-6.38(3H-Furan), 6.99-7.49(5H-Indole)
7	A7		3251(CH str.), 1620(C-C str.), 2270(C=C Str.) 1220(C-N str.), 1460(N-O str.),	
8	A8		1600(C-C str.), 2281(C=C str.), 1200(C-N str.), 3440(N-H str.)	

Spectral analysis (A1-A8)

Data for A1



IN-VITRO GLUCOSIDASE INHIBITORY ACTIVITY

In-vitro glucosidase inhibitory activity evaluation of synthesized compounds

α -Glucosidase Inhibition Assay

All the synthetic novel indole derivatives (A1–A8) were screened to evaluate their in vitro α -glucosidase inhibitory activity by using α -glucosidase enzyme. The majority of compounds exhibited a varying degree of α -glucosidase inhibitory activity with IC₅₀ values between 20.7 and 61.1 μ M when compared with standard acarbose.

In 96-well plate, reaction mixture containing 50 μ l phosphate buffer (100 mM, pH=6.8), 10 μ l α glucosidase (1 U/ml) and 20 μ l of varying conc. of extract (Baker's yeast) and fractions (0.1, 0.2, 0.3, 0.4, 0.5 mg/ml) was preincubated at 37°C for 20 min. The reaction was stopped by adding 50 μ l Na₂CO₃ (0.1 M). The absorbance of the released p-nitro phenol was measured at 405 nm using Multipal Reader. Acarbose at various conc. (0.1–0.5 mg/ml) was included as a standard. Without test substance was set up in parallel as a control and each experiment was performed in triplicates. The result were expressed as % inhibition, which was calculated using formula, Inhibitory activity (%) = $(1 - A_s/A_c) \times 100$ Where, A_s —absorbance in the presence of test substance, A_c —absorbance of control.

Compound	IC ₅₀ (mM $\pm$ SEMa)
A1	17.45 $\pm$ 1.2
A2	22.5 $\pm$ 0.6
A3	37.8 $\pm$ 1.1
A4	11.4 $\pm$ 0.5
A5	38.2 $\pm$ 2.1
A6	28.5 $\pm$ 0.4
A7	43.5 $\pm$ 0.9
A8	22.4 $\pm$ 0.6
Acarbose	30.8 $\pm$ 1.1

Result and Discussion

The table above shows the structures, yields, and melting temperatures of a novel chemical that was synthesised. The produced compounds had sharp melting points, showing that they were pure; the yield value of the compounds also indicated that the chemical procedures used to synthesise the compound were dependable. All of the spectrum data was consistent with the expected structure. In-vitro glucosidase inhibitor activity studies were performed on all of the produced compounds. As a standard control, the Acarbose was utilized [5–50].

Conclusion

1. The present research work is a Bonafide novel for the synthesis of indole.
2. The extensive literature review suggests the utilization of these heterocycles as a lead in treatment of wide variety of diseases and disorders.
3. The method of synthesis of these heterocycles starting from different substrate had been established.
4. Around Eight never derivatives of before mentioned heterocycles were synthesized.
5. The purity of synthesized compounds was checked with the help of TLC.
6. The physical constants (m.p.) of the synthesized compounds were determined using open capillary method.
7. The structures of the synthesized compounds were established by using IR, ¹H NMR and CHN analysis.
8. The synthesized compounds were screened for their In-vitro glucosidase inhibitory activity in treatment of diabetic Mellatis.
9. We investigated the importance of functional group substitutions, in the structural framework of the compounds for their In-Vitro glucosidase inhibitory activity. All compounds showed significant glucosidase inhibitory activity. The compounds (A1, A3 and A6) showed better activity.
10. The synthesized compounds were also subjected for QSAR

analysis the results found were in the range of less than 0.2 hence are acceptable.

Finally, the encouraging result of the glucosidase inhibitory activity displayed by these compounds may be of interest for further structural modifications to the lead compound and next level studies in the hope of. Finding a new potent glucosidase inhibitor.

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