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New Bioactive Aromatic Indole Molecules with Monosaccharide Core

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Abstract: 1,1,2-trimethyl-1H-benzo[e]indole is an important heterocyclic compound, it is available in reasonable price and can easily be modified to make a good intermediate for synthesis of other derivatives. It can be used as a starting material for the synthesis of a new series of compounds by coupling with other biomolecules such as monosaccharide amines after a simple modification. The current work aims to synthesize new potentially bioactive compounds by coupling 1,1,2-trimethyl-1H-benzo[e]indole with one or two molecules of both 2-deoxy-2-amino-d-glucose and 6-deoxy-6-amino-d-glucose. The mono-substituted derivative were prepared in two steps, the first step is the functionalization reaction to create two reactions centers via the treatment of 1,1,2-trimethyl-1H-benzo[e]indole (**1**) with $POCl_3$ to produce 2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene) malonaldehyde (**2**) with two reaction centers represented by aldehyde groups, while in the second step the latter was coupled with two amino sugars. Four new molecules resulted from this reaction, two mono-substituted derivatives (**3**,**5**) when we apply the last reaction for a short time, while the di-substituted molecules (**4**,**6**) take long time for the same reaction conditions in order to overcome the steric hindrance at one reaction center. The purity and characterization of the target molecules were confirmed using spectroscopic methods including 1H NMR and 13C NMR. The synthesized compounds, especially the di-substituted derivatives, show a good biological activity as antibacterial and antifungal agents and they can find their way in medical application as they are soluble in water due to the presences of sugar moiety in their structures.

Keywords: Vilsmeier-Haack, Schiff bases, malonaldehyde, Fisher projection, Howarth formula, steric hindrance, biomolecules, biological activity.

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INTRODUCTION

There are many biologically active compounds synthesized and reported from different heterocyclic compounds. As the bacterial and fungi by the time may become more familiar with the known bioactive compounds, the need to modify and find new bioactive compounds to overcome this problem has become important and has a wide range of the scientific interest. 1,1,2-trimethyl-1H-benzo[e]indole is an aromatic heterocyclic compound modified by many chemists and scientists to produce other useful compounds and derivatives in many applications, including biological activity. Wen-Hai Zhan et al. reported the synthesis of cyanine dye derivatives (C-Cy(1–4)) in which a coumarin moiety is attached to benzoindole via click chemistry (1). Yoichi Shimizu and coworkers, developed novel near-infrared NIR fluorophore-micelle complex probes. By using benzoindole for for synthesizing a novel lipophilic NIR fluorophores, which were encapsulated in an amphiphilic polydepsipeptide micelle "lactosome" (2), while Duanwen Shen and coworkers used the same material to develop near-infrared (NIR) dye that fluoresces at two different wavelengths (dichromic fluorescence, DCF) (3). Guillermo O. Menéndez and others presented water soluble and fluorescent biotinylated probe derived from a carbocyanine dye from benzoindole (4). Kaiquan Zhang et al. used benzoindole to developed a new type of fluorescent

probe (QcyCHO) featured with H_2S-triggered off-to-on near-infrared (NIR) fluorescence (5). Ludmila A. Oparina and coworkers reported the reaction of 3H-indoles with tertiary propargylic alcohols to give functionalized dihydrooxazolo[3,2-*a*]indoles (6). Nisha Narayanan and his team synthesized six squaraine dyes consisting of two different electron donor moiety including 1,1,2-trimethyl-1H-benzo[e]indole (7). Clare L. Lawrence et al. declared eighteen dyes were placed within classes based on their core subunit i.e. 2,3,3-trimethylindolenine, 1,1,2-trimethyl-1H-benzo[e]indole, or 2-methylbenzothiazole for antifungal activities (8). Kandasamy Ponnuvel et al. announced a merocyanine dye-based fluorescent probe have been synthesized for selective and sensitive detection of hypochlorous acid and imaging in live cells (9). Yury A. Sayapin and coworkers reported the synthesis of chemosensors based on 1H-indole, 1H-benzo[e]indole, and 1H-benzo[g]indole as fluorescence (10). Haribhau S. Kumbhar synthesized 1, 1, 2-trimethyl-1H benzo[e]indoline based β-enaminone boron complexes exhibited the intense fluorescence (11). Rasa Steponavičiūtė et al. reported the reaction of 1,1,2-trimethyl-1H-benzo[e]indole with acrylic acid and its derivatives was employed for the preparation of novel fluorescent building blocks (12). Rasa Steponavičiūtė was able to alkylate 1,1,2-trimethyl-1H-benzo[e]indole with bifunctional compounds, and investigated their chemical and optical properties (13). Waad Naim and coworkers presented the transparent and colorless dye-sensitized solar cells exceeding 75% average visible transmittance (14). Wang reported the synthesis of new benzo[e]indolinium cyanine dyes with two different fluorescence wavelengths (15). Xiangning Fang and coworkers provided a one-step condensation method for the synthesis of the fluorescent dye Indocyanine Green (ICG) with 92% yield using 1,1,2-trimethyl-1H-benzo[e]indole (16). In continuation with these efforts we aim to find a new modification for 1,1,2-trimethyl-1H-benzo[e]indole by functionalization and attaching two different amino glucose as mono and di-substitution targeting synthesis new bioactive derivatives for medical and pharmaceuticals application.

METHODOLOGY

Chemistry

Chemical and Solvents

All chemical, reagent and solvent were purchased from different companies and were used without any further purification.

NMR Spectroscopy and IR Spectrometry

The purity and characterization of the target compounds were done using spectroscopic methods including 1H and 13C NMR (Avance Neo Neo 400, Iran), IR spectrometer Perkin-Elmer Spectrum version 10.02 at the Department of Chemistry, Faculty of Science, Diyala University.

Programs and Software

Drawing the chemical structure and 2D investigation and finding were performed via ChemOffice Ultra 2006 (CambridgeSoft) and ChemSketch 2010 (Advanced Chemistry Development, Inc.).

Tools and Instruments

Follow up of the reactions performed via thin layer chromatography (TLC) using alumina plates (size 20×20 cm) percolated with silica gel and Fluorescence Analysis Cabinet Model CM-10 as a detector. The Stuart SMP10 electronic apparatus used to calculate the melting point of the final products (Department of Chemistry, Faculty of Sciences, University of Diyala).

General Methods

Functionalization

1,1,2-trimethyl-1H-benzo[e]indole (**1**) (1 eq.) was dissolved in about 15 mL of anhydrous dimethyl formamide (DMF) with cooling. Cooled solution of phosphorus oxytrichloride ($POCl_3$) in 15 mL of DMF added gradually to indole solution within about 30 min. at about 4 °C. The mixture was refluxed at about 85-90 °C. After about 4 h, TLC (3:1) n-hexane: ethyl acetate indicates the consumption of the starting material, the mixture poured into ice water and neutralized by sodium hydroxide (35% NaOH). Products precipitate, filtered off, washed with water, and dried in a 70 °C oven to give pale yellow crystals of 2-(1,1-dimethyl-1H-benzo[e]indol -2(3H)-ylidene) malonaldehyde (**2**) (17-19).

Coupling

Step1

2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene) malonaldehyde (**2**) (1 eq.) in 15-20 mL ethanol and solution of D-glucose amine (1 eq.) in 5-10 mL ethanol were mixed. Glacial acetic acid (1 mL) was added to the mixture before refluxing for about 10-12 hours. TLC 3:1 n-hexane: ethyl acetate indicates the end of the reaction in about 10-12 hours. The mono-substituted indole precipitate after reducing solvent, filtered, washed, and dried (20-22). Two derivatives were synthesized in this step:

*(2S, 3S, 4R, 5S)-2-((E)-((E)-2-(1, 1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3 oxopropylidene) amino)-3, 4, 5, 6-tetrahydroxyhexanal (**3**)*

2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene) malonaldehyde (**2**) (0.15 g, 0.00035 mmol) was coupled with 2-deoxy-2-amino-D-glucose according to general procedure mentioned in step-1 above to yield yellow crystals of (2S,3S,4R,5S)-2-((E)-((E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3 oxopropylidene) amino)-3,4,5,6-tetrahydroxyhexanal (**3**) (0.2 g, 0.00047 mmol, 83%) m.p. (208 °C). 1H NMR chemical shifts at (400 MHz, DMSO-d6, δ in ppm): δ = 13.46 (d, 1H, NH), 9.80 (s, 2H, -CH=O), 8.20 (d, 1H, -CH=N-), 8.04-7.17 (m, 6H, Ar-H), 5.65-3.19 (m, 10H, d-glucose-H) and 1.95 (s, 6H, 2x CH_3). The 13C-NMR spectra of this compound, exhibits the signals (100 MHz, DMSO-d6, δ

in ppm): δ =179.67 for 2CH=O, 133.01 for NH-CH=C, 156.66 for CH=N, 109.131 for Ar-C, 94.96 for O=C-C=C, 52.93 for CH_3-C-CH_3, 54-75 for d-glucose-C , 52.93 for CH_3CCH_3 and 22.29 for 2× CH_3. (For more details, see Figures S1 and S3).

*(2S, 3S, 4R, 5S)-6-((E)-((E)-2-(1, 1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3 oxopropylidene) amino)-2, 3, 4, 5-tetrahydroxyhexanal (**5**)*

2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene) malonaldehyde (2) (0.15 g, 000035 mmol) was coupled with 6-deoxy-6-amino-D-glucose according to general procedure mentioned in step-1 above to produce brown crystals of (2S,3S,4R,5S)-2-((E)-((2Z,3E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3-((2R,3R,4S,5R)-3,4,5,6-tetrahydroxy-1-oxohexan-2-ylimino) propylidene) amino)-3,4,5,6-tetrahydroxyhexanal (**5**) (0.21 g, 0.00049 mmol, 87%) m.p. (255 °C).1H NMR chemical shifts at (400 MHz, DMSO-d6, δ in ppm): δ = 13.46 (s, 1H, NH), 9.83 (s, 2H, -CH=O), 8.20 (d, 2H, -CH=N-), 7-8.5 (m, 6H, Ar-H, 2.88-5., 1.95 (s, 6H, 2x C$\underline{H}_3$). The 13C-NMR spectra of this compound, exhibits the signals (100 MHz, DMSO-d6, δ in ppm): δ = 179.68 for 2$\underline{C}$H=O, 133.01 for NH-$\underline{C}$H=C, 156.77 for $\underline{C}$H=N, 109-131 for Ar-, 89.34 for O=C-$\underline{C}$=C, 54.94, for CH_3-$\underline{C}$-CH_3, 61.75 for d-glucose-$\underline{C}$, 54.93 for $CH_3\underline{C}CH_3$ and 17.19 for 2× CH_3. (For more details see Supplementary Material)

Step 2

Mono-substituted indole (**3**) or (**5**) (1 eq.) in 15-20 mL ethanol of and solution of D-glucose amine (1 eq.) in 5-10 mL of ethanol were mixed. Glacial acetic acid (1 mL) was added to the mixture before refluxing for about 72 hours. TLC 3:1 n-hexane: ethyl acetate indicates the end of the reaction in about 10-12 hours. The di-substituted indole was precipitated after reducing solvent, filtered, washed, and dried. Two derivatives were synthesized in this step: -

*(2S,3S,4R,5S)-2-((E)-((2Z,3E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3-((2R,3R,4S,5R)-3,4,5,6-tetrahydroxy-1-oxohexan-2-ylimino) propylidene) amino)-3,4,5,6-tetrahydroxyhexanal (**4**)*

(2S,3S,4R,5S)-2-((E)-((E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3 oxopropylidene) amino)-3,4,5,6-tetrahydroxyhexanal (**3**) (0.15 g, 0.57 mmol) was further coupled with 2-deoxy-2-amino-D-glucose according to general procedure mentioned in step-2 to give orange crystals of (2S,3S,4R,5S)-2-((E)-((2Z,3E)-2-(1,1-dimethyl-1H-benzo [e] indol-2(3H)- ylidene) -3- ((2R,3R,4S,5R) -3,4,5,6-tetrahydroxy-1-oxohexan-2-ylimino) propylidene)amino)-3,4,5,6-tetrahydroxyhexanal (**4**) (0.155 g, 0.00026 mmol, 74%) m.p. (185 °C). 1H NMR chemical shifts at (400 MHz, DMSO-d6, δ in ppm): δ = 13.46 (s, 1H, NH), 9.79(s, 2H, -C$\underline{H}$=O), 7.95 (d, 2H, -CH=N-), 6.60-8.18 (m, 6H, Ar-$\underline{H}$), 2.58-4.85 (20$\underline{H}$, d-glucose-$\underline{H}$) (s, 5.23, 4H, C$\underline{H}_2$OH) (m,3.61,8H, $CH_2O\underline{H}$) ,(dd, 3.52,2H, CHO$\underline{H}$, 1.94 (s, 6H, 2x C$\underline{H}_3$) The 13C-NMR spectra of this compound, exhibits the signals (100 MHz, DMSO-d6, δ in ppm): δ = 179.68 for 2$\underline{C}$H=O, 137.86 for 2NH-$\underline{C}$H=C, 133.01 for $\underline{C}$H=N, 109.13-130.25 for Ar-C, 97.36 for O=C-$\underline{C}$=C, 54.93, for CH_3-$\underline{C}$-CH_3, 61.68-75.29 for d-glucose-$\underline{C}$, 54,93 for $CH_3\underline{C}CH_3$ and 22.28 for 2× CH_3 (For more details, see Figures S5 and S6).

*(2S,3R,4S,5S)-6-((2E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3-((2R,3R,4S,5R)-2,3,4,5-tetrahydroxy-6-oxohexylimino)propylide-neamino)-2,3,4,5-tetrahydroxyhexanal (**6**)*

(2S,3S,4R,5S)-2-((E)-((E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3-oxopropylidene) amino)-3,4,5,6-tetrahydroxyhexanal (**5**) (0.15 g, 0.00035 mmol) was further coupled with 2-deoxy-2-amino-D-glucose according to general procedure mentioned in step-2 to give greenish crystals of (2S,3R,4S,5S)-6-((2E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3-((2R,3R,4S,5R)-2,3,4,5-tetrahydroxy-6-oxohexylimino)propylide-neamino)-2,3,4,5-tetrahydroxyhexanal (**6**) (0.16 g, 0.00027 mmol, 76%) m.p. (193 °C). 1H NMR chemical shifts at (400 MHz, DMSO-d6, δ in ppm): δ = 13.46 (s, 1H, NH), 9.79 (s, 2H, -C$\underline{H}$=O), 7.95 (d, 2H, -CH=N-), 6.61-8.17 (m, 6H, Ar-$\underline{H}$), 2.58-4.87 (20$\underline{H}$, d-glucose-$\underline{H}$), 1.94 (s, 6H, 2x C$\underline{H}_3$) The 13C-NMR spectra of this compound, exhibits the signals (100 MHz, DMSO-d6, δ in ppm): δ = 179.68 for 2$\underline{C}$H=O, 137.86 for 2NH-$\underline{C}$H=C, 133.01 for $\underline{C}$H=N, 109.13-130.25 for Ar-C, 97.36 for O=C-$\underline{C}$=C, (54.93), for CH_3-$\underline{C}$-CH_3, 61.68-75.29 for d-glucose-$\underline{C}$, 54,93 for $CH_3\underline{C}CH_3$ and 22.28 for 2× CH_3 (For more details, see Figures S7 and S8).

Biological Activity

Material and Methods

Staphylococcus aureus and *Staphylococcus epidermidis* isolates were cultured on Blood agar and Mannitol salt agar. *Klebsiella pneumonia* and *Escherichia coli* isolates were cultured on MacConky agar and Eosin Methylene Blue agar, *Candida albicans* isolate was cultured on Sabouraud dextrose agar and candida chromogenic agar, to obtain pure isolates.

MacFarland turbidity standard

The preparing solution from the company (Biomeriex) was used in calibrating the number of bacterial cells, as it gives an approximate number of cells 1.5 x 10^8 cells/mL.

1) Muller Hinton agar medium was prepared by dissolving 38 g of agar in 1 L of distilled water and sterilized in an autoclave at 121 °C and under pressure (15 pounds) for 15 minutes, cooled and poured into sterile dishes and kept in the refrigerator until use.

2) Determination the antimicrobial activity of the target compounds by agar well diffusion method as follows:

3) A number of bacterial colonies were transported by loop to prepare the suspended bacteria and put it

in tubes contain brain heart infusion broth to activate the bacteria. The tubes were incubated for (18 - 24) h at 37 °C. The suspended bacterium was compared to the standard MacFarland and solution (1.5×10^8) cells/mL. After that the bacteria suspended was spread by a sterile swab, it was spread on the plates containing Muller Hinton agar and then the plate was left for a while to dry.

4) Holes were made with a diameter of 5 mm in the culture media by using sterilized a cork borer 100 µL of the material were added to each hole individually by micropipette and one well represent the negative control by adding DMSO only. After then, the dishes were incubated at 37 °C for 24 h.

5) The effectiveness of each concentration was determined by measuring the diameter of the inhibition zone around each hole in mm (23-25).

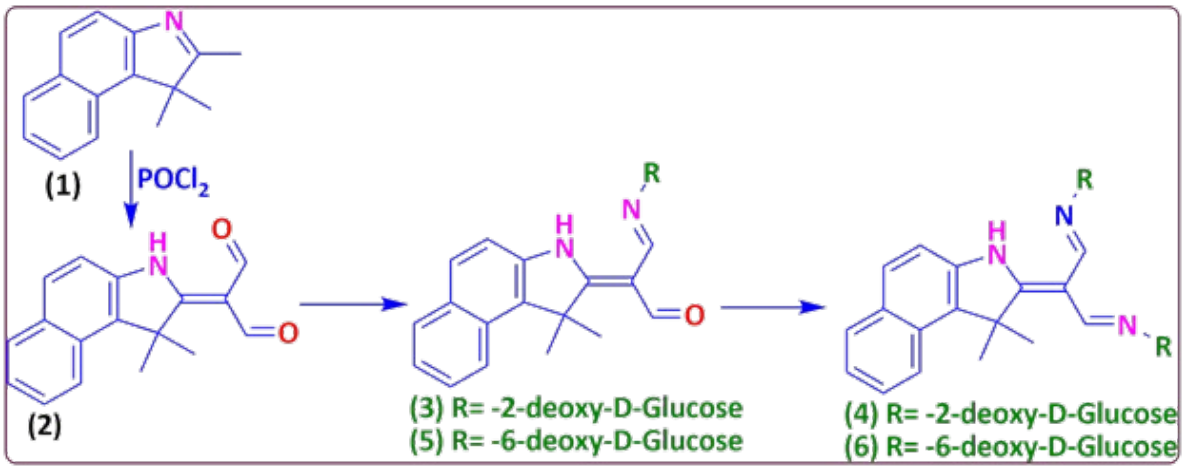
RESULTS AND DISCUSSION

Synthesis

There are too many aromatic heterocyclic derivatives which are useful for many applications in all fields of the life one of them is 1,1,2-trimethyl-1H-benzo[e]indole **1**, which is chosen as the starting material of the target synthesis for many reasons such as economy, availability, and accessibility. On the other hand, amino sugars, especially 2-deoxy-2-amino-D-glucose and 6-deoxy-6-amino-D-glucose are biochemical molecules chosen to attach with the heterocyclic starting material for the same reasons in addition their perfect chemical structures with multi hydroxyl group which may increase the solubility of the target compounds.

This coupling needs to modify the starting material to create new reaction centers, so that the functionalization of **1** was done via Vilsmeier-Haack reaction with of $POCl_3$ (phosphoryl chloride) in DMF to get **2** with two new reaction centers represented by aldehyde groups.

2 was coupled with the 2-deoxy-2-amino-D-glucose and 6-deoxy-6-amino-D-glucose via imines which are commonly called as Schiff bases or Schiff's bases to produce **5** respectively, with di-substituted amino sugar instead of expected di-substituted derivatives **4** and **6** in mild reaction conditions (Scheme 1) .



Scheme 1: Synthesis of mono and di-substituted heterocyclic derivatives.

In order to investigate the reasons for these unexpected products of the first step of the reaction, the 3D structure study of the precursor intermediate **2** shows that there is a steric hindrance at the aldehyde group close to the two methyl groups of the heterocyclic moiety, so the monosaccharide amine at the simple or mild conditions attach first the easy open aldehyde group away from the methyl group to produce the mono-substituted derivative as shown in Figure 1.

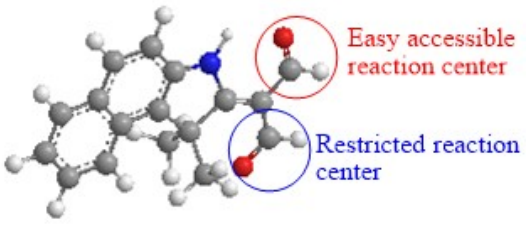


Figure 1: 3D structure of **2.**

Under hard conditions, it is possible to attach another amino monosaccharide to the hindered aldehyde group to yield compounds **4** and **6** respectively as shown in Scheme 1.

The purity and characterization of the mono-substituted derivatives **3** and **5** confirmed by IR , 1H NMR

and 13C NMR, proton NMR shows the chemical shift of the -NH at about 13-14 ppm, two aldehyde protons at about 8-9, -CH=N- at about 8-9, aromatic proton in between 7.0-8.5 ppm, the monosaccharides proton from 2-6 and the two methyl groups of the heterocyclic moiety at about 1-2 ppm (See Figures S1 and S2).

The 1H spectra of the di-sugar derivatives shows the chemical shift of the mentioned groups at the same positions with duplicated protons for sugar moieties and aldehyde groups, with appearance of the two -CH=N- proton chemical shifts. (See Figures S1 and S2)

13C NMR analysis confirms the structures as the number of carbon and the chemical shift fitting the suggested compounds, for the monosaccharide derivatives (**3**, **5**). The sugar aldehyde carbons appear at about 188 while indole aldehyde appears at 187, the 2NH-CH=C carbon list at 177-179, CH=N carbon located at about 153-155, aromatic carbons in between 110-132, sugar carbons appear from about 50-75, CH_3-C-CH_3 carbon and the two groups of methyl for the indole moiety at about 20-22 (See Figures S3 and S4).

The new derivatives can either be represented by Fisher Projection structure or by Howarth formula as shown in Figure S6, Supplementary Material. The 1H NMR analysis above shows clearly the chemical shift of the aldehyde protons and the absence of $\alpha \wedge \beta$configuration of the anomeric proton of glucose make the structure of the target compounds are compatible with Fisher projection rather than Howarth form (Figure 2).

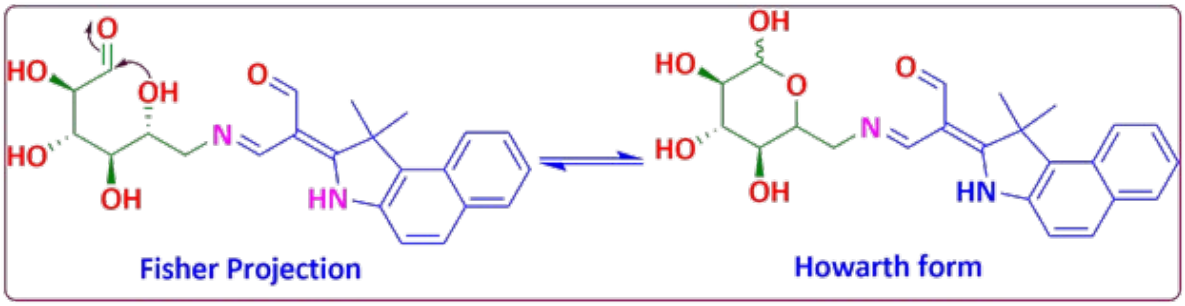


Figure 2: Fisher projection and Howarth form of compound (**5**).

The carbon and proton atoms number and their chemical shift of compounds **5** and **6**, are approximately the same carbon and proton number and chemical shift with double integration for sugar moieties in compered to compounds **3** and **5** and disappearance of one CH=N group from compounds **5** and **6**. (See Figures S5, S6, S7, and S8).

Finally, we can confirm the sugar-indole derivative can be accessible easily with a very simple process and this reaction can improve the solubility which can make such derivatives suitable for many applications especially in medical applications.

Biological Activity

The starting material and targets compounds were subjected to biological activity evaluation. The investigation shows that the starting material 1, 1, 2-trimethyl-1H-benzo[e]indole (**1**) does not show any biological activity by its natural stand structure but, the attachments of the biochemical such as amino monosaccharides led to new molecules with different degrees of bioactivity. The modification of the starting material and attachment with 2-deoxy-2-amino -d-glucose and 6-deoxy-6-amino -d-glucose produced two new compounds **3** and **5**, the investigation of those molecules with two gram positive bacteria *Staphylococcus aureus* and *Staphylococcus epidermidis* only compound **3** showed a good biological activity with *Staphylococcus aureus* while **5** is biologically inactive with this kind of bacteria, both of them showed inactivity with gram negative bacteria *Klebsiella pneumoniae* and *Escherichia coli* but, compounds **3** and **5** exist as a very good anti-fungal activity toward *Candida albicans.*

The modification of the precursor with two substitution of 2-deoxy-2-amino -d-glucose and 6-deoxy-6-amino -d-glucose yield two compounds **4** and **6** which show a good activity with all mentioned bacterial except compound **5** show poor results with *Klebsiella pneumoniae* and both show a great anti-fungal activity toward *Candida albicans.*

As a conclusion, the modification of 1, 1, 2-trimethyl-1H-benzo[e]indole **1** with two amino sugar molecules could be useful and considerable methods for synthesis of new bioactive compounds which can participate in the field of medical and pharmaceuticals applications (Table 1).

CONCLUSION

Biological derivatives based on available, economic and biodegradable monosaccharide with aromatic indole can be easily accessible within two to three steps reaction in acceptable yields. The new derivative show a good to moderate biological activity toward gram positive bacteria and gram negative bac-

teria, while they show activity toward fungi. It is possible for the new compounds in future to take the way in both medical and pharmaceuticals application to substitute the now known familiar for bacteria and fungi.

CONFLICT OF INTEREST

The researchers declare that there are no conflicts of interest regarding the current manuscript.

ACKNOWLEDGMENTS

The researches acknowledge and thankful to the University of Diyala, and the faculty of Sciences for submitting the entire requirements to do this research.

Table 1: The Biological Activity Investigation of Target Compounds.

No.	Gram Positive Bacteria								Gram Negative Bacteria								Fungi			
	S. aureus				*S. epidermidis*				*K. pneumoniae*				*E. coli*				*C. albicans*			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
3	16	14	13	R	R	R	R	R	R	R	R	R	R	R	R	R	26	24	24	23
4	15	14	13	11	R	R	R	R	R	R	R	R	R	R	R	R	27	24	24	22
5	15	15	14	13	16	11	R	R	R	R	R	R	13	11	R	12	26	23	22	22
6	18	18	17	R	15	14	14	11	12	11	11	12	16	16	14	18	27	23	21	20

Numbers indicate the diameter of the inhibition zone around each hole in mm.

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New Bioactive Aromatic Indole Molecules with Monosaccharide Core

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Supporting Material

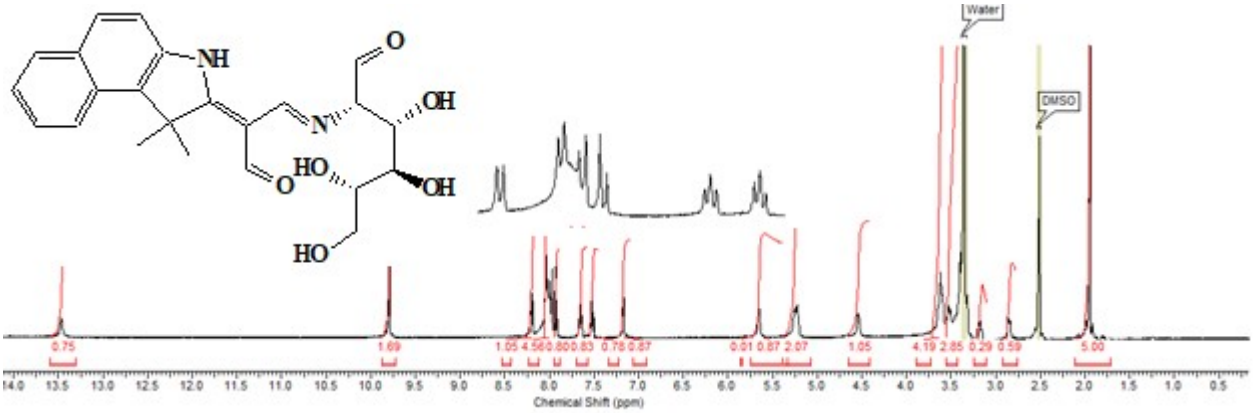

Figure S1: 1H NMR Spectrum for (2S,3S,4R,5S)-2-((E)-((E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3-oxopropylidene) amino)-3,4,5,6-tetrahydroxyhexanal (**3**).

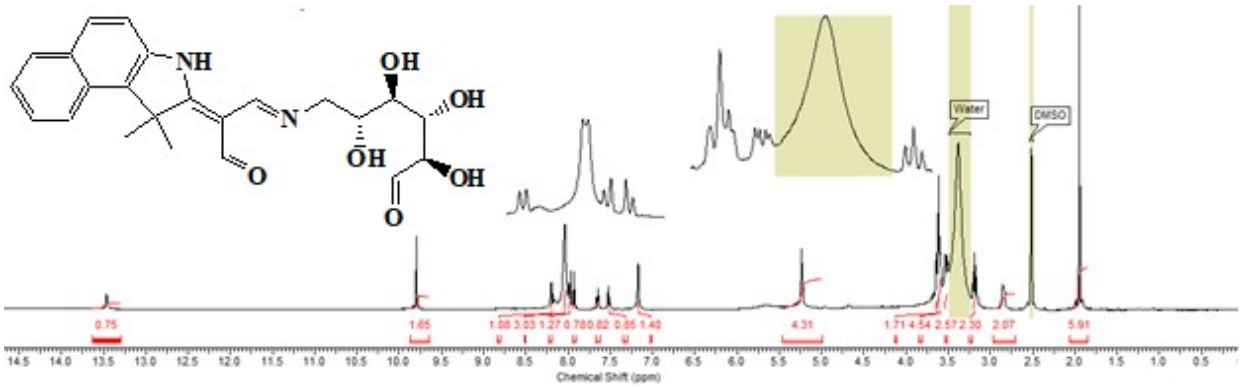

Figure S2: 1H NMR for (2R,3S,4R,5R)-6-((E)-((E)-2-(1,1-dimethyl-1H-benzo [e]indol-2(3H)-ylidene)-3-oxopropylidene) amino)-2,3,4,5-tetrahydroxyhexanal (**5**).

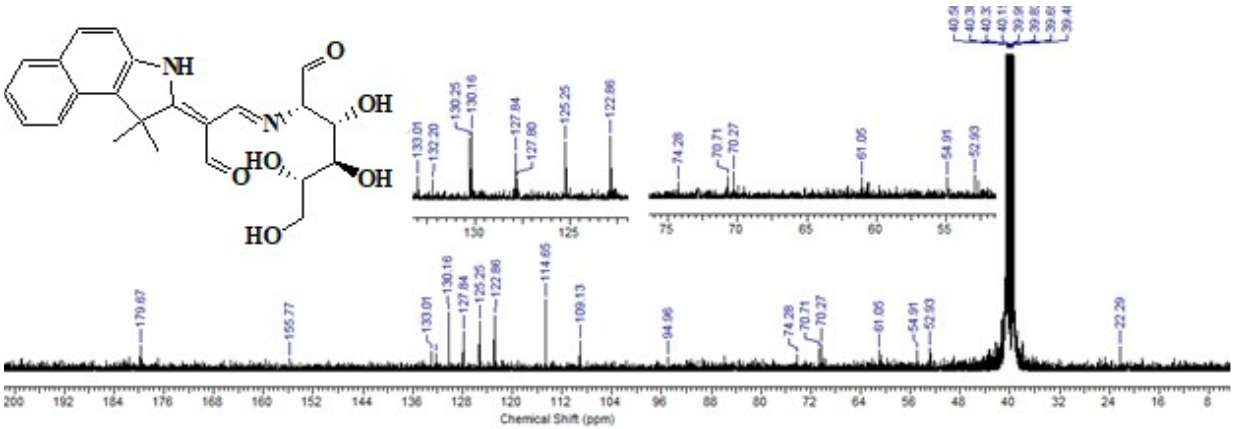

Figure S3: 13C NMR Spectrum for (2S,3S,4R,5S)-2-((E)-((E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3-oxopropylidene) amino)-3,4,5,6-tetrahydroxyhexanal (**3**).

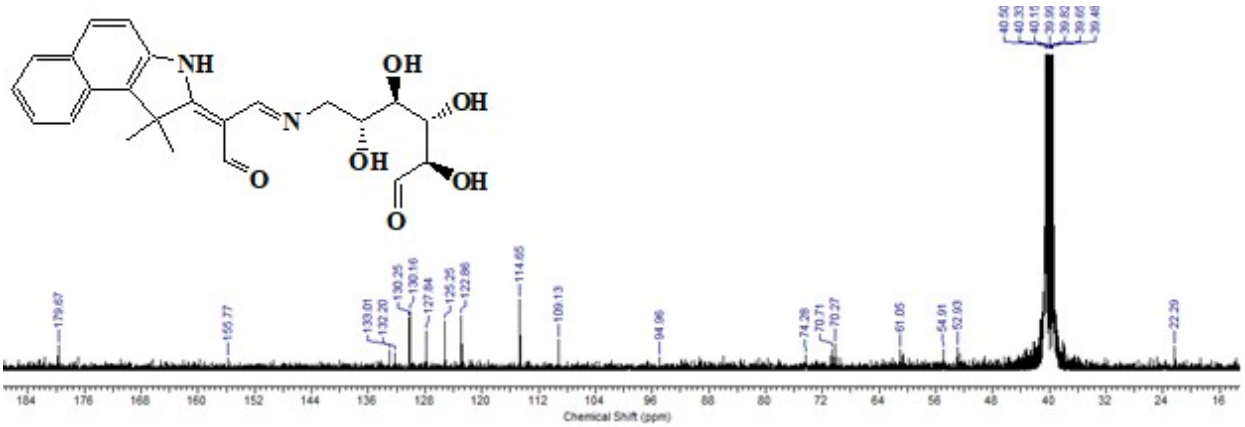

Figure S4: 13C NMR Spectrum for (2R,3S,4R,5R)-6-((E)-((E)-2-(1,1-dimethyl-1H-benzo [e]indol-2(3H)-ylidene)-3-oxopropylidene) amino)-2,3,4,5-tetrahydroxyhexanal (**5**).

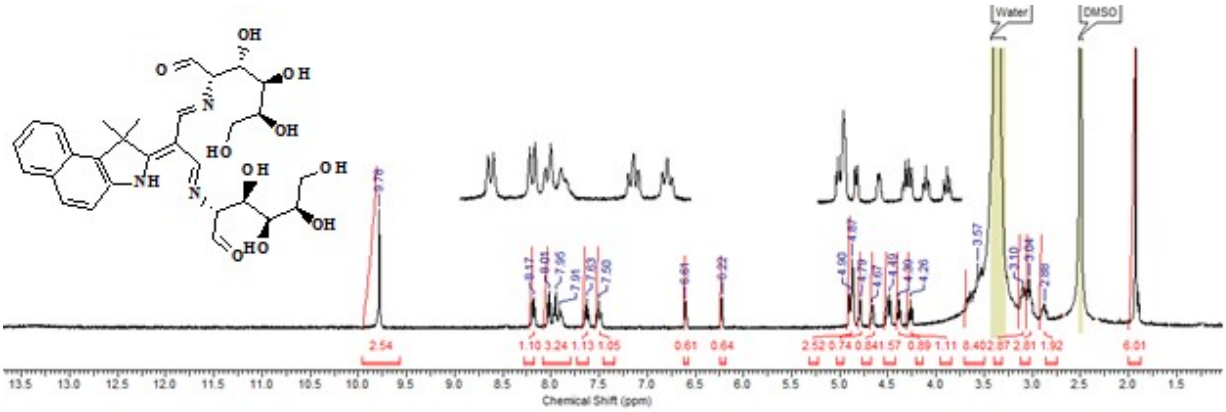

Figure S5: 1H NMR Spectrum for Compound (2S,3S,4R,5S)-2-((E)-((2Z,3E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3-((2R,3R,4S,5R)-3,4,5,6-tetrahydroxy-1-oxohexan-2-ylimino) propylidene) amino) -3,4,5,6-tetrahydroxyhexanal (4).

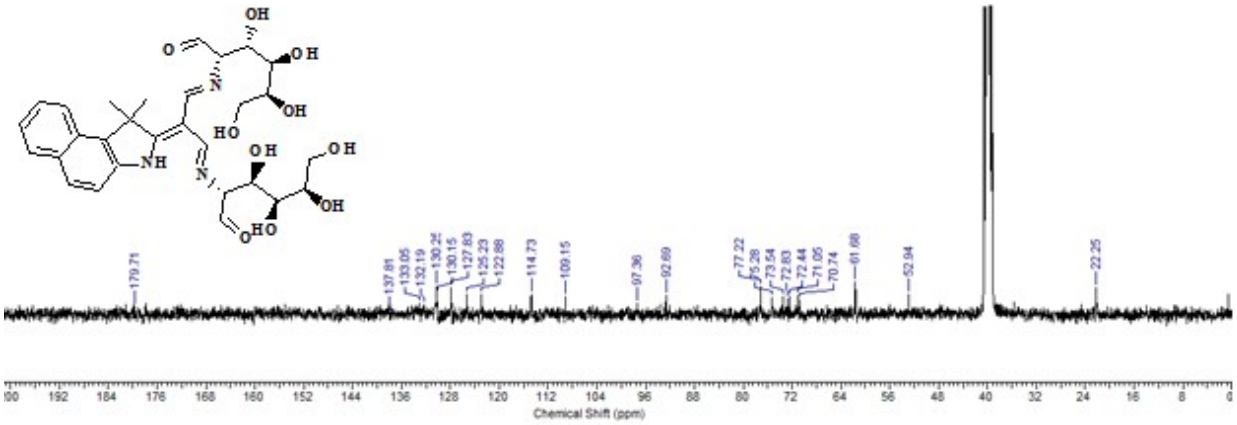

Figure S6: 13C NMR Spectrum for compound (2S,3S,4R,5S)-2-((E)-((2Z,3E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3-((2R,3R,4S,5R)-3,4,5,6-tetrahydroxy-1-oxohexan-2-ylimino) propylidene) amino) -3,4,5,6-tetrahydroxyhexanal (**4**)

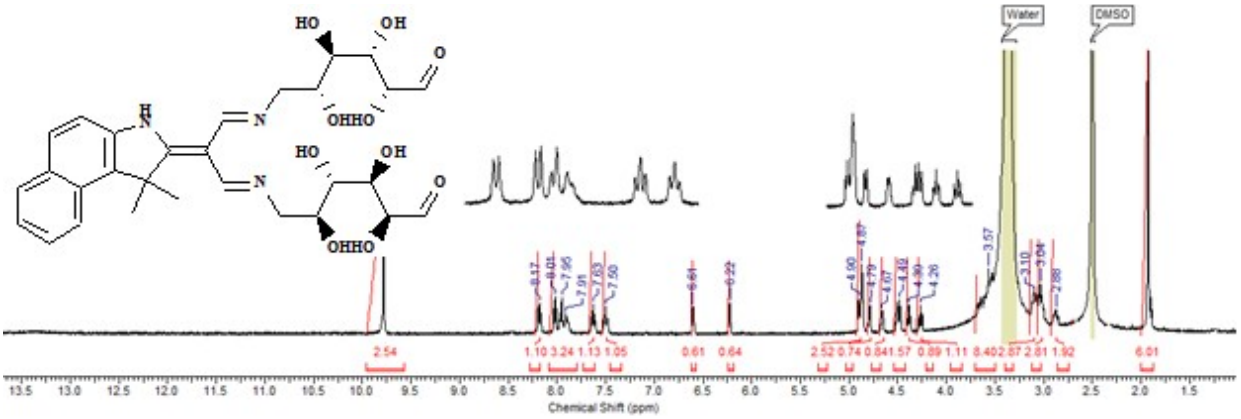

Figure S7: 1H NMR Spectrum for compound(2S,3R,4S,5S)-6-((2E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3-((2R,3R,4S,5R)-2,3,4,5-tetrahydroxy-6 oxohexylimino) propylideneamino) -2,3,4,5-tetrahydroxyhexanal (**6**).

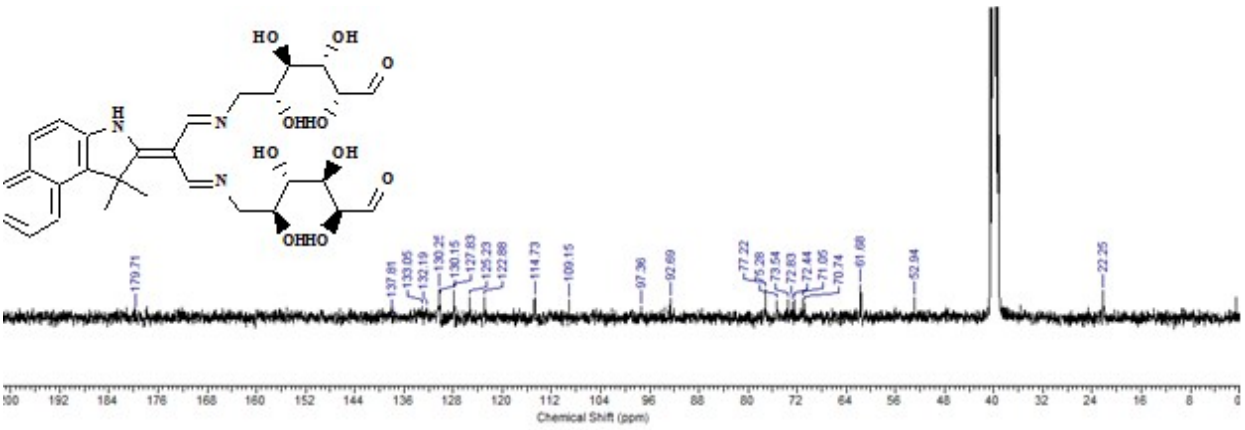

Figure S8: 13C NMR Spectrum for compound (2S,3R,4S,5S)-6-((2E)-2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3-((2R,3R,4S,5R)-2,3,4,5-tetrahydroxy-6 oxohexylimino) propylideneamino) -2,3,4,5-tetrahydroxyhexanal [6].