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Design, synthesis and characterisation of a disulphide appended sugar *bis*-triazole

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In this work, sugar-based bis-triazole appended disulfide was synthesized, characterized and the molecular structure is confirmed through different spectral techniques like NMR (^{1}H, ^{13}C), FTIR and mass spectroscopy. Since the target molecule possesses suitable core moiety, we anticipate that the synthesized sugar-based bis-triazole appended disulfide derivative can act as a sensor.

Keywords: Bis-triazole, Sensor, Sugar derivative

Mercury is a standout amongst the most lethal substantial metal elements. Mercury or methylmercury in particular is considered one of the hazardous chemicals or groups of chemicals of foremost public health fear. It is a naturally occurring element that is originates in earth's crust[1]. It exists in three unique structures: inorganic mercury, alkylmercury and basic mercury. Mercury tainting happens through different procedures, for example, the ignition of non-renewable energy sources, mining, and strong waste burning. The acquaintance of mercury in with the nourishment tie makes genuine risks to the humankind and also to the marine lives[2]. Exposure of a small amount of mercury causes toxic effects on the digestive and immune systems and neurological damage in human body. Mercury particles demonstrate a high fondness for thiol groups in proteins, prompting the glitch of cells and thus causing numerous medical issues[3]. Its amassing in the body can contribute to the improvement of a wide assortment of ailments, such as pre-birth cerebrum harm, genuine subjective and movement issue, furthermore, Minamata disease[4]. A molecular sensor or chemosensor is a molecule that signals the presence of matter or energy. A typical chemosensor contains a receptor capable to selectively bind the analyte and a site with some tuneable molecular property, which translates a recognition event (any molecular property) into a tuneable signal[5,6]. Fluorescent chemosensor is a molecular sensor that generates a fluorescent signal. Fluorescent chemosensors have been broadly used in different fields, for example, science, physiology, medication, and pharmacology, as the varieties of fluorescence signals can be seen through optical instruments and even by the naked eye progressively[7]. Fluorescent chemosensors are widely used for the detection of transition metals, over the previous decade more consideration has been centered on the improvement of fluorescent chemosensors for the recognition of Hg^{2+} ions. Because Hg^{2+} is known to be a fluorescence quencher[8], most fluorescent chemosensors recognize Hg^{2+} by fluorescence extinguishing through spin-orbit coupling[9]. Owing to their affectability, fluorescent chemosensors that recognize metal particles by fluorescence enhancement are all the more effortlessly checked than those that work by fluorescence quenching[10].

In general, synthesis of a five-membered heterocyclic systems particularly 1,2,3-triazoles exhibited good biological activities[11-14]. 1,3-dipolar cyclo additions of azide and alkyne using Cu(I)-catalyst commonly known as “click reaction” has been widely used for the construction of five-membered heterocyclic rings in one step[15,16]. It enables one to design simple to complex molecular designs enclosing 1,4-disubstituted triazole skeleton in one step. In this line, carbohydrate-based triazole molecules with standard drugs are always symbolized itself as a good drug candidate with increased therapeutic efficacy. Nowadays a great number of biologically active glycosylated 1,2,3-triazole derivatives have been synthesized which showed a decent pharmacokinetic properties. A number of carbohydrate-based 1,2,3-triazole core moieties containing drug-like molecules with good pharmacokinetic properties have been reported in the literature[17-21]. In addition, sugar particles merged into their layout and are versatile campaigners as cation sensor. Moreover, utilization of sugar particles would surrender higher water dissolvability, also sugars are

chiral substances having free hydroxyl groups that can come closure and are extraordinarily appropriate as cation-confining groups. A representative example of a water-soluble sugar (ribosyl)-based sensor is shown in Fig. 1[22]. The advantage of using carbohydrate based sensor is that they are biocompatible and abundance and of low cost. Moreover, there are hydroxyl groups and oxygen atom in a biologically benign sugar moiety which enhance its water solubility and make it suitable for binding with cation.

In this exertion, we have designed and synthesized a disulfide appended sugar bis-triazole derivative, which is expected to act as a good mercury sensor and the study in this direction is in progress.

Materials and Methods

All starting materials were obtained from commercial suppliers and used as received. D-Glucose was purchased from Merck, India. 4-(diethylamino)-2-hydroxybenzaldehyde and 3, 3'-dithiopropionic acid were purchased from Sigma Aldrich chemicals Pvt. Ltd, USA. Potassium hydroxide, acetic anhydride, and acetic acid were purchased from SRL, India. Methanol and ethanol were used after distillation. Column chromatography was performed on silica gel (100-200 mesh). NMR spectra were recorded on a Bruker DRX 300 MHz, and 400 MHz spectrometer. FTIR spectra were measured on Agilent Cary FTIR Spectrometer High-Resolution Mass Spectroscopy (HRMS) was performed on Thermo Fischer Scientific Exactive Plus Orbitrap mass spectrometer.

Synthesis of dimethyl-3,3'-disulfanediyl-di-propanoate, (2)

To the solution of 3,3'-dithiopropionic acid (3 g, 1.4 mmol, 1 eq) (1) in 50 mL of methanol and 6 drops of conc. H_2SO_4 were added. The reaction mixture was stirred under reflux for 4 h and monitored by TLC.

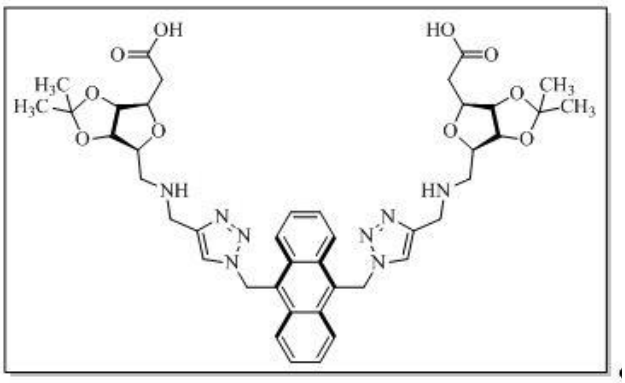


Fig. 1 — Representative example for a water-soluble fluorescent sensor[22]

After cooling to room temperature, the solvent was removed under vacuum and the remaining residue was extracted with ethyl acetate, washed thrice with distilled water finally with $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated to give ester (2) as a white solid (97% yield)[23].

Preparation of 3, 3'-disulfanediyl-di-(propanehydrazide), (3)

3,3'-Disulfanediyl-di-propanoate (**2**) (3.3g, 1.4 mmol, 1 eq) was dissolved in dry MeOH (50 mL). hydrazinehydrate (1.24 mL, 25 mmol, 6 eq) was added and the reaction mixture was stirred 18 h at room temperature. The resulting suspension was filtered and a white solid was obtained, which was washed with water (2 mL) and MeOH (5mL) then dried. 3, 3'-disulfanediyl-di-(propanehydrazide) (3) was obtained[24].

Preparation of 4-(diethylamino)-2-(prop-2-yn-1-yloxy)-benzaldehyde (5)

One gram of 4-(diethylamino)-2-hydroxybenzaldehyde (5.1 mmol, 1 eq) was treated with (0.7 g) alkyl bromide (0.7 g, 6.2 mmol, 1.2 eq) in the presence of 1.42 g of K_2CO_3 (17 mmol, 2eq) in DMF (10 mL) solvent. The solution was stirred vigorously at room temperature. The product formation was finalized by TLC and the reaction mixture was then poured into the crushed ice and brown colored precipitate was formed. The product was washed with 5 mL water and then extracted with diethyl ether. The organic layer was three times washed with distilled water and dried over Na_2SO_4. The product was purified by column chromatography (ethyl acetate/hexane) (Brownish red colour, 98% yield).[25] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, Al-CH_3, 6H), 3.42 (q, Al-CH_2, 2H), 5.32 (s, -OCH_2, 2H), 7.31 (s, Ar-H, 1H), 6.31 (d, Ar-H, 1H), 10.13 (s, Ald-1H, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.68, 185.87, 161.62, 152.79, 143.62, 129.82, 120.68, 113.18, 103.77, 92.84, 11.55, 43.85, 19.47, 74.13.

Preparation of sugar based triazole derivative, (6):

To the pure 4-(diethylamino)-2-(prop-2-yn-1-yloxy)benzaldehyde (5), 1 g (4.3 mmol, 1 eq) of sodium ascorbate (0.12 g, 0.6 mmol, 0.3 eq) and 0.053 g of copper sulphate pentahydrate (0.2 mmol, 0.1 eq) were added by dissolving in mixture of THF, n-BuOH, H_2O in the ratio of 1:1:1. To the above solution, 0.8 g of sugar azide (2.3 mmol) was added and stirred at room temperature vigorously. The product formation was finalized by TLC and the product was extracted by DCM (30 mL) and the

organic layer washed with distilled water thrice. The solvent was evaporated under reduced pressure and the product (6) was purified by column chromatography (hexane/ethyl acetate) to obtain a pale yellow colored solid as a product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, 2-CH_3, 3H), 3.42 (q, 2-CH_2, 4H), 4.02-4.18(Sac-H, 2H), 4.29-4.35(d, Sac-H, 2H), 5.28 (t, 8.72Hz, Sac-H, 1H), 5.31 (S, -OCH_2, 1H), 7.98(S, Ar-H, 1H), 7.70(d, 8.92Hz), 10.13 (s, CHO, 1H), δ 5.32 (s, -CH_2, 2H), δ 7.31 (s, 1H, Ar-CH), δ 6.31 (d, Ar-H, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.68, 185.87, 161.62, 152.79, 143.62, 129.82, 120.68, 113.18, 103.77, 92.84, 11.55, 43.85, 19.47, 74.13.

Preparation of penta-*O*-acetyl-*β*-D-glucopyranose

D-Glucose (1 g, 27.8 mmol) and acetic anhydride (10 mL, 0.53 mmol) was stirred at room temperature. Few granules of iodine (10 mg, 0.435 mmol) were added to this and stirring was continued till all of the solution turns clear. The clear solution was poured into crushed ice (100 mL) with stirring and a white solid was formed. Workup is done in dichloromethane. Anhydrous Na_2SO_3 was added to this. The organic layer is washed with $NaHCO_3$ solution and dried over anhydrous Na_2SO_4 layer to remove water and then distilled. (98% yield). ^{1}H NMR (300 MHz, $CDCl_3$):δ 6.34 (d, J= 3.3 Hz, Sac-H, 1H), 5.48 (t, J= 9.8 Hz, Sac-H, 1H), 5.18 to 5.08 (m, Sac-H, 2H), 4.28 (dd, J= 3.9 Hz, Sac-H, 1H), 4.14-4.08 (m, Sac-H, 2H), 2.19-2.03 (m, 15H, -$COCH_3$) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 172.7, 172.2, 171.9, 171.3, 91.6, 72.3, 71.7, 70.4, 64.0, 23.4, 23.2, 23.1, 23.0, 22.9 ppm.

Preparation of 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl-bromide

HBr (33% in AcOH, 12.5 mL) was added to the solution of penta-*O*-acetyl β-glucopyranose 4 (4.50 g, 10.6 mmol) in dichloromethane at 0^{o}C and the reaction mixture was allowed to warm to room temperature and continuously stirred for 1.5 h. The completion of the reaction was confirmed through TLC. The reaction mixture was then poured into crushed ice. Workup is done with dichloromethane and the organic layer was washed with anhydrous $NaHCO_3$. The organic layer was collected and then dried over anhydrous Na_2SO_4 and then distilled. The solvent was evaporated and purified by column chromatography (hexane/ethyl acetate; 2 : 1) (89%). ^{1}H NMR (300 MHz, $CDCl_3$):δ_H 6.60 (d, J = 4.1 Hz, Sac-H, 1H), 5.54 (t, J = 9.7 Hz, Sac-H, 1H), 5.14 (tt, J = 10.2, Sac-H, 1H), 4.84 (dd, J =10.0, 4.1 Hz, Sac-H, 1H), 4.29 (dd, J =13.6, J=3.6 Hz, Sac-H, 1H), 4.26 (m, Sac-H, 1H), 4.14 (t, J=13.9, Sac-H, 1H), 2.08-2.02 (s, 12H, -$COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 86.5, 72.1, 70.5, 70.1, 67.1, 60.9, 20.6, 20.6, 20.6, 20.5 ppm.

Preparation of 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl-azide

Sodium azide (0.97 g, 14.65 mmol) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide (4.20 g, 9.95 mmol) solution, in the presence of dry DMSO (50 mL) and stirred for 10 min at room temperature till it get dissolved. The reaction mixture was then poured to crushed ice and then extracted with dichloromethane. Organic layer is collected and washed with brine, dried over anhydrous Na_2SO_4 and then distilled. 2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosylazide as white solid was obtained with 84% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.23 (t, J= 9.5 Hz, 1H, Sac-H), 5.11 (t, J= 9.6 Hz, 1H, Sac-H), 4.96 (t, J= 9.2 Hz, 1H, Sac-H), 4.65 (d, J= 8.7 Hz, 1H, Sac-H), 4.28 (dd, J= 4.8 Hz, J=12.5 Hz, 1H, Sac-H), 4.17 (dd, J= 2.1 Hz, J= 12.5 Hz, 1H, Sac-H), 3.83-3.78 (m, 1H, Sac-H), 2.11-2.02 (m, 12H, -$COCH_3$) ppm.^{13}C NMR (75 MHz, $CDCl_3$):δ_C 170.6, 170.1, 169.3, 169.2, 87.9, 74.0, 72.6, 70.6, 67.9, 61.7, 20.7, 20.5 ppm.

Preparation of sugar based bis-triazole appended di-sulfide derivative, (7)

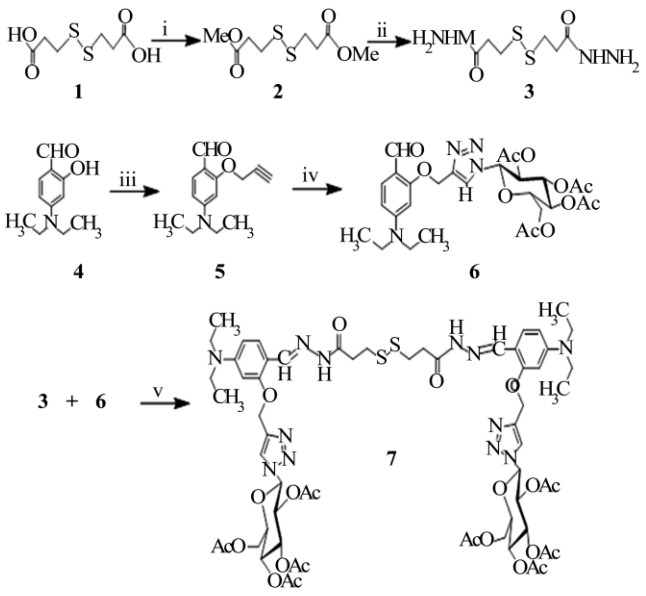
To the pure 3, 3'-disulfanediyl-di-propanehydrazide (0.5 g, 2.0 mmol, 1 eq), sugar-based triazole (6) derivative (2.5 g, 4.1 mmol, 2 eq) was added and dissolved in ethanol (10 mL). The reaction mixture was stirred for 4 h under a reflux condition. The product formation was monitored through TLC and the reaction mixture was cooled to room temperature for a few minutes after completion of the reaction. Then the workup was carried out using ethyl acetate, in which the organic layer was washed with distilled water (three times) and the combined organic layer was dried over Na_2SO_4. After the removal of the solvent by rotary evaporation the product was purified by column chromatography (ethyl acetate/hexane) and pure sugar-based *bis*-triazole appended disulfide derivative, 7 obtained as pale yellow solid with 86% of yield. ^{1}H NMR (300 MHz, $CDCl_3$):δ_H 6.33-6.35 (d, Sac-H, 2H), 6.20-6.23 (d, Sac-H, 2H), 5.90-5.95 (t, Sac-H, 2H), 5.52-5.54(d, Sac-H, 1H), 5.44-5.47 (d, Sac-H, 2H), 5.24-5.26 (s, Sac-H, 3H), 5.06-5.11 (t, Sac-H, 1H),4.90-4.93 (t, Sac-H, 1H), 4.27-4.30 (d, Ali-H, 2H), 4.13-4.19 (t, Ali-H, 2H), 4.03-4.04 (d, Ali-H, 2H), 4.26-4.27 (s, Ali-H, 1H), 4.16-4.23 (t,

Ali-H, 2H), 4.03-4.04 (d, Ali-H, 2H), 3.39 (s, Ali-H, 2H), 3.14-3.16 (d, Ali-H, 1H), 3.06-3.08 (d, Ali-H, 2H), 2.05-2.07 (s, Ali-H, 24H),1.87-1.89 (d, Ali-H, 8H), 1.191-1.197 (d, Ali-H, 12H), 9.79-9.81 (m, Ar-H, 1H), 8.95 (s, Ar-H, 1H), 8.22-8.28 (d, Ar-H, 1H), 8.15-8.16 (d, Ar-H, 1H), 7.98-8.01 (d, Ar-H, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 12.5, 12.6, 20.2, 20.6, 20.7, 29.6, 32.7, 32.9, 33.4, 33.9, 34.3, 34.7, 44.6, 44.8, 61.4, 62.0, 62.6, 66.9, 67.6, 67.8, 68.4, 70.0, 70.4, 71.1, 71.9, 72.4, 72.7, 73.0, 74.9, 75.0, 78.7, 77.1, 77.4, 85.5, 90.0,94.3, 95.1, 105.6, 109.3, 109.6, 109.8, 121.5, 121.8, 122.6, 127.2,140.6, 144.9, 145.0, 145.3, 150.6, 150.7, 158.4, 158.6, 167.0,169.3, 169.5, 169.7, 170.1, 170.6, 170.8, 172.8, 172.9.

Results and Discussion

Synthesis and characterization of sugar based bis-triazole di-sulfide appended derivative

Sugar-based bis-triazole appended disulfide, 7 was synthesized in five steps from readily available D-glucose. Disulfide precursor, 3 was synthesized from 3, 3'-dithiopropionic acid through esterification followed by the reaction with hydrazine. The other precursor triazole based sugar derivative, 6 was synthesized in two steps from 4-(diethylamino)-2-hydroxybenzaldehyde (Scheme 1). The molecular structure of both disulphide, 3 and triazole precursors, 6 was confirmed through spectral techniques. Formation of the expected product, sugar-based bis-triazole appended disulfide 7 is confirmed from NMR (^{1}H, ^{13}C), FTIR, and mass spectral analysis.



Scheme 1 — Synthesis of di-sulfide appended sugar bis-triazole derivative

1,3-Dipolar cycloaddition strategy was applied to synthesize sugar-based bis-triazole derivative, 7. *O*-Alkylation of aromatic *o*-hydroxyaldehydes led to the formation of the corresponding *O*-propargylated derivatives 5, in excellent yield. Copper catalysised alkyne-azidecycloaddition (CuAAC) of the *O*-propargyl-aldehyde with sugar-azide was promoted by $CuSO_4.5H_2O$ as the catalyst and sodium ascorbate as the reducing agent in a mixture of solvents [THF: H_2O: n-ButOH, 1:1:1], which resulted the corresponding sugar-triazole derivatives, 6. The formation of the triazole product, 6, was confirmed by NMR spectroscopic technique, where sharp singlets appears at δ 7.98 ppm which corresponds to the triazole proton and a peak at δ 10.31 ppm corresponds to the aldehyde proton. The ^{13}C NMR spectrum of compound 6, exhibited characteristic signals at δ 143.62 and 120.68 and 185.87 ppm, which were assigned to the C4 and C5 carbon atoms of the triazole ring, and aldehyde carbon, respectively. In addition, the molecular structure of compound, 6 is confirmed based on HRMS spectrum [m/z calculated-604.23751 and found-604.27704].

3,3'-Disulfanediyl-di-(propanehydrazide) 3, reacts with a sugar-triazole derivative bearing an aldehyde using ethanol as solvent gives the expected sugar-imine product, 7. The structure of the resulting sugar-imine derivative was characterized using FTIR, HRMS, ^{1}H and ^{13}C NMR spectral techniques. Formation of the imine core in compound, 7 was confirmed from the appearance of a peak at 1682 cm^{-1} in FTIR spectrum. The ^{1}H NMR spectrum of compound,7 shows a sharp singlet at δ 8.97 and 9.15 ppm, which is attributed to the imine proton, and the product formation was further confirmed from ^{13}CNMRspectrum by the appearance of a peak at δ 145 ppm which corresponds to the imine carbon. Moreover, HRMS analysis of the compound, 7 further confirms the structure.

Conclusions

In conclusion, the present precursor for sugar-based chemosensor, 7 was designed and synthesized by the 1, 3 dipolar cycloaddition of substituted alkyne and sugar azide. The disulfide appended sugar bis-triazole derivative consists of disulfide, amide, and sugar moieties, which can exhibit non-covalent interaction with a heavy metal ion such as mercury. The molecular structure of the standing materials and final sugar derivatives was confirmed using different

spectral techniques like ^{1}H & ^{13}C NMR, FTIR, and HRMS. Further studies of the sugar-based bis-triazole appended disulfide derivative as a fluorescent chemosensor to detect different transition metals especially mercury ions are in progress.

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Conflict of interest

The authors declare no conflict of interests in this study.

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