Research Article

Synthesis, Characterization And Antioxidant Activity Of 1,2,3- Triazole Derivatives From 1,2,:5,6-Di-O-Isopropylidene-D-Mannitol

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ABSTRACT

In this study, we synthesis of novel 1,2,3-triazole derivatives (HP_1 and HP_2) via the highly stable $CuSO_4{\cdot}5H_2O$-catalyzed Huisgen 1,3-dipolar cycloaddition reaction "click chemistry" between azides derived from sulfadiazine (BN_3 and BCN_3) in combination with a mannitol-based alkyne derivative (AP). Afterwards, the release of both acid-labile cis-acetal groups by dilute acetic acid led to corresponding deprotected derivatives DP_1 and DP_2.

FT-IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and thin-layer chromatography (TLC) were used to confirm the structures of all synthesized compounds. The antioxidant activities of the prepared compounds were screened in vitro using DPPH radical scavenging assay. Results: Compounds HP1 and HP2 exhibited strong antioxidant activity with IC_{50} values of below 10 µg/mL, furthermore; at its kinetic level indeed had more stability than compound (HP_1)Therefore, these results indicate that the incorporated structural modifications increased its capacity to donate electrons in comparison with what was observed for other synthesized derivatives and also paves new avenues toward realizing their potential pharmaceutical or biomedical applications.

Keywords:1,2,3-triazoles,1,2:5,6-Di-O-isopropylidene-D-mannitol,azide Sulfadiazine derivatives , Click chemistry, 1,3-dipolar cycloaddition.

INTRODUCTION

Triazoles are a class of five-membered nitrogen-containing heterocyclic compounds, which consists of three nitrogen atoms in 1,2,3-triazole and/or such as 1[2]-azolidin-4-one ring system part[20]. Due to their wide range of pharmacological activities such as anticancer [2], antibacterial [3], anti-HIV [4] antidiabetic, antimicrobial (6), anti-inflammatory and antidepressant activity, these heterocyclic frameworks are the focus of considerable interest in medicinal chemistry.

Besides their therapeutic relevance, triazole derivatives have also been thoroughly studied for their antioxidant capacity based on the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay [8] DPPH free radical has a dark violet color with an absorption maximum at 517 nm [9]. The radical is reduced when it interacts with antioxidant compounds resulting in a bathochromic shift from violet to pale yellow which can be assessed at sight and spectrophotometrically [10,11]. This way gives a good path to estimate the free radicals scavenging perform of these recently prepared molecules.

In the current study, new triazole derivatives are described prepared via reactions with newly synthesized D-mannitol-based derivatives and azides derived from sulfadiazines to develop different chemical structure / possible biological activity relationships [12].

MATERIAL AND METHODS

Chemicals

All the chemicals were Merck-group- BDH and Fluke –German from in Sialkot used in this study.

Laboratory devices

All measurements were carried out by:FT.IR-spectra, Fourier transform infrared shimadzu (8300) , ^{1}H-NMR &^{13}C-NMR-spectra in (ppm)-unit were obtained in DMSO solution using (Bruker, Ultra Shield 300 MKZ Switzerland), melting points, electro thermal 9300 ,melting point engineering LTD, U.K.

SYNTHESIS METHODS

1- Synthesis method of (2R,3R,4R,5R)-1,2,5,6-tetramethoxy-3,4-bis(prop-2-yn-1-yloxy) hexane[AP][13].

A mixture of 1,2:5,6-Di-O-isopropylidene-D-mannitol (2mmol,(0.51g)), NaOH(8mmol,(0.32 g)) and Toluene (7mL) were cooled at (-15℃)using salting ice bath while dropwise addition of Propargyl bromide (2.1mmol). The mixture was stirred

at ambient temperature for 28 hr. by the addition of cold water (25 mL) and extraction with DCM (3x 50mL). The organic layers were dried over anhydrous sodium sulfate (Na_2SO_4) and evaporated down under reduced pressure using a rotary evaporator, and purified by column chromatography (ethyl acetate: Cyclohexane 4:1).

Chemical Formula [Ap]: $C_{16}H_{26}O_6$; Yield=70 %, brawn wax, Molecular Weight: 314.38, R_f =0.48 (1:1ethyl acetate:n-hexane), time of reaction: 28 hrs.

2-General procedure of synthesis of 4-amino-N- (pyrimidin-2-yl)-3-(p- tolyldiazenyl) benzenesulfonamide [B] [14].

P-Toluidine (1.06gm,0.1mole)was dissolved in(4ml)of concentrated hydrochloric acid and (20ml) of distilled water. The mixture was cooled at ($0C^0$) in ice-water bath .A solution of sodium nitrite (0.68gm,0.1 mole) dissolved in (6ml) of distilled water .There was added a dropwise to the mixture with stirring. In the other beaker Sulfadiazine (2.5gm,0.1mole) dissolved in (2gm) of sodium hydroxide and (20ml) of distilled water and place this beaker in ice-water bath at ($0C^0$).The cold diazonium chloride was added to the coupling agent in small portions and stirred after each addition, A completing the addition, the reaction mixture was stirred at ($0C^0$) for (15)minutes .The brawn product was precipitated and filtered recrystallized from ethanol to give compound[B].

Chemical Formula[B]: $C_{17}H_{16}N_6O_2S$, Molecular Weight :368g \mol, yield 78% , m.p.258 C, Brawn ppt., and Rf= 0.74(toluene:ethanol,7:3)**.**

3-General procedure of synthesis of N-(2-((4-(azidomethyl) phenyl)diazenyl)-4-(N-(pyrimidin-yl) sulfamoyl) phenyl) acetamide [BN_3][15].

Compound [B] (6 g, 16.9 mmol) miscible in distilled water and hydrochloric acid (1:2.5 mL). A salt–ice bath was so prepared to cool the solution down to 0 °C. A solution of sodium nitrite (1.171 g, 16.9 mmol) in water was prepared separately and cooled to 0 °C this aqueous sodium nitrite solution is added dropwise into sulfadiazine with constant stirring. Following additional consecutive additions, the color of the reacting mixture slowly changed to orange. The reaction was then stirred for 45 min at 0 °C after the complete addition.

An aqueous solution of sodium azide(2 equiv; 2.207 g) is made and it was added to the reaction mixture dropwise later on time. Gas bubbles evolved through the addition process. The reaction mixture was stirred for an additional 2 h following complete addition, and the precipitate obtained by filtration with subsequent washing several times with distilled water.

Chemical Formula [BN_3]: $C_{19}H_{17}N_9O_3S$;Molecular Weight: 368.42 Yield=80%,Orang ppt.,m.p. = (163-165),R_f = 0.2(ethyl acetate:Cyclohexane, 4:1).

4- Synthesis of 2-chloro-N-(4-(N-(pyrimidin-2-yl)sulfamoyl)-2-(p-tolyldiazenyl)phenyl)acetamide [BC] [16].

Compound [B] (10 mmol, 3.35g) K_2CO_3(15mmol, 2 g) was dissolved in DMSO(100mL) and cooled down to ice bath at first then chloroacetylchloride (15mmol,1.7mL)was added dropwise into the active stirrer of above mixture After all followed by allowing it to warm up back to room temperature for additional 40 hrs while monitoring reaction progress using TLC with eluent [(ethyl acetate: Cyclohexane =4 :1)]. Reaction mixture was performed and then added cold D.W, extracted with dichloromethane (20 mL 3 times), dried by anhydrous sodium sulfate (Na_2SO_4)-filtration- Concentrated rotary evaporator.

Chemical Formula [BC]: $C_{19}H_{17}ClN_6O_3S$;Molecular weight:444.89g/mol, Yield=70%, Orange ppt. ,m.p.=(129-131). R_f = 0.48 (ethyl acetate: Cyclohexane 4:1).

5- Synthesis method of 2-azido-N-(4-(N-(pyrimidin-2-yl)sulfamoyl)-2-(p-tolyldiazenyl)phenyl)acetamide[BCN_3][17].

To a stirred solution of BC (22.11 mmol, 9.8g) and sodium azide(18 mmol,1.17g)dissolved in dimethyl sulfoxide(DMSO)(15 mL).This mixture was monitored by TLC [dichloromethane : n-hexane 2:3] during last stepat room temperature for73hr. Following these reaction regulations it was subjected to adding cold D.W., extraction, drying by anhydrous sodium sulfate (Na_2SO_4), filtering and concentration via rotary evaporator.

Chemical Formula [BCN_3]: $C_{19}H_{17}N_9O_3S$;Molecular weight:451.47g/mol ,Yield=83%, orange ppt.,m.p. = (124-126) ℃. R_f =0.25 (1:1 ethyl acetate:n-hexane).

6- Synthesis method of 1,2,3-triazole derivatives [HP_1-HP_2][18].

Sodium ascorbate (0.0396 g, 0.2 mmol) and $CuSO_4 \cdot 5H_2O$ (0.025 g, 0.01mol) was added to propargylic ether [AP] (10mL DMSO) in a round bottom flask Followed by addition of azide derivatives (BN_3 and BCN_3)(0.01mol) solution in DMSO (30 mL), the mixture was stirred at 60 °C for 37-130 hrs Controlled reaction using TLC (coursed until 1:4 ethyl acetate: cyclohexane). Dissolved in H2O (30mL), extracted with EtOAc 3×(30 mL); combined organic layers washed with saturated NaCl, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was flash chromatographed (silica gel, n-hexane / EtOAc; 2:1 → 1:2,) to afford the bis-1,2,3-triazole.

Chemical Formula[HP_1]: $C_{50}H_{54}N_{16}O_{10}S_2$,MolecularWeight:1103.20 ,Yield=60 %, Brawn ppt., m.p. =(157-159), R_f=0.48 (4:1 ethyl acetate: cyclohexane), time of reaction= 130hrs.

Chemical Formula [HP_2]: $C_{54}H_{60}N_{18}O_{12}S_2$, Molecular Weight: 1217.31, Yield=62%, Brawn ppt.,m.p.= (119-121)°C, R_f =0.32 (3:1 ethyl acetate: n-hexane), time of reaction= 37 hrs

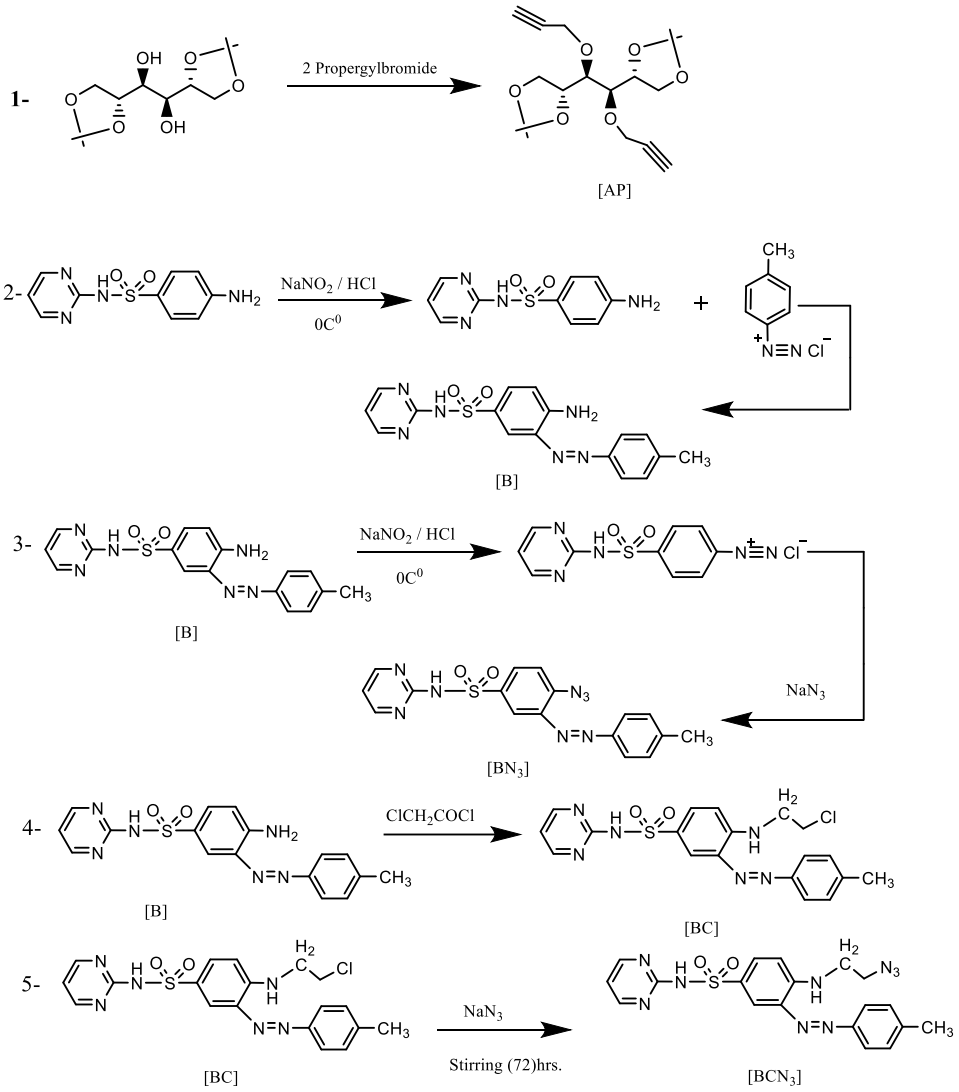
7-General procedure for de-isopropelidine of compounds [$DP_1$and DP_2][19].

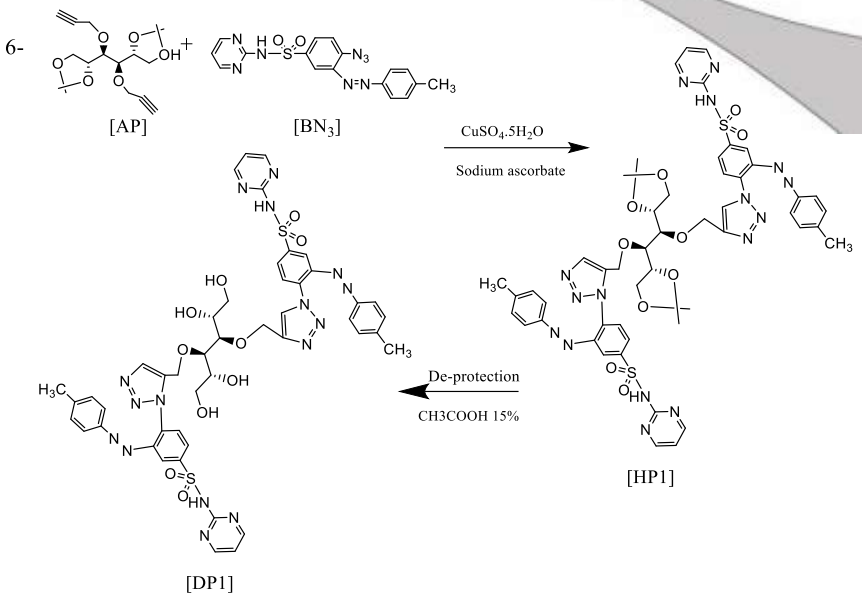
(0.01 mol) [$HP_1$and HP_2] dissolved in (30 mL) dilute acetic acid (15%), stirred until disappearance of starting material from TLC after (13-16 hrs.), added cold D.W.,extracted, organic layer dried over Na_2SO_4,and reduced in vacuum.

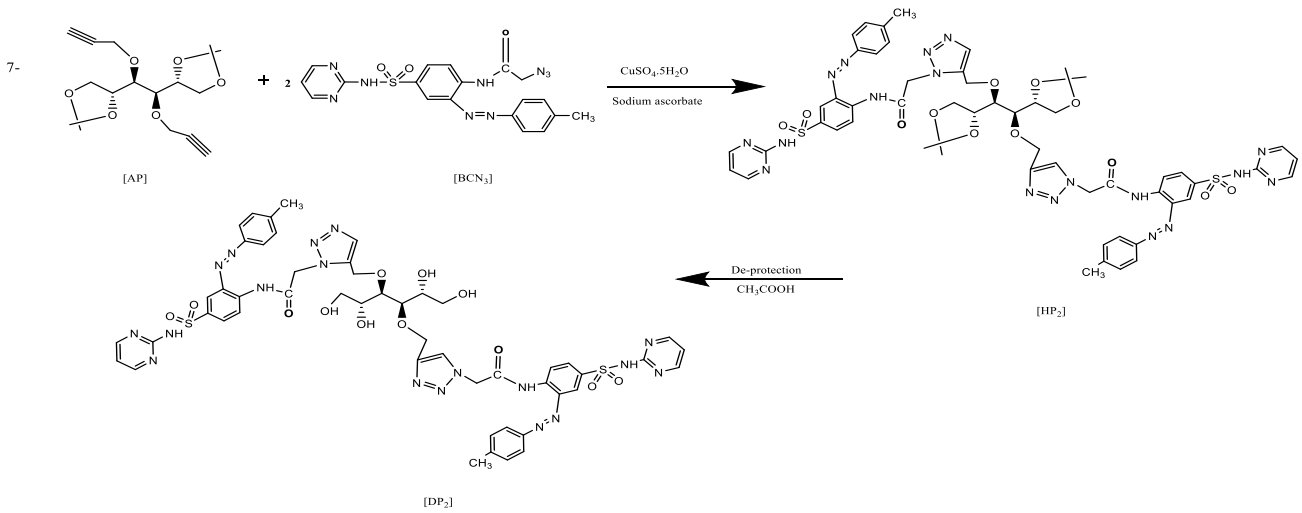
Chemical Formula[DP_1]: $C_{46}H_{46}N_{16}O_{10}S_2$**,** Molecular Weight: 1047.10 ,Yield=70 %, yellow ppt., m.p. = (142dec) , time of reaction= 13 hrs.

Chemical Formula [DP_2]:$C_{50}H_{52}N_{18}O_{12}S_2$MolecularWeight: 1161.20,Yield=70%,yellow ppt.,m.p.=(88dec)°C,time of reaction=16 hrs.

Scheme of reaction:







8-Antioxidant assay:

8.1-Preparation of DPPH (3mg/100mL) solution[20]:

30mg of DPPH dissolve in (1000 mL) beaker with 200mL of methanol. The volume was completed to the mark (1000 mL) with same solvent after transferred the solution to (1000 mL) volumetric flask.

8.2- Preparation stock solution (75 µg/mL) of Sample solution:

75 µ/mL of compounds (HP_1 and HP_2) prepared by dissolve 75 mg in a (1000 mL) beaker with 200mL of methanol. The volume was completed to the mark (1000 mL) with same solvent after transferred the solution to (1000 mL) volumetric flask.

8.3- Preparation (50 µg/mL) of Sample solution:

Transferred a (6.667 mL) stock solution to a (10 mL) volumetric flask and complete the volume by methanol to the mark.

8.4- Preparation (25 µg/mL) of Sample solution:

Transferred a (3.333 mL) stock solution to a (10 mL) volumetric flask and complete the volume by methanol to the mark.

8.5 -Determination of inhibition:

Mixing equal amount of sample solution (50 µg/mL) and DPPH solution tested intervals of 5, 10, and 15 min, the absorbance measured at λ_{max}=517 nm. The % inhibition was calculated by apply equation (1).

$$\%\ inhibition\ of\ activity\ of\ DPPH = \frac{A-B}{A} * X\ 100 \ldots\ldots \text{ equation (1)}$$

Where A is the control (DPPH and methanol) absorbed density and B is the sample absorbed density.

8.6 -Inhibitory Concentration Value 50% (IC_{50}) [21]:

After mixing equal amount of sample solution 25 µg/mL and DPPH solution, the absorbance measured at λ_{max}=517 nm and repeat same procedure with 50 and 75 µg/mL. The % inhibition was calculated by apply equation (2). The sample concentration draw in x-axis and the percentage of inhibition on y-axis. From the equation y=bx-a the value of IC_{50} calculated by using equation (2).

$IC50 = \frac{50-a}{b}$…….. Equation (2)

Where **a** = Intercept

b = Slope

RESULTS AND DISCUSSION

Compound [AP]:

The FTIR spectrum figure (1) show the appearance of new bands at (3286) cm^{-1} for terminal alkyne-carbon-hydrogen (≡CH), a new band at (2119) cm^{-1} for alkyne carbon-carbon (C≡C), a band at(2987,2850)$cm^{-1}$for$\upsilon(CH)_{aliph.}$,and(C-O-C)at(1058)cm^{-1}

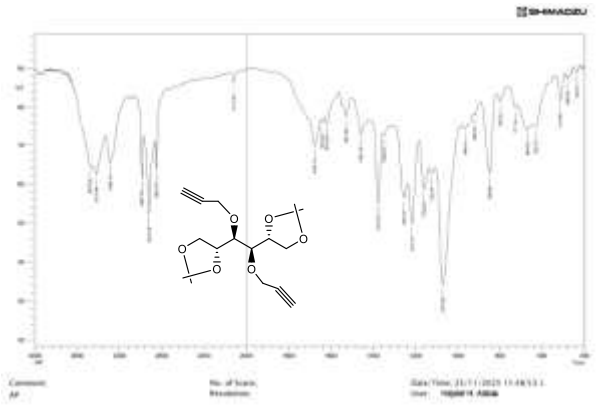
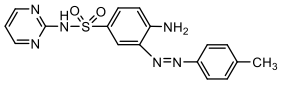


Figure (1): FTIR spectrum of compound [AP]

Compound [B]: The FT-IR spectrum was followed in figure(2) it showed appearance of two absorption band ,of the asymmetric and symmetric stretching vibration of (NH_2) group of sulfadiazine and spectra of these compounds showed the disappearance of two absorption band ,of the asymmetric and symmetric stretching vibration of (NH_2) group of (P-Toluidine) the absorption band (1489) cm^{-1} was due to (N=N) stretching band of azo group, ($NH_{2\ amine\ sulfonamide}$) 3418, (υ $N\text{-}H_{pyrimidine}$)3252, (υ $C{=}N_{pyrimidine}$) 1647, (υ $C{=}C_{aromatic}$) 3348, (υ C-N)1256 , (υ $N{=}N_{azo\ group}$) 1435, (υ C-S) 808, (υ $SO_{2asy\&sy}$) 1317,1145, (υ $CH_{3\ methyl\ group}$) 2933-2864.All of these absorption bands are another good evidence to formation our azo dyes compound [B]



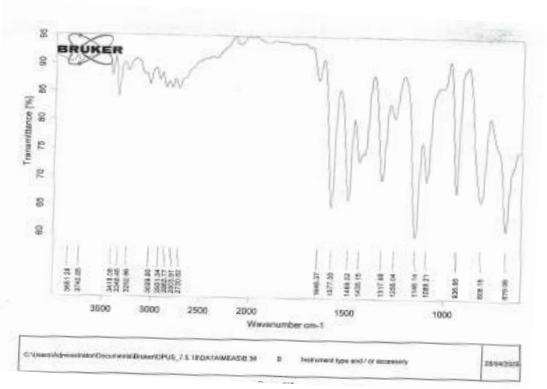


Figure (2): FTIR spectrum of compound [B]

Compound [BN_3]: Synthesis of new azido sulfa drugs (BN_3) synthesis by reaction [B] with sodium nitrate $NaNO_2$ and HCl in (0-5 ℃) to prepare diazonium salt after that the addition of sodium azide (NaN_3) at same temperature leads to synthesized new azide derivative and identified by disappearance of primary amine in [B] at 3358 cm^{-1} and appearance of special peak at 2119 cm^{-1} ,υ(NH) 3356 , $\upsilon(CH)_{aliph}$ 2941,2872,υ(C-H)Ar.3036,$\upsilon(SO_{2\mathbf{asy}\&sy.})$1330,1153,(υC-N)1253,(υN=N)1438,(υ C-S)679.and other peak as shown in figure(3).

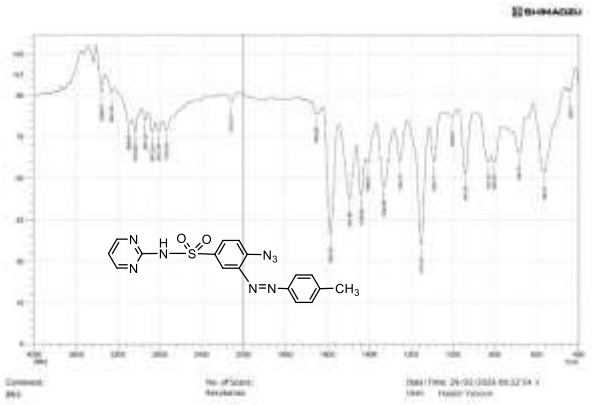


Figure (3): FTIR spectrum of compound [BN_3].

Compound [BC]: New amide according to S_N2 mechanism of reaction of [B] with cloroacetyl chloride to synthesis [BC].The FTIR spectrum shows the disappearance of primary amine at 3358 cm^{-1} for starting material [B] and the appearance of new peaks for the carbonyl amide group (υC=O) 1750 cm^{-1}, (υNH) 3366 cm^{-1}, (υCHAr.) 3031 cm^{-1},(υ$CH_{alph.}$)2947-2867 cm^{-1},(υC-Cl)677$cm^{-1}$and other peak as shown in figure (4).

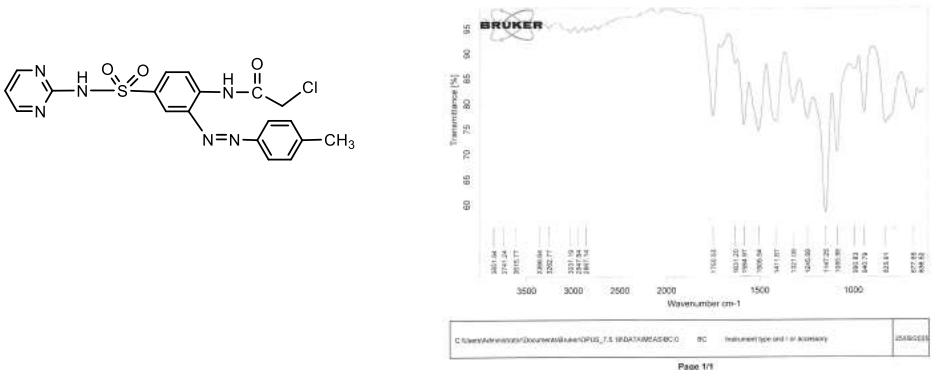


Figure (4): FTIR spectrum of compound [BC].

Compound [BCN_3]: Synthesis of new azido sulfa drug [BCN_3]according to S_N2 mechanism chloride in[BC] substituted by azido group (by using NaN_3 in DMSO) to synthesized new azide derivative and identified by disappearance C-Cl band at 677 cm^{-1} in [BC] and appearance of new band in 2112 cm^{-1} for new azide group ,and other peak (υNH)3375,(υ$CH_{Ar.}$)3034,(υ$CH_{alph.}$)2924,2852,(υC=O) 1757,(υC=C $_{aromatic}$)1589,(υ$SO_{2\ asy\&sy}$)1311,1155 (υC-N)1251,(υ N=N)1514,(υC-S) 698.as shown in FTIR spectrum in figure (5).

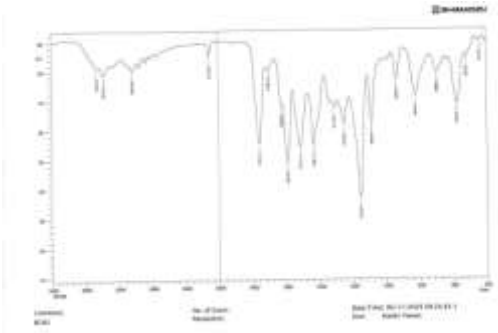


Figure (5): FTIR spectrum of compound [BCN_3].

Compound [HP_1 and HP_2]are identified by the disappearance of peak at 2108-2112 cm^{-1} for the azido group and 2119 cm^{-1} for propargylic derivative for starting materials and new peaks appearance as shown in FTIR spectrum figures(6and7) for the synthesis of [HP_1 and HP_2] and table (1).

Table(1): FTIR spectrum data of compounds [HP_1 and HP_2]

Comp.	υ$(CH)_{ar.}$	υ$(CH)_{aliph}$	υ(C=C)	υ(NH)	υ(C-O-C)	υ(C=O)
HP_1	3028	2922-2868	1591	3275	1089	1662
HP_2	3028	2941-2872	1593	3414	1251	1658

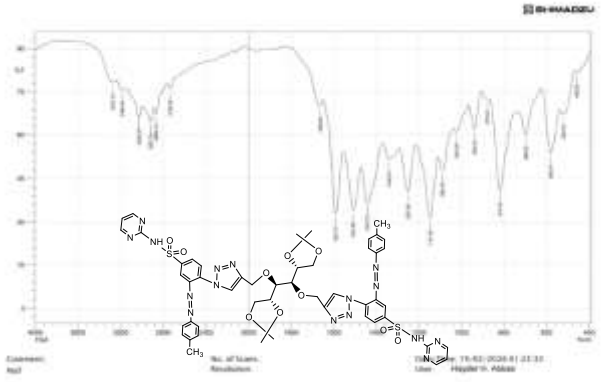


Figure (6): FTIR spectrum of compound [HP_1].

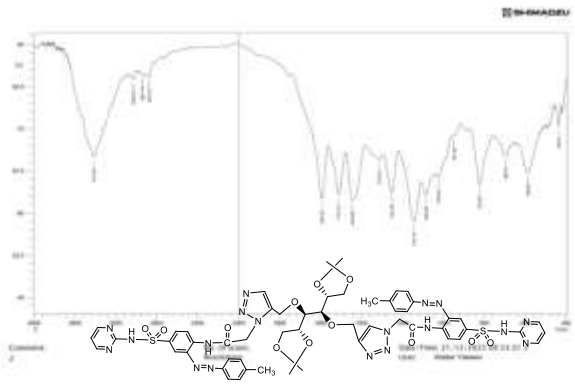
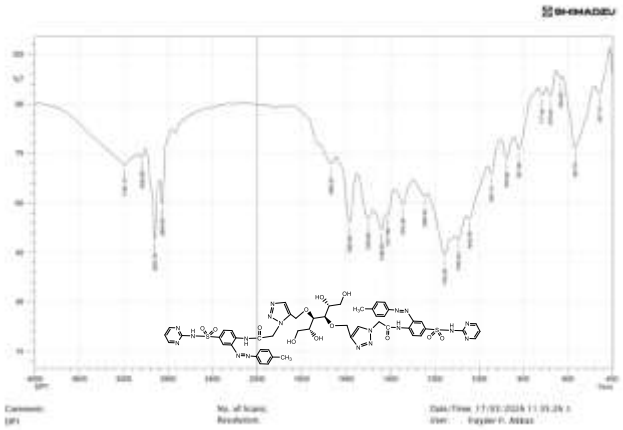


Figure (7): FTIR spectrum of compound [HP_2].

Compound [DP_1 and DP_2]: General de-protection of compounds Compound [HP_1 and HP_2]by using dilute acetic acid and shown in new peaks appearance as shown in FTIR spectrum figures (8-9) for the synthesis of [HP_1 and HP_2] and table (2).

Table(2): FTIR spectrum data of compounds [DP_1 and DP_2]

Comp.	**υ$(CH)_{ar.}$**	**υ$(CH)_{aliph}$**	**υ(C=C)**	**υ(C=O)**	**υ(OH) υ(NH)**
DP_1	3035	2922-2854	1583	1666	3194
DP_2	3032	2924 2858	1587	-------	3201



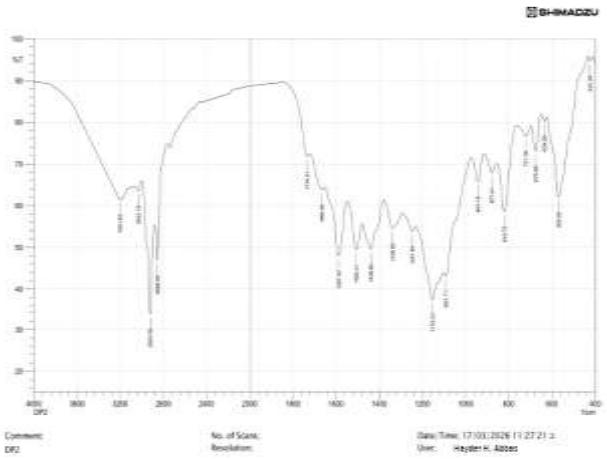
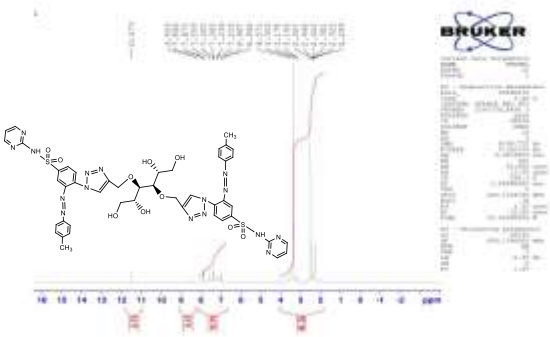


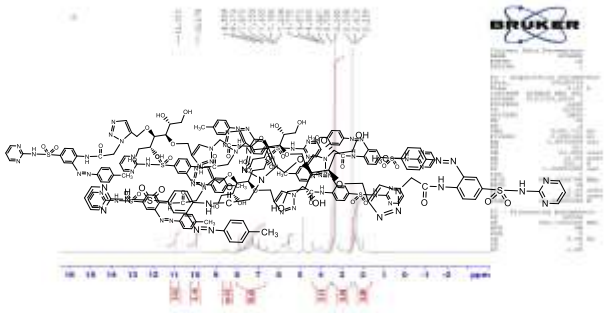
Figure (8): FTIR spectrum of compound [DP_1]. **Figure (9):** FTIR spectrum of compound [DP_2].

^{1}H-NMR (400 MHz, DMSO-d_6)[DP_1] δppm : 11.57 (-SO_2-NH), 6.94-7.89(-CH-Ar), 8.55 ($CH_{triazole}$), 4.57 (triazole−CH_2−O),3.35(-CH_2O), 3.17(sugar backbone protons(CH,CH_2) 4.57(OH),2.32 (CH_3),
^{1}HNMR (400 MHz, DMSO-d_6)[DP_2] δppm : 7.23 (-$CH_{triazole}$), 7.55-8.55(-CH-Ar), 4.35 (triazole−CH_2−O), 3.70 (-CH_2O) , 3.36 (CH-O-triazole), 2.41 (-CH_3),11.10 (-SO_2-NH),3.96(-OH sugar). figures (10-11) show the ^{1}HNMR spectrum of this derivatives.

Figure (10): ^{1}HNMRspectrum of compound [DP_1].

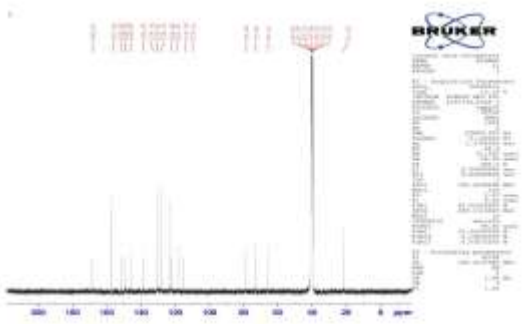


Figure(11): ^{1}HNMR spectrum of compound [DP_2].



^{13}C-NMR (400 MHz, DMSO-d6) [Dp_1] δppm:157.32(-C=N $_{pyrmidine}$),116.16 (Ar-C), 146.09 (Triazole carbons) , 21.61 (CH_3),78.49(CH-O sugar) , 72.88 (sugar carbons), 152.25 (C-OH).

^{13}C-NMR (400 MHz, DMSO-d6) [Dp_2] ppm: 156.15 (CO $_{amide}$) , 130.65 ($CH_{triazole}$),116.16-139.58 (CH-Ar), 159.55-78.49(CH-O), 71,68-78.49 (CH-OH),71.68(CH_2-N), 56.16(CH_2 aliphatic), 21.69(CH_3) . figures (12-13) show the ^{13}C-NMR spectrum of this derivatives.



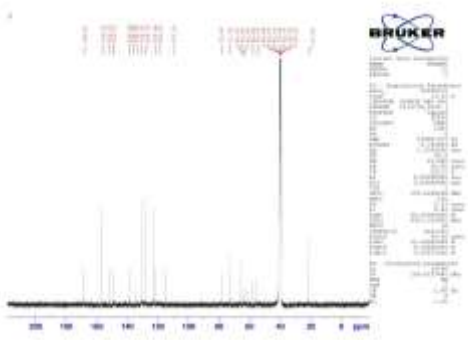


Figure (12):^{13}C-NMR spectrum of compound [DP_1]. Figure (13):^{13}C-NMR spectrum of compound [DP_2].

Antioxidant activates

1- Anti-Oxidant activates

The compound HP_1 (at50µg/mL) exhibited the highest scavenging percentages after 5 and 10 minutes compared to other concentrations and compound. However, HP_1 maintained a relatively stable and superior antioxidant activity throughout the incubation periods. On the other hand, the results showed that HP_2 (at25µg/mL) reached its peak scavenging activity at 15 minutes, showing a slight increase in inhibition over time. Overall ,the synthesized triazole derivatives showed significant antioxidant potential, with HP_1 being the most effective at the higher concentration. Table (3)showed Absorbance and Inhibition % of (HP_1-HP_2) at 5, 10, and 15 min

Table (3): Absorbance and Inhibition % of (HP_1-HP_2) at 5, 10, and 15 min

Control Absorbance =1.119 λ = 517 nm							
Compounds		After 5 min		After 10 min		After 15 min	
		Sample	% Inhibition	Sample Abs.	% Inhibition	Sample Abs.	% Inhibition
HP_1	50µg/mL	0.278	75.1563	0.279	75.0770	0.281	74.8882
	25µg/mL	0.289	74.1733	0.290	74.0840	0.291	73.9946
HP_2	50µg/mL	0.303	72.9222	0.304	72.8328	0.306	72.6541
	25µg/mL	0.288	74.2627	0.287	74.3521	0.286	74.4414

The synthesized triazole derivatives demonstrated potent antioxidant properties. HP_1 (at 50 µg/mL) exhibited the highest scavenging activity, exceeding 75% inhibition with stable kinetics across all incubation periods, indicating a rapid reaction with radicals. A dose-dependent relationship was observed for HP_1, as inhibition decreased at the lower concentration (25 µg/mL).

Conversely, the antioxidant capacity of HP_2 was remarkably stable reaching approximately 74% at 25 µg/mL with a slight increase after an incubation time of 15 minutes indicating remaining activity. HP_1 was overall the strongest derivative at highest concentration tested. Figure(14)The Standard Calibration Curve of (HP_1 and HP_2).

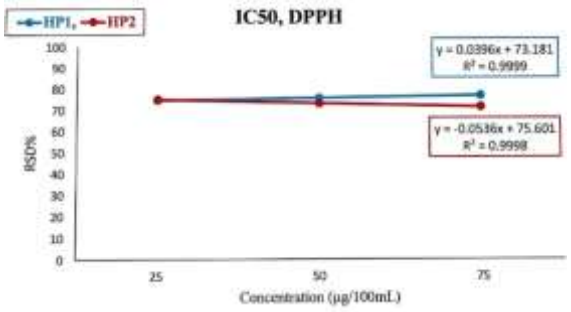


Figure (14): The Standard Calibration Curve of (HP_1 and HP_2)

2- Inhibitory Concentration Value 50% (IC_{50})

Apparently, the synthesized derivatives showed better antioxidant efficacy than Ascorbic acid and this is proven by their lower IC_{50} values. According to the standard classification of antioxidants, HP_1 and HP_2 are classified as "Very Active" antioxidants(IC_{50}<10 µg/mL), indicating their very high efficiency in removing free radicals. Linear Regression and IC_{50} Values of Different Purities (HP_1, HP_2) Derivatives-Hydrazoic.

Table (4): Linear regression and IC_{50} value of (HP_1 and HP_2) and ascorbic acid

Compounds	Linear Regression Equation	IC_{50} (µg/mL)
HP_1	Y =0.0396x + 73.181 R^2 = 0.9999	0.231
HP_2	y = -0.1654x + 75.601 R^2 = 0.9433	0.174
Ascorbic acid	y = 0.1654x + 48.122 R^2 = 0.9885	4.215

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