SYNTHESIS OF SOME NEW THEOPHYLLINE DERIVATIVES USING CLICK CHEMISTRY AND STUDY OF BIOLOGICAL ACTIVITY

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Abstract: *In this study, the authors chemically synthesized new theophylline derivatives and then evaluated them in vitro as antimicrobial agents. The target derivatives, theophylline derivatives conjugated with 1,2,3-triazole and piperazine moieties, were synthesized via sequential various reactions. Spectroscopically, the researchers employed FT-IR, ^{1}H NMR, and ^{13}C NMR techniques to get further insights into these derivatives; they also used the CHN technique to facilitate their structure identification. In addition, the authors conducted tests in vitro to evaluate the antibacterial activity of all the synthesized derivatives against E. coli and S. aureus. The study results obtained showed encouraging antibacterial efficacy.*
Keywords: *click reaction, antibacterial agent, theophylline, triazole derivatives.*
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Introduction

Copper-catalyzed alkyne-azide cycloaddition (CuAAC) reactions are known as "click" chemistry reactions, where they produce 1,2,3-triazoles. Click reactions' high reaction yield, broad substrate range, and ease of purification make them one of the most advantageous catalytic processes for the synthesis of 1,2,3-triazoles [1-4]. Simple copper salts such as CuI, $Cu(AcO)_2$, and CuSO4 are preferred as catalysts in the bulk of published protocols for these reactions [5-10]. For more than 80 years, methylxanthines, in particular theophylline, have been known to be effective bronchodilators for the treatment of acute asthma [11]. Theophylline (Fig. 1A), referred to as 1,3-dimethylxanthine, belongs to the purine class; it is a well-established bronchodilator medication that has been used to treat respiratory diseases like asthma and chronic pulmonary obstructive disease (COPD) [12-14]. Adenosine receptor antagonism is one of theophylline's modes of action [15]. Cyclic AMP and cyclic GMP intracellular concentrations rise as a result of theophylline's poor and non-selective inhibition of phosphodiesterases (PDEs) of cyclic nucleotides [16]. The drug's strong antagonistic action at adenosine receptors is its other well-documented pharmacological function [17]. Additionally, theophylline has been demonstrated to increase the release of interleukin-10 (likely through the inhibition of PDE), antagonize tumor necrosis factor alpha, inhibit the pro-inflammatory effects of prostaglandins, decrease intracellular calcium ion release, prevent nuclear factor-κB from translocating into the nucleus (which may lower the expression of inflammatory genes), stimulate apoptosis, and increase histone deacetylase activity [18-20]. In addition, theophylline and some of its derivatives (Fig. 1) are important heterocyclic scaffolds for the development of effective pharmacological treatments, including antimicrobial [21], antiviral (for HCV and COVID-19) [22, 23], antituberculosis properties [24], anti-cancer [25], and anti-inflammatory effects [26]. In the present study, we synthesize new derivatives of 1,2,3-triazole in addition to their biological activity evaluation.

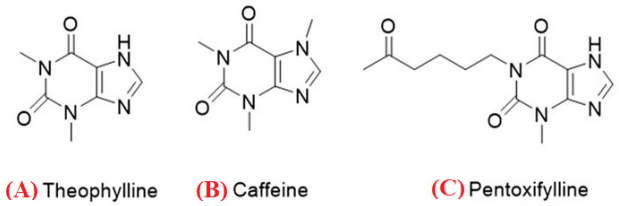


Fig. 1. Theophylline and some of its derivatives

Experimental part

Chemicals and Analytical Devices. The materials were provided by Sigma-Aldrich (USA), BDH (United Kingdom), and Merck (Germany). The measurement was obtained using a melting-point thermometer. A thin-layer chromatography (TLC) technique was employed to monitor the progress of the reaction using a 9:1 mixture of benzene and methanol as the eluent. After completion, the solvent had completely evaporated. The purification of the products was carried out using column chromatography. The column had a diameter of 2 cm and a length of 50 cm. Silica gel with a mesh size of 60-120 was used as the stationary phase. Different eluents were employed based on the separation observed on thin-layer chromatography (TLC). The spectra were obtained using a Shimadzu FT-IR (8300) spectrophotometer equipped with KBr discs in the range of 4000-400 cm^{-1}. The ^{13}C NMR and ^{1}H NMR spectra were obtained using a Bruker (400 MHz) NMR spectrophotometer in DMSO-d6. The chemical shifts were determined in parts per million (ppm) with respect to Tetramethylsilane (TMS).

Synthesis [27]. ***General procedure for Synthesis of azidic derivatives 2a and 2b.***

One of the aniline compounds (15 mmol), (8-amino theophylline **2a**, 4-nitroaniline **2b**) was individually dissolved in 30 ml of a solution containing 10% hydrochloric acid (HCl). The solution was then cooled in an ice bath to 0 C°, then 16.33 mmol of sodium nitrite ($NaNO_2$) dissolved in 5 ml ща distilled water was added. The mixture was stirred for an hour at 0 degrees Celsius. Then 20 mmol of sodium azide dissolved in 5 ml of distilled water was added. The reaction mixture was stirred for one to two hours and then checked by TLC to detect the completion of the reaction. After completion of the reaction, a solution was treated with 5%NaOH and then extracted with chloroform (3 × 15 ml). Next, the organic liquid obtained was dried with anhydrous magnesium sulfate ($MgSO_4$) and then concentrated into a solid by a vacuum device. The resulting compounds were purified on a short column of SiO_2 using methanol–chloroform as eluent.

Com. 2a: Yield 83% , mp.62-64ºC. IR, ν, cm^{-1}: 3414 (NH), 2951, 2850 (C-H), 2136 (N_3), 1697,1674 (C=O), 1570, 1527 (C=C).^{1}H NMR (DMSO-*d6*, ppm) δ: 6.60 s (1H, N-H), 5.83 s (1H, C_8-H), 4.62 s (1H, C_4-H), 3.20 s (3H, C_{10}-H), 2.78 s (3H, C_{11}-H). ^{13}C NMR (DMSO-*d6*, ppm) δ: 167.68 C-6, 159.63 C-3, 151.65 C-1, 79.66 C-8, 53.97 C-4, 36.38 C-11, 28.08 C-10. Anal. calc. for $C_7H_9N_7O_2$ (223.20 g/mol) : C, 37.67; H, 4.06; N, 43.93 Found: C, 36.03; H, 3.92; N, 43.25.

Com. 2b: Yield 81%; m.p. 67-69ºC. IR, ν, cm^{-1}: 3070 (C-H), 2120 (N_3), 1593 (C=C), 1516, 1346 (N-O). ^{1}H NMR (DMSO-*d6*, ppm) δ: 8.23 d (*J* = 8.6 Hz, 2H, C(3+5)-H), 7.33 d (*J* = 8.7 Hz, 2H, C(2+6)-H).^{13}C NMR (DMSO-*d6*, ppm) δ: 147.13 C-4, 144.48 C-1, 125.98 C-(3+5), 120.51 C-(2+6). Analytical calculation for $C_6H_4N_4O_2$ (164.12 g/mol): C, 43.91; H, 2.46; N, 34.14. Found: C, 44.92; H, 2.46; N, 33.53.

Synthesis of 7-(2-chloroacetyl)-1,3-dimethyl-3,4,5,7-tetrahydro-1H-purine-2,6-dione 4. In a round flask, theophylline 3 (2.77 mmol, 0.5 gm) was dissolved in 25 ml of DMF, and Et_3N (2.77 mmol) was added to the solution at 10ºC and stirred for 30 minutes. Chloroacetyl chloride with an equivalent amount of moles was added gradually and slowly to the solution and stirred for an hour at room temperature; after that, the mixture was stirred at 60 ºC and then followed by TLC. After completion of the reaction, a solution was treated with 5% NaOH and then extracted with chloroform. Next, the

organic layer was dried with anhydrous magnesium sulfate and then concentrated into a solid using a vacuum. The resulting compound was purified on a short column of SiO_2 using methanol–chloroform as eluent. Yield: 76%; m.p. 130-132 ºC. IR, ν, cm^{-1}: 2974 (C-H), 1705, 1666 (C=O), 1566 (C=N). ^{1}H NMR (DMSO-*d6*, ppm) δ: 8.81 s (1H, C_6-H), 6.71 s (1H, C_4-H), 5.76 s (1H, C_8-H), 3.86 s (2H, C_{13}-H), 3.35 s (3H C_{10}-H), 3.02 s (3H). ^{13}C NMR (DMSO-*d6*, ppm) δ: 168.60 C_{14}, 166.47 C_3, 154.86 C_1, 70.38 C_8, 55.76 C_4, 45.99 C_{13}, 34.56 C_{11}, 28.25 C_{10}. Analytical calculation for $C_9H_{11}ClN_4O_3$ (258.66 g/mol): C, 41.79; H, 4.29; N, 21.66. Found: C, 41.23; H, 4.16; N, 20.91.

Synthesis of 1,3-dimethyl-7-(2-(piperazin-1-yl)acetyl)-3,4,5,7-tetrahydro-1H-purine-2,6-dione 5. In a round flask, compound **4** (5 mmol) dissolved in 25 ml of DMF. Et_3N and piperazine are added to it with an equivalent amount of moles, and the mixture is stirred at 70 °C for a 3 hour (check by TLC). After completion of the reaction, a solution was treated with 5% NaOH and then extracted with chloroform. Next, the organic layer was dried with anhydrous magnesium sulfate ($MgSO_4$) and then concentrated into a solid using a vacuum. The resulting compound was purified on a short column of SiO_2 using methanol–chloroform as eluent. Yield: 72%; m.p. 185-187 ºC. IR, ν, cm^{-1}, 3200 (NH), 2978, 2850 (C-H), 1708, 1662 (C=O), 1566 (C=N). ^{1}H NMR (DMSO-*d6*, ppm) δ: 8.05 s (1H, C_6-H), 5.32 s (1H, C_4-H), 4.91 s (1H, C_8-H), 3.61 s (2H, C_{13}-H), 3.45 s (3H, C_{10}-H), 3.39 s (3H, C_{11}-H), 3.17 – 3.03 m (2H $C_{(15,16,18,19)}$-H), 2.54 s (1H, NH). ^{13}C NMR (DMSO-*d6*, ppm) δ: 161.70 C_{12}, 161.64 C_3, 154.88 C_1, 148.39 C_6, 82.60 C_8, 66.39 C_{13}, 55.79 C_4, 50.22 C_{15+19}, 45.96 C_{16}, 45.89 C_{18}, 34.67 C_{11}, 28.20 C_{10}. Analytical calculation for $C_{13}H_{20}N_6O_3$ (308.34 g/mol): C, 50.64; H, 6.54; N, 27.26. Found: C, 49.99; H, 6.17; N, 27.30.

Synthesis of 1,3-dimethyl-7-(2-(4-(prop-2-yn-1-yl)piperazin-1-yl)acetyl)-3,4,5,7-tetrahydro-1H-purine-2,6-dione 6. A mixture of compound **5** (5 mmol, 0.583 gm) with propargyl bromide (6 mmol, 1.111 gm) was dissolved in DMF (25 ml) and then stirred the reaction mixture for 16 h at 80 °C and monitored by thin layer chromatography (TLC). After the reaction was over, the mixture was cooled and then poured onto ice flakes. Then the organic layer was separated from the aqueous layer using chloroform; the excess solvent was removed by distillation under vacuum pressure to obtain a white precipitate after purification with absolute ethanol. Yield: 79%; m.p.169-171ºC. IR, ν, cm^{-1}, 3242 $(C\text{-}H)_{alkyne}$, 2978, 2850$(C\text{-}H)_{aliphatic}$, 2210 (C≡C), 1712, 1664 (C=O), 1566(C=N).^{1}H NMR (DMSO-*d6*, ppm) δ: 8.07-7.93 m (1H, C6-H), 5.18 s(1H, C4-H), 4.52 s (1H, C8-H), 3.64 d (*J* =4.8 Hz, 1H, C20-H), 3.42–3.35 m (5H, C(13+10)-H), 3.24 s (3H, C_{11}-H), 2.68 s (1H, C22-H), 2.47 t (*J* = 5.0 Hz, 4H), 2.41 t (*J* = 5.3 Hz, 4H).^{13}C NMR (DMSO-*d6*, ppm) δ: 161.73 C_{12}, 161.27 C_3, 154.86 C_1, 148.31 C_6, 83.94 C_{21}, 79.19 C_8, 72.34 C_{22}, 53.60 C_{13}, 53.51 C_4, 52.10 C $_{(15+19)}$, 50.91 C $_{(16+18)}$, 48.12 C_{20}, 36.30 C_{11}, 28.19 C_{10}. Analytical calculation for $C_6H_4N_4O_2$ (346.39 g/mol): C, 55.48; H, 6.40; N, 24.26. Found: C, 55.23; H, 6.27; N, 24.09.

General procedure synthesis of 1,2,3-triazole derivatives 7 and 8. A mixture of compound 6 (2 mmol) with one of the azide derivatives 2a or 2b (2 mmol) was dissolved in 15 ml of DMF. After half an hour, anhydrous copper sulfate (0.170 mmol) and sodium ascorbate (0.170 mmol) were added to the reaction mixture, and then it was refluxed at a temperature of 60°C for 8-10 hours. After the finish of the reaction (checked by TLC), the reaction mixture was cooled with ice, and the precipitate obtained was filtered and purified with absolute ethanol.

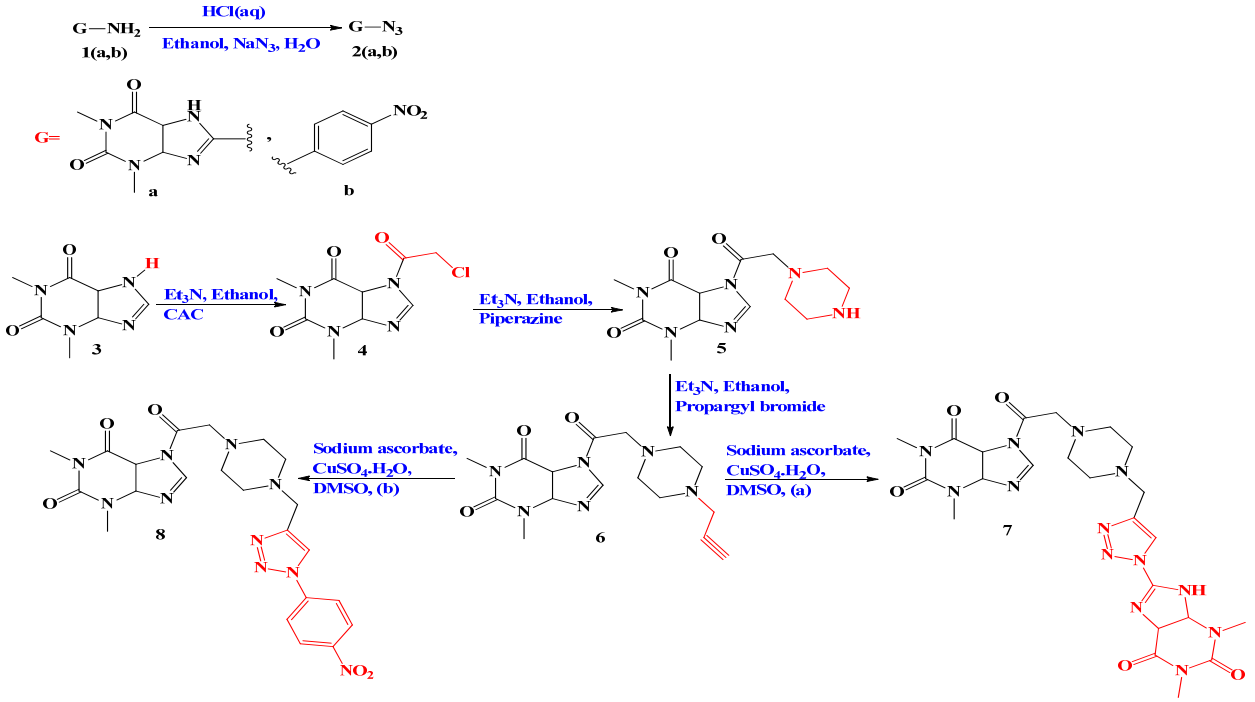
Com.7: Yield: 74%, mp.202-204ºC. IR, ν, cm^{-1}, 3396 (N-H), 2968, 2873 (C-H)ali., 1708, 1647 (C=O), 1570 (C=N), 1539(C=C), 1375 (C-N).^{1}H NMR (DMSO-*d6*, ppm) δ: 8.02 d (*J* = 29.6 Hz, 2H, $C_{(6+22)}$-H), 7.18 s (1H. NH), 6.12 s (1H, C_4-H), 5.40 s (2H, $C_{(28+8)}$-H), 4.10 (s, 1H, C_{29}-H), 3.74 (s, 2H, C_{20}-H), 3.40-3.37 m (8H, $C_{(13+35+10)}$-H), 3.23 s (3H, C_{11}-H), 2.95 s (3H, C_{34}-H), 2.44 m (4H, $C_{(15+19)}$-H), 2.37 m (4H $C_{(16+18)}$-H).^{13}C NMR (DMSO-*d6*, ppm) δ: 161.75 C_{12}, 161.68 C_{33}, 161.29 C_3, 155.02 C_{31}, 151.66 C_1, 148.67 C_6, 138.73 C-$_{26}$, 126.23 C_{21}, 123.37 C_{22}, 95.89 C_8, 70.82 C_{29}, 66.77 C_{28}, 57.16 C_4, 56.51 C_{20}, 54.65 C_{13}, 53.75 $C_{(15+19)}$, 53.00 C $_{(16+18)}$, 39.25 C_{11}, 30.19 C_{10}, 28.20 C_{34}, 27.95 C_{35}. Analytical calculation for $C_{23}H_{31}N_{13}O_5$ (569.59 g/mol): C, 48.50; H, 5.49; N, 31.97. Found: C, 47.88; H, 5.36; N, 31.76.

Com.8: Yield: 78, mp197-199ºC. IR, ν, cm^{-1}, 3078 (C-H), 2926, 2875 (C-H)ali., 1797, 1651 (C=O), 1599 (C=N), 1547 (C=C), 1504, 1396 (N-O), 1303 (C-N). ^{1}H NMR (DMSO-*d6*, ppm) δ: 8.38-7.42 m (6H, $C_{arom.}$-H), 5.80 s (1H, C4-H), 4.67 s (1H, C8-H), 3.71 s (1H, C20-H), 3.20 s (1H, C_{13}-H), 3.14-3.11 s (6H, $C_{(11+10)}$), 2.36 s (4H, C(16+18)-H), 2.01 s (4H, C(15+19)-H).^{13}C NMR (DMSO-*d6*, ppm) δ: 161.75 C_{12}, 161.67 C_{13}, 156.18 C_1, 150.17 C_6, 146.96 C_{29}, 142.19 C_{21}, 136.00 C_{26}, 126.85 C $_{(28+30)}$, 121.68 C_{22}, 119.83 $C_{(27+31)}$, 96.04 C_8, 58.11 C_{13}, 57.65 C_4, 55.15 $C_{(16+18)}$, 54.23 $C_{(15+19)}$, 45.95 C_{20}, 39.27 C_{11}, 28.12 C_{10}. Analytical calculation for $C_{22}H_{26}N_{10}O_5$ (569.59 g/mol): C, 51.76; H, 5.13; N, 27.44. Found: C, 51.12; H, 5.00; N, 27.28.

Antibacterial assay [28]. The following bacterial strains *(Staphylococcus aureus* and *Escherichia coli)* were employed in this study. The sensitivity of the bacteria to the compounds under investigation was ascertained using the well diffusion method. This method involved preparing the culture medium per the supplier's instructions using 100 µL of Muller-Hinton medium (70191-Merk-Germany). After that, the medium was put on plates and given time to solidify. Using a cork drill, five depressions with a diameter of 6 mm were created in the medium after solidification. The inhibition zones had to be kept apart from one another by leaving enough space between each well. Thereafter, 0.1 mL of the bacterial suspension was transferred to the nutrient agar medium and evenly spread across the plate surface using a sterile cotton swab in a laminar flow hood. After that, the contaminated plates were stored for roughly 30 min. Each well received a volume of 0.1 mL that contained 100 µM and 250 µM of the compounds that were tested for biological activity. Each neighboring well received a different concentration, while one well was used as a control and received the same volume of solution.

Results and discussion

The derivatives studied in this manuscript were synthesized in sequential steps, where two types of azide derivatives, **2a** and **2b**, were prepared using the diazonium salt of the corresponding amines. The derivative **4** was synthesized by reacting theophylline **3** with chloroacetyl chloride using Et_3N as a catalyst.



Scheme 1. The experimental steps for synthesis of compounds 2-8

After that, the derivative **5** was synthesized via a reaction of derivative **4** with piperazine in the presence of Et_3N as a catalyst. Next, derivative **5** was reacted with propargyl to synthesize and sodium ascorbate as catalysts. **Scheme 1** indicates the steps of the formation of these derivatives in sequence. In addition, structures of synthesized molecules were determined by derivative **6** using Et_3N as a catalyst. After that, azides **2a** and **2b** were introduced individually in a cycloaddition reaction with the derivative **6** using both hydrated copper sulfate different techniques (FT-IR, ^{1}H NMR, and ^{13}C NMR). The spectral data were included in the experimental section.

Table 1. Inhibition zones of antimicrobial activity for synthesized compounds in mm.

Antimicrobial activity				
E. coli (Gram-negative)			***S. aureus (Gram-positive)***	
No.	**Size mm**		**Size mm**	
	100 µM	**250 µM**	**100 µM**	**250 µM**
4	20	20	16	22
5	10	14	10	15
6	16	20	18	25
7	16	26	13	20
8	14	22	15	23
Cephalexin	22	26	12	15
Penicillin	11	15	20	25

Antibacterial Activity. Control of microbial populations is essential to prevent the emergence of diseases, infections, decomposition, spoilage, and contamination that they cause. Newly synthesized compounds were examined for their antimicrobial activity *in vitro* against bacteria (*Staphylococcus aureus* and *Escherichia coli*). Results of antimicrobial activity revealed that most of the tested compounds had moderate to strong activity. Compounds were appearing to have a strong effect against Escherichia coli, except derivative **5** was appearing to have a middling effect. In addition, compounds had a middling effect against Staphylococcus aureus compared to Cephalexin, as illustrated in Table 1.

Conclusion

Theophylline derivatives were synthesized in yields ranging from 72 to 82%. Some of the synthesized compounds exhibited encouraging antibacterial properties compared to that of standard reference, and this may be due to their structural properties that help in making morphological defects in the cell walls of bacteria. Fourier transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance ^{1}H NMR and ^{13}C NMR techniques were used to validate the chemical structures of the synthesized compounds.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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