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Synthesis of New 1,2,3-Triazole Glycosides-Based Quinoline System via Click Cycloaddition

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Abstract: The impact of novel compounds based small heterocyclic rings with important bioactivities promotes further research for designing and synthesizing new hybrid molecules. In the current investigation, new azido quinoline derivative has been synthesized from the commercially available 8-hydroxyquinoline. The obtained azido derivative was exploited via click chemistry to access three new 1,2,3-triazole glycosides by applying click chemistry reaction strategy. The newly synthesized compounds have been characterized by their spectral and analytical data involving ^{1}H, ^{13}C NMR and IR. The anticancer activity of the synthesized products were evaluated agains a pannel of human cancer cell lines and the results were formulated in the form of IC_{50} and percentage inhibition values.

Keywords: 1,2,3-triazole – glycosides - click – cycloaddition – anticancer – cytotoxicity

1. INTRODUCTION

Heterocycles are attractive species of molecules with distinctive traits, which have envolved since long time ago [1]. The importance of heteroatoms shows that they are a common part of many types of active pharmaceutical installation and excipients [2-5]. It can also be used as raw materials in the preparation of organic compounds. In medicinal chemistry, heterocycles, which are cyclic compounds of five or six atoms containing nitrogen, oxygen or sulfur atom, have an important role in discovery, drug, identification, synthesis and design of biologically active compounds.

Statistics show that about 85% of the entities that possess biological activity have a heterogeneous cycle [6]. Therefore, heterogeneous cycles are of great interest to chemists working in medicine to develop the drug chemical field and to work on more efficient methods of drugs invention. In a study of heterocyclic systems with a fixed composition versus to organic compounds, triazoles rings were assessed as highly important heterocyclic compounds for medication-related actions. In particular, triazole rings containing glycosides possess a wide range of biological properties, such as antimicrobial [7], antiparasitic [8], anticancer [9-10] and antituberculous [11] activities. Recently, 1,2,3-triazoles have been found to have α-glucosidase inhibitory activity [12]. As a result, 1,2,3-triazole glycosides are now useful in the search for new drugs, and the creation of bioactive carbohydrate-based molecules is now an important area of research [13].

In this work, we describe the synthesis of new 1,2,3-triazole glycosides via the click chemistry of an azido quinoline derivative with terminal alkynes of the acetylated D-glucose, D-galactose, and D-xylose, then studying their activity against a number of cancer cell lines.

2. MATERIALS AND METHODS

General methods

Melting Points were taken on a digital melting point apparatus, and they are uncorrected. Infrared spectra (KBr for solid or neat for liquid) were measured on a Bruker-Vector 22, Germany (Qassim University, college of science). ^{1}H- and ^{13}C-NMR signals were recorded NMR spectra were recorded on 400 MHZ (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer, referenced to TMS and the solvent shift (DMSO-d_6). Coupling constants are given in Hz and without signs. The elemental analyses of the synthesized compounds were found in their agreed ranges.

General Click Chemistry Procedure:

Quinolin-8-yl 2-bromoacetate 1.33g (10 mmol) and 0.975 g (25 mmol) of NaN_3 in a solvent mixture of EtOH: DMSO: H_2O (7:4:2), was stirred at room temperature. The reaction mixture was stirred and warmed at 50°C for 2h. The reaction progress was monitored by TLC using petroleum ether/ethyl acetate (70/30) as an eluent. Addition of ice-cold water after cooling will afford the product **3** as a yellowish oil after extraction using diethyl ether. The latter was transferred directly into a round bottom flask containing (1 equiv) of acetylinc sugar in a mix of solvents of H_2O/1-BuOH/CH_2Cl_2 (1:2:8) and the mixture was stirred until dissolved. Then (1 equiv.) of azide derivatives, (0.3 equiv.) of Na-ascorbate, (0.15 equiv.) of diisopropyl ethylamine, and (0.15 equiv.) of $CuSO_4.5H_2O$ were added and the reaction mixture was stirred in the dark for 2 days at RT. Then the mixture was warmed at 50°C for about 3h. After returning to room temperature, in a test tube, 0.5 mL of water and (0.15 equiv.) of sodium ascorbate were added, and in another test tube, we have added 0.5 mL of water and (0.075 equiv.) of $CuSO_4.5H_2O$. The contents of the two test tubes were then added to the mixture reaction with heating. Using chloroform/methanol (95/5) as the eluent, TLC was used to monitor the reaction's progress. The mixture reaction was extracted diluted with CH_2Cl_2 and the organic layer was washed with an aqueous ethylenediaminetetra acetic acid disodium

salt (EDTA-Na_2) solution (2 times), and aqueous saturated NaCl solution (2 times). After drying over Na_2SO_4 and filtration, the target compounds were obtained.

(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(2-oxo-2-(quinolin-8-yloxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (7)

Brown powder, Yield: 54%; M.p. 84-94 ºC; IR (cm^{-1}) v: IR (cm^{-1}) v: 1032 (C-O), 1205 (C-N), 1432 (C=C) 1733 (O-C=O), 3074 (Ar-H); ^{1}H NMR (400 MHz, DMSO-d_6) (ppm): 1.99, 2.00, 2.01, 2.02 (4s, 3H, CH_3), 3.99-4.11 (m, 2H, H-6',6''), 4.35-4.38 (m, 1H, H-5'), 4.88-4.91 (m, 1H, H-2'), 5.23 (t, 1H, J = 8.8 Hz, H-3'), 5.34 (s, 2H, -CH_2-N), 5.99 (d, 1H, J = 10.2 Hz, H-1'), 7.31 (m, 1H, qu.-H), 8.38 (d, 1H, qu.-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 19.9, 20.1, 20.2 (4CH_3), 65.2, 69.2, 70.5, 70.9, 72.2, 98.2 (sug-C), 116.8-152.8 (Ar-C), 164.7, 168.3, 168.5, 169.2, 170.3 (5C=O).

(2R,3R,4S,5R)-2-((1-(2-oxo-2-(quinolin-8-yloxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (8)

Yellow powder, Yield: 53%; M.p. 98-100 ºC; IR (cm^{-1}) v: 1032 (C-O),1215 (C-N), 1435 (C=C) 1744 (O-C=O), 3302 (Ar-H); ^{1}H NMR (400 MHz, DMSO-d_6) (ppm): ^{1}H NMR (400 MHz, DMSO-d_6) (ppm): 1.98, 2.01, 2.02, 2.04 (4s, 3H, CH_3), 3.96-4.10 (m, 2H, H-6',6''), 4.37-4.40 (m, 1H, H-5'), 4.88-4.92 (m, 1H, H-2'), 5.23 (t, 1H, J = 8.8 Hz, H-3'), 5.35 (s, 2H, -CH_2-N), 5.99 (d, 1H, J = 10.2 Hz, H-1'), 7.31-7.49 (m, 3H, qu.-H), 8.22-8.38 (m, 3H, qu.-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 20.5, 20.7, 20.9, 21.4 (4CH_3), 65.2, 69.2, 70.5, 70.8, 72.2, 97.8 (sug-C), 116.9-152.5 (Ar-C), 164.5, 168.4, 168.8, 169.2, 170.2 (5C=O).

(2R,3S,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(2-oxo-2-(quinolin-8-yloxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (9)

Yellow powder, Yield: 51%; 95-96 ºC; IR (cm^{-1}) v: 1065 (C-O), 1206 (C-N), 1433 (C=C), 1738 (O-C=O), 3105 (Ar-H); ^{1}H NMR (400 MHz, DMSO-d_6) (ppm): 1.99, 2.01, 2.03 (3s, 3H, 3CH_3), 3.98-4.11 (m, 2H, H-5',5''), 4.39-4.43 (m, 1H, H-4'), 4.88-4.99 (m, 1H, H-3'), 5.23-5.27 (m, 2H, H-2'), 5.43 (s, 2H, -CH_2-N), 6.01 (d, 1H, J = 9.8 Hz, H-1'), 7.32-7.49 (m, 3H, qu.-H), 8.20-8.35 (m, 3H, qu.-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 20.3, 20.8, 21.5 (3CH_3), 61.5, 69.4, 71.6, 73.2, 99.5 (sug-C), 116.6-151.5 (Ar-C), 164.5, 168.2, 168.3, 170.2 (4C=O).

Anticancer activity

Cytotoxic activity

The cytotoxic activity of the newly afforded derivatives was investigated to evaluate their cytotoxic activity on five various cancer cell lines such as SK-OV-3, A549, HT29, HCT116 and MCF7 in addition to normal cell line (RPE1) using the MTT assay [14,15]. The results were outlined numerically as described in table 1 as cytotoxic activity at 100 µM on the mentioned cell lines under investigation and the related IC 50 (µM) values for the products achieving more than 90% at 100 µM (table 2).

3. RESULTS AND DISCUSSION

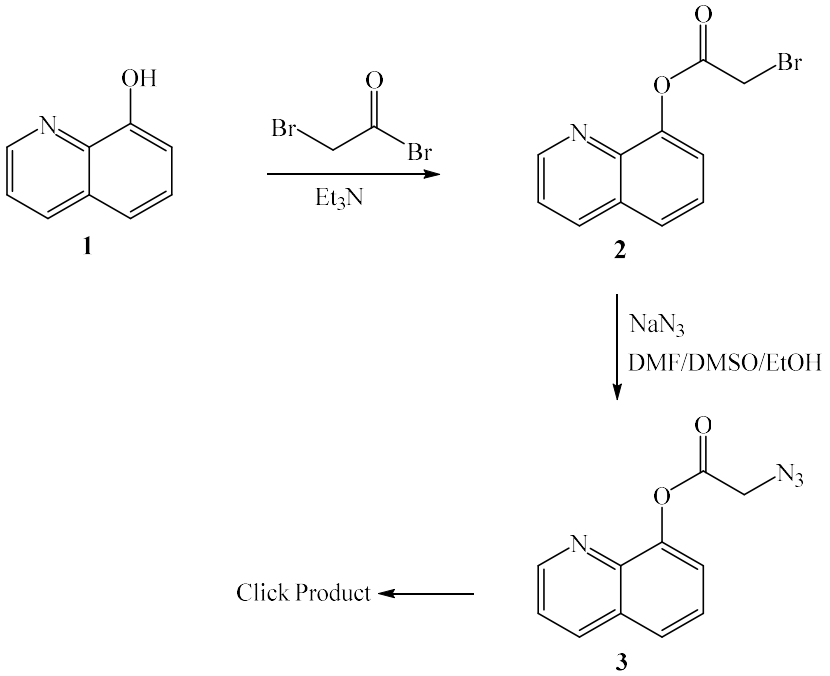
Chemistry

Molecular hybridization is an important designing strategy for the formation of targeted products derived from various cores with the aim for getting molecules incorporating effective motifs. The latter products are usually expected to possess potent bioactivities depending on the nature of the incorporated systems. Click chemistry approach was found a unique route for synthesizing multifunctional products in which a 1,2,3-triazole represents a linker joining different structural systems.

In the current investigation, 8-hydroxyquinline **1** was used as a starting compound for the formation of the required azide substrate for the proposed click reaction. Thus, compound **1** was reacted with 2-bromoacetyl bromide to lead to quinolin-8-yl-2-bromoacetate **2** in good yield according to the previously reported procedure [16]. The achievement of the required azido-functionality was processed by azidation of later acetate product and completed by using sodium azide in the presence of mixture of the mixed solvent DMSO/DMF/ethanol which was achieved after trying varied solvent systems, and afforded the derived azido derivative **3** in good yield which was further used instantly in the click reaction (Scheme 1). It was thought that the latter azide will be suitable reagent for the target click reaction to result, successfully, in the sugar-bases triazolyl-quinoline core.

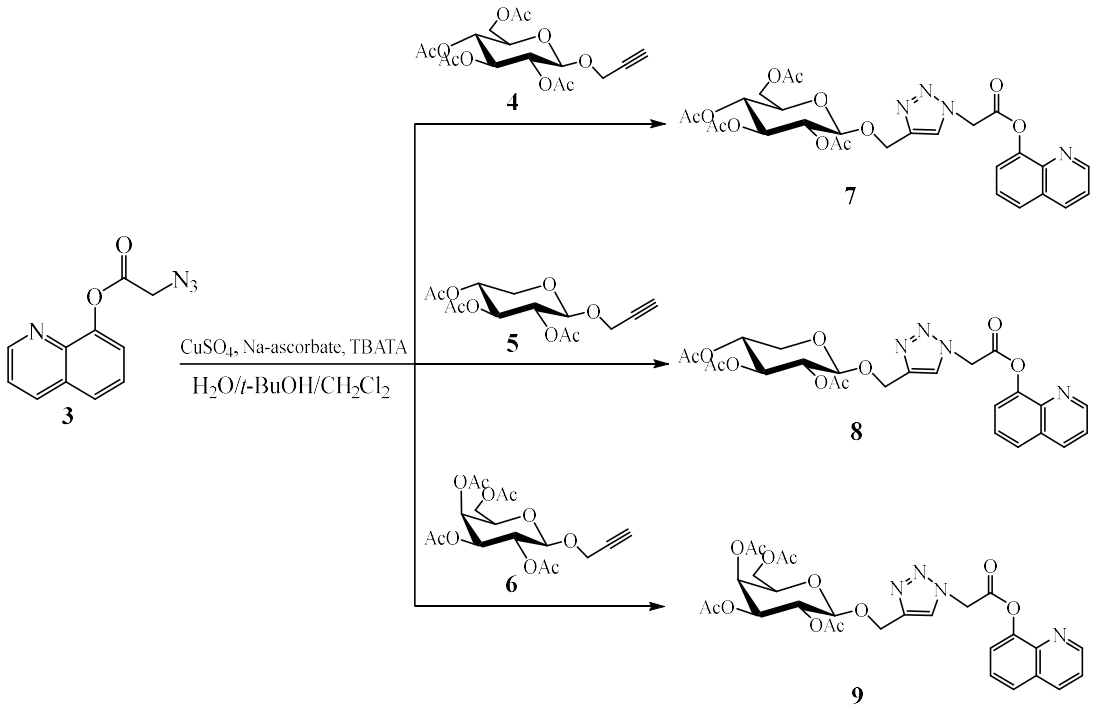
The azido derivative **3** is engaged in a click chemistry reaction with terminal alkynes of the acetylated D-glucose **4**, D-xylose **5**, and D-galactose **6** [17-18] afforded the desired 1,2,3-triazole Glycosides **7-9** (scheme 2).

The IR spectra of compounds **7-9**, show the absorption at 1733, 1744 and 1738 cm^{-1}, respectively, related to (C=O) group. The spectra displayed also stretching at 1032, 1065, 1435 cm^{-1} assigned to (C-O) and (C=C) respectively. The ^{1}H NMR spectra of compounds **7-9** showed a band at 2.01, 2.04 and 2.01 ppm, respectively, attributed to proton of acetate group. The spectra ^{13}C NMR of compounds **7-9** exhibit a singlet at 170.22 ppm corresponding to the carbonyl of acetate group and 169.32 ppm corresponding to the carbonyl of quinoline.



1 2 3

Scheme 1: Synthesis of azide based Quinoline system



Scheme 2: Synthesis of 1,2,3-triazole glycosides bases quinoline system

3.1. Anticancer activity

The afforded glycosides were investigated to study their cytotoxicity behavior against a number of cancer cell lines. The used cells in the current investigation are colorectal carcinoma (HCT116), breast adenocarcinoma (MCF7), SKOV, A549, HT29, human tumour cell lines. MTT assay protocol was applied in the current investigation. The results were presented in tables 1 and 2 outlining the observed percentage inhibition of the cytotoxicity activity at 100 μM and the related IC_{50} (μM) values, respectively on the cell lines under test.

The resulting data indicated the observed activity of compound **5** against most of the applied cancer cell lines (colorectal carcinoma (HCT116), breast adenocarcinoma (MCF7), SKOV, A549). The *N*-glycoside **6** revealed comparably lower activity showing good cytotoxic action regarding the cancer cells (colorectal carcinoma (HCT116), breast adenocarcinoma (MCF7), A549) than its analogue **5** which reflected more active behaviour. Compounds **4** showed the lowest activity against of all cancer cell lines.

The close structural similarity of the tested compounds promoted further trials to correlate the observed activity to the structural features of such tested products in spite of their low number. The difference between the 1,2,3-triazole glycosides 4-6 is in the orientation of the substituents in at C-4 in the sugar moiety (compounds **4** and **5**) or the number of carbons in the sugar residue (six carbons as compounds **4** and **5** as in compound **6**). Thus, the *N*-glycosides incorporating the O-acetylated galactopyranosyl moiety showed obviously higher activity then it isosteric analogue possessing the acetylated glucopyranosyl part. The triazole glycoside with the acetylated xylopyranosyl ring linked to the triazole system showed moderate activity which is still better than its isosteric analogue (compound **4**) with the same orientation at sugar C-4 but possessing more one carbon with its substituent (C-6).

Table 1. Percentage cytotoxicity of 100μM of the compounds on human tumor cell lines*

Compd.	SKOV	HCT116	MCF7	A549	HT29	RPE1
6	53.6±8.1	97.66±1.9	98.9±0.3	98.63±0.1	42.6±2.3	97.16±0.3
4	3.4±1.7	5.61±1.1	21.26±3.0	33.06±4.6	23.2±2.7	-
5	97±0.2	98.8±0.2	89.36±14.1	98.6±0.1	42.42±6	96.93±0.4

*The results are shown as average ± standard deviation

Table 2. The IC_{50} values of the compounds which gave more than 50% at 100µM

Compounds	SKOV	HCT116	MCF7	A549	HT29	RPE1
6	-	56.7±7.4, r^2=0.98	25.29±0.8, r^2=0.99	42.57±2.4, r^2=0.99	-	28.91±6.6, r^2=0.88
4	-	-	-	-	-	-
5	47.61±4.5, r^2=0.97	8.39±1.0, r^2=0.90	18.86±1.2, r^2=0.99	14.37±0.8, r^2=0.98	-	25.04±2.3, r^2=0.98
doxorubicin		2.2±1	12.8±1	0.9±0.5		

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Arabic Abstract

تحضير مركبات الكينولين الجديدة المرتبطة على 1،2،3-تريازول جليكوسيدات بواسطة الكيمياء النقرية.

الملخص: إن تأثير المركبات الجديدة المتصلة على حلقات حلقية صغيرة غير متجانسة ذات أنشطة حيوية مهمة يشجع على إجراء المزيد من الأبحاث لتصميم وتشييد جزيئات هجينة جديدة. في البحث الحالي، تم تصنيع مشتق أزيدو كينولين جديد من 8-هيدروكسي كينولين المتوفر تجاريًا. تم استغلال مشتق الأزيدو الذي تم الحصول عليه عبر كيمياء النقر للوصول إلى ثلاثة جليكوسيدات 1،2،3-تريازول جديدة من خلال تطبيق استراتيجية تفاعل كيمياء النقر. تم تشخيص المركبات المحضرة حديثا من خلال بياناتها الطيفية والتحليلية التي تشمل IR, NMR C^{13} and H^{1} تم تقييم النشاط المضاد للسرطان للمنتجات المصنعة مرة أخرى على مجموعة من خطوط الخلايا السرطانية البشرية وتمت صياغة النتائج في شكل IC_{50} وقيم التثبيط المئوية.

الكلمات الاستدلالية: 1،2،3-ترايازول – جليكوسيدات – النقر – إضافة حلقية – مضاد للسرطان – السمية الخلوية.