Egypt. J. Chem. Vol. 67, SI: M. R. Mahran, pp. **1221 - 1233** (2024)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis, Molecular Docking And Anticancer Activity Of New Substituted Pyridine-1,2,3-Triazole Hybrid *N*-Glycosides Via Click Chemistry

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Abstract

Cancer is still the most upsetting threat for human life and its fighting strategies have acquired intensive research. The design and synthesis of novel candidates for their possible potent anticancer activity has become a major objective in the drug anticancer discovery field. In the current research, new 1,2,3-triazole glycosides linked to substituted pyridine system were prepared vis click chemistry approach. A number of substituted acetylenic substrates incorporating varied structural features were applied for the click reaction. Various sugar moieties as acetylated glycopyranosyl forms provided the 1,4-disubstituted 1,2,3-triazole products possessing sugar, aryl- or heteroaryl substituents in the synthesized compounds. The 1,2,3-triazole glycoside **10** and its acetylenic precursor **6** possessing the biphenyl and thienyl rings in addition to the *O*-acetylated glucopyranosyl moiety showed the highest activity against A549, MCF7 and PC3 human cancer cell lines. Furthermore, the docking studies into EGFR and EGFR showing good binding modes with the protein active sites.

Keywords: 1,2,3-triazole; anticancer; pyridine; EGFR; Cytotoxicity; molecular docking

Introduction

The research identifying and developing novel anti-cancer candidates has gained intensive interest due to the threating behaviour of cancer as one of the leading causes of death worldwide. Generally, chemotherapy requires continued research since the current drugs for fighting such threat are associated with a cytotoxic action, killing cells, or even cell stabilizing, lowering their number in the body. Accordingly, an urgent demand for conducting comprehensive research for creation novel candidates with potent behaviour exhibiting the ability to noticeably decrease cancer cell numbers [1–5] showing minimum or no harmful action on normal cells.

Nitrogen heterocycles are still an enriched source for providing a variety of bioactive candidates such as agents of possible anticancer activity. Being an important functionalized pyridine system, nicotinonitrile based compounds possess bioactive and medicinal properties. Various bioactivities are associated to structural core including antimicrobial [6], cardiotonic [7], antioxidant [8], anti-inflammatory [9], anti-alzheimer [10], anticonvulsant [11], anti-parkinsonism [12], antitubulin agents [13], antiproliferative [14], antiprotozoal agent [15], Anti-H5N1 [16], and protein kinases inhibitor [17]. A variety of substituted pyridine derivatives were intensively studied as potential anticancer candidates, against human cancer cell lines. Bosutinib and neratinib are representative products incorporating a 3-cyanopyridine nucleus and an oxygenated alkyl-substitution side chain for drugs exhibiting anti-leukemia and anti-breast cancer actions, respectively [18-20].

1,2,3-Triazoles represent a group of important five-membered nitrogen heterocycles due to their structural features allowing them as potent heterocyclic motif leading to their unique biological and medicinal applications. 1,2,3-Triazole based products were

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Receive Date: 08 October 2024, Revise Date: 16 November 2024, Accept Date: 25 November 2024
DOI: 10.21608/ejchem.2024.326738.10597

revealed by their well-known bioactivities making such motif a useful building block in numerous structures [21–26]. The significance of the structural behaviour and bioactivity of 1,2,3-triazoles of therapeutic properties, particularly their anticancer action [27-30] directed much interest for their intensive study in view of synthetic and medical investigations.

On the other hand, sugar containing structures are significant natural polyfunctional compounds possessing numerous stereochemical characteristics as well as non-toxic behaviours since they are incorporated molecular recognition and intracellular processes [31-35]. The attachment of bioactive structural cores to a sugar moiety via a glycosidic linkage, of different binding modes, resulted in the formation of potent products provided a main objective in drug discovery field [36-42] possessing enhanced bioactivity. The later consequence was evidenced by the fact that various glycosides, such as glycosyl heterocycles, of potent antitumor properties via enzyme inhibition action mode [43-48]. Molecular hybridization was discovered as a promising strategy for designing potential compounds with hybrid structures incorporating various potential motifs. (Figure 1) presents potent anticancer compounds against human cancer cells and enzyme inhibitor involved in tumor formation process [49-53]. The above-mentioned significances related to the proposed hybrid targets stimulated our interest in the synthesis and investigation of anticancer activity of new pyridine-aryl- or heteroaryl-1,2,3-triazole-glycosyl hybrids against number of human cancer cell lines with the related molecular docking simulations.

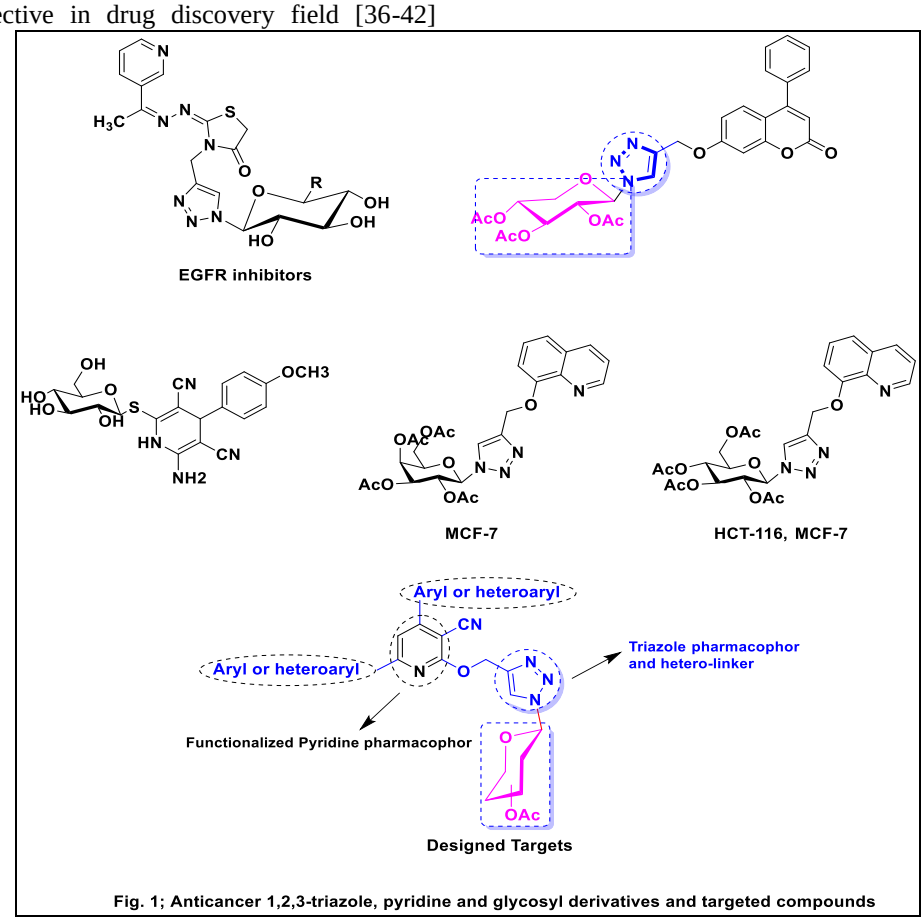


Fig. 1; Anticancer 1,2,3-triazole, pyridine and glycosyl derivatives and targeted compounds

RESULTS AND DISCUSSION

2.1. Chemistry

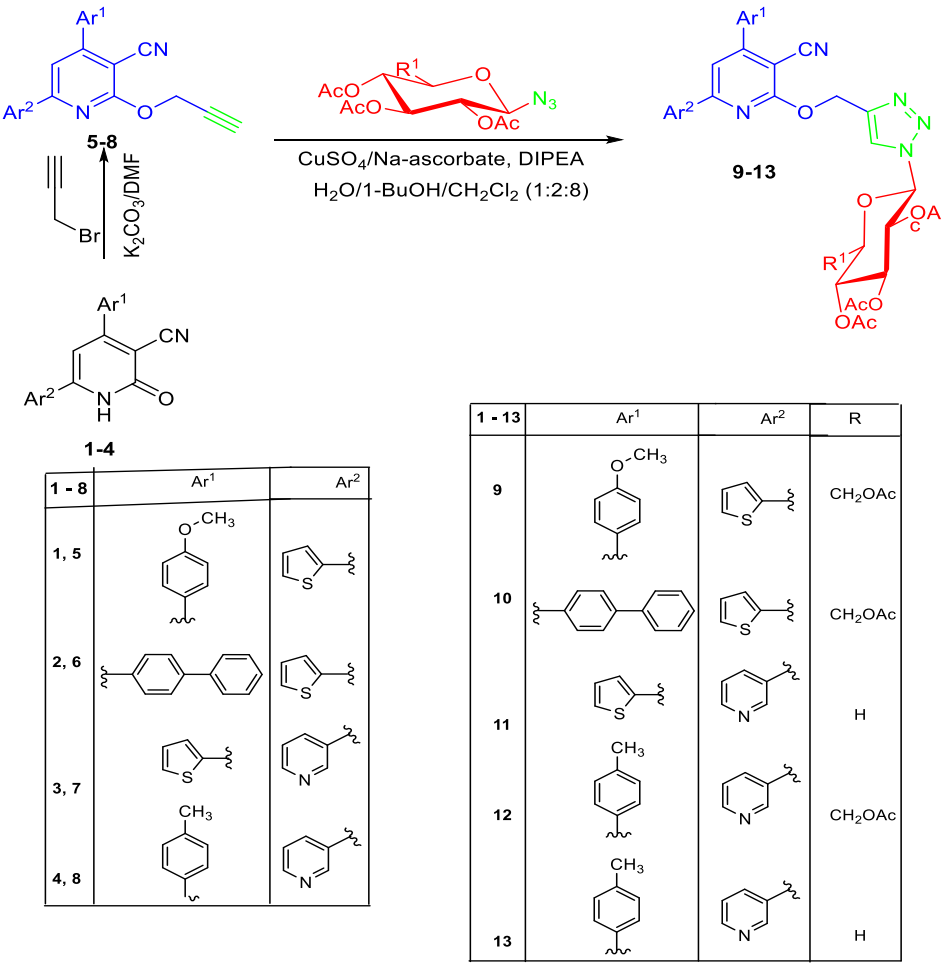
For achieving the targeted molecular hybridization approach in the planned newly designed products our research work was directed to the creation of novel target triazolyl-heteroaryl-glycosides. Because of their possible potent bio-effects against cancer cells, nitrogen functionalized heterocyclic core, the aryl and hetero-aryl substituted pyridine derivatives were used. Formation of the hybrid structures starts with the preparation of the suitable substrates and reagents in the applied reactions. Thus, in the current approach novel 1,2,3-triazole-thienyl-pyridine glycosyl hybrids are their of 1,2,3-triazole-aryl glycosidic analogues were synthesized from simple starting precursor.

The required terminal acetylenic substrates were prepared *via* alkylation reaction of the substituted pyridine compounds **1-4** using propargyl bromide as an alkylating agent. The substituted acetylenic substrates were selected on the basis of the incorporation of varied substituted aryl and/or

heteroaryl moieties. The latter are proposed to exhibit structural features that could enhance the bioactivity via achieving various interacting modes with the biological targets.

The spectral data confirmed the afforded regioselectivity of the alkylation process which proceeded towards formation of the *O*-alkyl substituted products. The observed results are in complete accordance with the previous reported results regarding the alkylation of similar reported substituted pyridine products [39]. The latter consequence also confirmed that the most stable fully aromatic *O*-substituted products are formed rather than the *N*-substituted analogs. The later terminal acetylenic compounds were fully characterized since the corresponding IR spectra showed the bands concerning the terminal alkynes (≡CH) the alkane (–CH), the nitrile (CN) and the alkynes (C≡C) at 3300, 3000-2800, 2260-2210 and 2260-2100 cm^{-1}, respectively, in addition to the disappearance of amide carbonyl band. ^{1}H NMR spectrum presented a singlet signal at 3.37 ppm assigned to the terminal acetylene proton, and another singlet signal attributed to the methylene protons at 4.68 ppm. The ^{13}C NMR spectra presented a signal at 53.8 ppm for the aliphatic carbon in the methylene group (OCH_2), also, showed two signals at 76.4, 78.7 ppm corresponding to the two carbons of the terminal acetylene.

The click reaction of the glycopyranozyl azides of 2,3,4,6-tetra-*O*-acetyl-*β*-D-gluco- or 2,3,4-tri-O-acetyl-β-D-xylopyranosyl azide derivatives, with the terminal alkyne compounds **5-8** was performed. A mixture of (DCM - *n*-BuOH - H_2O) as a solvent, DIPEA as a base, Na-ascorbate and $CuSO_4.5H_2O$ were used in the click process after investigation of different solvent systems. Although showing a degree of availability for reaction completion, a number of tested solvent systems, either pure single or mixed solvents such as methanol, DMSO, THF-DCM did not achieve the best reaction time and achieved reaction yield. The reaction resulted in the formation of the target glycosyl-1,2,3-triazoles **9-13** in 69% to 82%. The substituted-aryl and glycosyl-1,2,3-triazoles **9-13** are hybrid products in which the substituted pyridine and the sugar part are connected by the 1,2,3-triazole system linker.



1 - 8	Ar¹	Ar²
1, 5		
2, 6		
3, 7		
4, 8		

1 - 13	Ar¹	Ar²	R
9			CH_2OAc
10			CH_2OAc
11			H
12			CH_2OAc
13			H

Scheme. 1. Synthesis of substituted 1,2,3-glycosides based pyridine system.

The structures of the newly synthesized 1,2,3-triazole glycosides were determined by the spectroscopic methods FT-IR, ^{1}H NMR and ^{13}C NMR. The IR spectra of resulted glycosyl-1,2,3-triazoles **9-13** displayed an absorption at 1750-1680 cm^{-1} related to the acetoxy carbonyl band (C=O), also, showed a

stretching at 1350-1000 and 1300-1000 cm^{-1} attributed to the (C–N) and (C–O) groups, respectively, in addition to the disappearance of acetylene and terminal acetylene bands. The ^{1}H NMR spectra confirmed the assigned structure and presented number of singlet signals between 2.02 and 2.04 ppm assigned to the acetoxy groups protons, as well as, the singlet signal at 3.81 ppm for the methoxy protons. The spectra also showed several signals between 4.78 and 6.39 ppm for the sugar protons, moreover and a singlet signal at 7.18-7.62 attributed to the 1,2,3-triazol ring proton, in addition to the disappearance of the terminal acetylene proton band. The ^{13}C NMR spectrum showed one signal at 20.09-20.20 ppm and signals at 22.69-20.77 ppm attributed to the (CH_3) in the acetoxy groups, as well as the signal appeared at 55.8-xxx ppm ppm for the methoxy group. In addition, the spectra presented several signals in the range of 68.9-97.6 ppm assigned to the sugar carbons. Moreover, two characteristic signals at 122.1 and 143.0 for the triazole ring, furthermore, the spectrum showed four signals designated to the carboxylate carbons appears at 170.2 ppm.

2.2. Cytotoxicity

The cytotoxic evaluation of a number of the newly synthesized derivatives **6-8** and **9-13** was estimated against breast (**MCF-7**), human prostate carcinoma cells (**PC3**), lung (**A-549**), human normal (**BJ1**) cells. These evaluations were performed using the colorimetric MTT assay [54-55] comparing with doxorubicin, the standard medication, at a dosage of 100 µM, shown in the tables below. The effective concentration IC_{50} of the promising derivatives, which demonstrated cytotoxic activity of ≥50% at a concentration of 100 µM, was determined by additional screening against the target cells at concentrations ranging from 1000.78 µM.

The obtained data reflected the observation that most of the screened derivatives displayed moderate to weak cytotoxic activity against the three cancer cell lines. On the other hand, one of the screened 1,2,3-triazolyl-glycosides based pyridine scaffold possessing certain acetylated sugar moiety and its precursor i.e. acetylenic derivative afforded good and high potency definitely; the glycoside **10** and its acetylenic precursor **6**. The behavior was markedly obvious from the recorded results against the three cancer cell lines showing moderate and high activities, for the latter derivatives, respectively. The results are presented in the tables below.

The observed activity of tested compounds may provide a degree of correlation of the structural features of tested compounds to such activity results against cancer cells. The glycoside having the structure as 1,4-disubstituted -1,2,3-triazolyl-glycosides based pyridine core possessing since it has certain acetylated sugar parts and its precursor i.e. acetylenic derivative revealed improved and high potency (glycoside **10** and its acetylenic precursor **6)**. The behavior was markedly obvious from the recorded results against the three cancer cell lines showing moderate and high activities, for the latter derivatives, respectively. The results are presented in the tables below.

The activity of both compounds showed the effect of attachment of sugar moiety to specific substituted triazole base incorporated to pyridine system having certain aryl and heteroaryl substituents. In such cases the substitution in the pyridine system with a biphenyl and thienyl rings revealed markedly increased influence compared to the other products. The observation was also supported by the observed results of the acetylenic precursor which showed more potent activities than those revealed by the other structural analogs. The latter also showed the importance of such structural features. The effect of sugar, only in specific structures, was also shown by the relatively improved effect of the glycoside compared to other glycosidic structural analogs. The latter observed structural selectivity is interesting and needs more future studies in such concern.

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

Compound	MCF7	PC3	A549	BJ1
6	67.80±4.65	73.73±0.80	57.60±0.61	0.00±0.005
7	11.39±332	11.46±2.93	21.63±1.42	-
8	5.26±3.81	10.42±2.18	20.20±2.72	-
9	39.00±1.04	27.00±4.09	27.70±3.47	-
10	97.70±0.20	98.26±0.17	98.53±0.12	99.90±0.90
11	25.21±3.57	1.25±1.34	20.80±3.41	-
12	27.05±8.66	9.98±4.86	25.20±3.29	-
13	26.04±2.13	0±0.005	4.10±3.39	-

*The results are shown as average ± standard deviation.

Table 2. *The percentage cytotoxicity of the compounds on* ***MCF7*** *human tumor cell line at different concentrations*:*

Compound	100 µM	50 µM	25 µM	12.5 µM
6	67.80±4.65	51.63±0.06	38.83±0.12	23.30±0.87
7	11.39±332	9.18±1.35	6.91±0.37	1.85±1.96
8	5.26±3.81	2.41±0.48	2.96±1.17	0.67±1.16
9	39.00±1.04	34.52±0.47	27.10±1.84	21.72±2.71
10	97.70±0.20	89.60±.20	83.67±2.92	82.43±4.61
11	25.21±3.57	11.70±1.74	8.00±0.89	2.89±2.96
12	27.05±8.66	17.63±0.35	12.05±1.65	5.20±1.25
13	26.04±2.13	26.60±1.65	25.10±0.56	18.42±4.02

*The results are shown as average ± standard deviation.

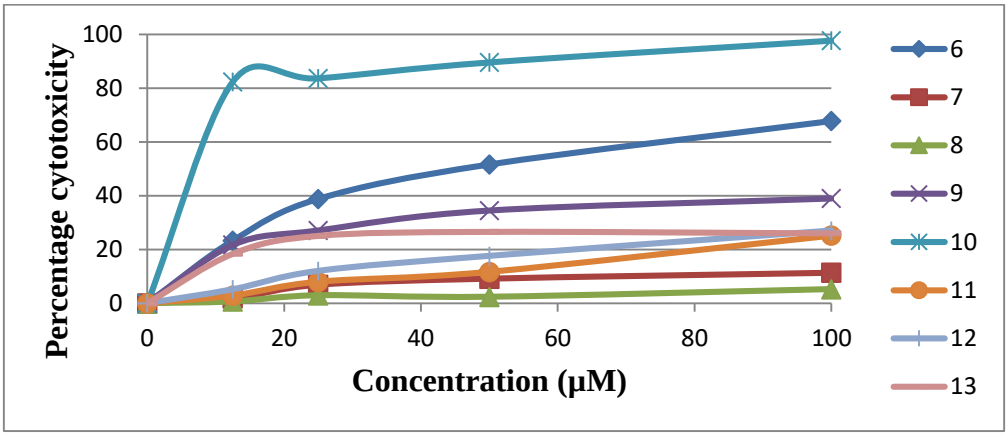


Fig.2. The percentage cytotoxicity of the compounds on **MCF7** human tumor cell line at different concentrations.

Table 3. *The percentage cytotoxicity of the compounds on* ***PC3*** *human tumor cell line at different concentrations*:*

Compound	100 µM	50 µM	25 µM	12.5 µM
6	73.73±0.80	46.50±2.75	14.73±2.65	11.40±7.16
7	11.46±2.93	8.90±2.17	7.35±2.39	2.47±3.03
8	10.42±2.18	7.36±0.31	1.65±0.80	0±0.005
9	27.00±4.09	12.20±1.37	5.85±0.80	1.45±2.51
10	98.26±0.17	87.13±4.88	66.69±1.60	60.63±14.27
11	1.25±1.34	1.70±0.61	0.71±0.61	0±0.005
12	9.98±4.86	3.19±1.10	0±0.005	0±0.005
13	0±0.005	0±0.005	0±0.005	0±0.005

*The results are shown as average ± standard deviation.

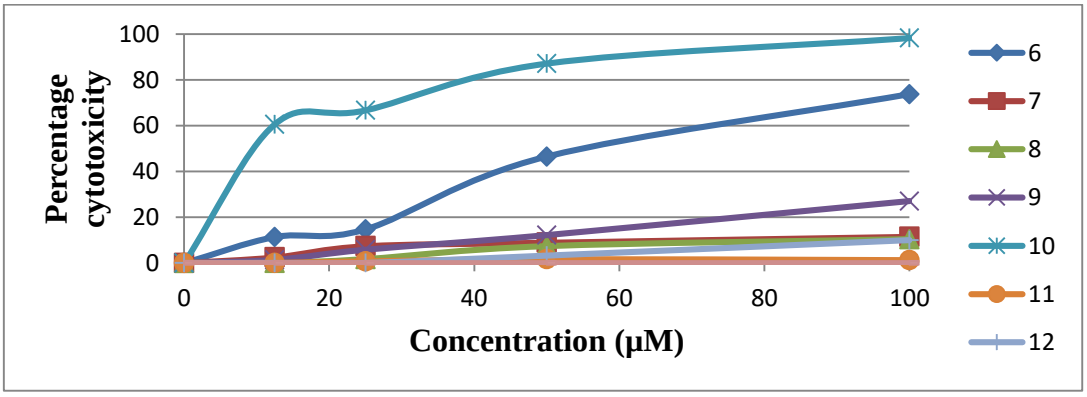


Fig. 3. The percentage cytotoxicity of the compounds on **PC3** human tumor cell line at different concentrations

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Table 4. *The percentage cytotoxicity of the compounds on* ***A549*** *human tumor cell line at different concentrations*:*

Compound	100 µM	50 µM	25 µM	12.5 µM	6.125 µM
6	57.60±0.61	45.40±2.29	33.73±2.57	32.73±2.98	-
7	21.63±1.42	19.23±0.95	17.53±1.00	15.72±1.84	-
8	20.20±2.72	18.53±2.35	16.33±2.77	0±0.005	-
9	27.70±3.47	19.40±1.87	18.17±1.25	22.20±1.83	-
10	98.53±0.12	93.17±1.70	89.33±1.95	87.27±0.55	83.43±2.83
11	20.80±3.41	14.77±1.10	12.18±3.31	12.53±1.04	-
12	25.20±3.29	22.53±3.60	20.98±2.64	18.77±2.47	-
13	4.10±3.39	7.46±1.59	8.57±2.58	7.72±2.26	-

*The results are shown as average ± standard deviation.

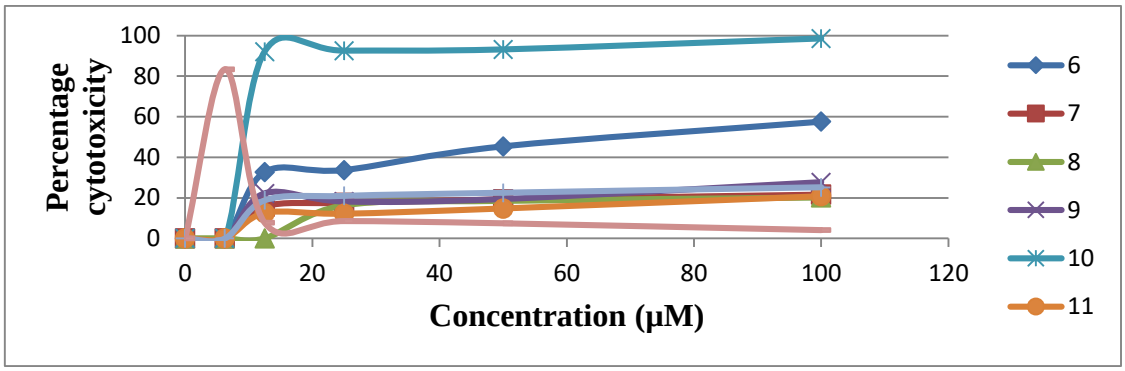

Fig. 4. The percentage cytotoxicity of the compounds on **A549** human tumor cell line at different concentrations.

Table 5. *The percentage cytotoxicity of the active compounds on* ***BJ1*** *normal human cell line at different concentrations*:*

comp.	100 µM	50 µM	25 µM	12.5 µM	6.25 µM	3.125 µM	1.6 µM	0.8 µM
6	0±0.005	0±0.005	0±0.005	0±0.005	0±0.005	0±0.005	0±0.005	0±0.005
10	99.00±0.10	99.07±0.03	97.87±0.75	96.77±1.89	51.90±9.02	19.63±3.06	6.77±2.85	13.22±4.88

*The results are shown as average ± standard deviation

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Table 6. *The IC_{50} values of the compounds which gave more than 50% at 100µM*:*

	MCF7	PC3	A549
6	-	56.12±5.96, r^2=0.97	65.16±15.10, r^2=0.89
10	-	9.65±4.83, r^2=0.77	0.75±6.50, r^2=0.93

*The results are shown as average ± standard deviation.

Interestingly, all tested compounds presented safety margins concerning their effects upon normal retinal pigment epithelial-1 (**BJ1**) cells. The 1,2,3-triazole glycoside incorporating the glucopyranosyl-part as sugar residue as N-glycosidic linkage possessing the glucosyl, the thienyl and methoxyphenyl exerted actions comparable to that of doxurobucine reflecting the influence of both hybrid systems.

2.3. Molecular docking

Two glycosyl products, one of the glycosides, which revealed markedly, improved activities and its structural isosteric analogue were used based upon the afforded cytotoxic results of the pyridine-1,2,3-triazole-glycoside hybrids. Thus, compounds **9** and **10**, were applied for the docking simulation in order to suggest the proposed possible binding affinities and theoretical possible mode of action. Simulation study done *via* MOE-Dock with respect to sites of EGFR and VEGFR-2 (PDB codes: 1M17 and 4ASD, respectively) [56-58] giving energy scores of -12.15 and -10.55 kcal/mol (RMSD 1.08 and 0.85 Å, respectively). The latter mode of action is similar to that proposed for the compounds in the current investigation. The docked targets **9** and **10** provided energy scores of -11.82 and -10.35 kcal/mol, respectively within the active site of EGFR and -9.92 and -11.35 kcal/mol, respectively within the active site of VEGFR-2. This promising energy scores revealed good fitting and binding affinity for both derivatives within the screened active sites.

By inspection of **Fig. 5** and **Fig. 6** relating to EGFR, the thiophene moiety at p-6 of pyridine moiety in derivative **9** afforded arene-H interaction with the

key amino acid **Met769**, while the *p*-methoxyphenyl scaffold at p-6 of pyridine, displayed arene-cation interaction with **Lys721**, **Fig. 5**.

The replacement of *p*-methoxyphenyl with biphenyl in compound **10** displaced the thiophene away from **Met769** and facilitate binding of **Lys721** with pyridine and 1,2,3-triazole moieties through arene-cation interactions **Fig. 6**.

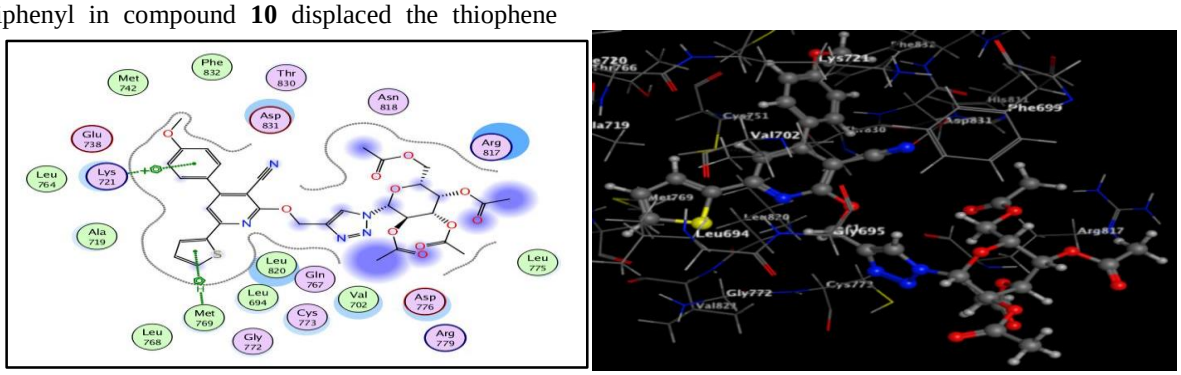

Fig. 5. 2D and 3D binding views of the pyridine-1,2,3-triazole-glycoside hybrid **9**.

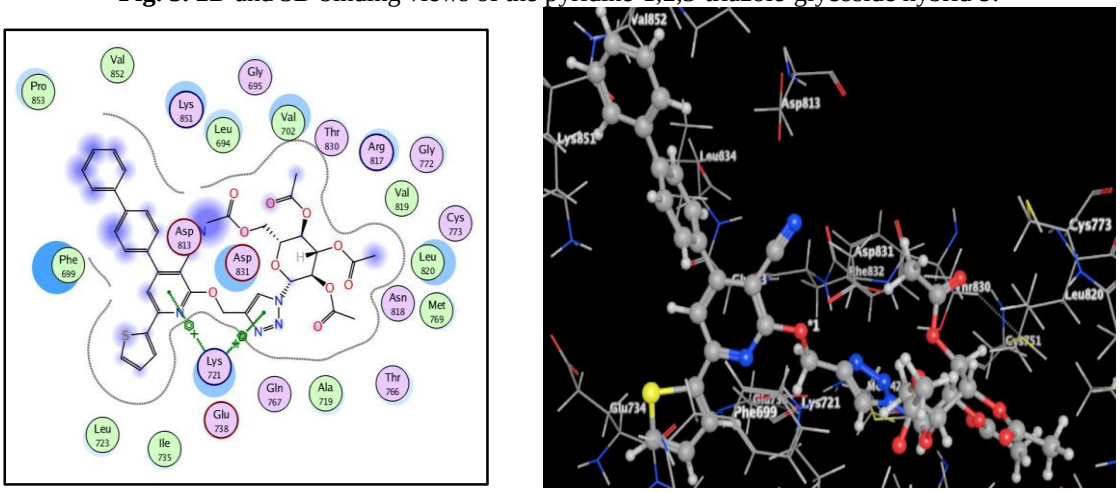

Fig. 6. 2D and 3D binding views of the pyridine-1,2,3-triazole-glycoside hybrid **10**.

Regarding to VEGFR-2, the sulfur atom of the thiazole scaffold in both derivatives **9** and **10** formed H-bond donors with the backbone of **Val889 (**distance: 2.83, 3.57 Å, respectively). On the other hand, the sugar part afforded H-bond donor with the backbone of **Asp814** in compound **9**, and exhibited two H-bond acceptors with the sidechains of **Ala881** and **Arg1027** in compound **10 (**distance: 3.18, 3.05 and 3.04 Å, respectively) **Fig. 7** and **Fig. 8**.

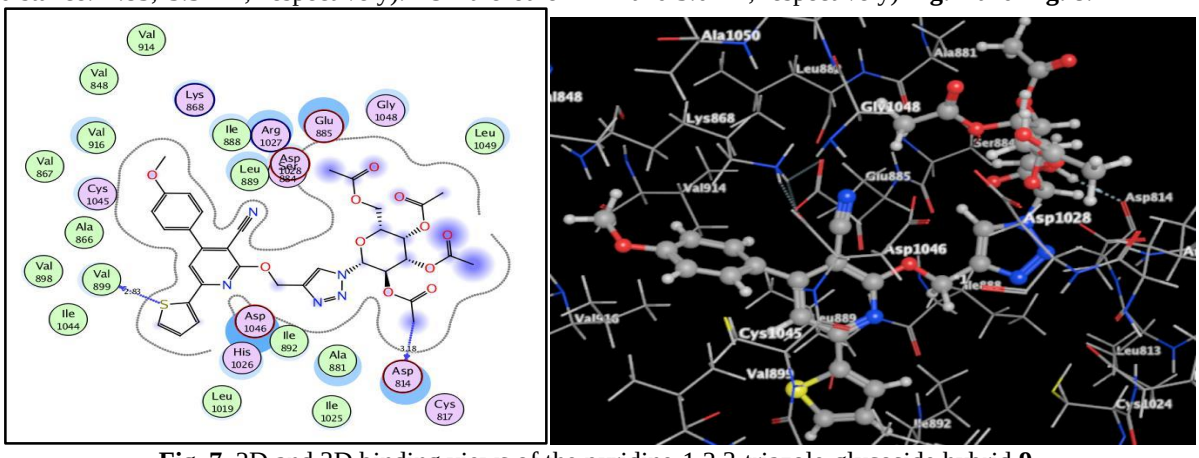

Fig. 7. 2D and 3D binding views of the pyridine-1,2,3-triazole-glycoside hybrid **9**.

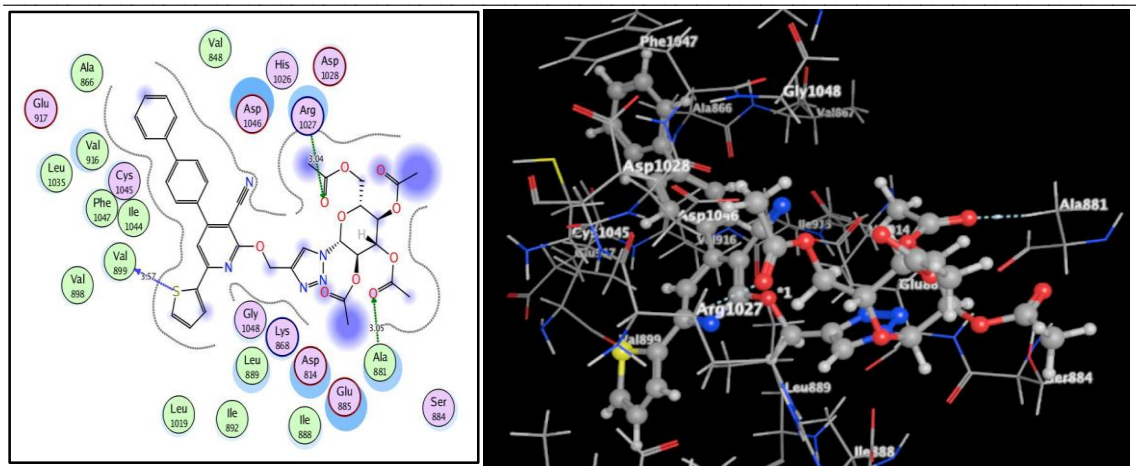

Fig. 8. 2D and 3D binding views of the pyridine-1,2,3-triazole-glycoside hybrid **10**.

EXPERIMENTAL

3.1. Generality

All apparatuses data were mentioned in sup. File. The synthetic procedure for the preparation of the starting substituted pyridine compounds **1-4** and the derived *O*-acetylenic compounds **5-8** were described in the supplementary file. 4-(4-Methoxyphenyl)-2-(prop-2-yn-1-yloxy)-6-(thiophen-2-yl)nicotinonitrile (**5**) was prepared as literature [59].

*3.1.1. **Synthesis of the O-Substituted pyridine terminal acetylenic compounds (5-8)***

The substituted pyridone compound **1-4** (3 mmol) was dissolved in DMF (20 mL) then the reaction flask was provided with anhydrous K_2CO_3 (3 mmol) followed by stirring for 50-60 min. To the latter mixture was then added gradually (over a period of 10 min) propargyl bromide (5 mmol) while stirring is continued in an ice bath. After stirring of the reaction content for 8 h at rt, it was added portion wise to an ice-cold water mixture with continues stirring for 30 min after which precipitate was formed. The precipitated product was filtered, washed with water, dried and recrystallized from ethanol to afford the acetylenic products **5-8**, respectively.

4-([1,1'-Biphenyl]-4-yl)-2-(prop-2-yn-1-yloxy)-6-(thiophen-2-yl)nicotinonitrile (6)

Phosphoric yellow crystal, Yield: 80%; M.p: 245-247 ºC; IR (ν_{max}, cm^{-1}): 3300 (≡CH), 3090 (=CH-Ar), 2955 (-CH), 2190 (C≡C), 2220 (C≡N), 1615 (C=N); ^{1}H NMR (400 MHz, DMSO) δ 3.66 (s, 1H, Acetylene-H), 5.29 (s, 2H, CH_2), 7.16 – 7.19 (m, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.44 (d, *J* = 5.2 Hz, 2H, Ar-H), 7.51 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.56 (d, *J* = 4.9 Hz, 1H, Ar-H), 7.64 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.73 (d, *J* = 4.2 Hz, 3H, Ar-H), 8.03 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO) δ 55.41 (OCH_2), 78.57 (C≡CH), 79.39 (C≡C), 92.20, 109.96, 114.52 (CN), 115.80, 124.31, 126.11, 126.44, 127.15, 127.79, 128.03, 129.19, 132.51, 135.34, 136.47, 149.52, 150.97, 151.71, 155.48 (Ar-C), 163.55 (C-O). Analysis calcd. for $C_{25}H_{16}N_2OS$ (392.48): C, 76.51; H, 4.11; N, 7.14. Found: C, 76.44; H, 4.06; N, 7.21.

6-(Prop-2-yn-1-yloxy)-4-(thiophen-2-yl)-[2,3'-bipyridine]-5-carbonitrile (7)

Brown crystal, Yield: 79%; M.p: 298-300 ºC; IR (ν_{max}, cm^{-1}): 3300 (≡CH), 3070 (=CH-Ar), 2955 (–CH), 2205 (C≡CH), 2218 (C≡N), 1612 (C=N); ^{1}H NMR (400 MHz, DMSO) δ 3.66 (s, 1H, Acetylene-H), 5.30 (s, 2H, CH_2), 7.59 (dd, *J* = 8.0, 4.8 Hz, 1H, Thio.-H), 7.77 (dd, *J* = 5.1, 1.5 Hz, 1H, Thio.-H), 7.83 (dd, *J* = 5.1, 2.9 Hz, 1H, Pyr.-H), 8.08 (s, 1H, Pyr.-H), 8.37 (dd, *J* = 3.0, 1.5 Hz, 1H, Pyr.-H), 8.64 (dt, *J* = 8.1, 2.0 Hz, 1H, Pyr.-H), 8.72 (dd, *J* = 4.8, 1.7 Hz, 1H, Pyr.-H), 9.48 (s, 1H, Pyr.-H); ^{13}C NMR (100 MHz, DMSO) δ 55.42 (OCH_2), 78.60 (C≡CH), 79.28 (C≡C), 92.20, 109.96, 114.52 (CN), 115.80, 124.31, 128.03, 129.11, 132.52, 135.35, 136.37, 149.22, 150.92, 151.75, 155.43 (Ar-C), 163.54 (C-O). Analysis calcd. for $C_{18}H_{11}N_3OS$ (317.37): C, 68.12; H, 3.49; N, 13.24. Found: C, 68.07; H, 3.56; N, 13.19.

6-(Prop-2-yn-1-yloxy)-4-(p-tolyl)-[2,3'-bipyridine]-5-carbonitrile (8)

Brown crystal, Yield: 80%; M.p: 260-262 ºC; IR (ν_{max}, cm^{-1}): 3300 (≡CH), 3100 (=CH-Ar), 2072 (–CH), 2195 (C≡CH), 2228 (C≡N), 1610 (C=N); ^{1}H NMR (400 MHz, DMSO) δ 2.42 (s, 3H, CH_3), 3.66 (s, 1H, Acetylene-H), 5.31 (s, 2H, CH_2), 7.10-7.14 (m, 1H, Ar-H), 7.42 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.59 (dd, *J* = 8.0, 4.9 Hz, 1H, Ar-H), 7.70 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.95 (s, 1H, Pyr.-H), 7.96-7.98 (m, 1H, Pyr.-H), 8.64 (dt, *J* = 8.1, 2.0 Hz, 1H, Pyr.-H), 8.72 (dd, *J* = 4.8, 1.7 Hz, 1H, Pyr.-H), 9.47 (s, 1H, Pyr.-H); ^{13}C NMR (100 MHz, DMSO) δ 21.38 (CH_3), 55.42 (OCH_2), 78.60, 79.31 (C≡C), 93.42, 115.22, 115.49, 124.35, 128.80, 129.14, 129.51, 129.93, 132.57, 133.06, 135.42, 140.75, 149.24, 151.74, 155.32, 157.30 (Ar-C), 162.78 (C-O). Analysis calcd. for $C_{21}H_{15}N_3O$ (325.37): C, 77.52; H, 4.65; N, 12.91. Found: C, 77.48; H, 4.67; N, 12.84.

3.1.2. Synthesis of the targeted 1,2,3-triazole glycosides via click chemistry reaction (9-13)

In a 100 mL round bottom flask the acetylenic substrates (1 equiv.) was placed in a mixture of H_2O/1-BuOH/CH_2Cl_2 (1:2:8), then stirred until complete dissolution was achieved. The sugar azide derivative (1 equiv.), Na-ascorbate (0.3 equiv.), DIPEA (0.15 equiv.), and $CuSO_4.5H_2O$ (0.15 equiv.) were added respectively. The addition of sodium ascorbate and $CuSO_4.5H_2O$ was performed in a separate concentrated solution of water. The reaction mixture was stirred in the dark for 2 days at rt. TLC has been used for following track of how the reaction was going and petroleum ether/ethyl acetate (90/10) was applied as an eluent. Once alkyne and azide reactants had been consumed work up was initiated by dilution of the resulting mixture with DCM then transference into a separating funnel. An aqueous ethylenediaminetetraacetic acid (EDTA) disodium salt (EDTA-Na_2) solution was added, then the organic phase was washed (2x) with water, and aqueous saturated NaCl solution (2x). Dryness of the separated organic layer over Na_2SO_4 and filtration, the target compounds were obtained **9**-**13**.

*2-((1-[2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl]-1H-1,2,3-triazol-4-yl)methoxy)-4-(4-methoxyphenyl)-6-(thiophen-2-yl)nicotinonitrile (**9**)*

Faint green powder, Yield: 75%; M.p: 139-141˚C; IR (ν_{max}, cm^{-1}): 3065 (=CH-Ar), 2945 (–CH), 2220 (C≡N), 1745 (C=O), 1610 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83, 2.03, 2.06, 2.07 (4s, 12H, CH_3CO), 3.88 (s, 3H, OCH_3), 4.01 (dd, *J* = 10.2, 5.0 Hz, 1H, H-6″), 4.15 (dd, *J* = 12.7, 2.2 Hz, 1H, H-6′), 4.28 (dd, *J* = 12.6, 4.9 Hz, 1H, H-5′), 5.25 (t, *J* = 9.6 Hz, 1H, H-3′), 5.45 (dt, *J* = 25.1, 9.5 Hz, 2H, H-4′, H-2′), 5.73 (s, 2H, CH_2), 5.89 (d, *J* = 9.0 Hz, 1H, H-1′), 7.03 – 7.06 (m, 2H, Ar-H), 7.15 – 7.17 (m, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 7.52 – 7.54 (m, 1H, Ar-H), 7.62 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.73 – 7.74 (m, 1H, Ar-H), 8.01 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.09, 20.53, 20.56, 20.69 ($4CH_3CO$), 55.44 (OCH_3), 61.49 (C-6), 67.61 (C-2), 70.14 (C-4), 72.65 (C-3), 75.11 (C-5), 85.71, 92.14 (C-1), 112.06, 114.43, 115.49, 121.82, 127.12, 128.15, 128.59, 129.83, 130.04, 143.05, 144.31, 152.73, 156.41, 161.18, 163.79 (Ar-C), 168.83, 169.36, 169.98, 170.59 (4C=O). Analysis calcd. for $C_{34}H_{33}N_5O_{11}S$ (719.72): C, 56.74; H, 4.62; N, 9.73. Found: C, 56.69; H, 4.59; N, 9.78.

4-([1,1'-Biphenyl]-4-yl)-2-((1-[2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl]-1H-1,2,3-triazol-4-yl)methoxy)-6-(thiophen-2-yl)nicotinonitrile (**10**)

Faint green powder, Yield: 77%; M.p: 142-144 ˚C; IR (ν_{max}, cm^{-1}): 3080 (=CH-Ar), 2950 (–CH), 2218 (C≡N), 1750 (C=O), 1604 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84, 2.03, 2.06, 2.07 (4s, 12H, CH_3CO), 4.01 (dd, *J* = 10.4, 5.0 Hz, 1H, H-6″), 4.15 (dd, *J* = 12.7, 2.2 Hz, 1H, H-6′), 4.29 (dd, *J* = 12.6, 4.9 Hz, 1H, H-5′), 5.26 (t, *J* = 9.6 Hz, 1H, H-3′), 5.45 (dt, *J* = 24.6, 9.5 Hz, 2H, H-4′, H-2′), 5.76 (s, 2H, CH_2), 5.90 (d, *J* = 9.1 Hz, 1H, H-1′), 7.17 – 7.19 (m, 1H, Ar-H), 7.27 (s, 1H, Ar-H), 7.43 (d, *J* = 5.2 Hz, 2H, Ar-H), 7.49 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.55 (d, *J* = 4.9 Hz, 1H, Ar-H), 7.65 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.75 (d, *J* = 4.2 Hz, 4H, Ar-H), 8.02 (s, 1H, Ar-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 20.09, 20.54, 20.56, 20.70 ($4CH_3CO$), 61.48 (C-6), 67.61 (C-2), 70.16 (C-4), 72.64 (C-3), 75.13 (C-5), 85.74, 92.42 (C-1), 103.72, 112.26, 115.24, 121.82, 127.10, 127.20, 127.30, 127.70, 127.96, 128.65, 128.81, 128.95, 130.23, 131.68, 134.74, 136.49, 139.98, 141.29, 142.95, 143.05, 144.26, 150.69, 152.98, 156.42, 163.77 (Ar-C), 168.84, 169.36, 169.98, 170.59 (4C=O). Analysis calcd. for $C_{39}H_{35}N_5O_{10}S$ (765.79): C, 61.17; H, 4.61; N, 9.15. Found: C, 61.21; H, 4.57; N, 9.20.

*6-((1-[2,3,4-Tri-O-acetyl-β-D-xylopyranosyl]-1H-1,2,3-triazol-4-yl)methoxy)-4-(thiophen-2-yl)-[2,3'-bipyridine]-5-carbonitrile. (**11**)*

Pale yellow powder, Yield: 77%; M.p: 155-157 ˚C; IR (ν_{max}, cm^{-1}): 3058 (=CH-Ar), 2955 (–CH), 2225 (C≡N), 1752 (C=O), 1614 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85, 2.05, 2.07 (3s, 9H, CH_3CO), 3.58 (d, *J* = 11.2 Hz, 1H, H-5″), 4.30 (dd, *J* = 11.9, 5.6 Hz, 1H, H-5′), 5.19 (s, 2H, CH_2), 5.39 – 5.45 (m, 2H, H-3′, H-4′), 5.78 (dd, *J* = 14.0, 5.8 Hz, 2H, H-2′, H-1′), 7.18 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.47- 7.50 (m, 2H, Ar-H), 7.64-7.65 (m, 2H, Ar-H), 7.73-7.75 (m, 2H, Ar-H), 7.99 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.13, 20.65, 20.77 ($3CH_3CO$), 65.55 (C-5), 68.36 (C-2), 70.31 (C-4), 72.02 (C-3), 75.05, 86.35 (C-1), 92.41, 109.77, 112.23, 112.43, 115.20, 121.76, 124.17, 127.09, 127.20, 127.30, 127.34, 127.70, 127.95, 128.57, 128.65, 128.81, 128.95, 129.35, 130.26, 130.40, 134.70, 134.75, 137.36, 139.99, 142.89, 142.94, 143.03, 143.06, 152.94, 152.97, 156.40, 163.27, 163.76 (Ar-C), 168.93, 169.76, 169.95 (3C=O). Analysis calcd. for $C_{29}H_{26}N_6O_8S$ (618.62): C, 56.31; H, 4.24; N, 13.59. Found: C, 56.28; H, 4.19; N, 13.63.

6-((1-[2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl]-1H-1,2,3-triazol-4-yl)methoxy)-4-(p-tolyl)-[2,3'-bipyridine]-5-carbonitrile. (**12**)

Pale yellow powder, Yield: 79%; M.p: 144-146 ˚C; IR (ν_{max}, cm^{-1}): 3100 (=CH-Ar), 2935 (–CH), 2228 (C≡N), 1748 (C=O), 1610 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84, 2.00, 2.01, 2.05 (4s, 12H, CH_3CO), 2.22 (s, 3H, CH_3), 4.14-4.20 (m, 2H, H-6″, H-6′), 4.23 – 4.25 (m, 1H, H-5′), 5.26 (dd, *J* = 10.4, 3.3 Hz, 1H, H-3′), 5.55 (s, 2H, CH_2), 5.58 – 5.60 (m, 1H, H-4′), 5.80 (d, *J* = 2.8 Hz, 1H, H-2′), 5.87 (d, *J* = 9.3 Hz, 1H, H-1′), 7.51 – 7.57 (m, 4H, Ar-H), 7.62 (s, 1H, Ar-H), 8.02 (d, *J* = 6.2 Hz, 4H, Ar-H), 8.46 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.20, 20.52, 20.67, 20.69 ($4CH_3CO$), 61.24 (C-6), 66.83 (C-2), 67.80 (C-4), 70.75 (C-3), 74.09 (C-5), 86.28, 93.05 (C-1), 109.47, 113.29, 115.33, 116.30, 121.82, 126.82, 127.00, 127.34, 128.91, 134.84, 136.17, 144.04, 150.85, 151.54, 155.54, 164.26 (Ar-C), 169.03, 169.86, 170.08, 170.39 (4C=O). Analysis calcd. for $C_{35}H_{34}N_6O_{10}$ (698.69): C, 60.17; H, 4.91; N, 12.03. Found: C, 60.09; H, 4.96; N, 11.98.

6-((1-[2,3,4-tri-O-Acetyl-β-D-xylopyranosyl]-1H-1,2,3-triazol-4-yl)methoxy)-4-(p-tolyl)-[2,3'-bipyridine]-5-carbonitrile. (**13**)

Yellow powder, Yield: 76-77%; M.p: 152-154 °C; IR (ν_{max}, cm^{-1}): 3055 (=CH-Ar), 2940 (–CH), 2225 (C≡N), 1745 (C=O), 1615 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83, 2.03, 2.07 (3s, 9H, CH_3CO), 2.45 (s, 3H, CH_3), 4.00 – 4.05 (m, 1H, H-5″), 4.15 – 4.20 (m, 1H, H-5′), 4.27 – 4.32 (m, 1H, H-4′), 5.28 (d, *J* = 10.0 Hz, 1H, H-3′), 5.43 – 5.46 (m, 1H, H-2′), 5.80 (s, 2H, CH_2), 5.90 (d, *J* = 8.9 Hz, 1H, H-1′), 7.28 (s, 1H, Ar-H), 7.36 (d, *J* = 7.9 Hz, 3H, Ar-H), 7.57 (t, *J* = 6.3 Hz, 4H, Ar-H), 7.97 (s, 1H, Ar-H), 8.44 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.11, 20.56, 20.72 ($3CH_3CO$), 21.42 (CH_3), 67.61 (C-5), 70.16 (C-2), 72.59 (C-4), 73.97 (C-3), 75.16, 87.89 (C-1), 94.19, 102.55, 106.89, 109.41, 114.12, 114.98, 120.11, 121.64, 128.07, 128.28, 129.79, 129.84, 132.89, 134.80, 140.77, 141.66, 144.20, 151.35, 155.42, 157.40, 163.98 (Ar-C), 169.36, 169.97, 170.60 (3C=O). Analysis calcd. for $C_{32}H_{30}N_6O_8$ (626.63): C, 61.34; H, 4.83; N, 13.41. Found: C, 61.28; H, 4.79; N, 13.45.

3.2. ***Molecular docking***

All details are mentioned in the supplementary file. [56-58]

Conclusions

In this investigation, new products of targeted hybrid structures incorporating triazolyl-glycoside-heteroaryl and their related substituted pyridine scaffold were efficiently, synthesized using the click approach under mild conditions. The latter strategy was applied using the thienyl-pyridine or aryl-pyridyl hybrids with azido sugars. The cytotoxicity activity evaluation of the newly synthesized 1,4-disubstituted glucosyl-1,2,3-triazoles incorporating the derived hybrids as thienyl, pyridyl and aryl parts was estimated against (MCF-7), (PC-3) and (BJ-1) cancer cell lines and (RPE-1) comparing to doxorubicin to calculate their IC_{50}. Certain products possessing the heteroaryl or aryl, glycosyl moieties with 1,2,3-triazole linker revealed good activity. The performed molecular docking resulted in achievements of binding modes of the structural features of the most potent derivatives with the molecular protein targets.

Conflicts of interest

"There are no conflicts to declare".

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