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Synthesis, Molecular Docking And Anticancer Activity Of New Pyridyl-1,2,4-Triazole-Thioglycosides And Their Pyridyl-[1,2,4]Triazolo[1,5-A]Pyridine-Glycoside Analogues

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Abstract

Cancer remains a main threat for human life and requires intensive research for discovering and developing treatment strategies. The design and synthesis of novel functionalized and hybrid structures as candidates for anticancer activity investigation have been proven in the literature as an efficient approach for providing a variety of compounds. In the current work, new compounds of hybrid structures incorporating aryl- or heteroarylpyridine, 1,2,4-triazole, glycosyl moieties have been prepared via a stepwise pathway starting from simple available starting compounds. The anticancer activity against MCf-7, PC3 and A549 human cancer cell lines revealed that substituted 1,2,4-triazole-thiol based substituted pyridine structure and the *N*-glycosyl derivative of the 1,2,4-triazolopyridine compounds exhibited the most potent activities against MCF-7 and A549 cancer cells. Molecular docking into EGFR active site and showed good binding affinities via various modes.

Keywords: Pyridine; 1,2,4-triazole; glycosides; cancer; molecular docking; cytotoxicity.

Introduction

Cancer represents one of the critical threats for human health due to the extreme deficiency of potent and safe treatments. Molecular hybridization, a strategy aiming for the incorporation of more than one motif in one hybrid structure was found as an efficient tool for providing more safer and active anticancer candidates, simulated more research in chemotherapy strategy for treatment of the cancer threat.

As a versatile nitrogen heterocyclic motif, 1,2,4-triazoles and their related fused heterocyclic derivatives have been widely recognized, particularly, as neuroprotectant [1], antioxidant [2], antimalarial [3], anti-leishmanial [4], antimicrobial [5], antiviral [6,7], anticonvulsant [8], anticancer [9,10] and g-aminobutyric acid-A (GABA-A) a-2, a-3 and a-5 containing receptor antagonists [11] and their synthesis gain interest [12]. Nitrogen system incorporating derivatives exert their actions as efficient pharmacophores by interacting with the biological receptors with high affinity owing to their dipole character, hydrogen bonding capacity, rigidity and solubility. It is an integral part of a variety of drugs available in clinical therapy, including anticancer (anastrozole), aromatase inhibitor (letrozole) and anticonvulsant (loreclezole) [13,14]. Their ability to target EGFR and CDK-2/cyclin A2 allows them to become potent anticancer agents. For example, heterocycles incorporating triazole moieties have demonstrated significant activity against HepG-2 and MCF-7 cancer cell lines, with IC50 values as low as 8.3 μM [15]. Additionally, triazole-based compounds have demonstrated antiviral properties against HIV and hepatitis C [16,17].

The Pyridine ring system possessing compounds exhibited various bioactivities, one of which is anticancer activity [18-21], providing them a versatility features as critical molecules in pharmaceutical research for anticancer. Pyridines are particularly known with their ability to serve as core structures in many FDA-approved drugs, including anticancer agents like sorafenib and crizotinib [22-25]. Their cytotoxic effects are enhanced when hybridized with triazole groups, as seen in pyridine-triazole

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hybrids, which exhibit potent activity against multiple cancer cell lines [22, 26]. Pyridines have also been identified for their neuroprotective effects in treating neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Notably, nicotine, a well-known pyridine alkaloid, enhances cognitive function by modulating neurotransmitter release [27, 28].

Triazolopyridines, have emerged as a class of compounds with remarkable anticancer, antifungal, and antiviral properties. These compounds have demonstrated selective cytotoxicity against various cancer cell lines, including HeLa, human colon cancer, and lung adenocarcinoma [26,29]. They have been revealed as potential tubulin polymerization inhibitors, allowing them as valuable candidates for treating cancers by preventing cancer cell division [26, 30]. Compound **II** showed VEGFR2 kinase inhibitory action, and the [1,2,4]triazolo[1,5-a]pyridine displayed favorable physicochemical properties. Furthermore, **IV** inhibited VEGFR2 kinase [30]. Triazolopyridine derivatives were designed and synthesized, indicating analog **IV** as a potent RORt inverse agonist [31]. A series of compounds based on 1,2,4-triazolo[1,5-a]pyridine scaffold and discovered that CEP-33779 is a novel, selective, and orally bioavailable inhibitor of JAK2 [32]. Thus CEP-33779 can be used in anticancer therapy [33] and rheumatoid arthritis treatment [34]. Wyatt et al. identified 2-acylamino-6-aryl[1,2,4]triazolo[1,5-a]pyridines as inhibitors of the leishmania cdc 2-related protein kinase CRK3 [35].

Owing to the above forementioned significances related to the observed impact of the individual or incorporated heterocyclic cores as well as our interest [36-41] in the synthesis of biologically active glycosyl heterocycles, simulated our interest to design, synthesize and investigate the anticancer activity of new 1,2,4-triazole-pyridine-triazolopyridine-glycosyl hybrids against a number of human cancer cell lines.

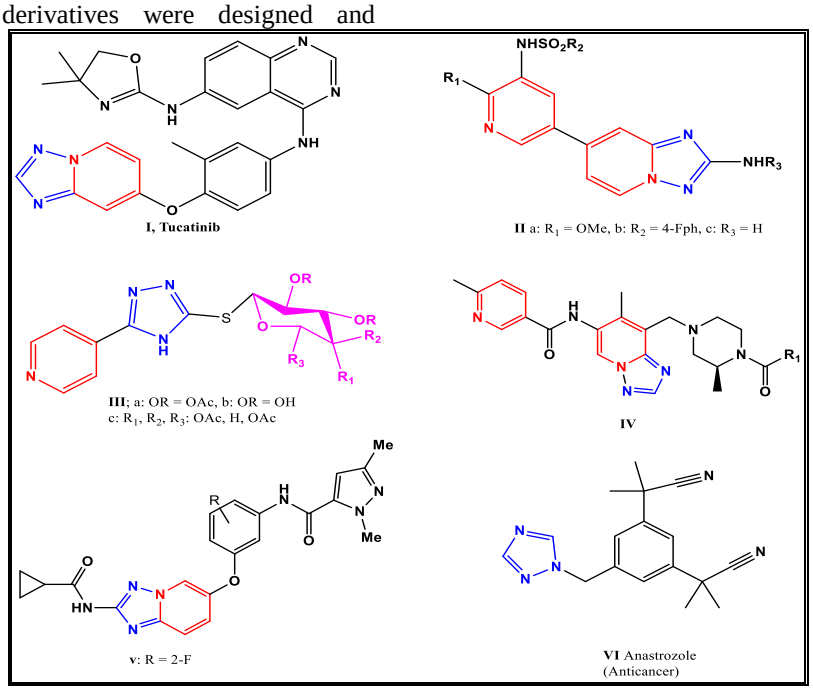


Figure 1: Anticancer 1,2,4-triazoles, pyridine and triazolopyridine compounds

Results and Discussion

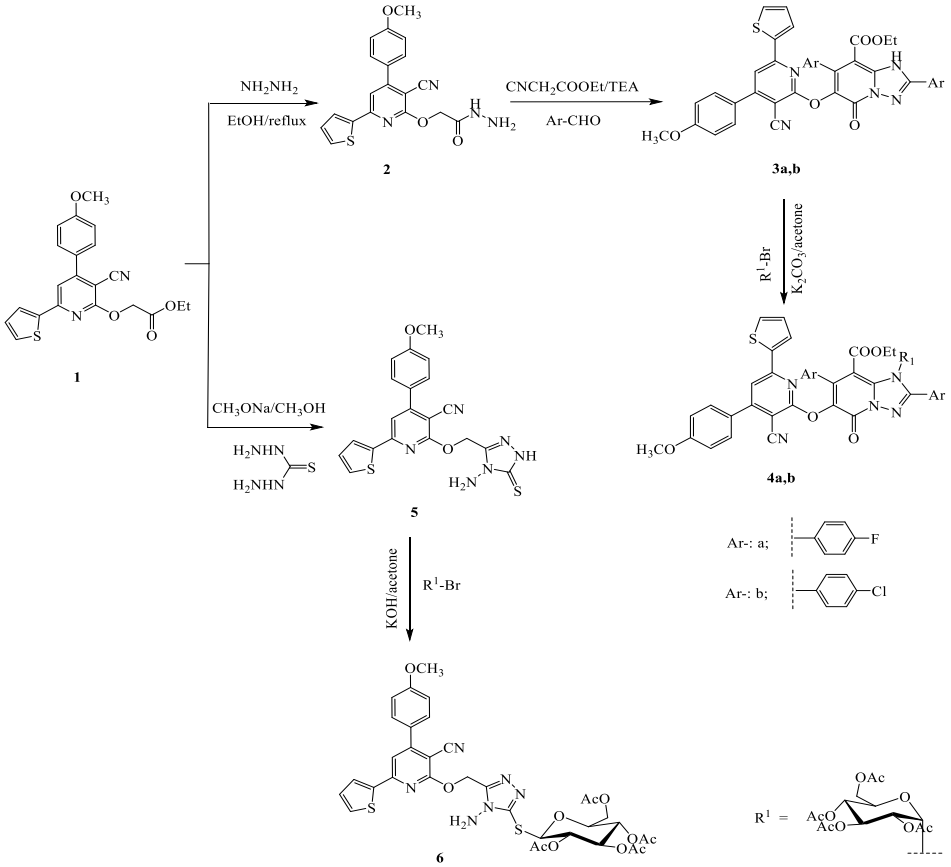
In this investigation, the ester **1** and hydrazine hydrate were reacted to result in the formation of the hydrazide **2** [42]. Reacting the latter with ethyl cyanoacetate, and either *p*-chlorobenzaldehyde or *p*-fluorobenzaldehyde in basic medium afforded the bicyclic product **3a,b**. Reaction of the resulting triazolopyridine products with tetra-*O*-acetyl-*D*-glucopyranosyl bromide resulted in the formation of the *N*-glycoside derivatives **4a,b**. The Infrared (IR) spectra of compounds **3a** and **3b** show absorption peaks at 3214 and 3244 cm $^{-1}$, which are assigned to the (NH) group. The other absorption peaks occur at 2218 cm^{-1} for the CN group, 1675 and 1703 cm^{-1} for the carbonyl group. The ^{1}H NMR spectrum presents signals at 5.34, 5.57 ppm for (NH), and aromatic protons have signals ranging from 7.16-7.71 ppm. A signal at 8.08 ppm is discerned for a CH proton on the pyridine ring. In the ^{13}C NMR spectrum, the carbon of the C=N group is indicated by a signal at 163.81 ppm, while the characteristic cyanide group signal is observed at 114.82 ppm. Infrared (IR) spectral data for compounds **4a** and **4b** reveal absorption peaks, attributed to the (C=O) acetyl group, at 1749 and 1747 cm^{-1}. A peak corresponding to the cyanide group is also observed at 2219 cm^{-1}. ^{1}H NMR spectra display signals between 1.92-2.01 ppm, assigned to acetate group protons, and 4.71-5.39 ppm, attributed to sugar protons. A signal at 8.07 ppm corresponds to a CH proton on the pyridine ring. The anomeric proton signal was observed at 5.39 with a coupling constant 8 accounting for the *β*-conformation. For ^{13}C NMR, signals for the carbon atoms of the acetate groups are found at 20.07 and 21.0 ppm. Sugar carbon signals range from

69.0-86.1 ppm and 70.18-84.41 ppm for **4a** and **4b**, while carbonyl group signals are distinct at 170.2 and 186.09 ppm.

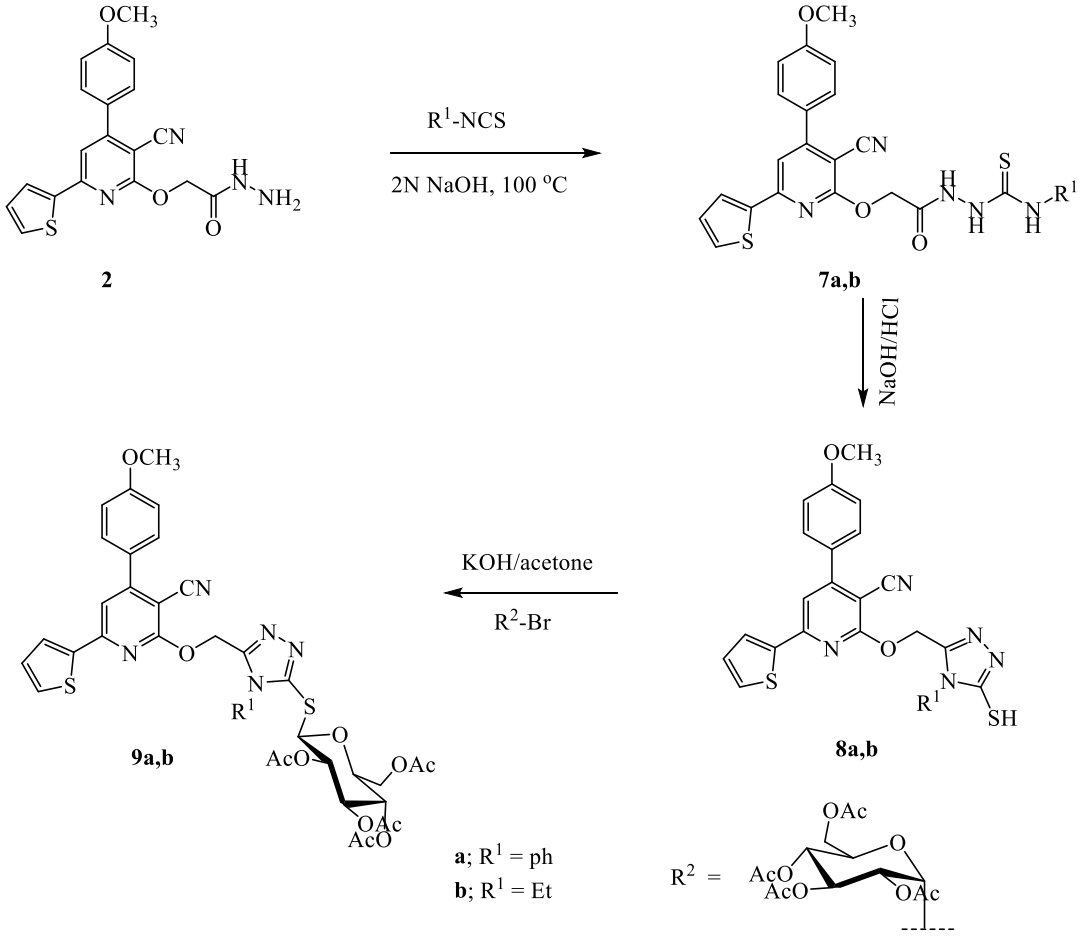
The substituted 1,2,4-triazole derivative **5** was prepared starting with the ester **1** via reaction with thiocarbohydrazide, Compound **5** was then used as a substrate for preparation of the *S*-glycoside compound **6** via reaction with 2,3,4,6-tetra-*O*-acetyl-*D*-glucopyranosyl bromide The IR spectrum of **5** displays peaks at 1251, 1688 and 2219 cm^{-1}, correlating with the (C-O), (C=N) and (CN) functional groups, respectively. The ^{1}H NMR analysis reveals aromatic protons resonating occurring from 7.16 to 7.73 ppm, and a specific resonance at 8.09 ppm associated with the pyridine ring proton. As for the ^{13}C NMR spectrum, it reveals a C=N carbon signal at 169 ppm and a distinct cyanide group signal at 114.82 ppm. The Infrared (IR) spectrum of the thioglycoside **6** exhibits an absorption peak at 1741 cm^{-1}, corresponding to the (C=O) of the acetyl group in the sugar part. The ^{1}H NMR spectrum indicates a signal between 1.94-2.01 ppm, attributable to the protons of the acetate groups, and between 4.70-5.47 ppm for the sugar protons. The anomeric proton signal was observed at 5.47 with a coupling constant 7 accounting for the *β*-conformation of the sugar attachment to the triazole ring in the diglycosidic linkage. The ^{13}C NMR spectrum demonstrates four separate signals at 20.74, 20.83, 20.94, and 21.02 ppm for the carbon atoms of the acetate groups, and a distinct carbonyl group signal at 170.50 ppm.

Upon heating thr hydrazide **2** with isothiocyanate derivatives, compounds **7a, b,** were generated, which were refluxed in a basic solution affording the 1,2,4-triazole products **8a,b**, respectively. Glycosylation via interaction with 2,3,4,6-tetra-*O*-acetyl-*D*-glucopyranosyl bromide in acetone. produced the *S*-glycoside products **9a,b**. The IR spectra of compounds **7a** and **7b** show NH group peaks in addition to CN and C=O bands. Both **7a** and **7b** ^{1}H NMR spectra have an OCH_3 group signal at 3.86 ppm and unique NH group signals as well as the signals assigned for the remaining hydrogens. The Infrared (IR) spectra for compounds **8a** and **8b** reveal the presence of cyanide (CN) absorption peaks at 2216 and 2218 cm-1, respectively.

The proton ^{1}H NMR spectra of **8a** and **8b** showed the signal assigned for the CH_2 linked to oxygen, and a signal at for the SH group in addition to the aryl and thienyl; protons. The proton ^{1}HNMR spectra for compounds **9a,b,** showed the signals within the range of 1.97-2.15 ppm and 1.94-2.04 ppm, respectively, attributed to the acetate group protons. Additionally, sugar proton signals appear between 4.70-5.81 ppm for compounds **9a, 9b** in addition to the remaining hydrogen signals of the assigned structure. The H-1 (assigned as sugar anomeric proton hydrogen) signal was revealed at 5.91-6.01 showing a value of *J* as 7 Hz indicating the *β*-attachment mode of the attached sugar to the triazole ring in the diglycosidic linkage of the formed thioglycosides.



Scheme 1: Synthesis of 1,2,4-triazolopyridine and 1,2,4-triazole glycosides



Scheme 2

2.2 Cytotoxicity

The cytotoxic potential of the newly developed derivatives was tested against a variety of human cancer cell lines, including breast **(MCF-7)**, **(A-549)**, and prostate cancer cells **(PC3)**, as well as normal human **(BJ1)** cells. These evaluations were performed using the colorimetric MTT assay 76-78 and benchmarked against the standard medication, doxorubicin, at a dosage of 100 μM (as outlined in Table 1). For those derivatives displaying a cytotoxic activity of ≥50% at a concentration of 100 μM, the IC_{50}, or effective concentration, was further determined. This was accomplished through additional screenings involving exposure of the target cells to concentrations ranging from (1000.78 μM).

Compound **8b** was revealed as the most potent compound within the investigated series against the studied human cancer cell lines **(MCF-7)**, **(PC3)**, and (**A549)**. The cytotoxicity inhibition percentage were comparable of such compounds to that recorded for the reference drug. Interestingly, all tested compounds presented safety margins concerning their effects upon normal human **(BJ1)** cells.

Through a comprehensive analysis of various compounds and their impacts on cancer cell lines **MCF-7**, **PC3**, and **A549**, several noteworthy observations were made. The compound **153b** exhibited the most potent activity against **MCF-7** cells but showed no impact on **PC3** cells. On the flip side, compound **7b** had the least impact on **MCF-7** cells. Compound **8b** demonstrated strong cytotoxic effects across all three cancer cell lines, particularly in **MCF-7** and **A549** cells, but it, along with **9a**, had the least impact on **PC3** cells. Compounds **4a** and **4b** also displayed strong activity in both **MCF-7** and **A549** cells but were moderate against **PC3** cells. Interestingly, compound **8a** was effective against **MCF-7** and **PC3** but showed significantly reduced activity against **A549** cells, where **7a** and **3b** had the least impact. Moreover, compound **7b** exhibited weak cytotoxic activity across all cell lines tested. It is worth noting that compounds **2**, **7b** showed no activity against **PC3** cells. In contrast, compounds like **8b** and **9b** were highly active against **PC3** cells.

For the impact on **BJ1** cells, only compounds **4a** and **4b** showed any activity, both exhibiting strong effects. Compounds **6** and **8b** showed the least impact on **BJ1** cells. This suggests that these specific compounds may have a wider cytotoxic profile, affecting not just cancer cells but also normal cells. Further studies could explore these relationships in more detail, potentially leading to more effective and targeted anti-cancer agents

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

Compounds	MCF-7	PC3	A549	BJ1
2	18.35Â±2.05	0.00Â±0.005	18.67±4.65	-
3a	23.17Â±2.58	0.77Â±1.34	11.67±9.01	-
3b	21.00Â±3.73	20.48Â±0.49	9.21±5.45	-
4a	57.83Â±1.97	15.87Â±3.06	52.23±2.38	96.46±0.16
4b	54.31Â±1.98	14.77Â±1.68	60.33±0.91	96.13±0.25
5	30.00Â±3.31	15.22Â±0.61	32.10±1.87	-
6	49.28Â±4.13	14.44Â±6.09	37.30±3.74	0.0±0.005
7a	29.61±0.59	8.43±1.74	21.7±0.50	-
7b	13.85±2.39	0±0.005	7.60±5.53	-
8a	45.20Â±3.66	23.78Â±2.24	10.64±5.54	-
8b	63.30Â±3.93	35.45Â±4.86	62.80±2.75	0.00±0.005
9a	14.55Â±1.06	0.42±0.10	19.47±6.10	-
9b	34.67±1.29	29.03±2.16	26.36±1.49	-

*The results are shown as average ± standard deviation

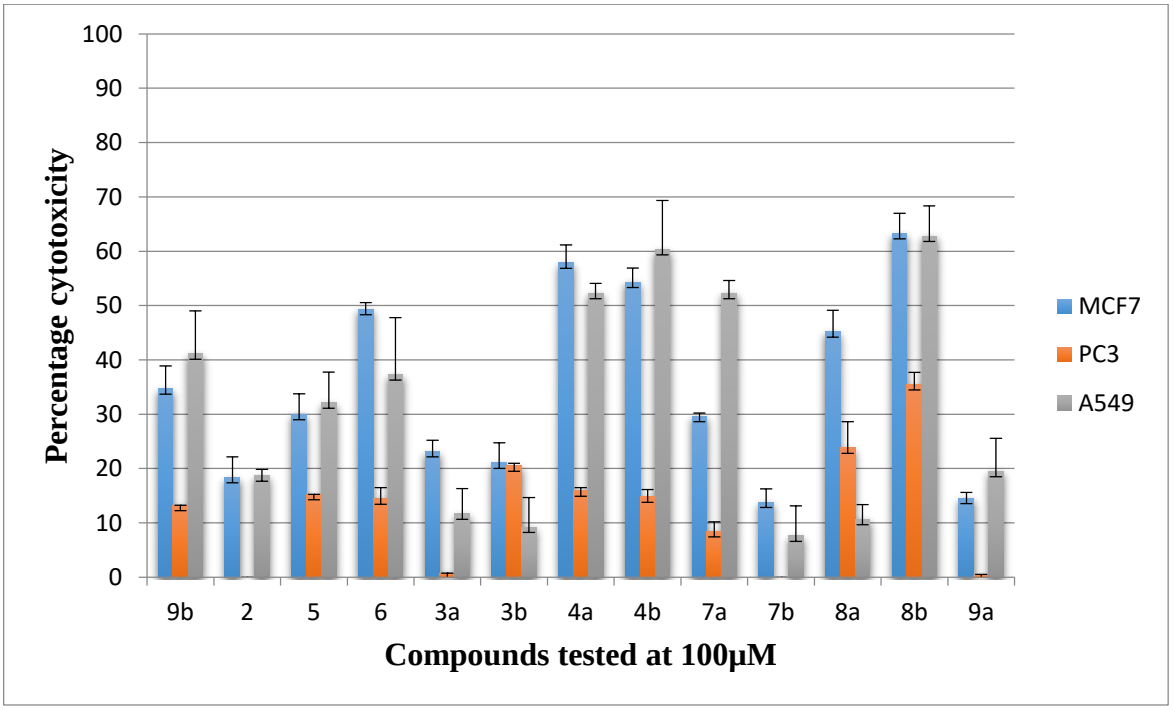


Figure 2. Percentage inhibitions of tested compounds at 100µM.

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

Compounds	MCF-7	A549
4a	45.09±11.00, r^2=0.95	61.12±19.45, r^2=0.89
4b	53.00±13.00, r^2=0.86	50.42±5.6, r^2=0.96
8b	4.77±0.5, r^2=0.98	10.29±5.00, r^2=0.94
Doxorubicin	45.02	48.8

*The results are shown as average ± standard deviation.

Structure Activity Relationship

The observed cytotoxicity results against the human cancer cells applied in the current investigation, were correlated to the structural features defined in the most potent investigated products providing a vision of the possible SAR correlation. It was found that the 1,2,4-triazole-5-thione incorporating ethyl-substitution at 1,2,4-triazile-*N*[4] revealed, obviously, more potent activity than its phenyl-substituted analogue against MCF-7 and A549 cells accounting for the selectivity according to the nature of the substituents as an alky partner. The enhanced activity results of the functionalized 1,2,4-triazolopyridine-*N*-glycosides **4a,b** reflects the

importance of the incorporating sugar moieties for activity and the role of the sugar part. The latter consequence is obvious and observed by the marked loss of activity of triazolopyridines **3a,b** as precursors of the active glycosides. There is a relative increase of activity of the p-fluoro substituent against MCF-7 slightly higher than its chloro-analogue.

2.3 Molecular Docking

All details were mentioned in sup. File. [41-46]

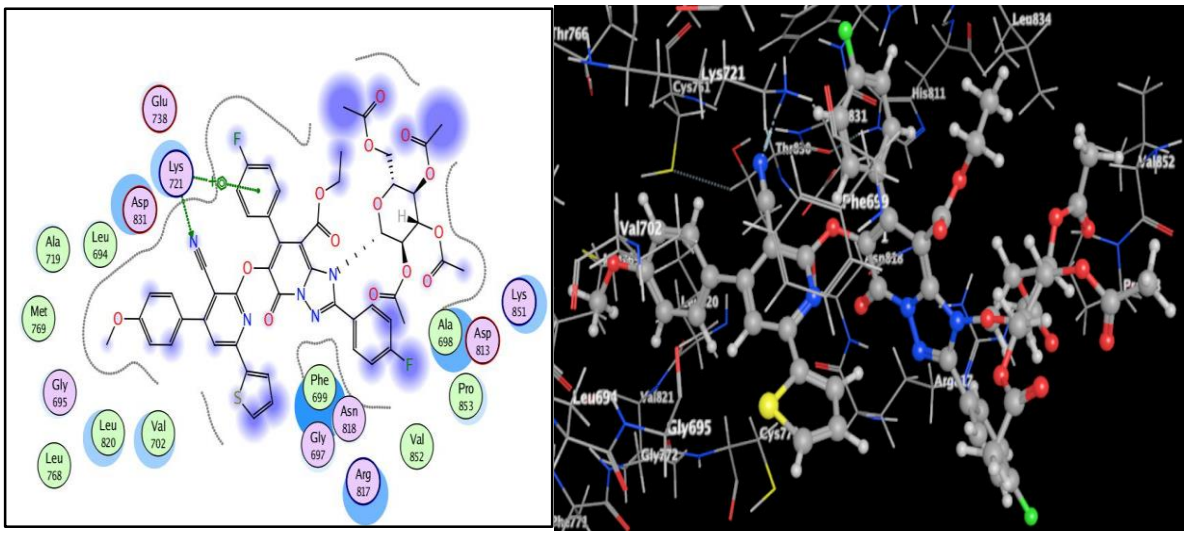


Figure 3. 2D and 3D Binding Models of Compound 4a with EGFR.

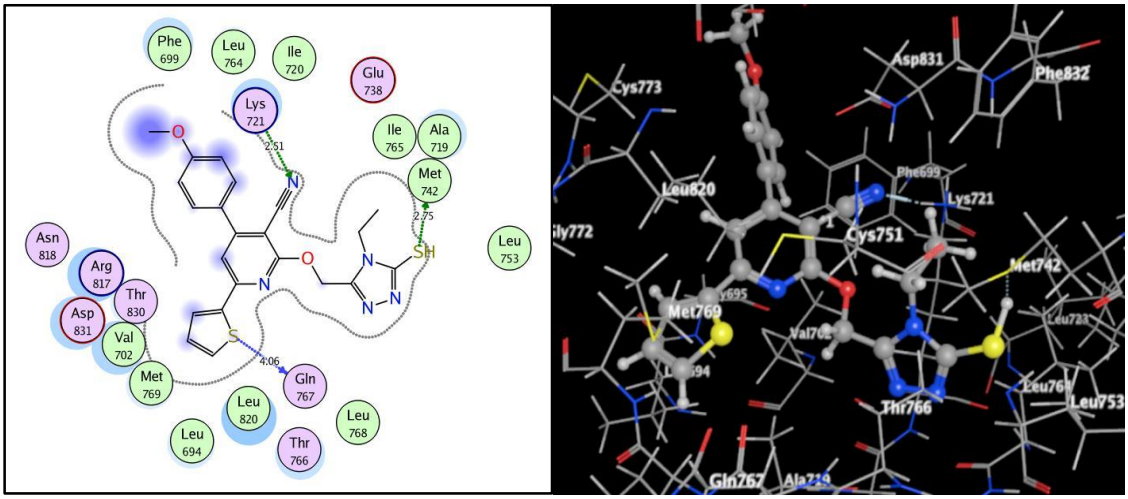


Figure 4. 2D and 3D Binding Models of Compound **8b** with EGFR.

Experimental

Chemistry

All details and procedures of synthesis of compounds were mentioned in sup. File.

Synthesis of compound *2-((3-cyano-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyridin-2-yl)oxy)acetohydrazide* **2** [42].

*Ethyl 6-(((3-cyano-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyridin-2-yl)oxy)methyl)-2,7-bis(4-fluorophenyl)-5-oxo-1,5-dihydro-[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate **3a***

withe powder, Yield 46%; M.p. 231-233 ºC; IR (KBr): 3309 (Ar-H), 3214 (NH), 2218 (CN), 1675, 1609 (2C=O), 1255 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 1.23 (t, *J* = 8.0 Hz, 3H, CH_3), 3,86 (s, 3H, OCH_3), 4.27 (q, *J* = 8.0 Hz, 2H, CH_2O), 4.93 (s, 2H, CH_2), 7.16 (d, *J* = 7.5 Hz, 4H, H_{Ar}), 7.23 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 7.70-7.72 (m, 5H, H_{Ar}), 7.76 (s, 1H, H_{Ar}), 7.83 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 8.08 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 9.38 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 14.92 (CH_3), 55.91 (OCH_3), 60.53, 64.72, ($2CH_2$), 85.46, 91.67, 93.82, 112.67, 114.82, 116.85, 118.0, 120.42, 121.49, 124.61, 129.13, 129.45, 130.63, 131.83, 131.83, 133.88, 142.90, 147.56, 148.84, 149.61, 151.33, 152.78, 153.78, 155.54, 156.07, 161.33, 163.82 (Ar-C), 166.95 (C=O); Analysis calcd. for $C_{39}H_{27}F_2N_5O_5S$ (715.73): C, 65.45; H, 3.80; N, 9.79. Found: C, 65.34; H, 3.71; N, 9.85.%.

*Ethyl 2,7-bis(4-chlorophenyl)-6-(((3-cyano-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyridin-2-yl)oxy)methyl)-5-oxo-1,5-dihydro-[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate (**3b**)*

white powder, Yield 45%; M.p. 218-221 ºC; IR (KBr): 3310 (Ar-H), 3244(NH), 2218 (CN), 1703, 1676 (C=O), 1257 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 1.23 (t, *J* = 8.0 Hz, 3H, CH_3), 3,87 (s, 3H, OCH_3), 4.27 (q, *J* = 8.0 Hz, 2H, CH_2), 4.93 (s, 2H, CH_2), 7.16 (d, *J* = 7.5 Hz, 4H, H_{Ar}), 7.23 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 7.70-7.73 (m, 5H, H_{Ar}), 7.76 (s, 1H, H_{Ar}), 7.83 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 8.08 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 9.38 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 15.23 (CH_3), 55.92 (OCH_3), 64.72, 69.19 ($2CH_2$), 87.36, 94.43, 99.07, 112.66, 114.82, 116.85, 120.27, 124.98, 125.44, 128.15, 129.12, 129.44, 130.62, 131.83, 133.23, 134.07, 134.49, 135.17, 135.70, 136.27, 142.89, 148.58, 150.45, 155.16, 156.45, 161.33, 163.14 (Ar-C), 166.95 (C=O); Analysis calcd. for $C_{39}H_{27}Cl_2N_5O_5S$ (748.64): C, 62.57; H, 3.64; N, 9.36. Found: C, 62.56; H, 3.54; N, 9.44.%.

(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(6-(((3-cyano-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyridin-2-yl)oxy)methyl)-8-(ethoxycarbonyl)-2,7-bis(4-fluorophenyl)-5-oxo-[1,2,4]triazolo[1,5-a]pyridin-1(5H)-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate ***4a***

White powder, Yield 42%; M.p. 186-188 ºC; IR (KBr): 3222 (Ar-H), 2219 (CN), 1749, 1688 (2C=O), 1235 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 1.24 (t, *J* = 8.0 Hz, 3H, CH_3), 1.92, 1.95, 1.99, 2.01 (4s, 12H, $4COCH_3$), 3,86 (s, 3H, OCH_3), 4.02;4.21 (m, 2H, H-6", H-6'), 4.24 (q, *J* = 8.0 Hz, 2H, CH_2), 4.51 (s, 2H, CH_2), 4.71-4.73 (m, 1H, H-5'), 4.89 (t, *J* = 7.0 Hz, 1H, H-3'), 5.08 (d, *J* = 7.0 Hz, 1H, H-4'), 5.22 (d, *J* = 8.0 Hz, 1H, H-2'), 5.39 (d, *J* = 8.0 Hz, 1H, H-1'), 7.14-7.24 (m, 4H, H_{Ar}), 7.27-7.49 (m, 4H, H_{Ar}), 7.53-7.67 (m, 4H, H_{Ar}), 7.71-7.74 (m, 3H, H_{Ar}), 8.07 (s, 1H, H_{Ar}), ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 14.2 (CH_3), 20.7, 21.0 ($4CH_3CO$), 55.8 (OCH_3), 61.8 (CH_2O), 62.4 (C-6), 69.3 (C-2), 69.9 (CH_2O), 71.1 (C-4), 73.1 (C-3), 77.3 (C-5), 86.1 (C-1), 88.4, 93.2, 108.6, 114.6, 114.8, 115.4, 115.6, 124.2, 127.0, 127.6, 128.0, 128.1, 128.9, 129.6, 130.5, 131.3, 142.4, 147.0, 148.9, 151.8, 152.3, 154.2, 156.4, 161.1, 162.1, 164.3, 164.8 (Ar-C), 165.1 (C=O), 170.2 (4C=O); Analysis calcd. for $C_{53}H_{45}F_2N_5O_{14}S$ (1046.02): C, 60.86; H, 4.34; N, 6.70. Found: C, 60.93; H, 4.41; N, 6.62.%.

(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(2,7-bis(4-chlorophenyl)-6-(((3-cyano-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyridin-2-yl)oxy)methyl)-8-(ethoxycarbonyl)-5-oxo-[1,2,4]triazolo[1,5-a]pyridin-1(5H)-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate ***4b***

White powder, Yield 41%; M.p. 140-143 ºC; IR (KBr): 3166 (Ar-H), 2219 (CN), 1747 (C=O), 1667 (C=O), 1234 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 1.24 (t, *J* = 8.0 Hz, 3H, CH_3), 1.92, 1.95, 1.99, 2.01 (4s, 12H, $4COCH_3$), 3,86 (s, 3H, OCH_3), 4.02;4.23 (m, 2H, H-6", H-6'), 4.19 (q, *J* = 8.0 Hz, 2H, CH_2), 4.52 (s, 2H, CH_2), 4.72-4.74 (m, 1H, H-5'), 4.93 (t, *J* = 7.0 Hz, 1H, H-3'), 5.08 (d, *J* = 7.0 Hz, 1H, H-4'), 5.31 (d, *J* = 8.0 Hz, 1H, H-2'), 5.39 (d, *J* = 8.0 Hz, 1H, H-1'), 7.12-7.19 (m, 4H, H_{Ar}), 7.26-7.48 (m, 4H, H_{Ar}), 7.54-7.67 (m, 4H, H_{Ar}), 7.70-7.76 (m, 3H, H_{Ar}), 8.08 (s, 1H, H_{Ar}); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 15.5 (CH_3), 20.5, 20.8, 21.0 ($4CH_3CO$), 55.9 (OCH_3), 60.8 (CH_2O), 61.4 (C-6), 69.9 (C-2), 70.1 (CH_2O), 71.3 (C-4), 73.8 (C-3), 77.1 (C-5), 86.4 (C-1), 88.9, 93.1, 108.2, 114.1, 114.9, 115.4, 115.7, 124.1, 127.0, 127.7, 128.1, 128.4, 128.9, 129.5, 130.4, 131.7, 142.6, 147.1, 148.9, 151.4, 152.1, 154.2, 156.1, 161.5, 162.9, 164.3, 164.6 (Ar-C), 165.4 (C=O), 170.1 (4C=O); Analysis calcd. for $C_{53}H_{45}Cl_2N_5O_{14}S$ (1078.92): C, 59.00; H, 4.20; N, 6.49. Found: C, 58.93; H, 4.11; N, 6.56.%.

*2-((4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methoxy)-4-(4-methoxyphenyl)-6-(thiophen-2-yl)nicotinonitrile (****5****)*

White powder, Yield 66%; M.p. 181-183 ºC; IR (cm^{-1}) v: 3092 (Ar-H), 2938 (CH), 2219 (CN), 1688 (C=N), 1251 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 3.74 (s, 3H, NH_2, NH), 3,86 (s, 3H, OCH_3), 5.10 (s, 2H, OCH_2), 7.16 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 7.23 (dd, *J* = 7.5, 1.5 Hz, 1H, H_{Ar}), 7.72-7.74 (m, 2H, H_{Ar}), 7.81-7.84 (m, 2H, H_{Ar}), 8.09 (s, 1H, H_{Ar}),; ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 55.92 (OCH_3), 64.07 (CH_2), 91.18, 112.96, 114.82, 115.76, 128.00, 129.31, 129.54, 130.70, 132.07, 142.73, 152.75, 156.63, 157.0, 161.40 (Ar-C), 163.42 (C=N), 169.08 (C=S); Analysis calcd. for $C_{20}H_{16}N_6O_2S_2$ (436.51): C, 55.03; H, 3.69; N, 19.25. Found: C, 54.93; H, 3.78; N, 19.17.%.

*(2S,3S,4R,5S,6R)-2-(Acetoxymethyl)-6-((4-amino-5-(((3-cyano-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyridin-2-yl)oxy)methyl)-4H-1,2,4-triazol-3-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (****6****)*

oily substance; IR (cm^{-1}) v: 2934 (C-H), 1741 (C=O), 1639 (C=N), 1206 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 1.94, 1.96, 1.98, 2.01 (4s, 12H, $4COCH_3$), 3.98 (s, 3H, OCH_3),), 4.01-4.06 (m, 1H, H-6"), 4.10-4.14 (m, 1H, H-6'), 4.70-4.73 (m, 1H, H-5'), 4.89-4.94 (m, 1H, H-4'), 5.01 (t, *J* = 7.0 Hz, 1H, H-3'), 5.22 (s, 2H, CH_2), 5.36 (d, *J* = 7.0 Hz, 1H, H-2'), 5.38 (s, 2H, NH_2), 5.47 (d, *J* = 7.0 Hz, 1H, H-1', anomeric), 7.25 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 7.46 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 7.55-7.61 (m, 3H, H_{Ar}), 8.59 (s, 1H, H_{Ar}); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 20.74, 20.83, 20.94, 21.02 ($4CH_3$), 55.02 (OCH_3), 62.58 (C6), 66.73 (CH_2), 68.01 (C2), 70.28 (C4), 73.18 (C3), 83.64 (C5), 89.47 (C1, anomeric), 94.18, 118.91, 122.21, 126.49, 127.25, 128.52, 129.48, 129.98, 130.36, 130.90, 133.92, 134.60, 149.42, 150.37, 153.33, 159.41, 162.11, 163.67 (Ar-C), 169.70, 169.99, 170.42, 170.58 (4C=O); Analysis calcd. for $C_{34}H_{34}N_6O_{11}S_2$ (766.80): C, 53.26; H, 4.47; N, 10.96. Found: C, 53.18; H, 4.52; N, 11.01.%.

*(2-((3-cyano-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyridin-2-yl)oxy)acetyl)-N-phenylhydrazine-1-carbothioamide (****7a****)*

White powder, Yield 50%; M.p. 193-194 ºC; IR (cm-1) v: 3220, 3289 (NH), 2214 (CN), 1697 (C=O), 1298 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 3.86 (s,

3H, OCH_3), 5.13 (s, 2H, CH_2), 7.16-7.18 (m, 5H, H_{Ar}), 7.32 (d, *J* = 7.5 Hz, 3H, H_{Ar}), 7.40 (br s, 1H, NH), 7.71-7.77 (m, 4H, $4H_{Ar}$), 8.08 (s, 1H, H_{Ar}), 9.74, 10,39 (s, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 55.93 (OCH_3), 64.55 (CH_2), 91.62, 100.61, 112.89, 114.85, 127.02, 127.40, 128.10, 128.58, 128.66, 129.27, 129.43, 130.65, 131.72, 139.45, 142.72, 152.89, 156.43, 161.38, 163.79 (Ar-C), 167.38 (C=O), 183.24 (C=S); Analysis calcd. for $C_{26}H_{21}N_5O_3S_2$ (515.61): C, 60.57; H, 4.11; N, 13.58. Found: C, 60.63; H, 3.99; N, 13.66.%.

*2-(2-((3-Cyano-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyridin-2-yl)oxy)acetyl)-N-ethylhydrazine-1-carbothioamide (**7b**)*

White powder, Yield 54% ; M.p. 212-213 ºC; IR (cm-1) v: 3367, 3275, 3140, (NH), 2964 (CH), 2217 (CN), 1690 (C=O), 1265 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 1.01 (t, *J* = 8.0 Hz, 3H, CH_3), 3.40 (q, *J* = 8.0 Hz, 2H, CH_2) 3.86 (s, 3H, OCH_3), 5.07 (q, *J* = 8.0 Hz, 2H, CH_2), 7.16-7.18 (m, 2H, H_{Ar}), 7.25 (d, *J* = 7.5 Hz, 1H, H_{Ar}), 7.71-7.73 (m, 3H, H_{Ar}), 7.77 (br s, 1H, NH), 7.84-7.85 (m, 1H, H_{Ar}), 8.10 (s, 1H, H_{Ar}), 9.29, 10.16 (br s, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 14.86 (CH_3), 38.88 (CH_2), 55.93 (OCH_3), 64.54 (CH_2), 91.27, 101.11, 112.90, 114.85, 115.94, 128.08, 129.31, 129.53, 130.65, 131.79, 142.73, 152.83, 156.44, 161.38, 163.78, 166.41 (Ar-C), 167.78 (C=O), 174.64 (C=S); Analysis calcd. for $C_{22}H_{21}N_5O_3S_2$ (467.56): C, 56.51; H, 4.53; N, 14.98. Found: C, 56.42; H, 4.42; N, 15.07.%.

*2-((5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)methoxy)-4-(4-methoxyphenyl)-6-(thiophen-2-yl)nicotinonitrile (**8a**)*

Yellow powder, Yield 53%; M.p. 165-168 ºC; IR (cm-1) v: 2930 (CH), 2216 (CN), 1257 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 3.85 (s, 3H, CH_3), 5.51 (s, 2H, CH_2), 7.12-7.16 (m, 4H, H_{Ar}), 7.23-7.26 (m, 2H, H_{Ar}), 7.46-7.51 (m, 2H, H_{Ar}), 7.65-7.71 (m, 4H, H_{Ar}), 8.07 (s, 1H, H_{Ar}), 13.89 (s, 1H, SH); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 55.91 (OCH_3), 68.14 (CH_2), 93.2, 112.09, 114.74, 114.81, 127.63, 128.7, 128.37, 129.46, 130.63, 131.92, 143.71, 145.89, 150.05, 154.63, 156.4, 160.76, 164.39, 168.55 (Ar-C); Analysis calcd. for $C_{26}H_{19}N_5O_2S_2$ (497.59): C, 62.76; H, 3.85; N, 14.07. Found: C, 62.83; H, 3.76; N, 13.98.%.

*2-((4-Ethyl-5-mercapto-4H-1,2,4-triazol-3-yl)methoxy)-4-(4-methoxyphenyl)-6-(thiophen-2-yl)nicotinonitrile (**8b**)*

Light yellow powder, Yield 45%; M.p. 214-216 ºC; IR (cm-1) v: 2935 (CH), 2218 (CN), 1258 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 1.33 (t, *J* = 8.0 Hz, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.11 (q, *J* = 8.0 Hz, 2H, CH_2), 5.69 (s, 2H, CH_2), 7.16 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 7.25 (dd, *J* = 7.5, 1.5 Hz, 1H, H_{Ar}), 7.72 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 7.83 (s, 1H, H_{Ar}), 7.86 (d, *J* = 7.5 Hz, 1H, H_{Ar}), 8.14 (d, *J* = 7.5 Hz, 1H, H_{Ar}), 13.89 (s, 1H, SH); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 15.86 (CH_3), 27.29 (CH_2), 55.69 (OCH_3), 68.28 (CH_2), 91.39, 112.97, 114.22, 114.82, 121.11, 128.02, 129.53, 129.77, 130.68, 131.95, 152.98, 156.60, 160.04, 161.40 (Ar-C); Analysis calcd. for $C_{22}H_{19}N_5O_2S_2$ (449.55): C, 58.78; H, 4.26; N, 15.58. Found: C, 58.84; H, 4.32; N, 15.49.%.

*(2S,3S,4R,5S,6R)-2-(acetoxymethyl)-6-((5-(((3-cyano-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyridin-2-yl)oxy)methyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate **9a***

oily substance; IR (cm-1) v: 2930 (CH), 2216 (CN), 1747 (C=O), 1257 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 1.91, 1.99, 2.01, 2.02 (4s, 12H, $4COCH_3$), 3.85 (s, 3H, CH_3), 3.98-4.00 (m, 1H, H-6''), 4.12-4.14 (m, 1H, H-6'), 4.68-4.73 (m, 1H, H-5'), 4.86-4.93 (m, 1H, H-4'), 5.22 (s, 2H, CH_2), 5.37 (t, *J* = 7.0 Hz, 1H, H-3'), 5.81 (d, *J* = 7.0 Hz, 1H, H-2'), 6.01 (d, *J* = 7.0 Hz, 1H, H-1', $_{anomeric}$), 7.14-7.17 (m, 3H, H_{Ar}), 7.26 (t, *J* = 7.5 Hz, 2H, H_{Ar}), 7.71-7.74 (m, 4H, H_{Ar}), 7.83 (s, 1H, H_{Ar}), 7.85-7.87 (m, 2H, H_{Ar}), 8.15 (d, *J* = 7.5 Hz, 1H, H_{Ar}); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 20.7, 21.0, 21.2, 21.4 ($4CH_3CO$), 55.93 (OCH_3), 64.54, 68.5 ($2CH_2$), 68.6 (C6), 70.3 (C2), 73.3 (C4), 79.7 (C3), 89.2 (C5), 91.71 (C1, $_{anomeric}$), 112.90, 114.85, 115.94, 128.08, 128.7, 129.31, 129.53, 130.65, 131.79, 142.73, 145.5, 147.1, 150.5, 152.83, 156.44, 161.38, 163.78 (Ar-C), 170.2 (4C=O); Analysis calcd. for $C_{40}H_{37}N_5O_{11}S_2$ (827.88): C, 58.03; H, 4.51; N, 8.46. Found: C, 57.94; H, 4.43; N, 8.53.%.

*(2S,3S,4R,5S,6R)-2-(acetoxymethyl)-6-((5-(((3-cyano-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyridin-2-yl)oxy)methyl)-4-ethyl-4H-1,2,4-triazol-3-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate **9b***

White crystals, Yield 35%; M.p. 180-182 ºC; IR (cm-1) v: 2930 (CH), 2216 (CN), 1747 (C=O), 1257 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 1.49 (t, 3H, CH_3), 1.98, 1.99, 2.02, 2.03 (4s, 12H, $4COCH_3$), 3.84 (s, 3H, CH_3), 4.11-4.15 (m, 2H, H-6'', H-6'), 4.69 (m, 1H, H-5'), 5.04 (t, *J* = 7.0 Hz, 1H, H-4'), 5.17 (s, 2H, CH_2), 5.23 (s, 2H, CH_2O), 5.34 (d, *J* = 7.0 Hz, 1H, H-2'), 5.39 (t, *J* = 7.0 Hz, 1H, H-3'), 5.91 (d, *J* = 7.0 Hz, 1H, H-1', $_{anomeric}$), 7.33-7.47 (m, 4H, H_{Ar}), 7.53 (d, *J* = 7.5 Hz, 1H, H_{Ar}), 7.59 (d, *J* = 7.5 Hz, 1H, H_{Ar}), 7.93 (d, *J* = 7.5 Hz, 1H, H_{Ar}), 8.59 (s, 1H, H_{Ar}); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 13.39 (CH_3), 20.7, 21.0, 21.2, 21.4 ($4CH_3CO$), 31.1 (CH_2), 55.93 (OCH_3), 64.54, 68.5 ($2CH_2$), 68.6 (C6), 70.3 (C2), 73.3 (C4), 79.7 (C3), 89.2 (C5), 91.71 (C1, $_{anomeric}$), 112.90, 114.85, 115.94, 128.08, 129.31, 129.53, 130.65, 131.79, 142.73, 148.7, 152.83, 156.44, 157.6, 161.38, 163.78 (Ar-C), 170.2 (4C=O); Analysis calcd. for $C_{36}H_{37}N_5O_{11}S_2$ (779.84): C, 55.45; H, 4.78; N, 8.98. Found: C, 55.39; H, 4.82; N, 9.07.%.

Conclusion

Novel functionalized heteroaryl– and aryl-substituted pyridine derivatives, their derived 1,2,4-triazoles and 1,2,4-triazolopyridine glycosides, were efficiently synthesized via a multistep synthetic approach starting

from simple and available starting materials. According to the observed results, it was concluded that, the *N*-glycosyl derivatives of the 1,2,4-triazolopyridine bases substituted pyridine core revealed markedly increased activities and thus reflecting the importance of the glycopyranozyl sugar part for activity against MCF-7 and A549 cancer cells. Molecular docking simulations into EGFR enzyme active site showed good binding affinities via various interaction modes with various functionalities in such active site. On the other hand, the process of substitution at N^4-1,2,4-triazole with ethyl substituent in the 1,2,4-triazole-5-thiol structure resulted in more potent product than the aryl-substituted analogue accounting for the importance of the substituent nature as an alkyl partner. The afforded forementioned observations in the current investigation could be a useful basis for future studies on modified analogues with such main structural features.

Conflicts of interest

"There are no conflicts to declare".

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