Journal of Qassim University for Science
2024, *Vol 3* (Issue 1), pp. 177-203
Received: 15 February 2024
Revised: 15 March 2024
Accepted: 30 March 2024

JQUS

Pyrimidine-1,2,3-Triazole Hybrid Glycosides: Click Based Synthesis and Biological aspects.

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Abstract: Application of click chemistry for the construction of hybrid structure incorporating 1,2,3-triazole nucleus was extensively studied as a powerful strategy for designing a variety of targeted structures. The currents review focused on the synthetic pathways of compounds possessing two important motifs: pyrimidine and 1,2,3-triazole systems and their derived sugar derivatives as glycoside analogues. The reported bioactivities of the formed hybrid products were highlighted.

Keywords: Pyrimidine; 1,2,3-Triazole; Glycosides; Click.

1. INTRODUCTION

Pyrimidine is a heterocyclic organic compound widely spread in nature since pyrimidine-type nucleobases are basic cores in nucleic acids and other biological systems. The importance of pyrimidine motif extended also to the fact that pyrimidine pharmacophore-based products possess a variety of bioactivities. Pyrimidines were synthesized by the cyclization of β-dicarbonyl compounds with N-C-N compounds [1], Biginelli reaction [2] in addition to other methods depending on condensation of carbonyls with diamines [3]. Recently, pyrimidine derivatives were synthesized by reacting certain amides with carbonitriles under electrophilic activation of the amide with 2-chloro-pyridine and trifluromethane sulfonic anhydride [4]. Compounds containing a pyrimidine moiety have been found to have a variety of biological activities act as anti-viral [5], anti-cancer [6], anti-fungal [7], anti-malarial [8], anti-depressants and anti-convulsant [9], anti-thyroid [10], anti-Inflammatory [11], anti-alzheimer [12], anti-Angiogenic [13], anti-Hepatitis [14] activity.

1,2,3-Triazoles are heterocyclic compounds containing three nitrogen atoms that can act as an alternative of peptide bond which prompts their stability and enhances biological activity [15] resulting

in interested leads in organic and medicinal chemistry research [16]. These compounds have variety pharmacological properties, such as anti-HIV [17], anti-tubercular [18], anticancer [19], antibacterial [20], antifungal [21] activities.

Sugar molecules are important poly functional natural compounds with diverse stereochemical properties characterized by their non-toxic behaviours and play important roles in intracellular functions and molecular recognition [22-26]. When a glycoside attachment was achieved by linking bioactive molecules to a glycosyl moiety, potent products could be resulted which represents a major objective in drug discovery field [27-31]. The later fact was obvious in the synthesis of glycoside with potent and antitumor activities via inhibition of the enzymes [32–36].

Click chemistry was first discovered in 1999 by barry Sharpless. Cu catalyzed and ruthenium-catalysed reactions are mainly classified into four different reactions like cycloaddition, addition, carbonyl chemistry, nucleophilic substitution [37]. The Huisgen reaction of 1,3-dipolar cycloaddition reactions in which azide and alkyne are reacted together and form a substituted 1,2,3-triazol ring lacked for stereoselectivity of products. When the latter was catalyzed by Cu(I) or, in some cases, with ruthenium catalyst [38], 1,2,3-triazoles were easily synthesized with very easily available solvents like water at room temperature [39,40]. The click approach acquired considerable interest in organic and medicinal chemistry owing to the unique nature of the produced molecules and possibility of linking variant molecules via the important 1,2,3-triazole linker [41-45].The serine proteases are the best and the most prominent among the proteases in plants. Serine proteases inhibitors are considered as defending components in plants [6] they inhibit serine proteases either partially or completely [5]. Serine proteases are mainly considered as enzymes for cancer development; thus, serine proteases inhibitors which are derived from plants can be used as drugs for diseases instead of chemicals. [14,15]. In fact, serine protease inhibitors have received a great interest for their multiple applications in biotechnology and biomedicine that focused mainly on therapeutics. Moreover, therapeutic serine protease inhibitors have proven their effectiveness in treating immune, inflammatory, respiratory diseases, and HIV. Also, they prevent pathogens and provide protection to plants by being used in pest control. Recent findings have demonstrated proteolysis control as a pharmacologically valid tool. In one of the studies, the findings suggest that serine protease inhibitors camostat can be used to treat patients with pancreatitis, and it is considered as an industrial drug, since it may inhibit the replication of influenza A/H1N1 and A/H3N2 viruses in primary human tracheal epithelial (HTE) cells through the inhibition of hemagglutinin cleavage which is essential for virus entry into the cell and the start of its replication [16]. However, to avoid the effects of chemical drugs, it is essential to search for serine protease inhibitors in natural sources. Furthermore, a novel serine protease inhibitor gene was isolated from *Hevea brasiliensis* leaves and has been used against antifungal *Trichophytonrubrum* that cause the disease Athlete's foot [17].

Rhamnus frangula L, which is known as (Glossy buckthorn) from family *Rhamnaceae*, is a shrub that grows from 3-6 meters in wetland and upland, used as laxative and can be found as a component in

herbal laxative preparations. Some studies have shown that the plant is antifungal and antioxidant [18 –20]. A previous study published in 2017 by Abir et *al* [20] shows that they have purified a protease inhibitor extracted from *Rhamnus frangula*. A biochemical characterization was done and they determined its molecular weight of 22 kDA and its N-terminal sequence. They also showed that it inhibits different types of human and commercial proteases. All these results obtained pushed us to go further with a molecular characterization of the gene coding for this inhibitor. This knowledge will certainly contribute to the design of better approaches to further characterize this inhibitor in order to apply it in pharmaceutical formulations and to use it as a drug for several types of diseases.

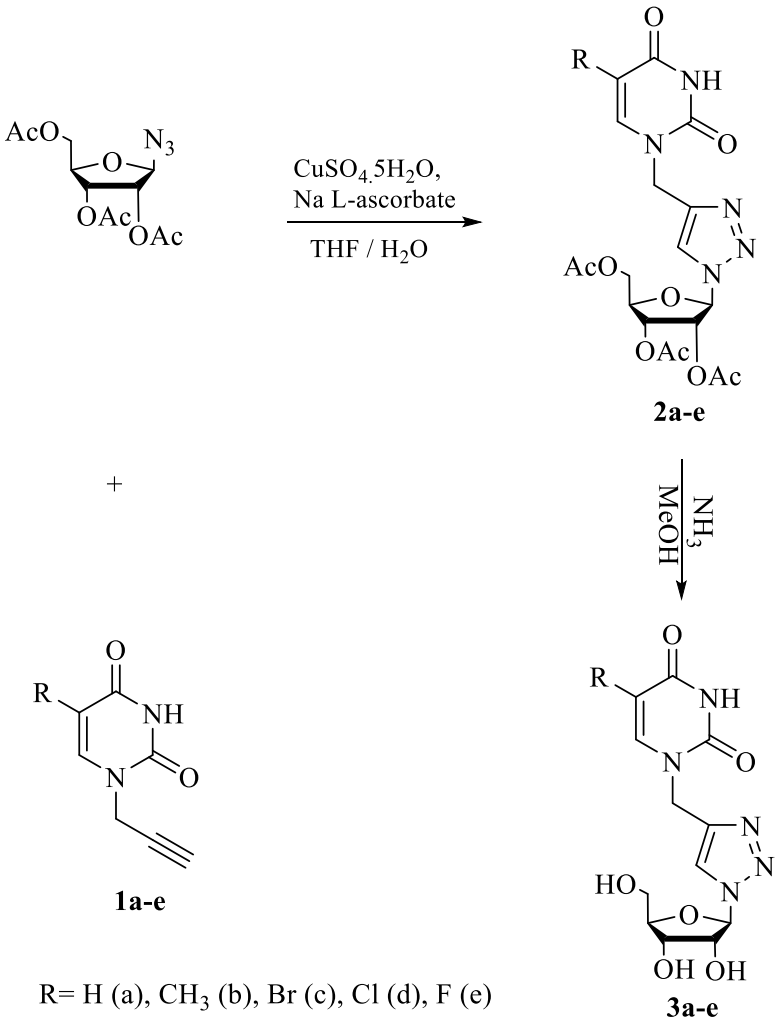
2. MATERIALS AND METHODS

2. **Click Bases Synthetic approach**

2.1. $CuSO_4.5H_2O$ - Na-ascorbate system

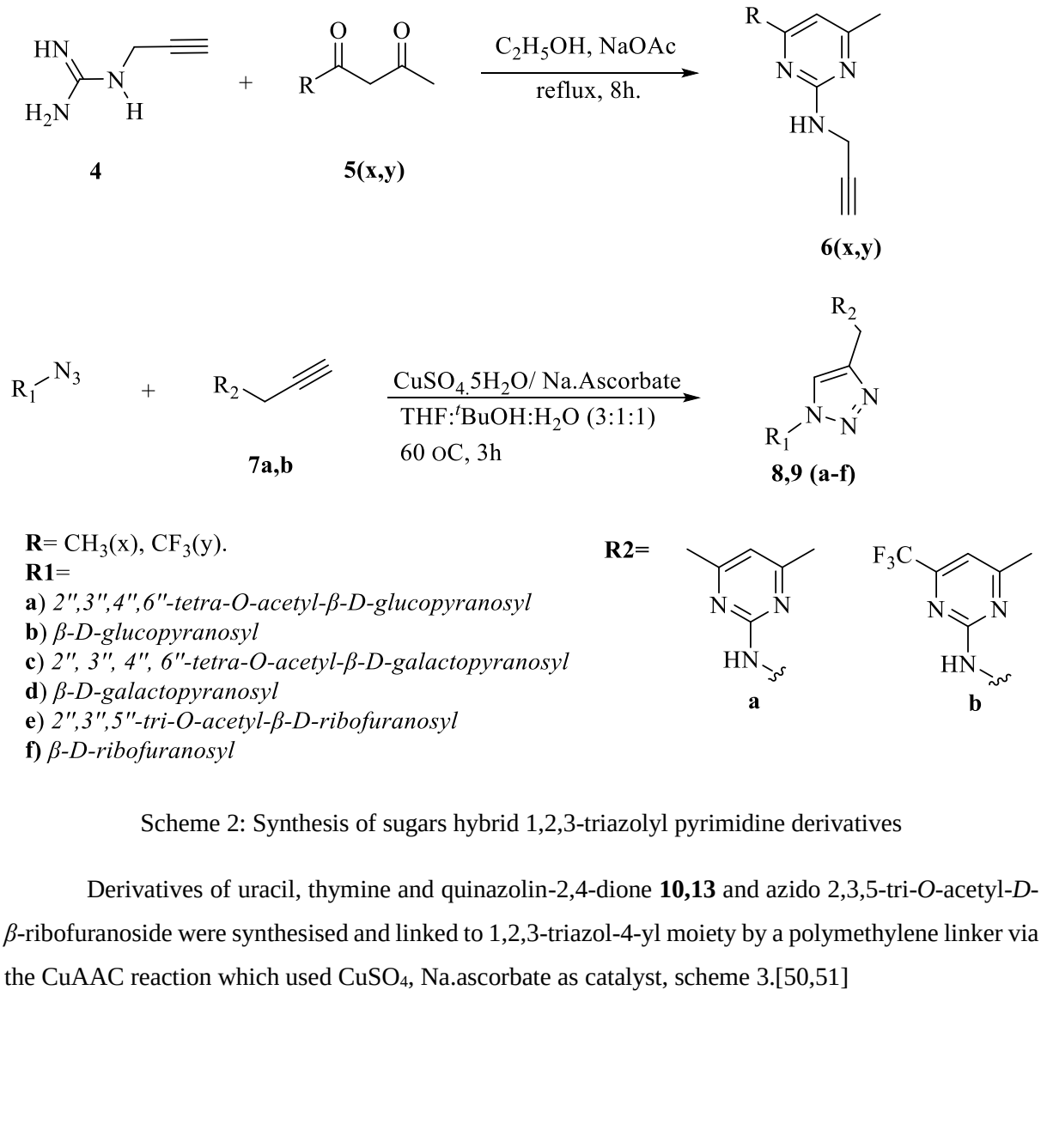
Click reactions are successfully catalysed by Cu (I) species and the difficulty in various cases for maintaining the stability of such ions promoted the use of an effective method for their *in-situ* fresh generation. The most widely applied systems for the latter purpose is $CuSO_4.5H_2O$ - Na-ascorbate system. by using click reaction chemistry, Copper-catalyzed azide-alkyne cycloaddition (CuAAC) was utilized to link propargyl uracil derivatives with the protected azido ribofuranose in the presence of catalytic amounts of $CuSO_4.5H_2O$ and sodium ascorbate.

The Cu(I)-catalyzed [2+3] dipolar cycloaddition reaction occurred with full regioselectivity, to obtain the 1,4-disubstituted 1,2,3-triazoles derivatives **2a–e**. then by using saturated methanolic ammonia solution, which converted the acetyl groups of the protected nucleosides to obtain free hydroxyl analogues **3a-e**, in 75% yield, scheme 1.[46]



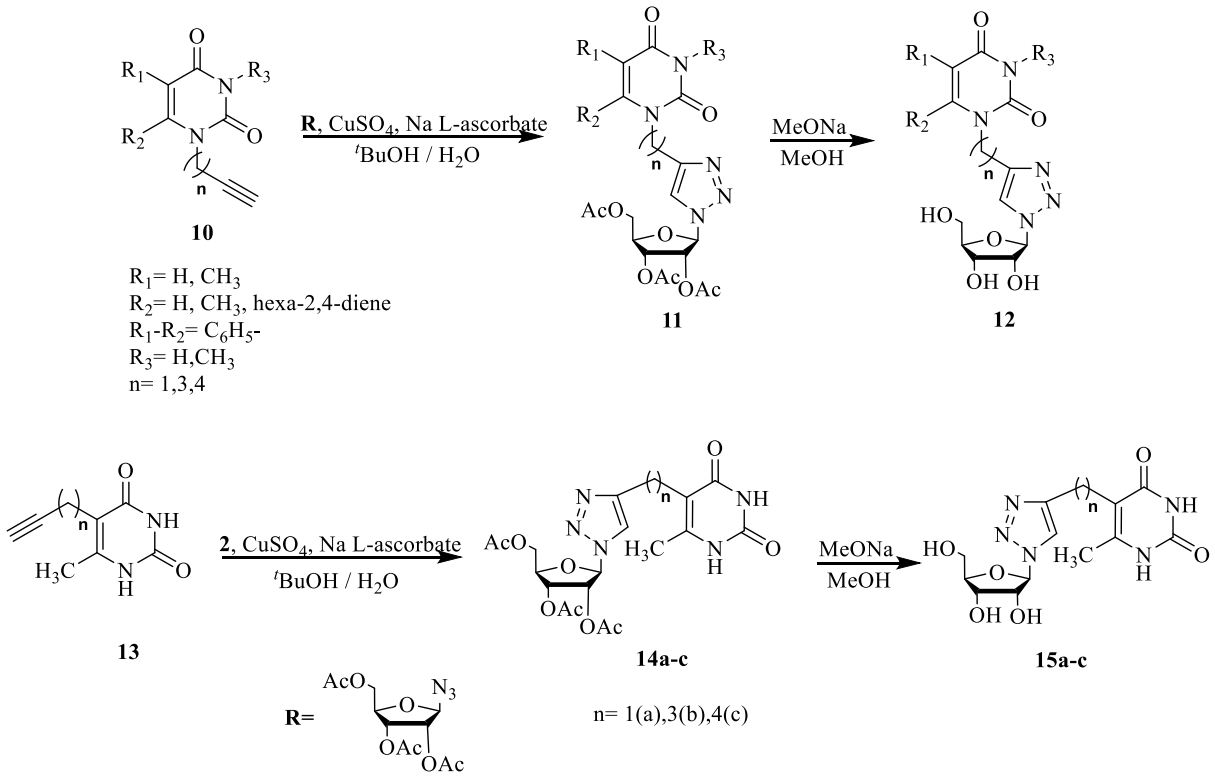
Scheme 1: Synthesis of *D*-ribofuranosyl-1,2,3-triazol uracil derivatives

2-Propargylamino pyrimidine derivatives **6x,y** were synthesised by reaction of *1H-pyrazole-1-carboxamidine hydrochloride* or *1H-pyrazole-1-carboxamidine* with propargyl amine in two steps. [47,48], 1,4-Triazole pyrimidine derivatives linked sugars moiety were formed by reaction of 2-propargylamino pyrimidine derivatives **7a,b** and azido-sugars to give **8,9(a-f)** in the presence of $CuSO_4$/(sodium *L*-ascorbate) which Known by click reaction, scheme 2.[49]



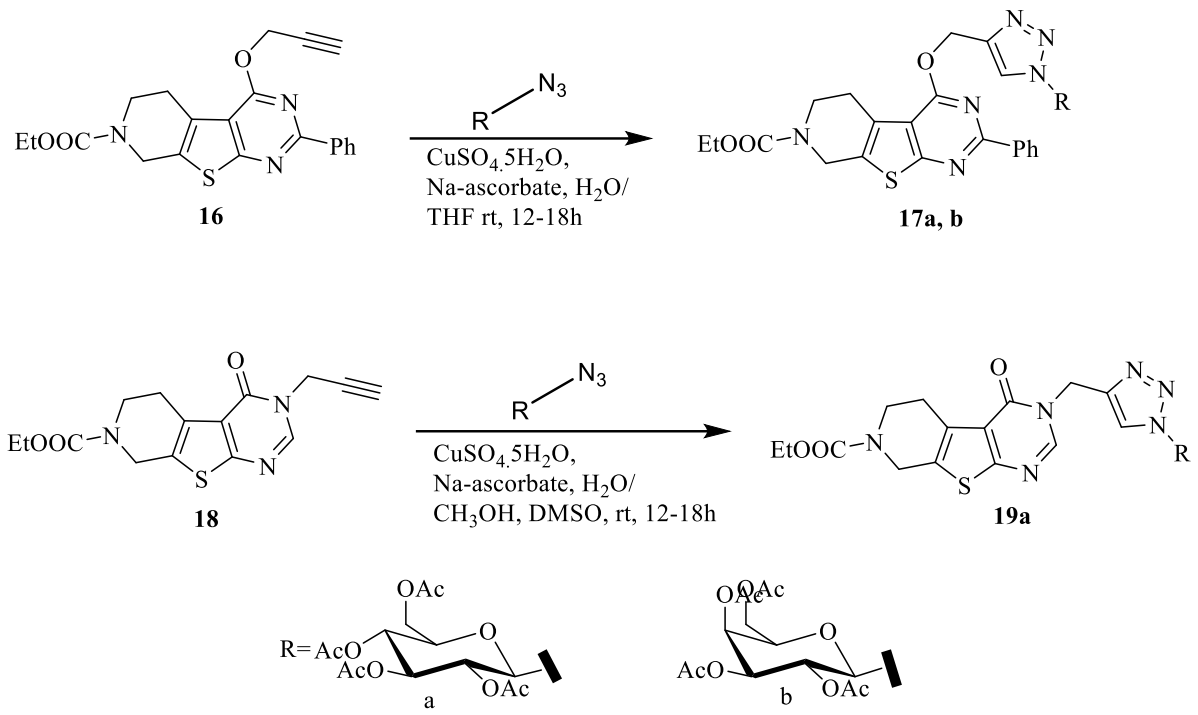
Scheme 2: Synthesis of sugars hybrid 1,2,3-triazolyl pyrimidine derivatives

Derivatives of uracil, thymine and quinazolin-2,4-dione **10,13** and azido 2,3,5-tri-*O*-acetyl-*D*-*β*-ribofuranoside were synthesised and linked to 1,2,3-triazol-4-yl moiety by a polymethylene linker via the CuAAC reaction which used $CuSO_4$, Na.ascorbate as catalyst, scheme 3.[50,51]



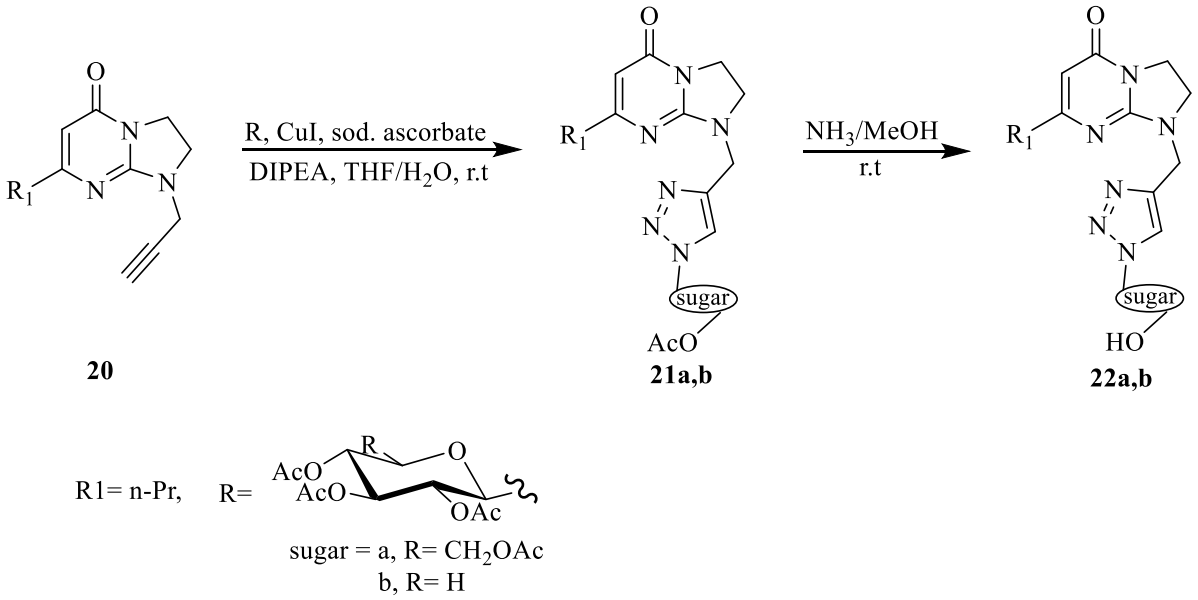
Scheme 3: Synthesis of 1,2,3-triazolyl nuclosides analogues linked with uracil derivatives

Pyridothienopyrimidinones derivatives **16, 18** and 1-azido-2,3,4,6-tetraacetyl-β-D-hexoses (glucose or galactose) linked by 1,2,3-triazoles were synthesized under Cu-catalyzed alkyne/azide click (CuAAC) reaction conditions that ($CuSO_4.5H_2O$/Na-ascorbate, suitable solvents) at room temperature. (scheme 4) [52]



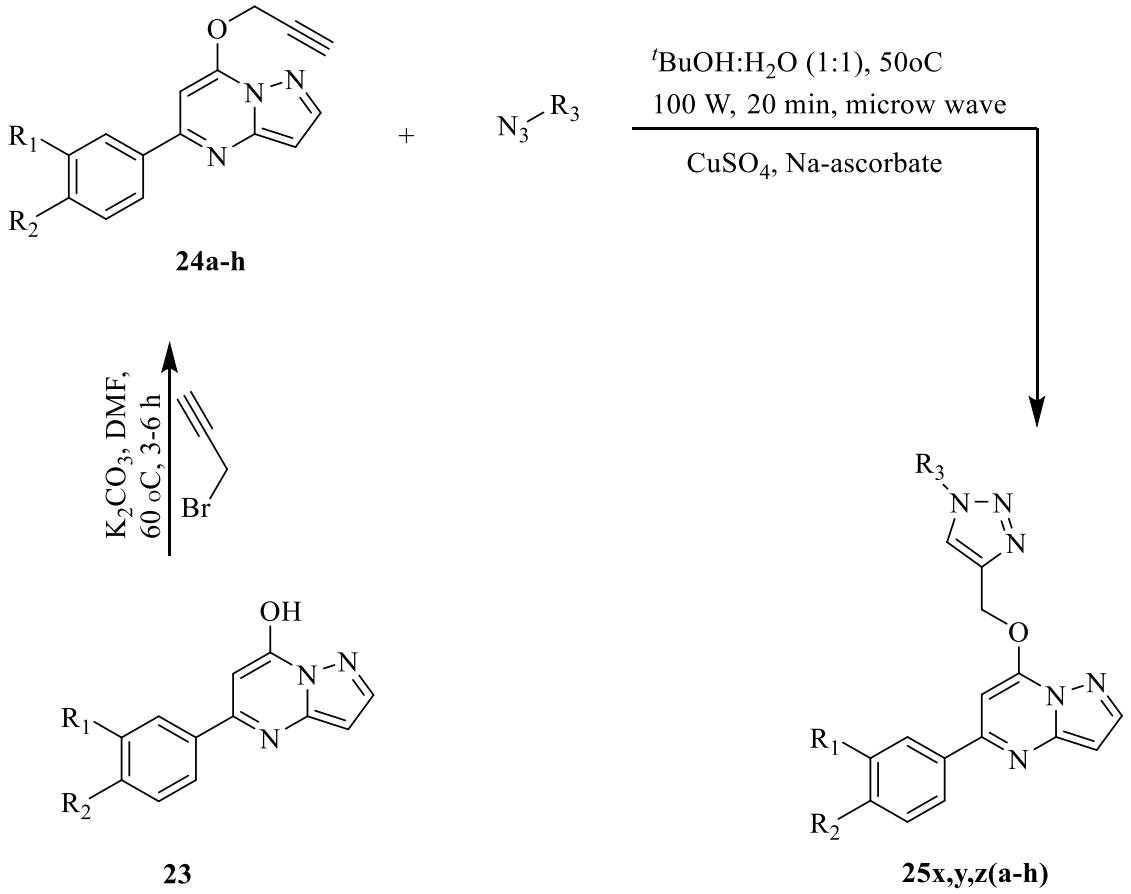
Scheme 4: Synthesis of *D*- galactose 1,2,3-triazol hydropyrido thienopyrimidine derivatives

The pyrimidin derivative 7-propyl-2,3-dihydroimidazo[1,2-a]pyrimidin-5(1*H*)-one reacted with propargyl bromide in a basic medium to obtain acetylenec compound **20**, then obtain the target acetylated 1,2,3-triazole-*N*-glycosides **21a,b**, in 71 and 73% yields, respectively, by click reactions of compound 21 with a sugars azide, such as 2,3,4,6-tetra-*O*-acetyl-*D*-gluco- or *D*-xylopyranosyl azide. The acetylated 1,2,3-triazole glycosides **21a,b** were deacetylated by reaction with a saturated methanolic ammonia solution to obtain the 1,2,3-triazole-*N*-glycosides pyrimidin derivatives **22a,b**, scheme 5. [53]



Scheme 5: Synthesis of glycosides linked 1,2,3-triazol dihydroimidazo pyrimidin

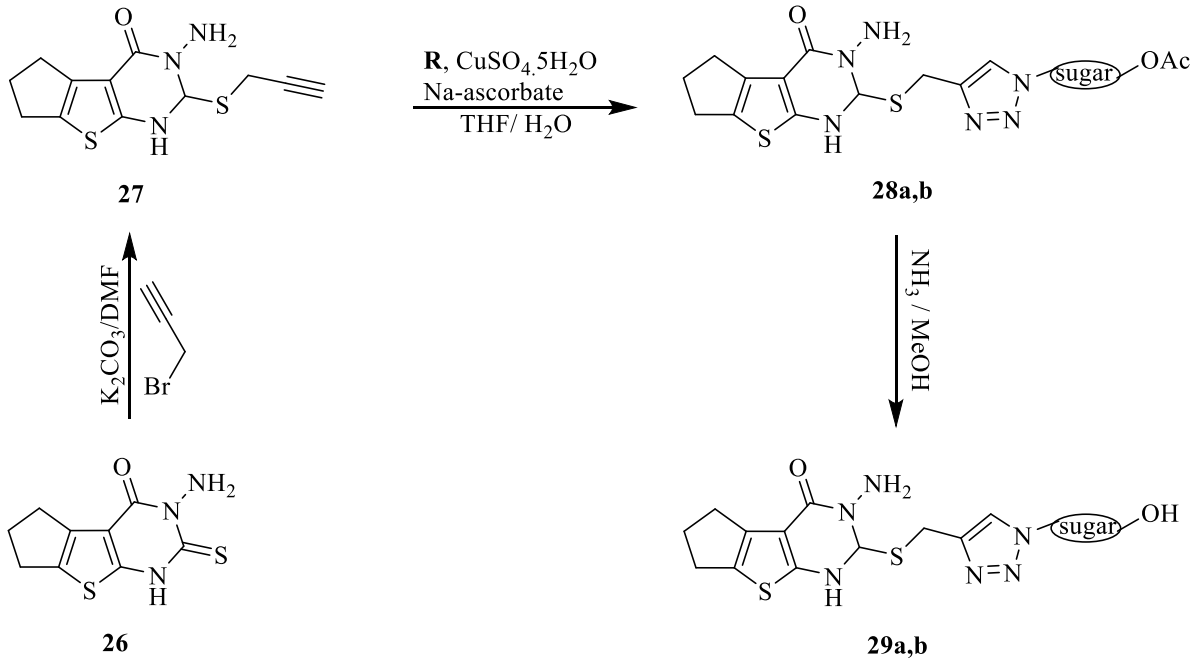
A series of pyrazolo[1,5-*α*]pyrimidine based triazole linked glycohybrids **25x-z (a-h)** were synthesized by CuAAC reaction after preparing 7-*O*-propargylated pyrazolo[1,5-*α*]pyrimidines derivatives **24a-h** which reacted with 1-azido-2,3,4,6-tetra-*O*-acetyl- D-glucose, D-galactose and D-mannose, by using $CuSO_4.5H_2O$/Na-ascorbate, ^{t}-BuOH-H_2O (1:1), 50 °C, 100 W, μW, 20 min, in excellent yield (91-98%) (scheme 6). [54]



R1= H
R2= CH3(a), OCH3(b), Br(c), Cl(d), CF3(e), isopropyl(f), -C4H4-(g), -OCH2O-(h)
R3= *[2,3,4,6-tetra-O-acetyl-b-D-glucopyranosyl](x),*
[2,3,4,6-tetra-O-acetyl-b-D-galactopyranosyl](y),
[2,3,4,6-tetra-O-acetyl-b-D-mannopyranosyl](z).

Scheme 6: Synthesis of triazole-linked glycosides hybrid of pyrazolo pyrimidines derivatives

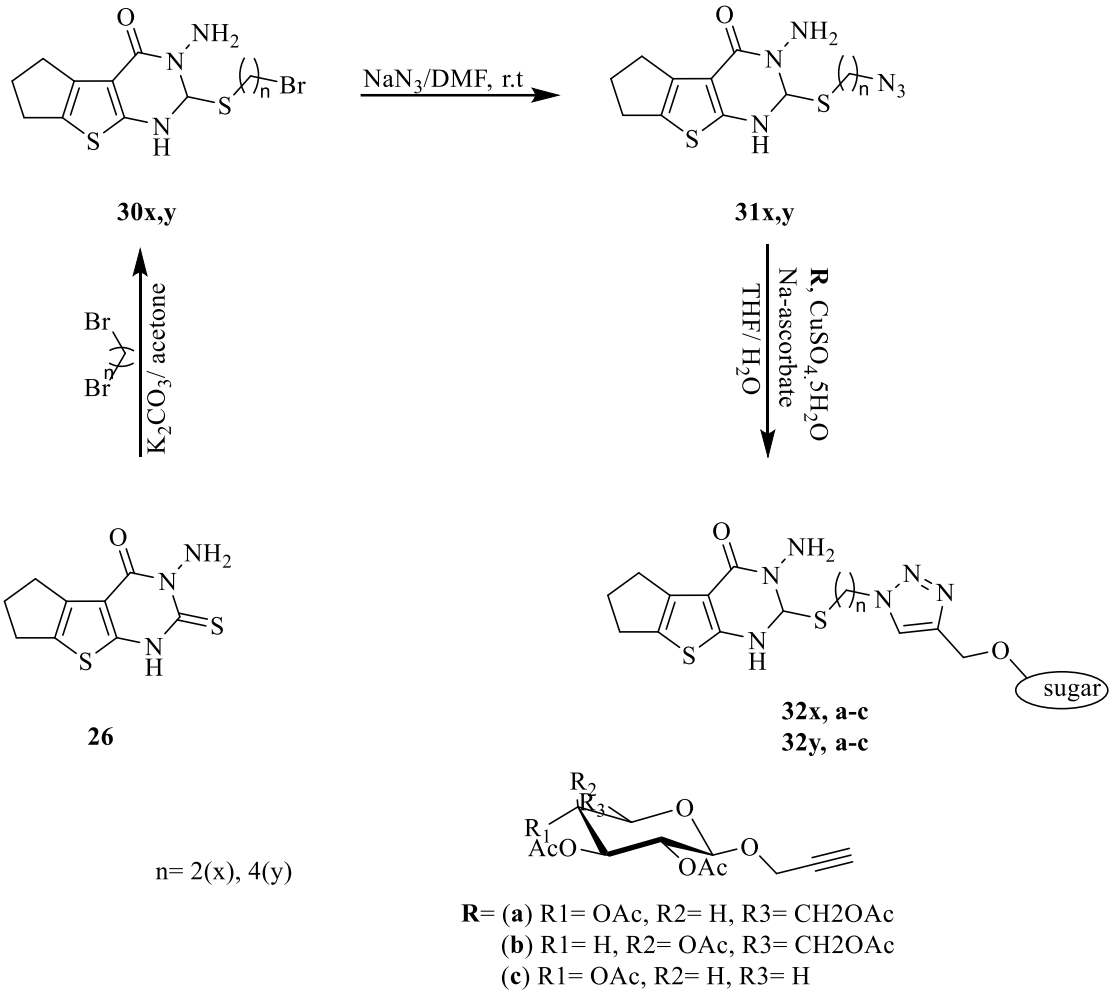
They synthesized two different derivatives of 1,2,3-triazole linked thienopyrimidine hybrid with different sugars via catalysed click dipolar cycloaddition strategy, that the first derivative when *3-amino-2-thioxothieno[2,3-d]pyrimidin-4-one* **26** reacted with propargyl bromide to afford acetylenic thienopyrimidine compound **27**, which reacted after that with tetra-*O*-acetyl-*β*-*D*-gluco- and tri-*O*-acetyl-*β*-*D*-xylopyranosyl azides, which lead to the synthesised of the targeted 1,2,3- triazole glycoside derivatives **29a,b**, in 65–60% yield, respectively, scheme 7. [55]



R= *2,3,4,6-Tetra-O-acetyl-b-D-glucopyranosyl* ***(a)***,
2,3,4-Tri-O-acetyl-b-D-xylopyranosyl ***(b)***

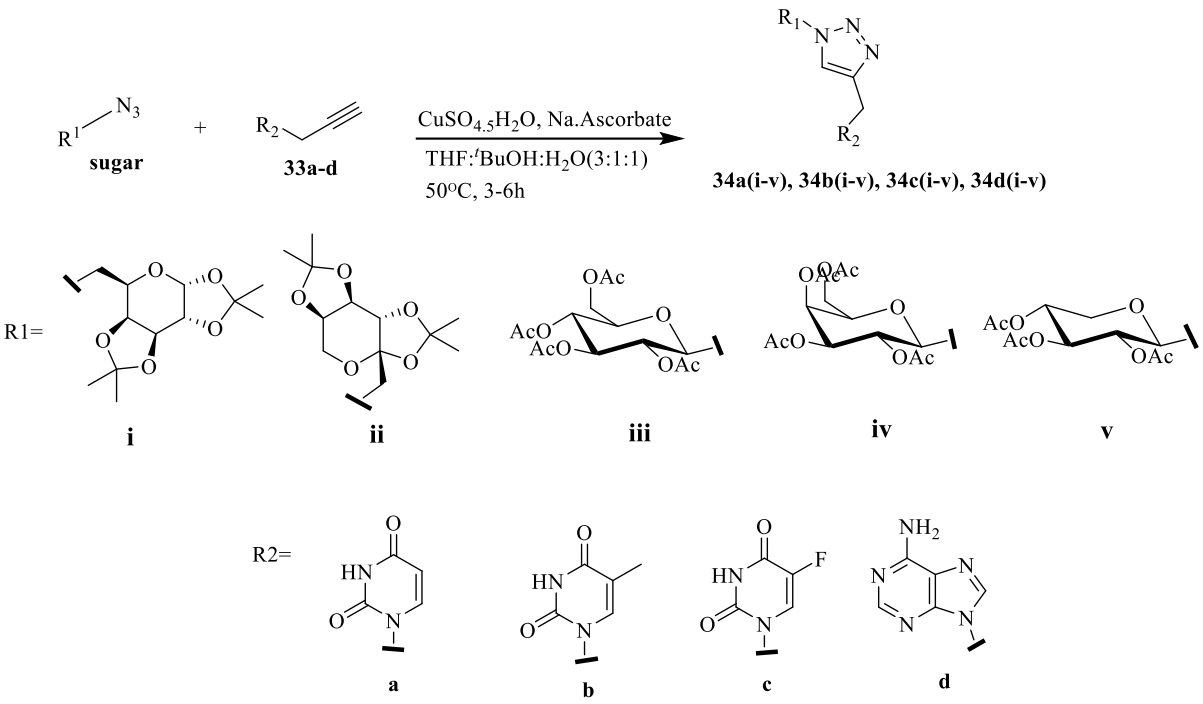
Scheme 7: Synthesis of triazole glycosides based thienopyrimidine system.

The second derivative was synthesised by halo-alkylation of *3-amino-2-thioxothieno[2,3-d]pyrimidin-4-one* **26** which reacted with 1,2-dibromoethane or 1,4-dibromobutane, then with sodium azide and obtained the required azide compounds **31x,y** which reacted with acetylated acetylenic sugars, galactose, or xylose to afforded the targeted glycosyl 1,2,3-triazoles incorporating thienopyrimidine moiety **32x,y(a-c)**, scheme 8. [56]



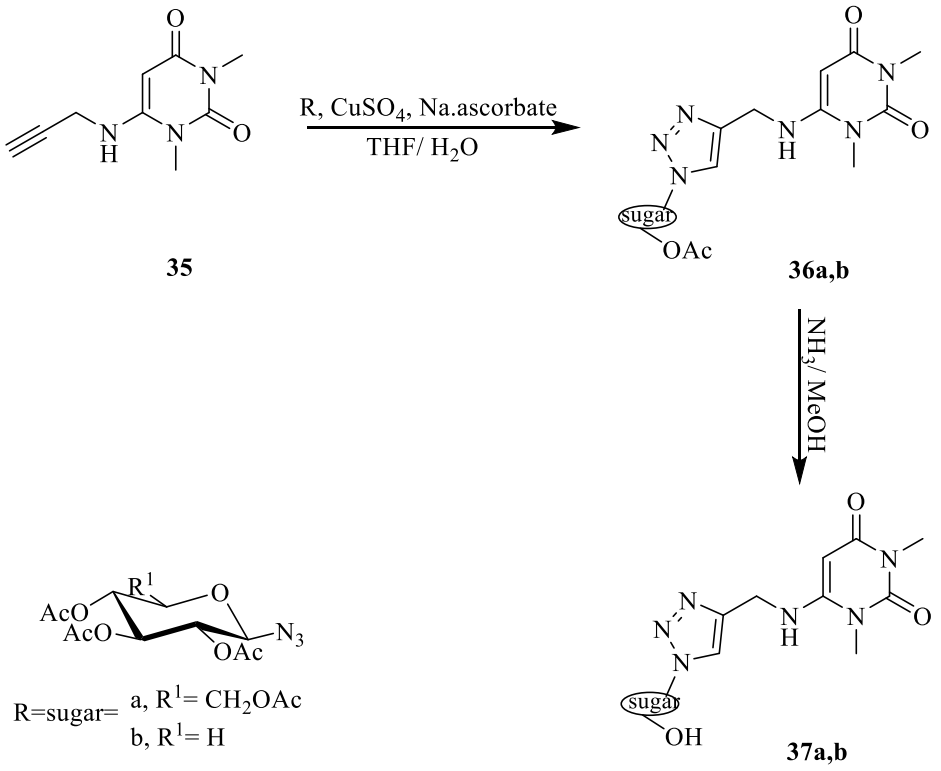
Scheme 8: Synthesis of cyclopenta thieno pyrimidinone linked glycosyl triazoles derivatives

1,4-Disubstituted-1,2,3-triazole pyrimidine bridged nucleosides **34a-d(i-v)** were synthesized *via* the CuAAC reaction in the presence of $CuSO_4.5H_2O$/Na-ascorbate in good yield (80-94%), from monopropynylated uracil, thymine, 5-fluorouracil, adenine **33a-d** nucleobases with azidosugars obtained according to the literature [57-62], which have a pyranose ring with D-*galacto*-, D-*fructo*-, D-*gluco*-, D-*xylo*, configurations (scheme 9). [63]



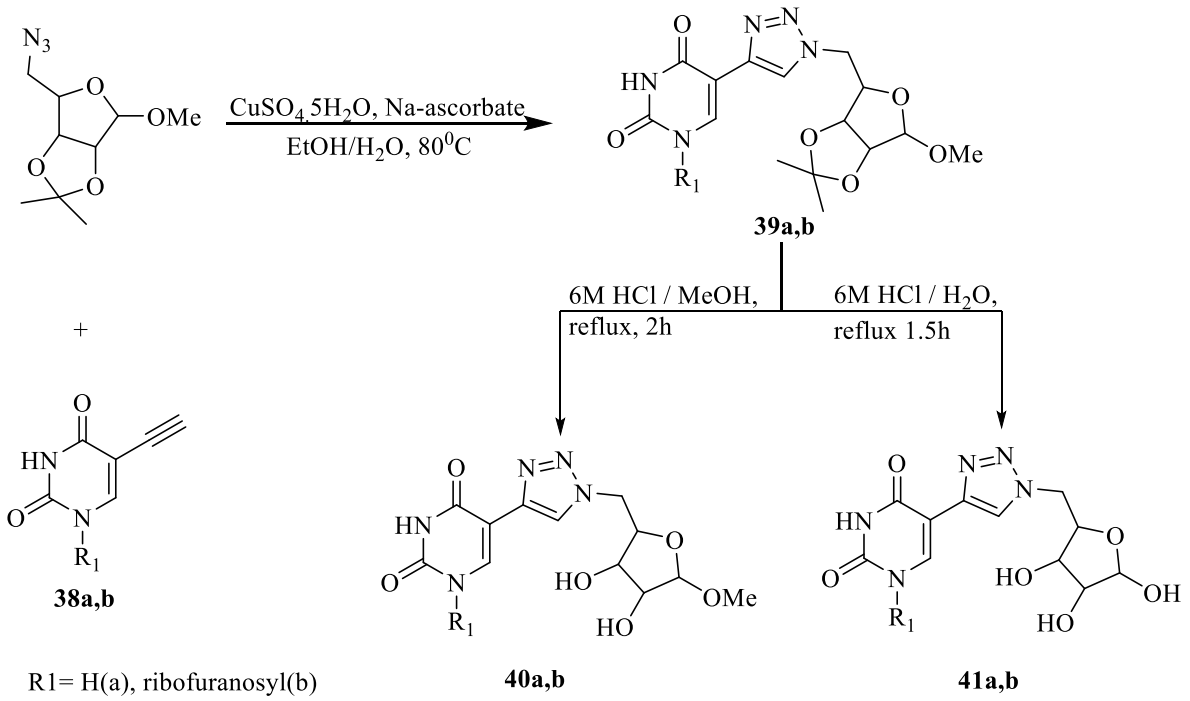
Scheme 9: synthesis of 1,2,3-triazole bridged purine and pyrimidine nucleosides derivatives

The propargylation reaction of aminopyrimidine derivative with propargyl bromide obtained acetylenic part derivative **35** which react with the azido-sugars that; 2,3,4,6-tetra-*O*-acetyl-*D*-glucopyranosyl or 2,3,4-tri-*O*-acetyl-*D*-xylopyranosyl azides under click conditions, in 72–74% yield to achieve compound **36a,b** which deprotected by using methanolic ammonia solution to form the corresponding free hydroxy 1,2,3-triazole-*N*-glycosides **37a,b**, scheme 10. [64]



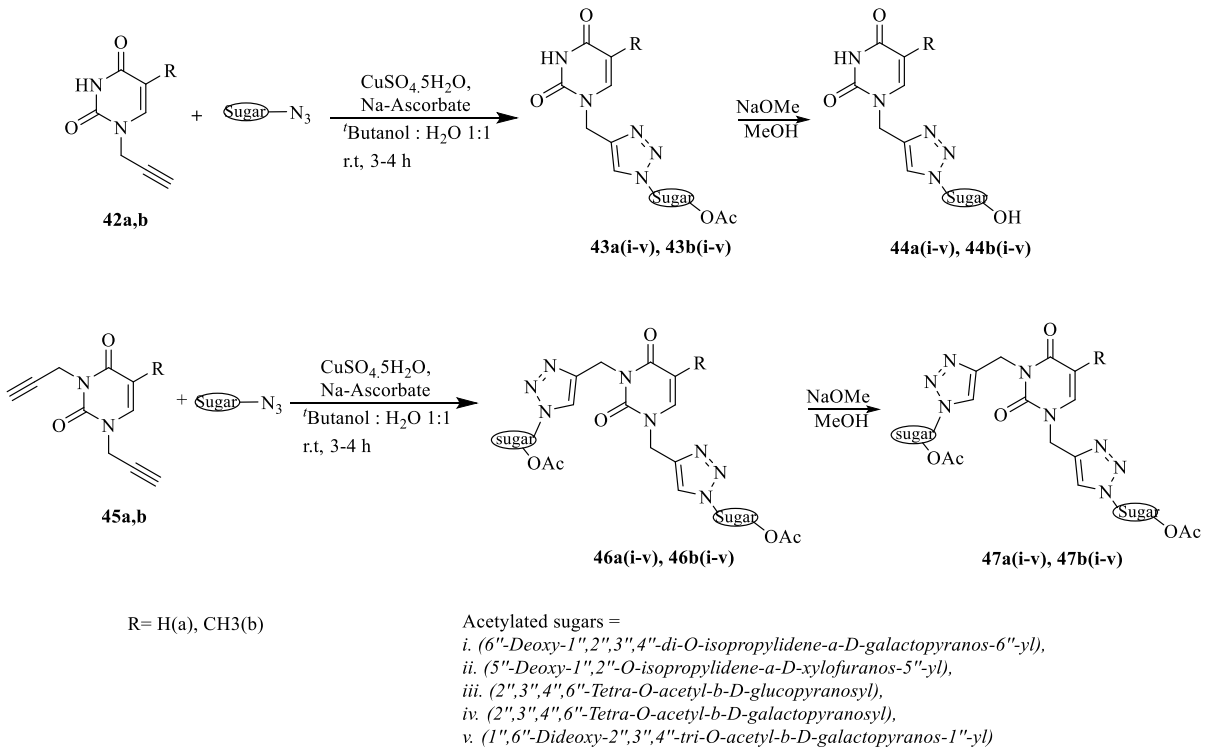
Scheme 10: Synthesis of Glycosides 1,2,3-triazol pyrimidinedione derivatives

The ribose pyrimidine ring derivative linked via triazole **39a,b** were synthesised by using CuAAC reaction of 5-ethynyluracil 4, 5-ethynyluridine **38a,b** with 5-azido sugar which were catalysed by $CuSO_4.5H_2O$ and sodium ascorbate which were carried out in a 1:1 mixture of water and ethanol at 80 ^oC for 1 h, giving the targeted compound **39a,b**. The isopropylidene protection groups were broken by treating with 6M Hydrochloric acid in Methanol alcohol, giving conjugates **40a,b** (82%) and **41a,b** (99%), scheme 11. [65]



Scheme 11: synthesis of uracil or uridine 1,2,3-triazole ribofuranoside derivatives

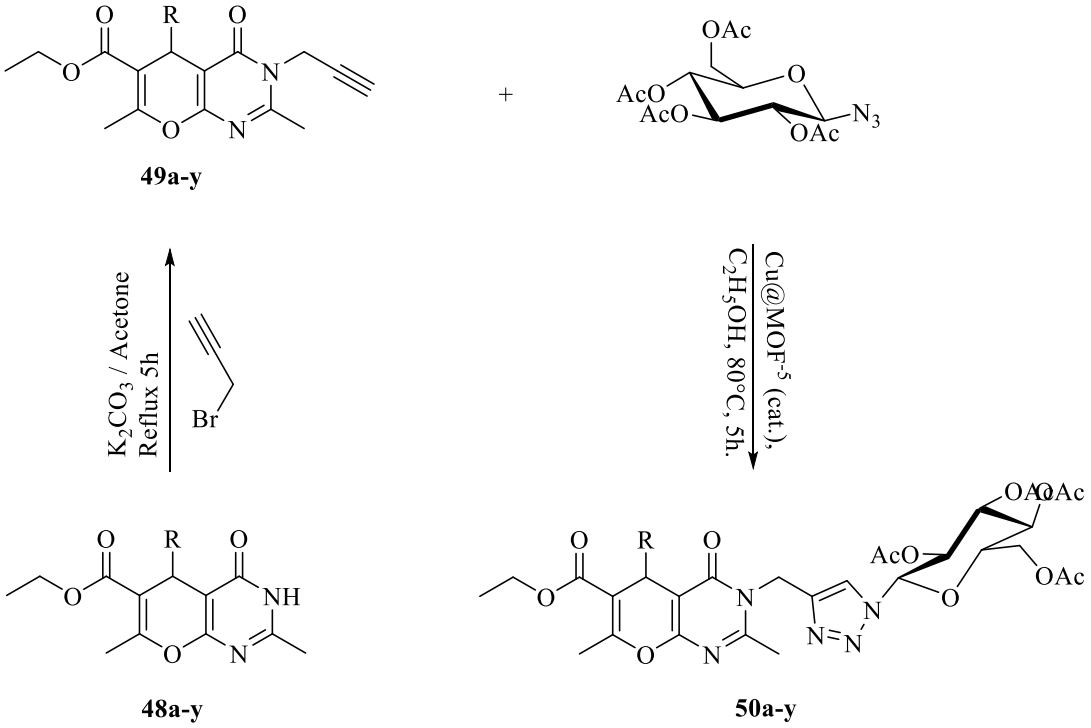
The targeted acetylenic pyrimidines **42,45(a,b)** were synthesised and reacted with different sugars azide derivatives via click reaction to obtained a new 1,2,3-triazole pyrimidines sugar **43-47a,b(i-v)**, the CuAAC reactions were achieved in ^{t}-BuOH/H_2O (1:1) using equimolar quantities of the reactants, $CuSO_4.5H_2O$ (10 mol%) and sodium ascorbate (20 mol%) at room temperature, scheme 12. [66,67]



Scheme 12: synthesis of 1,2,3-triazole pyrimidine nucleoside analogues derivatives

2.2. Click reaction catalysed by Cu@MOF-5

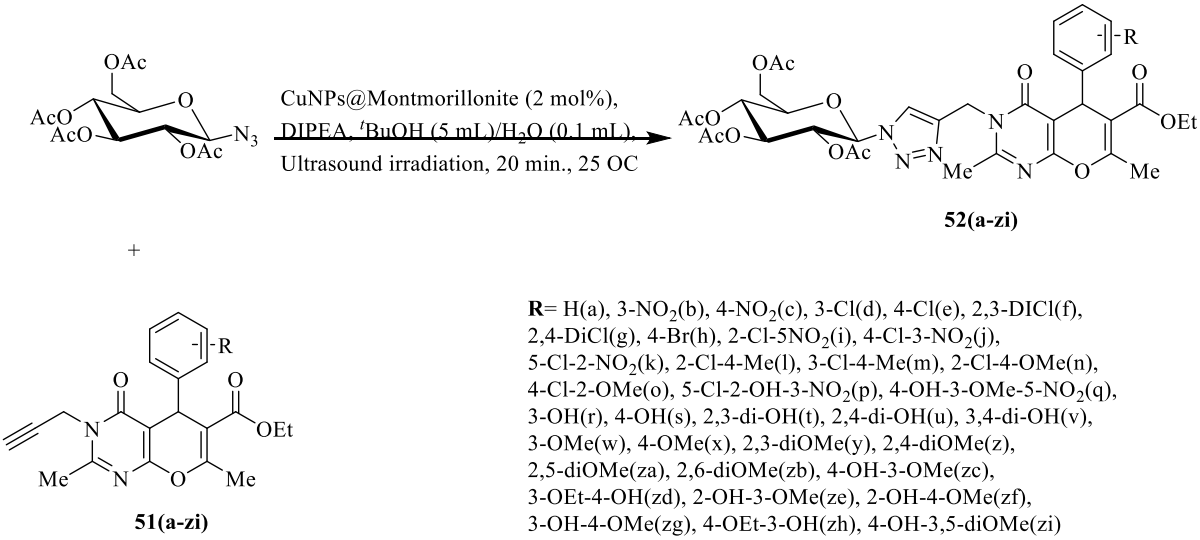
The click reaction of 3-propargyl-4-*H*-pyrano[2,3-*d*]pyrimidine derivatives **49a-y** has been accomplished by reaction with *2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl azide* to obtained the targeted 1,2,3-triazole pyrimidine sugar compounds **50a-y**, The processes were catalyzed by using the metal-organic framework Cu@MOF-5 in absolute ethanol for 4−5h at room temperature, scheme 13. [68]



R= H(a), 4-NO_2(b), 3-NO_2(c), 2-NO_2(d), 2,3-dichloro(e), 4-Cl(f), 3-Cl(g), 2-Cl(h), 4-Br(i), 4-Me(j), 4-iPr(k), 4-OH(l), 3-OH(m), 2-OH(n), 4-OMe(o), 3-OMe(p), 2-OMe(q), 2,4-NMe_2(r), 3,5-diMe(s), 3-OEt-4-OH(t), 3-OMe-4-OH(u), 3,5-diOMe-4-OH(v),3-OH-4-OEt(x), 3-OMe-4-OH-5-NO_2(y)

Scheme 13: synthesis of 1,2,3-triazoles glucose linked pyrano-pyrimidine derivativ

A series of 36 analogs derivatives of *4-H-pyrano[2,3-d]pyrimidine* hybrid 2,3,4,6-Tetra-*O*-acetyl-*β*-*D*-glucopyranosyl azide linked 1,2,3-triazole derivatives **52a-zj** were synthesized by click chemistry between these *N*-propargyl derivatives and sugar azide, by using CuNPs@Montmorillonite as a catalyst under ultrasound condition in the mixture of DIPEA in ^{t}-BuOH/H_2O at 25 °C for 20 min. This study showed that this catalyst system gave the highest yield with a shorter reaction time that (yield of 97.2% for 20 min., scheme 14. [69]



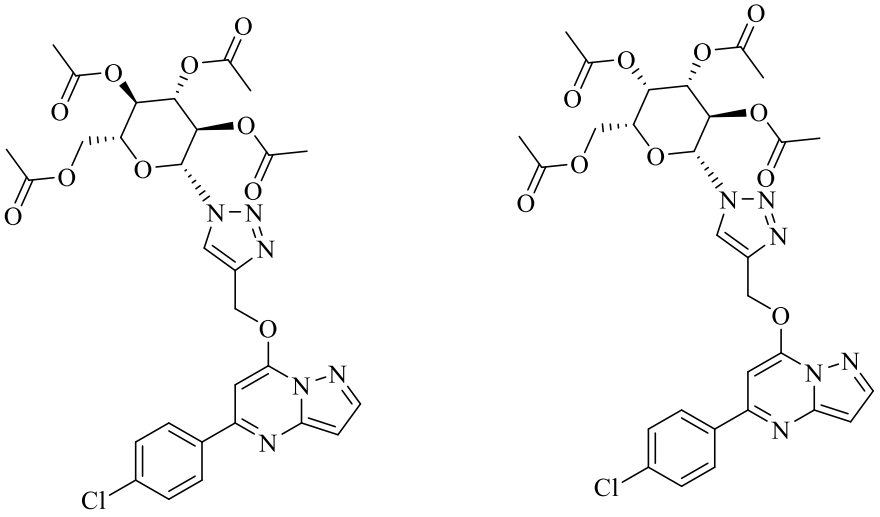
Scheme 14: synthesis of pyrano pyrimidine 1,2,3-triazoles glucose derivativ

3. Biological activity

3.1. Cytotoxicity activity (Anti-proliferative activity):

3.1.1. *Anti breast cancer (MDA-MB231) and (MCF-7) cell-lines.*

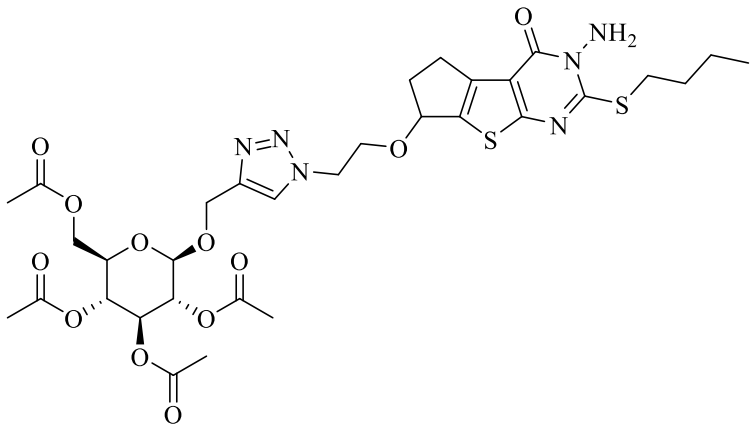
Compound (**27yd**) showed the most potent anti-cancer activity with IC_{50} value of 29.1 μM against MDA-MB231 cell line and compound (**27xd**) showed best inhibitory activity against MCF-7 cell line with IC_{50} value of 15.3 μM. [54]



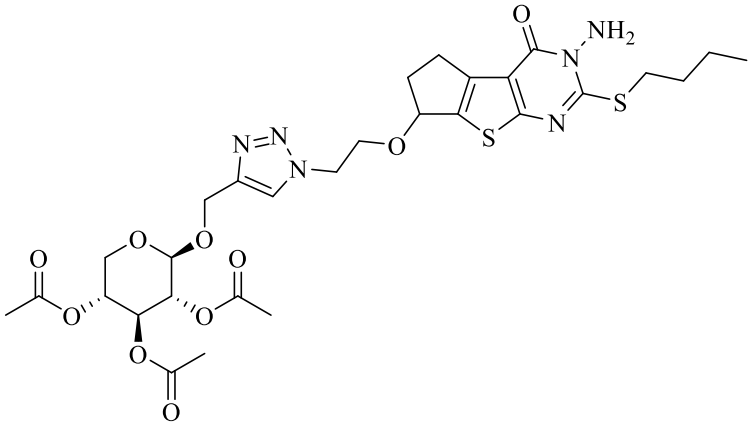
27xd **27yd**

3.1.2. *Anti-human colon cancer cell line (HCT-116 cell line)*

Compounds **34a** and **34c** showed significant cytotoxic activities against HCT-116 cell lines. [56]



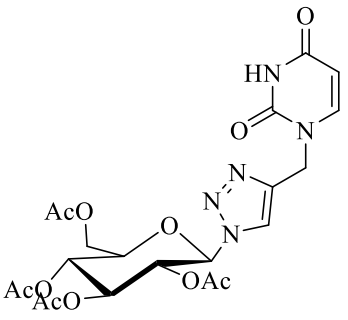
34a



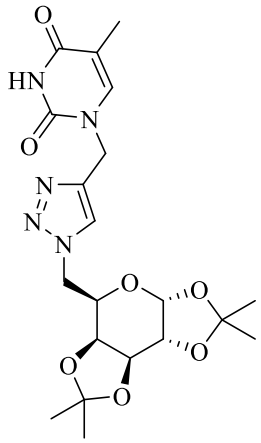
34c

3.1.3. *Anti-human hepatoma cell line (Hep 3B)*

Compounds ***(36a-iii)*** and ***(36b-i)*** were identified as potential hits against Hep3B cell. [63]



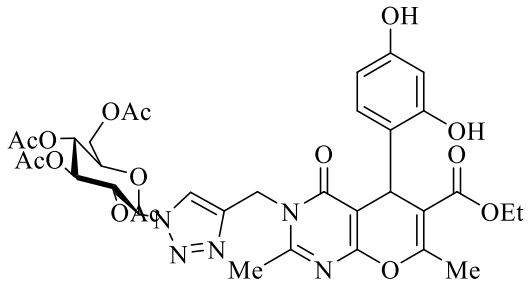
(36a-iii)



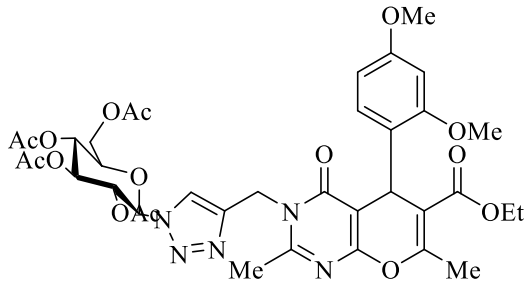
36b-i

3.1.4. *Anti HeLa (cervical cancer cells lines) and enzyme assay*

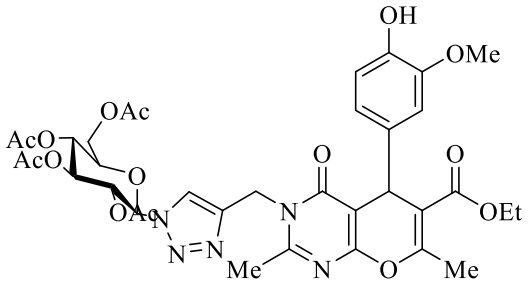
Compound **55zf** showed good activities against HeLa cancer cell lines, Compounds **55v, 55z, 55zc**, and **55zf** exhibited substantial inhibitory activity against EGFR and HER2 tyrosine kinases in comparison to Lapatinib. [68,69]



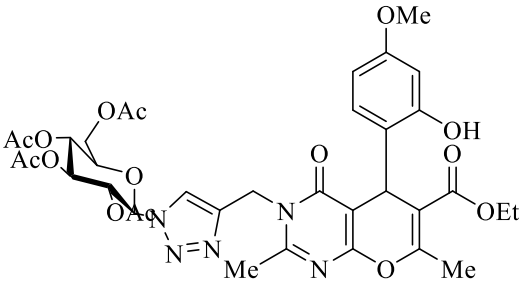
55v



55z



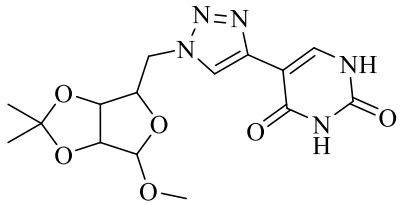
55zc



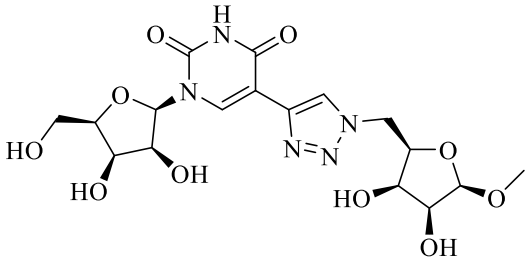
55zf

3.1.5. Anti-tumour cell lines activity

Compounds **42a** and **44b**, showed that low anti-proliferative activity on the tumour cell lines. [60]



42a

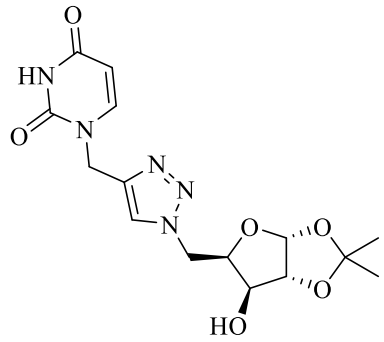


44b

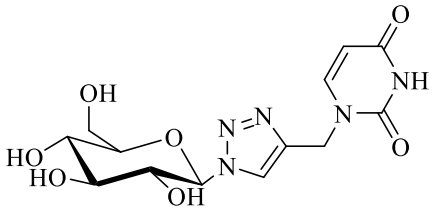
3.2. Antidiabetic activity:

3.2.1. *α-Glucosidase inhibitory enzyme*

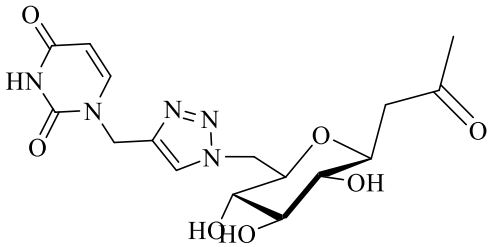
Compounds **50a(ii), 47a(iii), 47a(i)** and **50a(v)** exhibited very good inhibition of α-glucosidase enzyme comparable to the standard drug acarbose. [67]



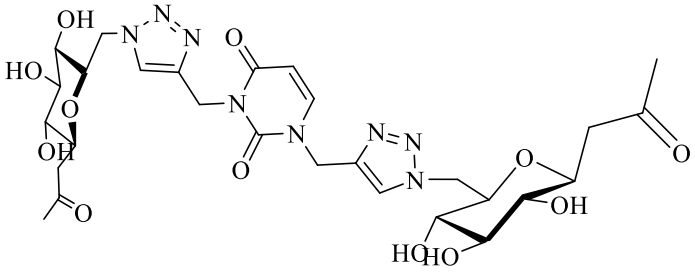
50a(ii)



47a(iii)



47a(i)

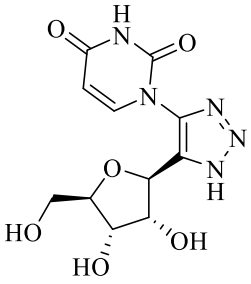


50a(v)

3.3. Antiviral activity:

3.3.1. *Enzyme inhibition activity against Ribonuclease A* (*RNase A)*

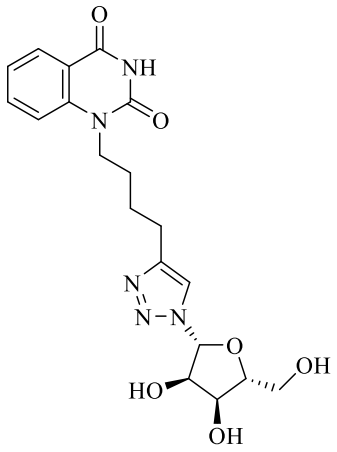
(**4a**) compound is the most potent competitive inhibitors of RNase A with low l M inhibition constant (Ki) values being with Ki = 1.6 l M. [46]



4a

3.3.2. *Aantiviral activity against Influenza A virus [A/PR/8/34/(H1N1)] and coxsackievirus B3.*

Compound (**14**) was the best values of IC_{50} (inhibiting concentration) and SI (selectivity index). against influenza virus A/PR/8/34/(H1N1) and coxsackievirus B3. [50,51]

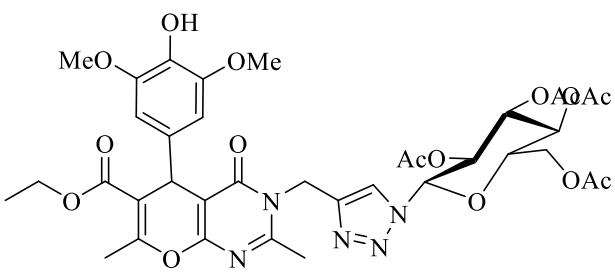


14

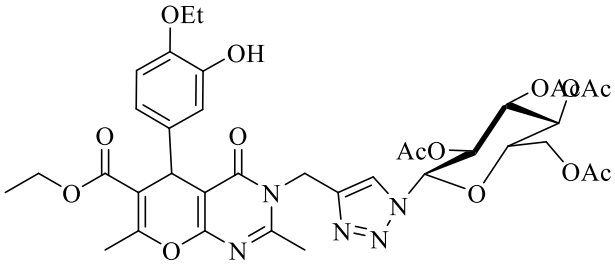
3.4. Anti-tuberculosis:

3.4.1. *Mycobacterium tuberculosis Protein Tyrosine Phosphatase (Mtb PtpB) inhibition*

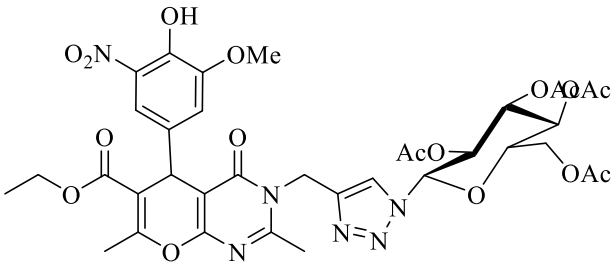
Compounds **53v, 53x** and **53y** were showed the most active against *Mycobacterium tuberculosis* protein tyrosine phosphatase B (MtbPtpB) inhibition. [68,69]



53v



53x



53y

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الملخص باللغة العربية

جليكوسيدات هجينة من البيريميدين-1،2،3- ترايازول: التركيب القائم على النقر والنشاط البيولوجية.

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تمت دراسة تطبيق الكيمياء النقرية لبناء بنية هجينة تتضمن نواة 1،2،3- ترايازول على نطاق واسع كاستراتيجية قوية لتصميم مجموعة متنوعة من الهياكل المستهدفة. ركزت مراجعة التيارات على المسارات التركيبية للمركبات التي تمتلك اثنين من العناصر المهمة: البيريميدين وأنظمة 1،2،3- ترايازول ومشتقاتها السكرية كمنظورات جليكوسيد. تم تسليط الضوء على الأنشطة الحيوية الهامة للمنتجات الهجينة المشكلة.

الكلمات المفتاحية: بيريميدين؛ 1،2،3- ترايازول؛ جليكوسيدات ؛ النقر.