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Quinazolines Linked to Sugar Derivatives as Nucleoside Analogs, Synthesis and Biological Aspects

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Abstract

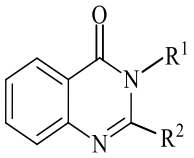
Quinazolines compounds are a significant class of multifunctional medicinal agents in the biological and pharmaceutical industries. Quinazoline-incorporating compounds have recently gained significant attention due to their various applications, especially in diverse bioactivities. Quinazolines derivatives have a range of pharmacological effects, making such heterocyclic systems an essential core in bioactive structures. Techniques for synthesizing or modifying this ring structure were always evolving and intriguing. They were of considerable interest as intermediates in the synthesis of various beneficial heterocyclic compounds. The incorporation of sugar in modified cyclic and acyclic forms with the structure of a heterocyclic quinazolines system revealed potential structures with various bioactivities. Cancer is the world's largest and most serious healthcare problem, identified by aberrant cell proliferation caused by an imbalance between cell division and cell death. There have been many chemotherapeutic drugs developed to treat cancer, but quinazolines derivatives are one of the most potent and have few side effects.

Keywords: quinazolines, quinazolines-c-nucleosides, 1, 2,3-triazolylnucleosides, propagylated quinazolines, anticancer, antimicrobial, antiviral.

1. Introduction

Quinazolines is a heterocyclic molecular structure with two rings that have pyramiding and benzene fused together. Quinazoline[s] skeleton is found in a variety of alkaloids, most frequently as 4-(3H)-quinazolinone moieties[1]. Due to their wide spectrum of biological features, 4-(3H)-quinazolinone **(1)** together with associated quinazolines **(2)** are a class of fused heterocyclic that are of great interest[2-5]. Quinazolines are regarded as a "privileged structure" for drug development similar to benzodiazepines, because of their demonstrated anticancer, anti-inflammatory, diuretic, and anti-hypersensitive, anticonvulsant properties, as demonstrated by a recent thorough review on the chemistry of 2-heteroaryl and heteroalkyl-4(3H)-quinazolinone [6, 7].

According to studies indicate that aromatic quinazolines can inhibit tyrosine kinase, which can be useful in regulating the growth of tumors [8]. The creation of novel techniques for ring synthesis has recently been prompted by this[9].



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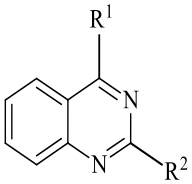

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There are four isomers of this family of bicyclic aromatic ring structures, known by their structural formula, that are composed of a benzene ring connected to an aromatic ring containing two nitrogen atoms. Examples of these are pyridazine,

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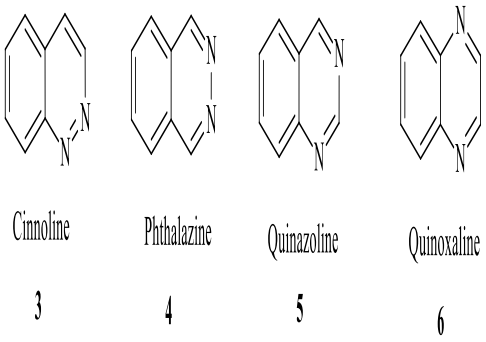
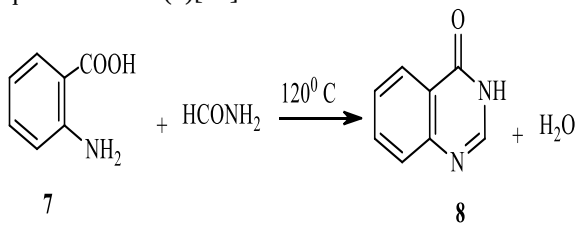
pyramiding, and pyrazine. These isomers, which are also referred to as diazanaphthalenes, can be distinguished by the heterocyclic ring's nitrogen position. The molecular compound crinoline (3) has a heterocyclic double-ring structure made up of two rings: pyridazine and benzene. Phthalazine (4), which is additionally known as benzopyridazine or benzo-orthodiazine, has a pyridazine ring and a benzene ring. Quinazolines (5) is a compound made up of two fused six-member simple aromatic rings, a benzene ring, and a pyramiding ring. Quinoxaline (6), recognized as a benzopyrazine, is made up of two rings: a pyrazine ring and a benzene ring.



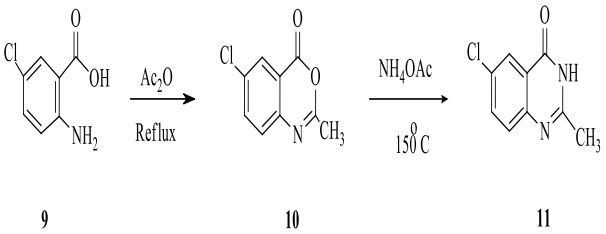
2. Synthetic approaches

The most widely used method of synthesizing 4-(3H)-quinazolinone is the cyclization reaction that V. Niementowski first reported in 1895. Anthranilic acid (7) was heated to 120°C with excess formamide, resulting in the elimination of water and almost a quantitative conversion to 4-(3H)-quinazolinone (8)[10].



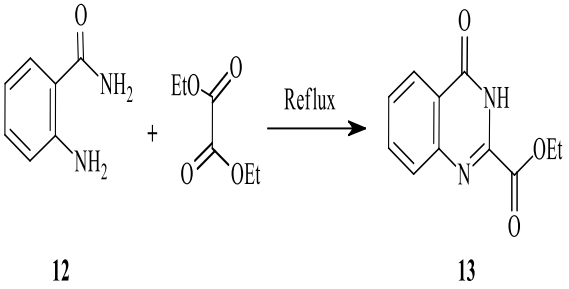
scheme 1.

Benzol-oxazinone (10) is produced by combining 5-choloranthranilic acid (9)with acetic anhydride,although at higher temperatures, 6-chloro-2-methyl quinazoline-4 (3H)-one (11) is provided by treating this mixture with ammonium acetate [11].



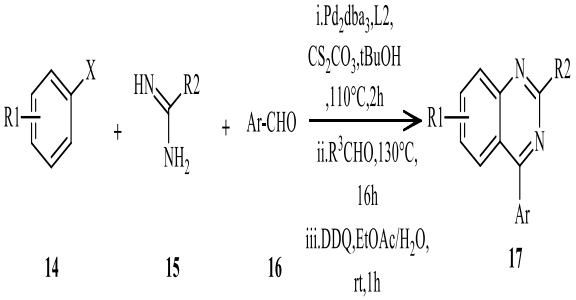
Scheme 2.

Anthranilamide(12)and diethyl oxalate are used under refluxing in the production of 2-carboethoxy-quinazolinone-4(3H)-one (13) as reported [12].



Scheme 3.

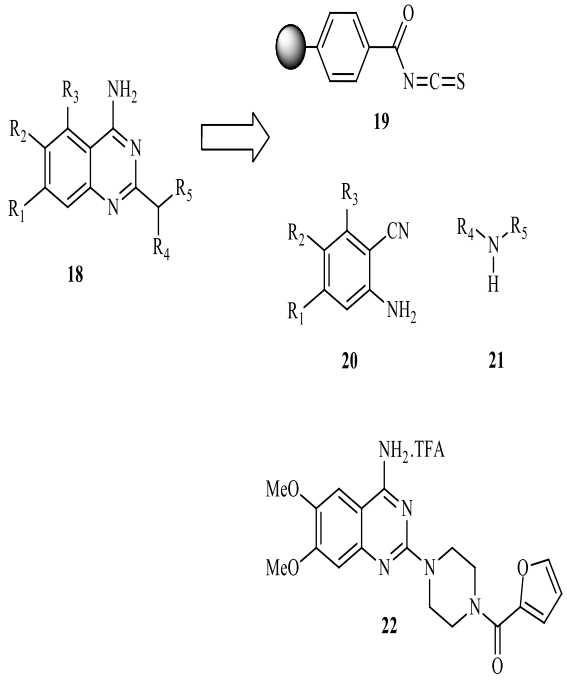
The palladium-catalyzed coupling process is a frequently employed and effective technique for the creation of C-C and C-heteroatom bonds in chemical synthesis and laboratories. It is particularly important in the pharmaceutical industry. Quinazolines derivatives were synthesized in a single pot using a palladium catalyst[13].



Scheme 4.

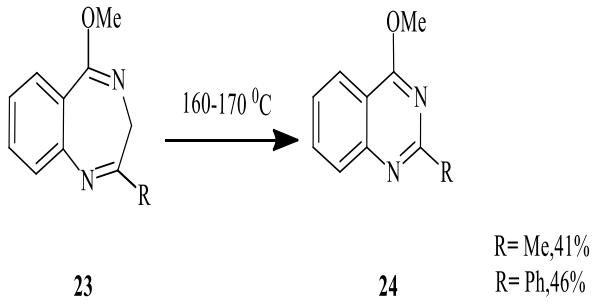
The manufacture of 2,4-diamino quinazolines**(18)** in good yields and purity was madeby the solid-phase synthesis described. Using functionalized 2-aminobenzonitriles **(20)** and amines **(21)** as the essential building blocks in the synthesis, an acyl isothiocyanate resin **(19)** was used

to achieve this. Using this method made it possible to synthesize an α-1 antagonistprazosin**(22) (Scheme 5)**.



Scheme 5.

4-Methoxyquinazolines **(24)** are the sole products obtained when heating 5-methoxy-3H-benzo[e][1,4]diazepine **(23)** in biphenyl ether for 6 hours at 160–170 °C. The yields of these products are moderate[14]. This is an example of quinazolines ring synthesis via ring contraction **(Scheme 6)**.



Scheme 6.

3. Quinazolines Derivatives as Anticancer agent

Numerous medications are available to prevent the spread of malignant tissue and this particular class of compounds. In pharmaceutical and biological chemistry, quinazolines play a significant role as anticancer drug agents that aid in tumor removal while protecting healthy tissues [15-17].

These chemical compounds have the power to inhibit a protein's activity, making them effective inhibitors of the EGFR protein, which is responsible for the growth of tumors. EGFR was discovered on the cancer cell's surface. For example, the DNA of cells that produce pigment can be harmed by UV radiation from the Sun shining directly on the skin [18].

The benzyl functional group was added to quinazolines moieties, which were discovered to be effective antitumor agents. As a result, benzyl-4(3H) quinazolinone analogs demonstrated broad-spectrum, potentially selectively active growth inhibitors against malignant cells **(fig.1)** [19-21].

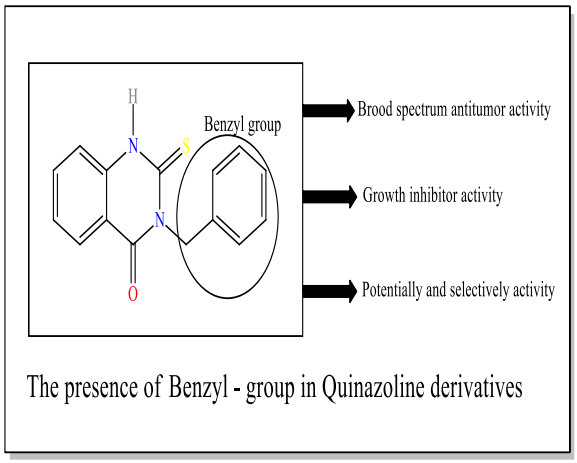


Fig. 1.

Quinazolines compounds have widespread application in the pharmaceutical and healthcare sectors as a prominent class of multifunctional therapeutic agents. Cancer is the world's greatest risk healthcare problem, characterized by aberrant cell proliferation caused by an unbalance between cell division and cell death. Many chemotherapeutic drugs have been manufactured for the therapy of cancer, but quinazolines derivatives are among the most effective and have few side effects.

4. Bioactivities of quinazolines

Antimicrobial therapies primarily hinder the formation of proteins, metabolites, cell walls, and nucleic acids, as well as causing damage to the plasma membrane. The several structural changes surrounding multiple halo-shaped- substituent's of quinazolines have a variety of positive applications and help treat various microbiological infections. In conclusion, scientists anticipate developing these stronger quinazoline molecules to treat a variety of fatal diseases **(fig. 2)**[22-24].

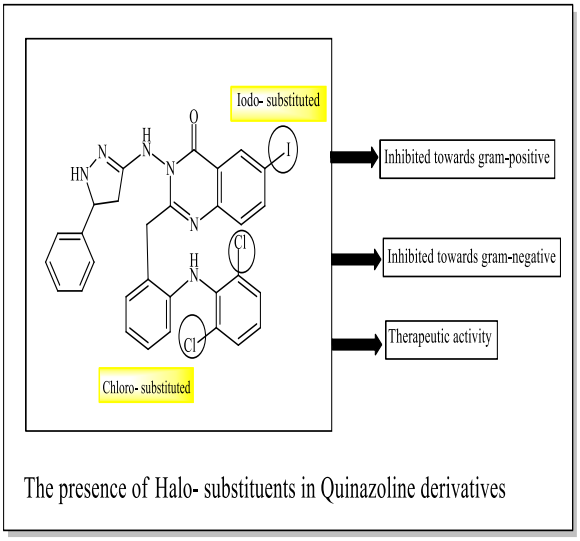


Fig. 2.

Quinazolines anti-inflammatory medications primarily have nitrogen and sulfur linkages as the primary functional groups in their chemical structures, which inhibit certain enzymes that cause inflammation**(fig.3)**[25].

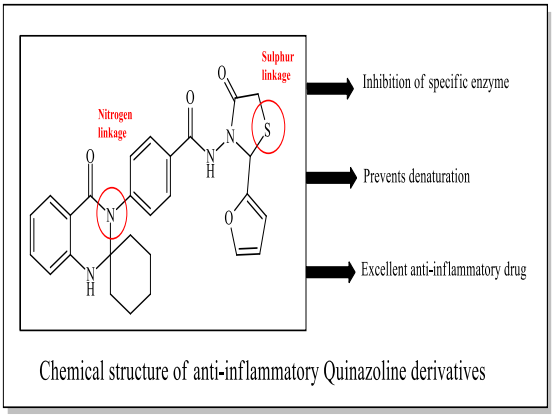


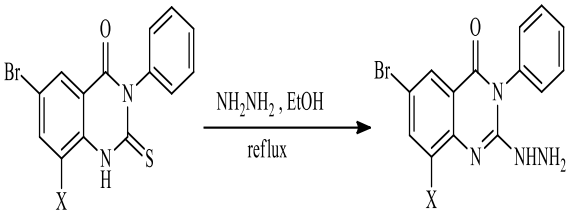
Fig. 3.

5. Quinazoline Incorporating Sugar Moieties

The importance of synthesized compounds with modified or functionalized heterocyclic systems attached to sugar parts is due to their characteristic structural feature mimicking the structure of nucleosides. The latter type of compounds was revealed by a variety of bioactivities such as antiviral, antimicrobial, anticancer activities, and other applications related to enzyme inhibition activities.

Modification of the heterocyclic system and/or the sugar part was useful strategies for the generation of a variety of nucleoside analogs. Simple methods for the production of several different quinazolinehydrazones and glycosides have been published taking into consideration the quinazolines and sugar moieties revealing respective biological actions. The latter was among an expansion of wide interest and pursuits of synthesizing quinazolines derivatives of modified structures incorporating such motifs [26-29].

The hydrazine derivatives **(27)** and **(28)** were prepared by reacting the quinazoly-thione key structure with hydrazine hydrate **(Scheme 7)**.

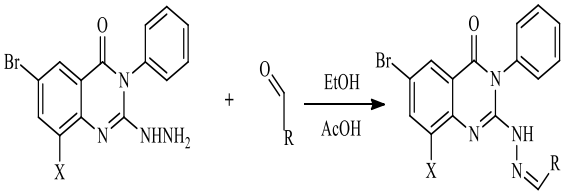


25 X = H
26 X = Br
27 X = H (72%)
28 X = Br (67%)

Scheme 7. Synthesis of 2-hyrazino-3-phenyl-3*H*-quinazolin-4-ones **27** and **28**

The functionalized hydrazones were generated in favourable yields by condensing 6-bromo- and 6,8-dibromo-2-hydrazino-3-phenyl-3*H*-quinazolin-4-ones with D-sugars in the presence of a catalytic amount of glacial acetic acid [30]. Catalytic catalysts in addition to equimolar concentrations of D-glucose, D-galactose, D-mannose, D-xylose, and D-arabinose (monosaccharide **(29a–e)** lead to condensation of **27**and **28**in ethanol [31, 32].

A four-hour addition of glacial acetic acid to the reflux settings generated yields ranging from 57–71% of**(30a-e)** and **(31a-e)**hydrazones, respectively **(Scheme 8)**.



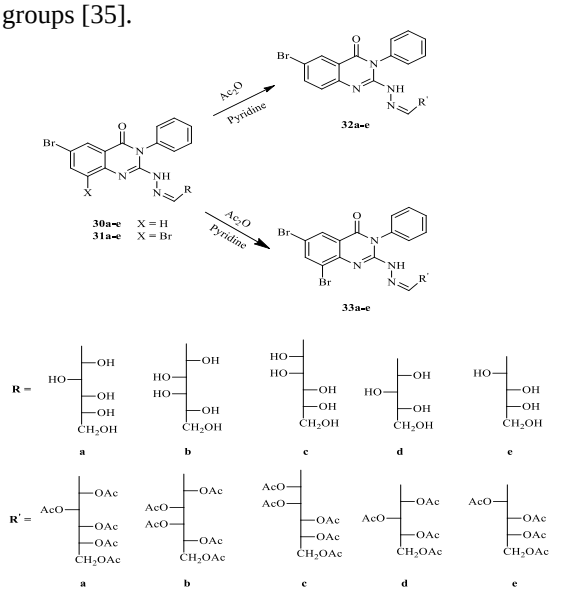
27 X = H
28 X = Br
29a-e
30a-e X = H
31a-e X = Br

Scheme 8. Synthesis of hydrazones 30 and 31

Reports state that sample infrared spectra displayed bands of absorption caused by the sugar

residue's NH and hydroxyl groups' stretching vibration. The ^{1}H NMR spectra of **(30)** and **(31)** had noticeable doublet bonds that indicate the presence of CH-N protons**.** The NH protons produced interchangeable singlet signals.

The corresponding acetylated hydrazones**(32a–e)(Scheme 9)** were generated in yields ranging from 62–68% by utilizing newly distilled acetic anhydride in dry pure pyridine at ambient temperature to acetylate hydrazones**(30a–e)[33]**. The spectroscopic results proved that peracetylation existed at both the NH groups and the polyol residue [34]. Despite this, acetylating **(31a–e)** produced 53–73% of the associated acetylated hydrazones**(33a–e)** when subjected to identical conditions **(Scheme 8)**, pointing that peracetylation had only happened at the polyol residue and had no influence on the NH groups [35].



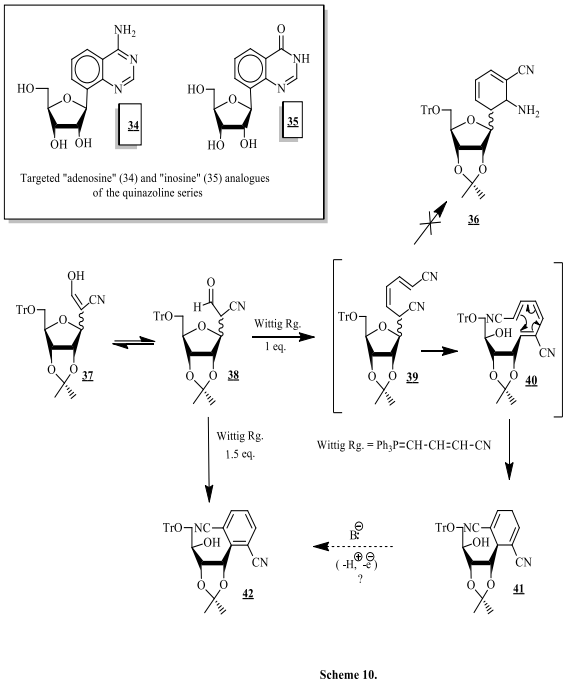
Scheme 9 Synthesis of acetyl hydrazones derivatives 32 and 33.

Infrared spectra of **(32)** and **(33)** displayed strong bands of absorption, which are related to the carbonyl groups of the ester (O–C–O) expansion vibrations. The ^{1}H NMR spectra of **(32)** show that there were no exchangeable signals containing the NH protons. On the other hand, the **(33)**^{1}H NMR spectra revealed convertible singlet signals, that resonated simply because of the NH protons.

6. Anticancer quinazolines sugar derivatives

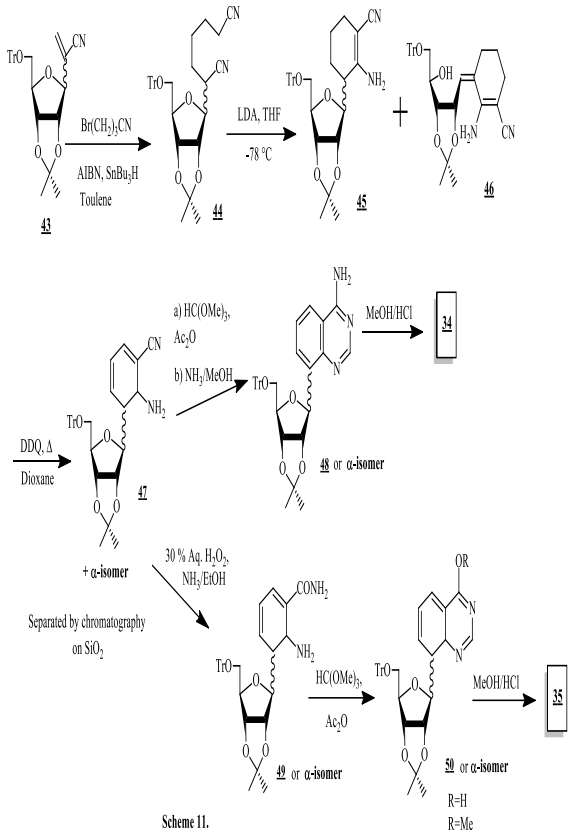
Research studies pointed out that 4-Bromobutyronitrile reacted with C-ribose acrylonitrile**(43)** and gave rise to the quinazolines C-nucleoside constituents of adenosine **(34)** and inosine **(35)** via a radical[36]. The pivotal intermediate 6-ribosylated anthranilonitrile (**47)** and its α-isomer came out by aromatization with DDQ following base-catalyzed Ziegler-Thorpe cyclization of the compound **(44)**. By initially heating a pyramiding ring onto **(47)** or the associated 0-amino-amide, and then deblocking along with MeOH/HCI, to afford compounds**(34)** and (**35)**.

Investigations illustrated that the initial strategy for acquiring the required o-amino nitrile intermediate **(36)** was to synthesize 1, 3-diene **(39)**, which would theoretically go through a Thorpe-Ziegler type of reaction. The synthesis of 1,3-dicyanobenzene derivative**(42)** involved the treatment of synthetic precursor **(37)** with 1.5 equivalents of an appropriate γ-cyanophosphorane at ambient temperature.



Scheme 10.

Finally, the synthesis of **(34)** and **(35)** was effectively completed by employing the fully saturated dinitrile **(44)** in a conventional Thorpe Ziegler cyclization procedure. Thesis of pyrido [4, 3-d] pyrimidine C-nucleosides **(42)**, the synthetic precursor, has an 88% yield. **(44)** Cycle using equation 1.2. Both products **(45)** and **(46)** from the LDA; THF combination were aromatized in dry THF at -78 0C to get o-aminonitrile **(47)** and its β-isomer. After undergoing treatment with 30% H_2O_2 and conc. ammonia in ethanol at ambient temperature, the aminonitrile **(47)** (or its α-isomer) easily altered into the related amide **(49)** (53% for the P- and eighty percent for the α-isomer). By treating the o-amino carboxamide **(49)** (or its isomer) at 65 0C employing ethanoic anhydride and trimethyl orthoformate, the moiety of quinazoline was generated. The outcome was 70% yields regarding the inhibited inosine analogue **(50)** (R=H) and 90% for the α-isomer.

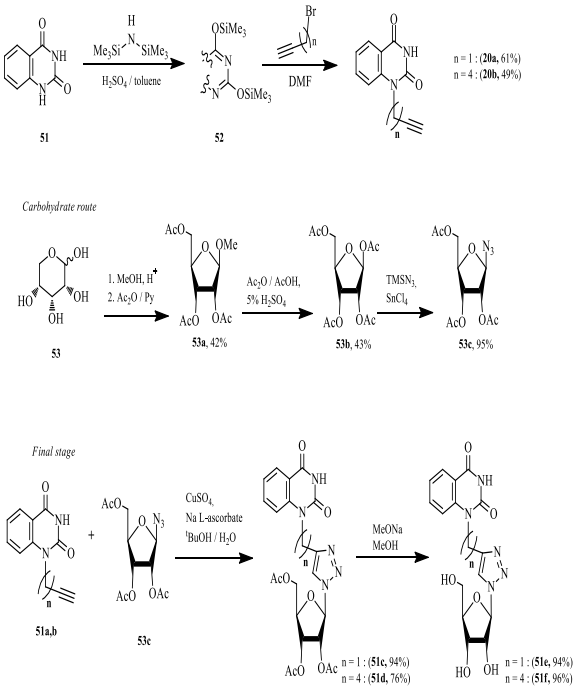


Scheme 11.

Investigations were conducted that determined the breadth of biochemical function in this novel category of analogues of C-nucleosides. It was discovered that 4-amino quinazoline nucleoside **(34)** exhibited strong growth inhibitory effects against several malignant tissue lines at concentrations equivalent to those of 9-deazaadenosine. This revelation suggests that **(34)** and adenosine share several structural similarities and that **(34)** may function as an antimetabolite [37].

As stated in reports, Hexamethyldisilane (HMDS) and thymine were first applied to uracil or thymine to achieve selectivity during the alkylation procedure [38].Alkylation was successfully performed by treatment with an adequate alkyl halide in 1,2-dichloroethane or DMF [39].

The principal objective of the carbohydrate pathway was the development of 2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosylazide**(53c)(Scheme 12)** via an adequate strategy. To synthesize a combination of α- and β-anomers of methyl 2, 3, 5-tri-*O*-Acetyl-D-ribofuranoside **(53a)**, silica gel was used to separate the two compounds by chromatographic procedure. Initially, D-ribose**(53)**underwent methylation to form D-α/β-ribofuranoside which was later per-*O*-acetylated [40]. Subsequently, replacement of methoxy group with an acetoxy group in the sugar **(53a)** by reacting with pure ethanoic acid and acetic anhydride in addition to H_2SO_4[41]. About 95% of the protected azido ribofuranose**(53c)** was obtained by reacting trimethylsilylazide ($TMSN_3$) with β-D-ribofuranose 1,2,3,5-tetraacetate **(53b)** in the existence of tin tetrachloride [42].



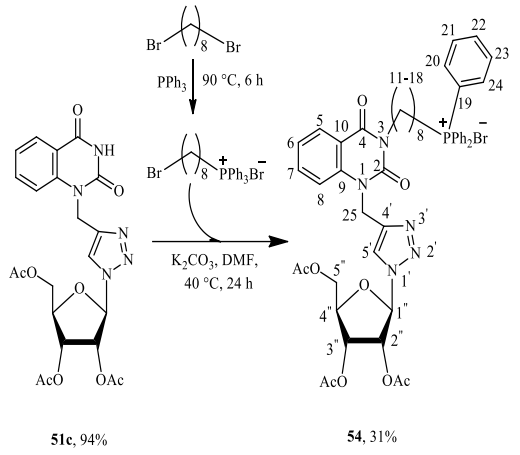
Scheme 12. Convergent synthesis of 1,2,3-triazolyl nucleoside analogues containing quinazolin-2,4-dione.

The resulting 1,2,3-triazolyl nucleoside analogues demonstrated anticancer characteristics. The revealed IC_{50} values were higher than 100 mM and consequently, nucleoside analogsespecially **(51c-f)** and **(51a-c)** have enormous potential as a foundation for the creation of cutting-edge therapeutic drugs.

Regarding investigations, two steps were involved in the synthesis of the target compounds **(51c)** and (**54)**. The first stage of the Cu alkyne-azide cycloaddition (CuAAC) process yielded pyrimidine nucleosides **(51c)** 1,2,3-triazolyl analogues. N^1-propargyl derivatives of azide 2, 4-dione quinazoline-3, 6-methyluracil **(51a)**, and thymine were synthesized using the previously mentioned techniques in the process[43, 44].

In the subsequent phase, 8-bromoocty l- and 10-bromodecyltriphenylphosphonium bromides have interacted with 1,2,3-triazolyl nucleoside analogue **(51c)**. Reports pointed out that to get the desired 1,2,3-triazolyl nucleoside analogue TPP-conjugates **(54)**, The 1,8-dibromoctane and 1,10-dibromodecane were heated along with triphenylphosphine for six hours at a temperature of 90°C[45, 46]. To facilitate better penetration into cells through lipid-rich cell membranes, prodrug

models of nucleoside equivalent with protected polar groups were being developed[47]. For this reason, investigations elucidated that the hydroxyl groups' acetyl protection in 1,2,3-triazolyl nucleoside equivalent **(54)**was not eliminated.



Scheme 13. Syntesis of the target TPP-conjugate of 1,2,3-triazolyl nucleoside analog 54

It has been realized that the quinazoline substituent's' cancer-fighting properties were increased when the sugar moiety was included.

TPP-conjugate of 1,2,3-triazolyl nucleoside analogue **(54)** was also evaluated for in vitro cytotoxicity against six human cancer cell lines: M− HeLa cervical epitheloid carcinoma, MCF-7 breast adenocarcinoma, A549 pulmonary adenocarcinoma, HuTu-80 duodenal adenocarcinoma, PC3 prostate adenocarcinoma, PANC-1 pancreatic carcinoma as well as a diploid human cell strain WI-38 composed of fibroblasts.

TPP-conjugate**(54)**showed cytotoxicity against the HuTu-80 cell line which corresponded to the cytotoxicity of the reference drug doxorubicin and exceeded the cytotoxicity of the reference compound – drug fluorouracil against the same cancer cell lines by 7–10 times.

7. Antiviralquinazoline sugar derivatives

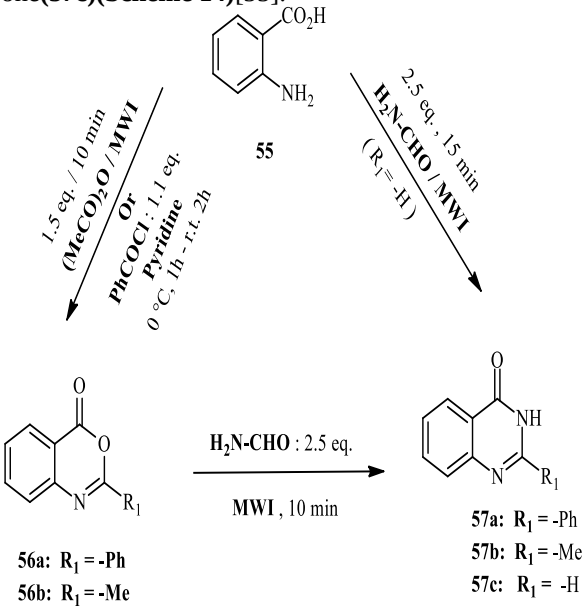
Studies state that the nucleoside ribofuranosyl-1,2,3-triazol-4-yl moiety **(51e–f)** analogues have been synthesized and tested againstH1N1, influenza virus A/PR/8/34. These analogues were connected to quinazoline-2,4-dione via a poly methylene linker. On the other hand, a nucleoside analogue with a butylenes linker, **(51f)** (n = 4), showed a moderate amount of efficacy against the influenza virus [48].

8. Formation of Protected Nucleosides and Acyclonucleosides:

Quinazolinone derivatives and related products comprise a significant category of heterocyclic chemical compounds that exhibit diverse biological responses. Such as antihypertensive, diuretic, anticancer, anti-inflammatory, and anti-convulsant qualities [2, 4, 49].

It has been reported that 1,4-disustituted-1,2,3-triazoloquinazoline ribonucleosides or acyclonucleosides were produced synthetically under microwave circumstances, by 1,3-dipolar cycloaddition of different *O*- or *N*-alkylated propargyl-quinazoline and 1'-azido-2',3',5'-tri-*O*-benzoylribose or activated alkylating agents[50].Consequently, a suggestion of basic structural modifications was enhanced.

Anthranilic acid **(55)** was successfully utilized as an available start to create the targeted derived quinazoline products. The acid and benzoyl chloride were first reacted between 0 and 5 °C in pyridine in anhydrous nature for sixty minutes before 2-phenylbenzoxazinone **(56a)** was formed. After that, the reaction mixture was stirred at ambient temperature for two hours [51, 52]. As an alternative, 2-methylbenzoxazinone **(56b)** was used via the microwave-induced combination of acetic anhydride and Anthranilic acid [53, 54]. After applying formamide treatment to the benzoxazinones, quinazolinone **(57a–b)** were produced by microwave stimulation. At the same time, Anthranilic acid and 2.5 equivalents of formamide were condensed using microwave stimulation to assist in making quinazoline-4-one**(57c)(Scheme 14)**[55].



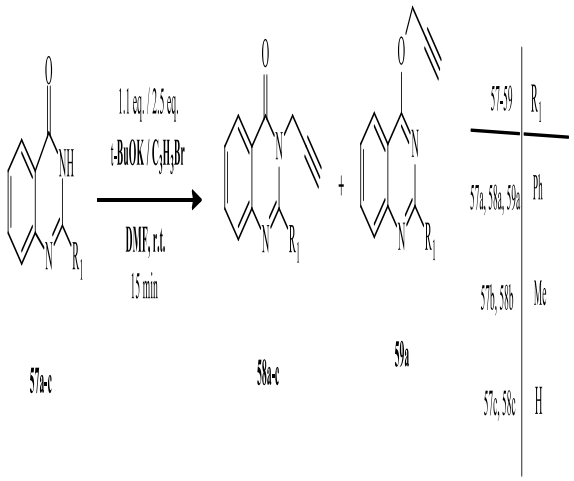
Scheme 14. Synthesis of benzoxazinones 56a,b.

Compound **(57a)** was produced in high yield. It was confirmed by ^{1}H-NMR and ^{13}C-NMR spectra.

9. 1,2,3-Triazole-quinazoline Hybrid Derivatives

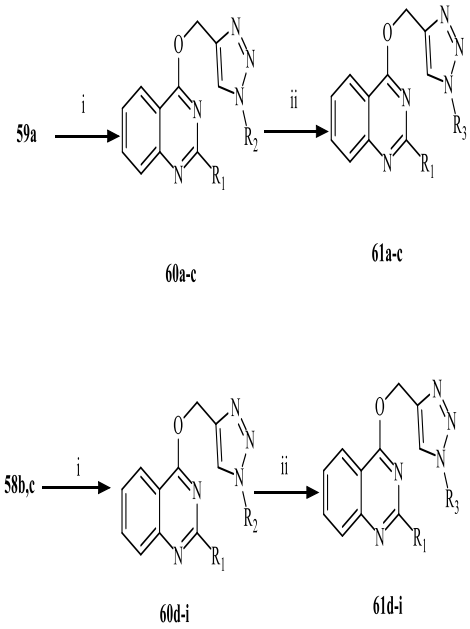
Since the advent of click chemical interactions in the world of therapeutic chemistry, there has been an increased interest in the use of 1,2,3-triazole as a desirable spacer or linker group to combine two pharmacological agents and construct unique dual-purpose compounds that defy oxidation, reduction, or hydrolysis [56]. Additionally, because the units of 1,2,3-triazoles are largely absent from natural products exhibiting outstanding stability to metabolic changes, they were utilized in a wide variety of pharmaceuticals.

It has been found that Propargyl bromide was employed in this inquiry to treat **(57a–c)** when potassium *t*-butoxide was present. Their investigative activities and also those for the alkylphosphonates were assessed as anti-HIV and anti-HCV activities [57-62]. The synthetic procedure employed DMF as an efficient medium for the reactants and catalytic systems **(Scheme 15)**[63-65]. When 2-methylquinazolin-4-ones **(56b)** and **(56c)** were alkylated, only N-propagylated quinazolines were formed; there was no evidence of *O*-propagylated isomers. Alkylation of the quinazolinone **(56a)** primarily produces *O*-propargylation, yielding *O*- and *N*-alkylated products **(59a)** and **(58a)** in 58 and 23 ratios.



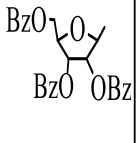
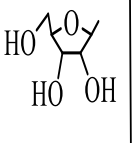
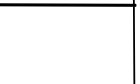
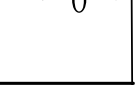
Scheme 15. Synthesis of alkylated quinazolines 58a-c and 59a.

The Propagylated quinazolines **(58)** and **(59)** were used in the 1,3-dipolar cycloaddition process to link the quinazoline nucleus with 1,2,3-triazole, resulting in compound**(60)**. The azide of sugar and pseudo-sugar engaged with propagylated quinazolines triple bonds when exposed to microwave radiation; in the absence of a solvent applying CuI as an efficient catalyst in this reaction **(Scheme 16)**.



Scheme 16. Synthesis of 1,2,3-triazoles-quinazoline 60a-i and 61a-i.

Reaction conditions; (i) **59a /58b-c** (1 mmol), alkylazide(2.5 mmol), Et_3N (1.1 mmol), CuI (0.1 eq), MWI (400W, 2min); (ii) **60a,d,g** (1 mmol), NaOMe (1 eq), MeOH, r.t (30 min) or **60b-c,e,f,h,i** (1 mmol), K_2CO_3 (1eq), MeOH, r.t (15 min).

Compound No.	R_1	R_2	R_3
60a, 61a	Ph		
60d, 61d	Me		
60g, 61g	H		
60b, 61b	Ph		
60e, 61e	Me		
60h, 61h	H		
60c, 61c	Ph		
60f, 61f	Me		
60i, 61i	H		

^{1}H-NMR spectrum of **(60a)** revealed the presence of -CH_2-N (Triazole) that appeared as triplet signals. The X-ray crystallography investigation confirmed the **(61c)** structure successfully.

Analogs of 1,2,3-triazolyl nucleosides have been produced in which the 1,2,3-triazole ring performs as more than simply serving as an ineffectual link between the sugar residue and the nucleic base[66]. The moiety of 1,2,3-triazole quickly binds to biological objectives utilizing dipole interactions and the creation of hydrogen bonds. Herpes simplex virus, cytomegalovirus, hepatitis B and C viruses, and human immunodeficiency viruses have all been monitored using nucleoside parallels in addition to a range of malignancies [67].

Propagylated nucleobases are used for constructing a variety of 1,2,3-triazole acyclonucleosides by 1,3-dipolar cycloaddition, and their strong HIV activity is assessed [68].

The reported click chemistry research program included in vitro tests to assess these derivatives' anti-HCV behaviour. The endeavour aimed to create novel hybrid molecules by fusing 1,2,3-triazole and quinazolinone, two heterocyclic[69, 70]. The anti-HCV qualities of the new compounds were also assessed.

Corresponding to research, a set of analogs **(Scheme 17)** that set up either substituted benzyl residues (compounds **(75)** and **(76)**) or substituted benzoyl groups (compounds **(63)** and**(64)** at the quinazoline-2,4-dione skeleton's N3 were synthesized[71].This was motivated by recent success in synthesizing homonucleoside analogues **(72)**.

N^1-Allyl-*N*^{3}-benzoylquinazoline-2,4-dione **(79a)** was produced by three methods, yielding a 20% total.Starting with quinazoline-2,4-dione and utilizing benzoyl chloride for selective *N*^{1}-debenzoylation and allylation, followed by bis-*N*^{1}, *N*^{3}-benzoylation. The *N*^{1}–*N*^{1}-debenzylation procedure was the littlest effective stage in producing *N* ^{1}-allyl–*N*^{3}–benzoyl quinazoline-2,4-diones**(79a–79d)**[72, 73].

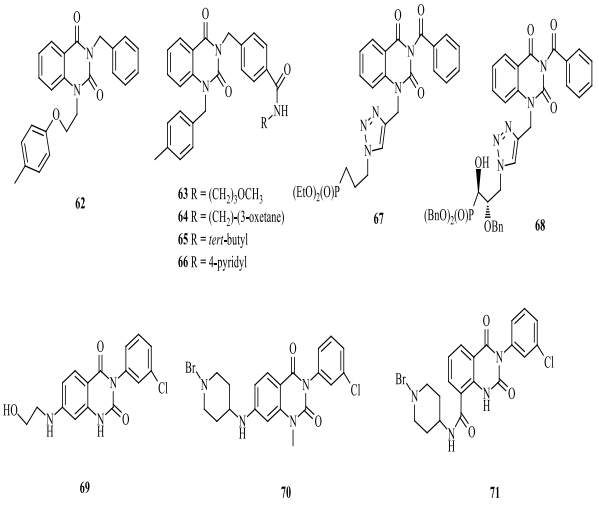
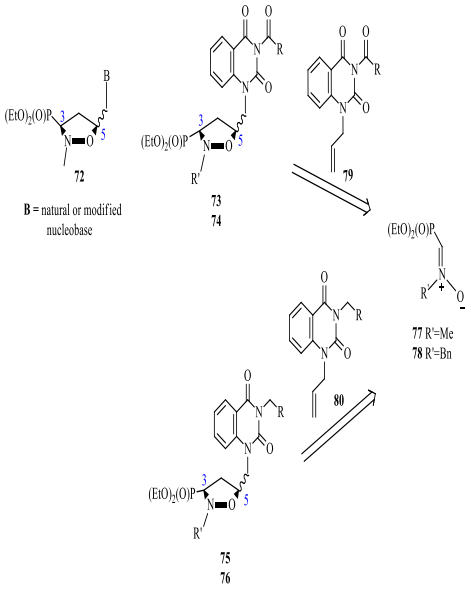
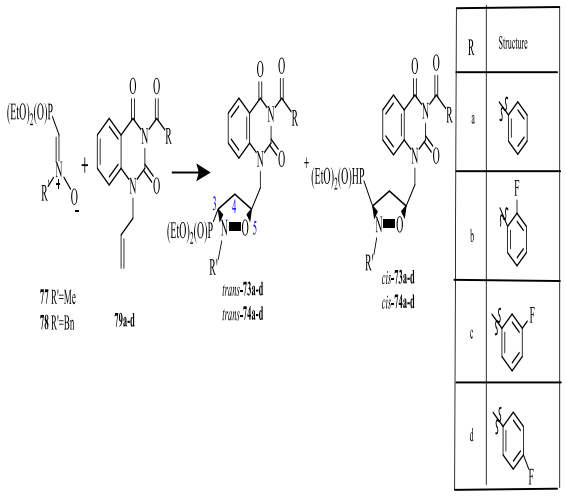


Fig 4. Examples of quinazoline-2,4-dione derivatives exhibiting antiviral activity.



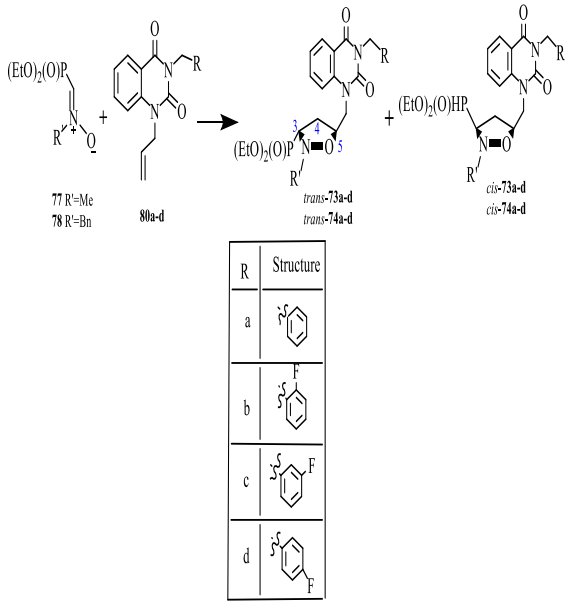
Scheme 17. Retrosynthesis of quinazoline-2,4-diones 73-76.

In toluene or toluene-ethanol at sixty degrees Celsius, nitrones **(77)**(R' = Me) or **(68)** (R' = Bn) underwent 1,3-dipolar cycloaddition with the corresponding N1-allyl-N3-benzoylquinazoline mixtures, where the trans-isomer prevailed (e.g., **trans-73** and **cis-73**, **trans-74** and **cis-74**) **(Scheme 18**).



Scheme 18. Reaction and conditions: a) toluene-ethanol, 60 °C, 72 h.

Under the identical incidents, as stated earlier for compound **(79)**, 1,3-dipolar cycloaddition of nitrones **(77)** (R'= Me) or**(78)** (R= Bn) with the referring N^1-allyl-N^3-benzylquina zoline-2,4-diones **80a-d**have resulted. With good to exceptional yields as a whole and relatively diastereoselectivities (i.e., 28–60%), the diastereoisomericcycloadducts**trans-75** and **cis-75**, or **trans-76** and **cis-76** (**Scheme 19),** were designed.



Scheme 19. Reaction and conditions: a) toluene-ethanol, 60 °C, 72 h.

When *N*-substituted C-(diethoxyphosphoryl) nitrones were cycloadditionally added to *N*-allylated quinazoline-2,4-diones functionalized at N^3 with substituted benzoyl or benzyl groups, moderate to good diastereoselectivities (d.e. 28=68%) were seen. The produced isoxazolidine phosphonates were tested for their antiviral efficacy against a range of DNA and RNA viruses. **Trans-374c**, **cis-74c/trans-74c** (86:14), **trans-76b/trans-76b** (87:13), and **trans-76d/cis-76d** (95:5) were the compounds that exhibited the highest level of activity against the TKÍ and TK VZV strains (mean EC50 values in the range of 3.0e8.7 mM). The isoxazolidines**trans-73a**, **cis-73a**, **trans-74a**, **trans-74d**, and **cis-76a**/**trans-76a** (50:50) had EC50 values ranging from 6.9 to 8.5 mM to 10.7 to 13.2 mM for the VZV TKÍ strain.

The distinct isomers of quinazoline-2,4-dione - pairs that were obtained were assessed for their capability to inhibit an abundance of DNA and RNA viruses employing several cell-based assays: herpes simplex virus-1 (KOS strain), herpes simplex virus-2 (G strain), and human being's embryonic lung (HEL) cells.

Human Skin Tiny Vessel Endothelial Cells Preserved (HMEC-1), human cervix cancer HeLa, human lymphocyte CEM, and murine leukemia L1210 were utilized to ascertain the cytostatic inhibitory dosage (IC50) that yields fifty percent reduction when it comes to cell division.

The delivered isoxazolidine phosphonates have undergone testing in vitro against multiple RNA as well as DNA viruses and diverse versions demonstrated potential against the varicella-zoster virus as well as human's hepatitis B virus. The compounds that exhibited the greatest magnitude of action against the TK+ VZV strain were **trans-39d/cis-39d** (95:5) (EC50 = 3.0 mM) and **cis-76b/trans-76b** (87:13) (EC50 = 4.7 mM). Furthermore, EC50 values for a few medications ranged from >3 to >14.5 mM, indicating some effectiveness regarding the human cytomegalovirus.

Compound **(82)** was evaluated for its effectiveness against a variety of viruses, comprising varicella zoster (TK+ and TK-), cytomegalo, vesicular stomatitis, sindbis, puntatoro, coxsackie B4, reo, herpes simplex 1 (TK+ and TK-), herpes simplex 2, human a lack of immunity and vaccinia [74].

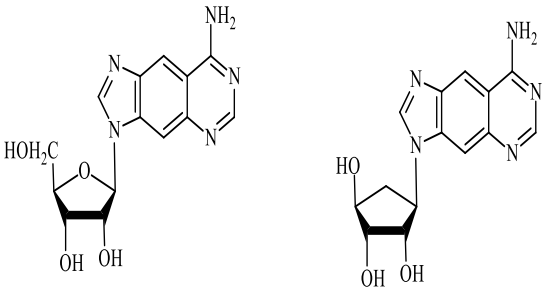
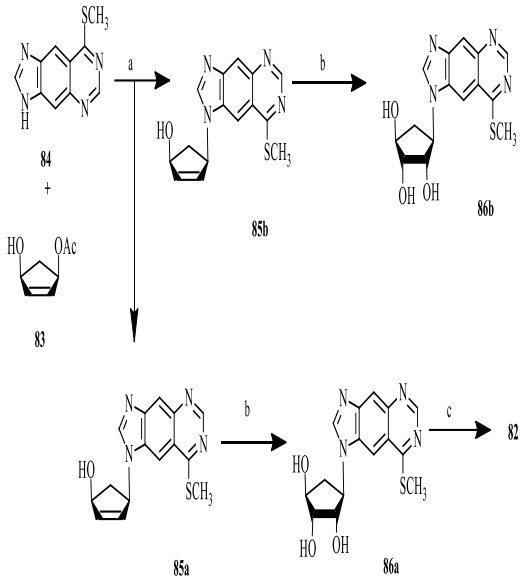
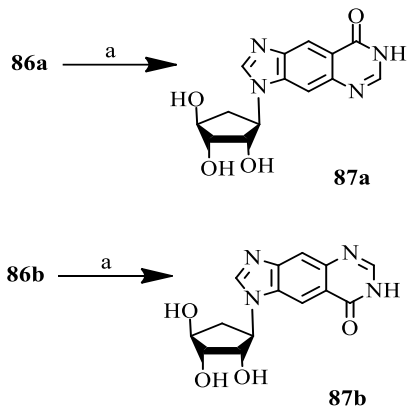


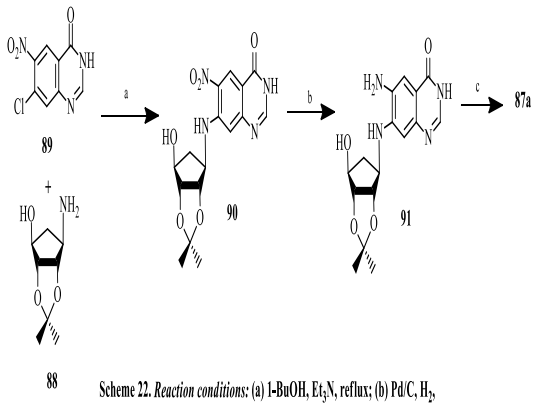
Fig. 5



Scheme 20. *Reaction conditions:* (a) NaH, $Pd(PPh_3)_4$, DMSO/THF; (b) OsO_4, NMO, THF/H_2O; (c) NH_3/MeOH, 110°C.



Scheme21. ***Reaction conditions:*** **(a) 1N HCl, reflux.**



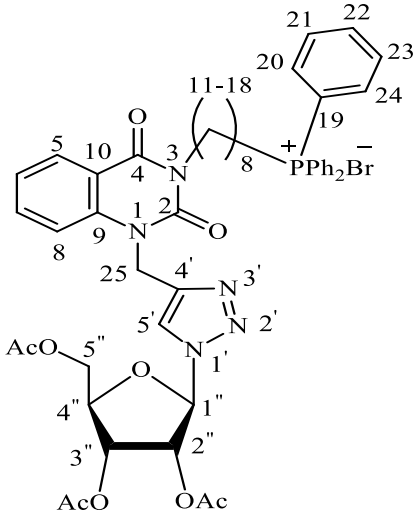
Scheme 22. *Reaction conditions:* (a) 1-BuOH, Et_3N, reflux; (b) Pd/C, H_2, 45 Psi; (c) (i) EtO_3CH, HCl, rt, (ii) H_2O, 80°C.

10. Antimicrobialquinazoline sugar derivatives

It has been noticed that when sugar's moiety was attached to quinazoline substituents, the activity toward microorganisms was enhanced.

Significant antibacterial efficacy against MRSA strains resistant to amoxicillin and ciprofloxacin was demonstrated by compound **(54)**[75, 76].

The produced TPP-conjugate **(54)** was tested for its in vitro antibacterial effectiveness against a variety of Gram-positive bacteria, including Bacillus cereus (Bc), Enterococcus faecalis (Ef), Staphylococcus aureus (Sa), MRSA-1, and MRSA-2. Salts of phosphorus have shown both antibacterial [77-79].



54

Quinazoline derivatives have acquired a wide spotlight and have been published in highly concerned articles over earlier periods[80].

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