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SYNTHESIS OF GLYCOSIDES CONTAINING QUINAZOLIN-4(3*H*)-ONE RING SYSTEM

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Abstract – Reactions of various aminoquinazolin-4(3*H*)-ones with monosaccharides in the presence of a catalytic amount of glacial acetic acid afforded the corresponding *N*-glycosylamines as a mixture of α- and β-anomers. Acetylation of this mixture gave the corresponding *β*-glycoside acetates. However, *β*-glycoside acetates could be obtained directly from reactions of per-*O*-acetyl-α-D-glucosyl bromides with quinazolin-4(3*H*)-one derivatives which deacetyalted to the corresponding β-glycosides. A series of *S*-glycosides have been synthesised from reaction of per-*O*-acetyl-α-D-glucosyl bromides with quinazolinethiones.

CONTENTS

1. INTRODUCTION

Glycosidase inhibitors are always of interest in view of potential applications in treatment of certain diseases.[1-5] In particular, some competitive inhibitors of α-glucosidases, such as 1-deoxynojirimycin and castanospermine, showed anti-HIV activity.[6] One of such compounds, *N*-butyl-1-deoxynojirimycin underwent clinical investigations.[7] The anti-HIV activity of this compound was thought to result from its inhibition of α-glucosidases involved in the processing of *N*-linked oligosaccharides on the viral coat during assembly. It prevents successful completion of the viral coat and hence reproduction of the infectious virus.[8] Recently, a number of glycosides[9-27] have been synthesised with the aim that they might have possible application as biologically active agents.

Quinazoline and its synthetic analogues have been found to exhibit interesting biological activities.[28-36] Some of these include activity as antimicrobial,[37-44] antimalarial,[45,46] antibacterial,[47,48] anticonvulsent,[49,50] antidepressant,[51] antiinflammatory,[52-54] antifungal,[55,56] antifolate,[57,58] antihypertensive,[59,60] biocidal,[61-63] plant-growth regulator,[64] herbicidal,[65] nervous system,[66-69] anticancer,[70,71] and anti-HIV agents.[72] However, the literature shows that there are relatively few examples in which quinazolin-4(3*H*)-ones are linked with sugar moieties. In view of the potential activities of quiazolin-4(3*H*)-ones we have investigated the synthesis of a range of such compounds.[73-88] This report concentrates on the work

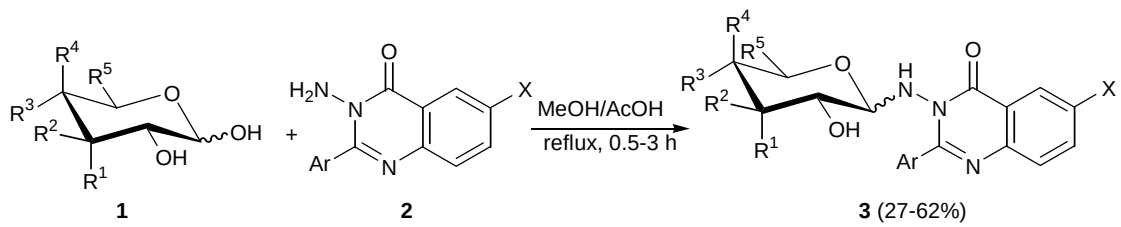
published on the synthesis of *N*-glycosyl amines, *N*- and *S*-glycosides containing quinazolin-4(3*H*)-one ring system.

2. *N*-GLYCOPYRANOSYL AMINES OF AMINOQUINAZOLIN-4(3*H*)-ONES

N-Glycosylamines were first prepared by Schiff by heating aniline or 4-toluidine with dry D-glucose at low temperature.[89,90] This method was modified by Sorokin who introduced the most generally used method for preparation of *N*-glycosylamines,[91,92] in which a mixture of amine and reducing sugar was heated under reflux in ethanol or methanol containing up to 10% of water and a small amount of acid as a catalyst. This method was used by Irvine and Gilmour to prepare *N*-phenyl- and *N*-*o*-carboxyphenyl-D-glucosyl amines.[93-95] Ellis and Weygand introduced a simple and general modification, in which a mixture of the amino compounds and monosaccharide heated under reflux in ethanol or methanol in the presence of a catalytic amount of glacial acetic acid to produce the corresponding of *N*-glycosylamine.[96-98] Recently, a number of *N*-glycosylamines having quinazoline ring system have been synthesised using this simple procedure.

2.1. *N*-Glycopyranosylamines of 3-amino-2-arylquinazolin-4(3*H*)-ones

Reactions of a number of monosaccharides (**1**), namely D-glucose, D-galactose, D-xylose and D-ribose, with 6-substituted 3-amino-2-arylquinazolin-4(3*H*)-ones (**2**) in boiling methanol in the presence of a catalytic amount of glacial acetic acid for 0.5-3 h afforded the corresponding 2-aryl-3-[*N*-(D-glycopyranosyl)]aminoquinazolin-4(3*H*)-ones (**3**) (Scheme 1) in 27-60% yields (Table 1).[99,100]



1 **2** **3** (27-62%)

Scheme 1

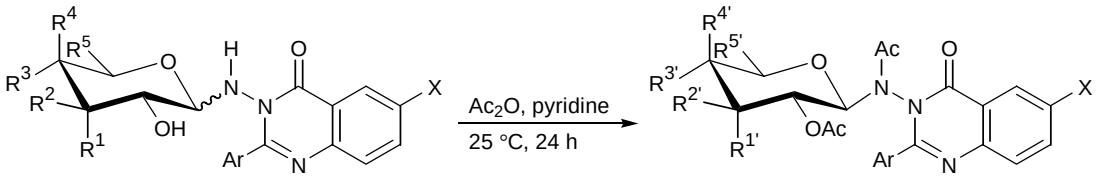
As expected, in solution, the *N*-glycopyranosylamines (**3**) were mixtures of α- and β-anomers in unequal

proportions as has often observed before for *N*-glycosylamines.[96] This conclusion was confirmed by NMR spectra of compounds (**3**). The spin-spin coupling constant *J*(1,2) for the predominating anomer was in the range of 7-9 Hz, which corresponds to diaxial orientation of the H-1 and H-2 protons of the sugar moieties, verifying the β-configuration with $^4C1$(D) conformation for this anomer. The small value (3-4 Hz) of *J*(1,2) in the minor anomer was consistent with its α-configuration and the same conformation.[99,100]

Table 1: Synthesis of *N*-glycopyranosylamines (**3**) according to Scheme 1

Product	Ar	X	R^1	R^2	R^3	R^4	R^5	Yield (%)	α:β
3a	Ph	H	H	OH	OH	H	CH_2OH	27	1:4
3b	Ph	Br	H	OH	OH	H	CH_2OH	60	1:4
3c	Ph	H	H	OH	H	OH	CH_2OH	40	1:3
3d	Ph	Br	H	OH	H	OH	CH_2OH	52	1:4
3e	Ph	Br	H	OH	OH	H	H	56	1:6
3f	Ph	H	OH	H	OH	H	H	40	1:6
3g	Ph	Br	OH	H	OH	H	H	52	1:5
3h	2-ClC_6H_4	H	H	OH	OH	H	CH_2OH	50	1:3
3i	4-BrC_6H_4	H	H	OH	OH	H	CH_2OH	62	1:4
3j	4-MeC_6H_4	H	H	OH	OH	H	CH_2OH	35	1:4

Acetylation of **3** using acetic anhydride in anhydrous pyridine at room temperature for 24 h gave the corresponding 2-aryl-3-[*N*-acetyl-*N*-(per-*O*-acetyl-β-D-glycopyranosyl)]aminoquinazolin-4(3*H*)-ones (**4**) (Scheme 2) in 66-88% yields (Table 2). The NMR and microanalyses showed that the acetylation took place on both the hydroxyl groups of the sugar moieties and the NH residues.[99,100]



3 **4** (66-88%)

Scheme 2

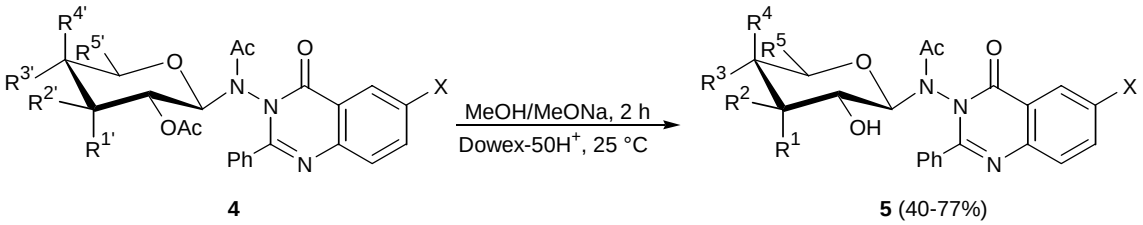
The NMR spectra verified the β-configuration and $^4C1$(D) conformation for compounds (**4**). The ambient temperature NMR spectra of compounds (**4**) showed the presence of two (*exo*- and *endo*-) sterically hindered rotamers due to hindered rotation about the N-N bond.[101,102] The barriers to rotation about the

N-N bond in 3-acylaminoquinazolin-4(3*H*)-ones and 3-diacylaminoquinazolin-4(3*H*)-ones reported and found to be as high as for hydrazine derivatives (14.7~20.6 Kcal mol^{-1}).[103,104]

Table 2: Synthesis of β-D-glycopyranosyl acetates (**4**) according to Scheme 2

Product	Ar	X	$R^{1'}$	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$	Yield (%)	*exo*:*endo*
4a	Ph	H	H	OAc	OAc	H	CH_2OAc	70	1:3
4b	Ph	Br	H	OAc	OAc	H	CH_2OAc	75	1:3
4c	Ph	H	H	OAc	H	OAc	CH_2OAc	80	1:4
4d	Ph	Br	H	OAc	H	OAc	CH_2OAc	82	1:3
4e	Ph	Br	H	OAc	OAc	H	H	66	1:3
4f	Ph	H	OAc	H	OAc	H	H	75	1:4
4g	Ph	Br	OAc	H	OAc	H	H	81	1:4
4h	2-ClC_6H_4	H	H	OAc	OAc	H	CH_2OAc	72	1:3
4i	4-BrC_6H_4	H	H	OAc	OAc	H	CH_2OAc	88	1:3
4j	4-MeC_6H_4	H	H	OAc	OAc	H	CH_2OAc	66	1:3

Deacetylation of compounds (**4a,b**) and (**4f-j**) by the use of Zemplen's method,[105] using sodium methoxide in the presence of an ion-exchange resin (Dowex-$50H^+$) at room temperature, afforded the corresponding 3-[*N*-acetyl-*N*-(β-D-glycopyranosyl)]amino-2-phenylquinazolin-4(3*H*)-ones (**5**) (Scheme 3) in 40-77% yields (Table 3).[99,100] No deacetylation took place on *N*-Ac group.



4 **5** (40-77%)

Scheme 3

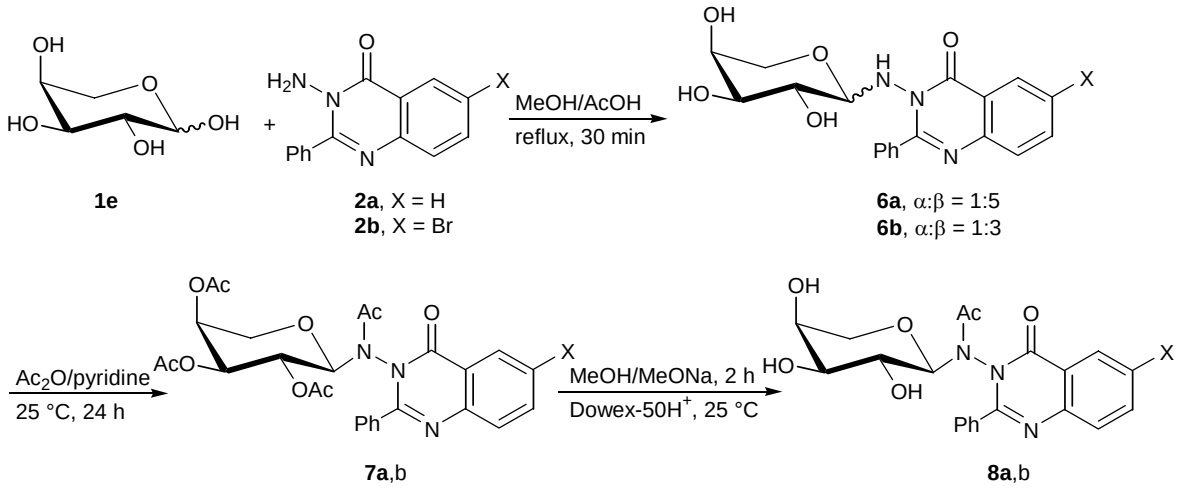
Table 3: Synthesis of β-D-glycopyranosyl derivatives (**5**) according to Scheme 3

Product	X	R^1	R^2	R^3	R^4	R^5	Yield (%)	*exo*:*endo*
5a	H	H	OH	OH	H	CH_2OH	40	1:4
5b	H	H	OH	H	OH	CH_2OH	40	1:4
5f	H	OH	H	OH	H	H	40	1:4
5g	Br	H	OH	OH	H	CH_2OH	46	1:3
5h	Br	H	OH	H	OH	CH_2OH	52	1:3
5i	Br	H	OH	OH	H	H	77	1:5
5j	Br	OH	H	OH	H	H	52	1:5

The ambient temperature NMR spectra of compounds (**5**) showed the presence of two (*exo*- and *endo*-)

sterically hindered rotamers due to hindered rotation about the N-N bond. The ^{1}H-NMR signals for these rotamers coalesced to one set of signals at higher temperature in DMSO-d_6 (65 °C).

On the other hand, reactions of **2a,b** with L-monosaccharides such as L-arabinose (**1e**) gave 2-phenyl-3-[*N*-(L-arabinopyranosyl)]aminoquinazolin-4(3*H*)-one (**6a**) and 6-bromo-2-phenyl-3-[*N*-(L-arabinopyranosyl)]aminoquinazolin-4(3*H*)-one (**6b**) (Scheme 4) in 22 and 30% isolated yields, respectively.[99,100] The NMR spectra of compounds (**6a,b**) verified the α-configuration and $^4C1$(L) conformation of the pyranoside structure was the predominating species.



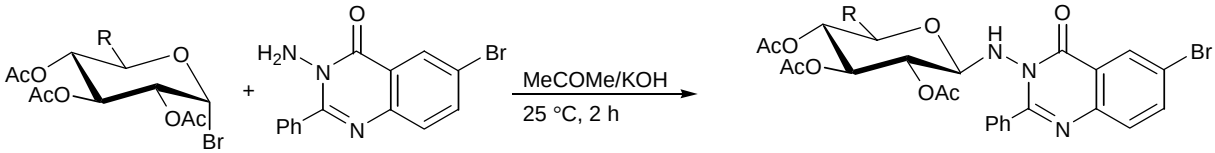
1e **2a**, X = H; **2b**, X = Br **6a**, α:β = 1:5; **6b**, α:β = 1:3 **7a**,b **8a**,b

Scheme 4

Acetylation of **6a,b** afforded the corresponding 2-phenyl-3-[*N*-acetyl-*N*-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)]aminoquinazolin-4(3*H*)-one (**7a**) and 6-bromo-2-phenyl-3-[*N*-acetyl-*N*-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)]aminoquinazolin-4(3*H*)-one (**7b**) (Scheme 4) in 50 and 62% isolated yields, respectively. The NMR spectra of **7a,b** verified the α-configuration and $^1C4$(L) conformation. Deacetylation of **7a,b** afforded 3-[*N*-acetyl-*N*-(α-L-arabinopyranosyl)]amino-2-phenylquinazolin-4(3*H*)-one (**8a**) and 6-bromo-3-[*N*-acetyl-*N*-(α-L-arabinopyranosyl)]amino-2-phenylquinazolin-4(3*H*)-one (**8b**) (Scheme 4) in 22 and 30% yields, respectively. Again, the ambient temperature NMR spectra of **8a,b** showed the presence of two (*exo*- and *endo*- in the ratio of 1:3) sterically hindered rotamers due to hindered rotation about the N-N bond, but the ^{1}H-NMR signals of the two rotamers were coalesced to one set of signals at higher temperature.

The anticarcinogenic activities of compounds (**3-8**) against the percentage growth of a wide variety of cancer cells were investigated under different concentrations. The bromo derivatives (**3b, 3g, 3j, 5b** and **5d**) showed the maximum measured effect against leukaemia/lymphoma cancer cells.[99,100]

On the other hand, reactions of **2b** with per-*O*-acetyl-α-D-glycopyranosyl bromides (**9**) in acetone in the presence of KOH at room temperature gave the corresponding *N*-per-*O*-acetyl-β-D-glycopyranosylamines (**10a,b**) in only 25% yields (Scheme 5).[106]

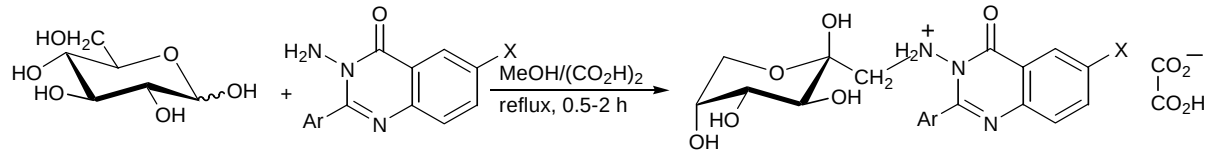


9 **2b**

10a, R = CH_2OAc (25%)
10b, R = H (25%)

Scheme 5

However, it was found that reactions of **2** with D-glucose (**1a**) in the presence of oxalic acid afforded Amadori rearrangement products (**11**) (Scheme 6) in 30-65% yields (Table 4).[107] Products (**11**) were also obtained from reactions of *N*-glucopyranosides (**3**) and oxalic acid in methanol under reflux conditions.[107] Amadori rearranged products arise from a complete conversion of *N*-substituted aldosylamines to *N*-substituted 1-amino-1-deoxy-2-ketoses or hemiacetal ring structure in the presence of an acid.[108]



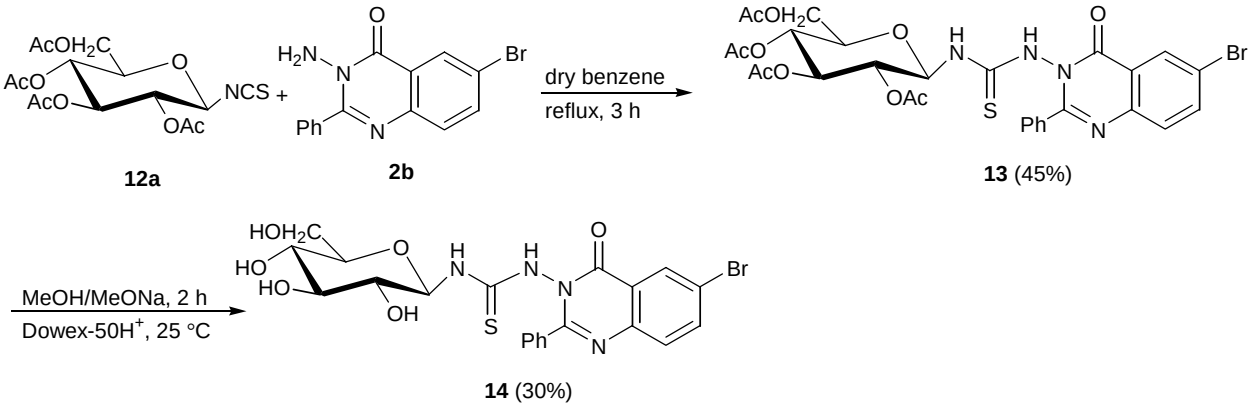
1a **2** **11**

Scheme 6

Table 4: Synthesis of products (**11**) according to Scheme 6

Product	Ar	X	Yield (%)
11a	Ph	H	30
11b	Ph	Br	55
11c	2-ClC_6H_4	H	58
11d	2-ClC_6H_4	Br	65
11e	3-ClC_6H_4	H	52
11f	4-MeC_6H_4	H	32

Reaction of 3-amino-2-phenylquinazolin-4(3*H*)-one (**2a**) with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**12a**) in dry benzene under reflux conditions gave *N*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[2-phenylquinazolin-4(3*H*)-one-3-yl]thiourea (**13**) in 45% yield (Scheme 7).[109] Deacetylation of **13** gave *N*-(β-D-glucopyranosyl)-*N*′-[2-phenylquinazolin-4(3*H*)-one-3-yl]thiourea (**14**) in 30% yield (Scheme 7).



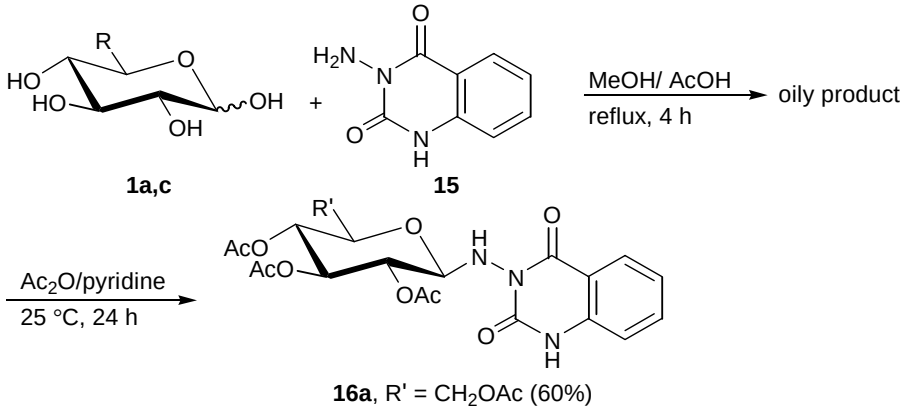
12a **2b** **13** (45%)

14 (30%)

Scheme 7

2.2. *N*-Glycopyranosylamines of 3-aminoquinazoline-2,4(1*H*,3*H*)-dione

Reactions of 3-aminoquinazoline-2,4(1*H*,3*H*)-dione (**15**) with D-glucose (**1a**) and D-xylose (**1c**) in boiling methanol in the presence of a few drops of glacial acetic acid as a catalyst for 4 h, followed by solvent evaporation, gave oily materials.[110] However, these oily products were purified by their acetylation to the corresponding acetate derivatives using a mixture of acetic anhydride and pyridine at room temperature (Scheme 8).[118]



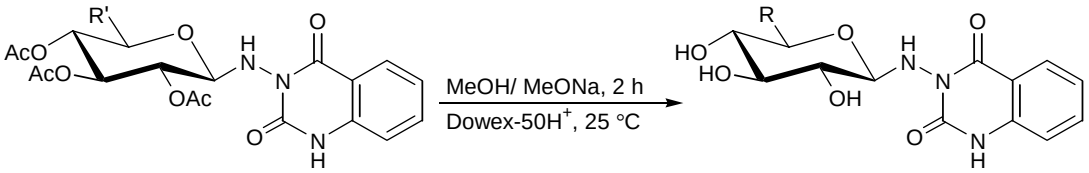
1a,c **15**

16a, R' = CH_2OAc (60%)
16b, R' = H (65%)

Scheme 8

3-[*N*-(tetra-*O*-Acetyl-β-D-glucopyranosyl)]aminoquinazoline-2,4-(1*H*,3*H*)-dione (**16a**) and 3-[*N*-(tri-*O*-acetyl-β-D-xylopyranosyl)]aminoquinazoline-2,4-(1*H*,3*H*)-dione (**16b**) were obtained in 60 and 65% yields, respectively (Scheme 8).[110] The acetylation took place on the sugar hydroxyl groups without affecting the NH hydrogen.

Deacetylation of **16a,b** using sodium methoxide in the presence of ion-exchange resin afforded the corresponding *N*-β-D-glycopyranosylamines (**17a,b**) in 60 and 55% yields, respectively (Scheme 9).[110] The NMR spectra verified the β-configuration and $^4C1$(D) conformation for *N*-glycosides (**16**) and (**17**).

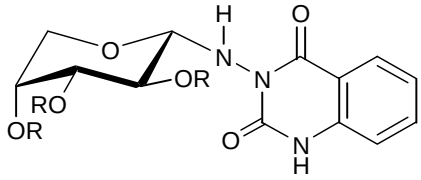


16a,b

17a, R = CH_2OH (60%)
17b, R = H (55%)

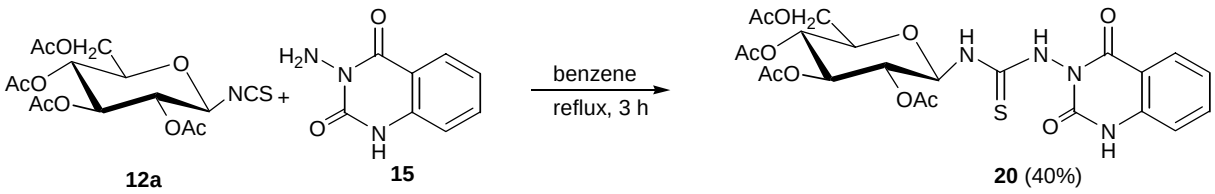
Scheme 9

On the other hand, reaction of **15** with D-arabinose (**1f**) in methanol in the presence of a few drops of glacial acetic acid as a catalyst under reflux conditions for 4 h gave **18**, which acetylated to **19**.[110] The NMR spectra of compounds (**18**) and (**19**) verified the α-configuration with $^1C4$(D) conformation. The α-configuration with $^1C4$(D) conformation was found to be thermodynamically more stable than the corresponding α-configuration with $^4C1$(D) conformation.



18, R = Ac (50%)
19, R = H (70%)

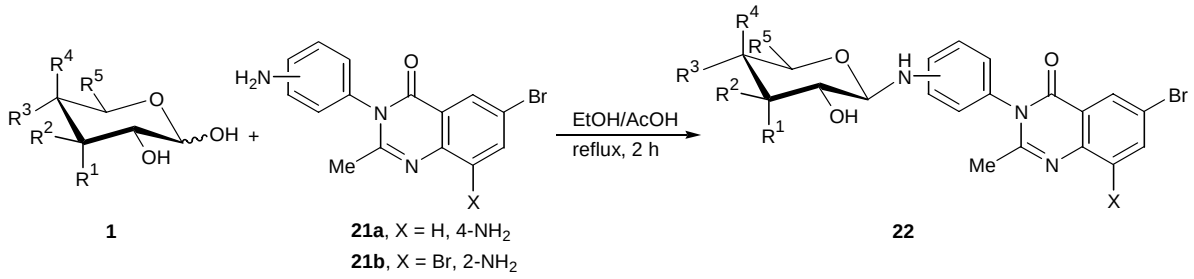
It was found that reaction of **15** with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**12a**) in dry benzene under reflux conditions gave *N*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[quinazolin-2,4(1*H*,3*H*)-dione-3-yl]thiourea (**20**) in 40% yield (Scheme 10).[109]



Scheme 10

2.3. *N*-Glycopyranosylamines of 3-(4-aminophenyl)- and 3-(2-aminophenyl)-2-methylquinazolin-4(3*H*)-ones

Reactions of 3-(4-aminophenyl)-6-bromo-2-methylquinazolin-4(3*H*)-one (**21a**) and 3-(2-aminophenyl)-6,8-dibromo-2-methylquinazolin-4(3*H*)-one (**21b**) with monosaccharides (**1**) in ethanol containing a few drops of glacial acetic acid under reflux conditions for 2 h afforded the corresponding 3-(*N*-β-D-glycopyranosyl)aminophenyl-2-methylquinazolin-4(3*H*)-ones (**22**) stereoselectively (Scheme 11) in 52-75 yields (Table 5).[111] The ^{1}H-NMR spectra of **22** showed that *J*(1,2) was approximately 8 Hz, which consistent with the β-configuration and $^4C1$(D) conformation.

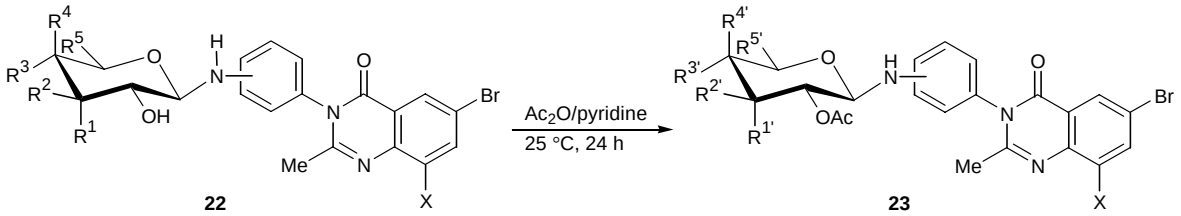


Scheme 11

Table 5: Synthesis of β-D-glycopyranosylamines (**22**) according to Scheme 11

Product	-NH-	X	R^1	R^2	R^3	R^4	R^5	Yield (%)
22a	4	H	H	OH	OH	H	CH_2OH	72
22b	4	H	H	OH	H	OH	CH_2OH	70
22c	4	H	H	OH	OH	H	H	75
22d	4	H	OH	H	OH	H	H	65
22e	2	Br	H	OH	OH	H	CH_2OH	52
22f	2	Br	H	OH	H	OH	CH_2OH	65
22g	2	Br	H	OH	OH	H	H	75
22h	2	Br	OH	H	OH	H	H	55

Acetylation of **22** with acetic anhydride in pyridine gave the corresponding 3-[*N*-(per-*O*-acetyl-β-D-glycopyranosyl)]aminophenyl-2-methylquinazolin-4(3*H*)-ones (**23**) (Scheme 12) in good yields (Table 6).[111] The acetylation took place on the sugar hydroxyl groups without affecting the NH hydrogen.

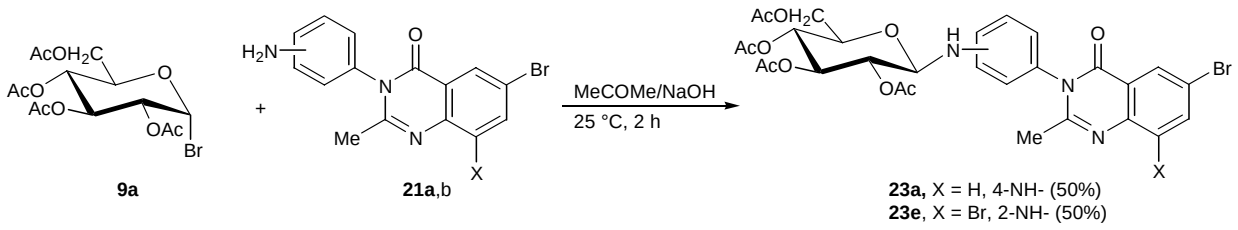


Scheme 12

Table 6: Synthesis of β-D-glycopyranosylamines (**23**) according to Scheme 12

Product	-NH-	X	$R^{1'}$	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$	Yield (%)
23a	4	H	H	OAc	OAc	H	CH_2OAc	85
23b	4	H	H	OAc	H	OAc	CH_2OAc	87
23c	4	H	H	OAc	OAc	H	H	88
23d	4	H	OAc	H	OAc	H	H	80
23e	2	Br	H	OAc	OAc	H	CH_2OAc	85
23f	2	Br	H	OAc	H	OAc	CH_2OAc	82
23g	2	Br	H	OAc	OAc	H	H	82
23h	2	Br	OAc	H	OAc	H	H	80

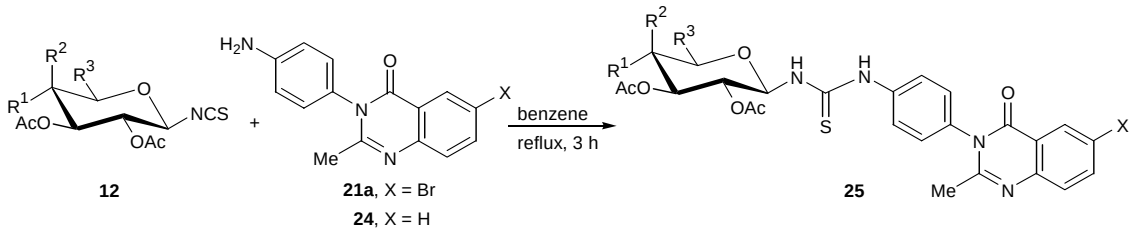
Deacetylation of **23** gave back the corresponding *N*-β-D-glycopyranosylamines (**22**).[111] Compounds (**23a**) and (**23e**) were also obtained in 50% yields from the direct reactions of **21a** and **21b** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**9a**) (Scheme 13).[111]



Scheme 13

Reactions of 3-(4-aminophenyl)-2-methylquinazolin-4(3*H*)-one (**24**) and 3-(4-aminophenyl)-6-bromo-2-methylquinazolin-4(3*H*)-one (**21a**) with a number of per-*O*-acetyl-β-D-glycopyranosyl isothiocyanates (**12**) in dry benzene under reflux conditions gave the corresponding *N*-(per-*O*-acetyl-β-D-glycopyranosyl)-*N*′-[4-(2-methylquinazolin-4(3*H*)-one-3-yl)phenyl]thioureas (**25**) (Scheme 14) in 60-

75% yields (Table 7).[109]

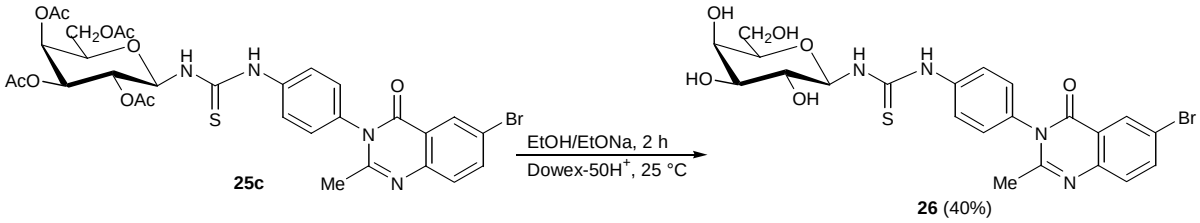


Scheme 14

Table 7: Synthesis of β-D-glycopyranosyl thioureas (**25**) according to Scheme 14

Product	X	R^1	R^2	R^3	Yield (%)
25a	H	OAc	H	CH_2OAc	60
25b	Br	OAc	H	CH_2OAc	70
25c	Br	H	OAc	CH_2OAc	65
25d	Br	OAc	H	H	75

Deacetylation of **25c** gave *N*-(β-D-galactopyranosyl)-*N*′-[4-(6-bromo-2-methylquinazolin-4(3*H*)-one-3-yl)phenyl]thiourea (**26**) in 40% yield (Scheme 15).[109]

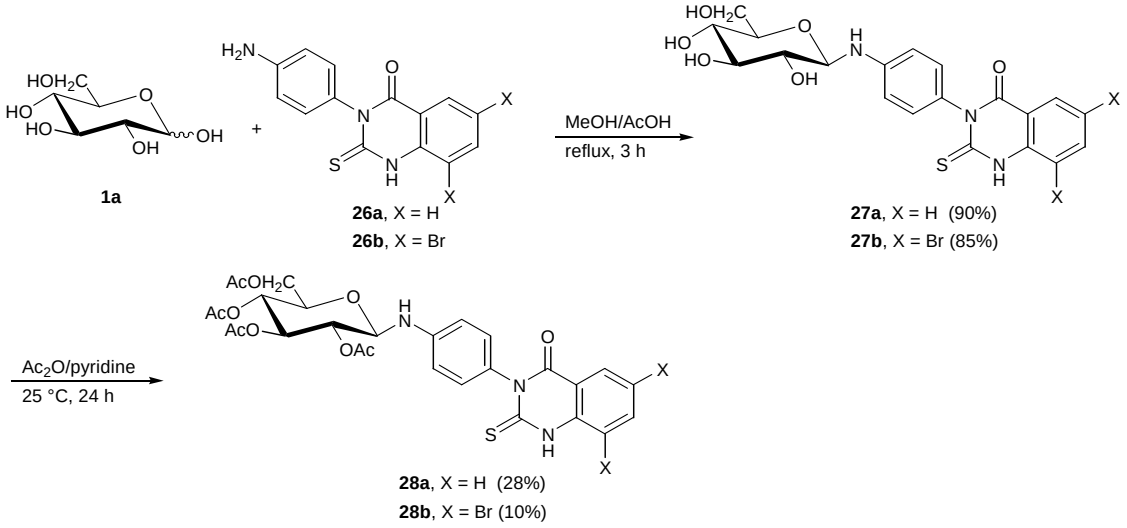


Scheme 15

2.4. *N*-Glycopyranosylamines of 3-(4-aminophenyl)-2-thioquinazolin-4(3*H*)-ones

Condensation of D-glucose (**1a**) with 3-(4-aminophenyl)-2-thioquinazolin-4(3*H*)-one (**26a**) or 3-(4-aminophenyl)-6,8-dibromo-2-thioquinazolin-4(3*H*)-one (**26b**) in methanol containing a catalytic amount of glacial acetic acid afforded 3-[4-*N*-(β-D-glucopyranosyl)]aminophenyl-2-thio-quinazolin-4(3*H*)-one (**27a**) and 6,8-dibromo-3-[4-*N*-(β-D-glucopyranosyl)]aminophenyl-2-thioquinazolin-4(3*H*)-one (**27b**) in 90 and 85% yields, respectively (Scheme 16).[112] Compounds (**27a,b**) were acetylated using acetic anhydride in pyridine at room temperature.[112] It was found that acetylation had taken place on the hydroxyl groups without affecting the NH groups, to give 3-[4-*N*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-

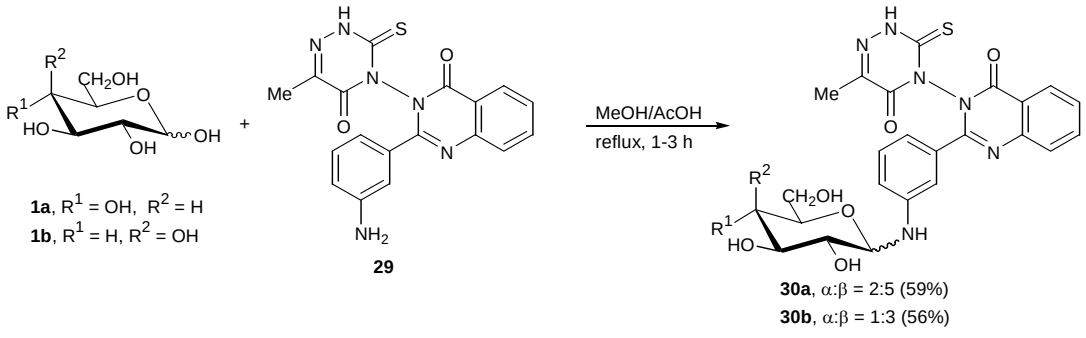
glucopyranosyl)]aminophenyl-2-thioquinazolin-4(3*H*)-one (**28a**) and 6,8-dibromo-3-[4-*N*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)]aminophenyl-2-thioquinazolin-4(3*H*)-one (**28b**) (Scheme 16).[112] A series of experiments was conducted under different reaction conditions in order to improve the yields of **28a,b**, but none of these conditions was successful.



Scheme 16

2.5. *N*-Glycopyranosylamines of 2-(3-aminophenyl)-3-[6-methyl-5(4*H*)-3-thio-1,2,4-triazin-4-yl]quinazolin-4(3*H*)-one

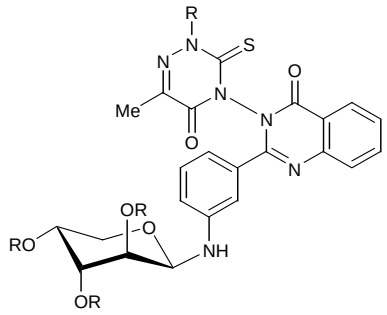
Reactions of 2-(3-aminophenyl)-3-[6-methyl-5(4*H*)-3-thio-1,2,4-triazin-4-yl]quinazolin-4(3*H*)-one (**29**) with D-glucose (**1a**) and D-galactose (**1b**) in methanol under reflux conditions gave the corresponding *N*-glycopyranosylamines (**30a**) and (**30b**) as α- and β-anomeric mixtures in 59 and 56% isolated yields, respectively (Scheme 17).[113]



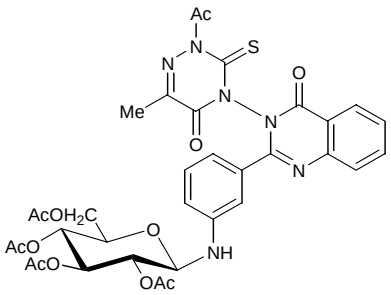
Scheme 17

The anticarcinogenic activities of compounds (**30**) against the percentage growth of a wide variety of cancer cells were investigated under different concentrations. However, none of these compounds showed significant anti-cancer activity.[113]

On the other hand, reaction of **29** with D-arabinose (**1f**) in methanol under reflux conditions for 1 h gave *N*-β-arabinopyranoside (**31**) stereoselectively in 61% isolated yield.[113] The ^{1}H-NMR spectrum of compound (**31**) showed that the anomeric proton resonated as a broad signal at 5.33 ppm, while C1′ resonated as a doublet at 85.2 ppm in its ^{13}C-NMR spectrum. These values are consistent with the β-configuration and $^{4}C1$(D) conformation. Acetylation of **30a** and **31** using acetic anhydride in pyridine at room temperature for 24 h gave the corresponding per-*O*-acetyl-β-glycopyranosylamines (**32**) and (**33**) in 40 and 48% yields, respectively.[113] It was found that acetylation took place on the hydroxyl groups of the sugar moieties and the NH group of the triazine ring.



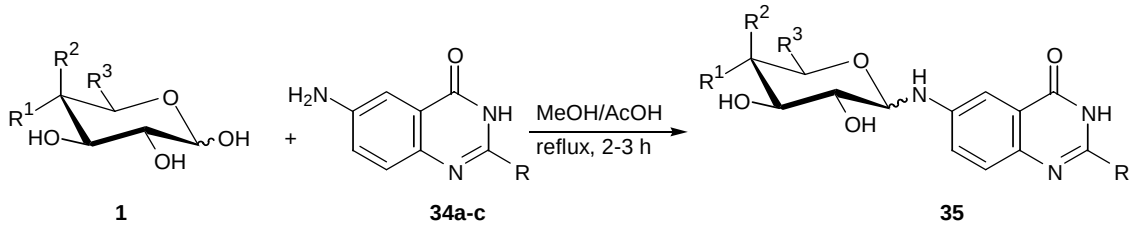
31, R = H (61%)
33, R = Ac (48%)



32 (40%)

2.6. *N*-Glycopyranosylamines of 6-aminoquinazolin-4(3*H*)-ones

Reactions of 6-aminoquinazolin-4(3*H*)-ones (**34a**), 6-amino-2-ethylquinazolin-4(3*H*)-ones (**34b**) and 6-amino-2-phenylquinazolin-4(3*H*)-ones (**34c**) with D-glucose, D-galactose and D-xylose (**1**) in methanol in the presence of a few drops of glacial acetic acid as a catalyst under reflux conditions afforded the corresponding 6-[*N*-(D-glycopyranosyl)]aminoquinazolin-4(3*H*)-ones (**35**) as mixtures of α- and β-anomers (Scheme 18) in good yields (Table 8).[113,114]



1 34a-c 35

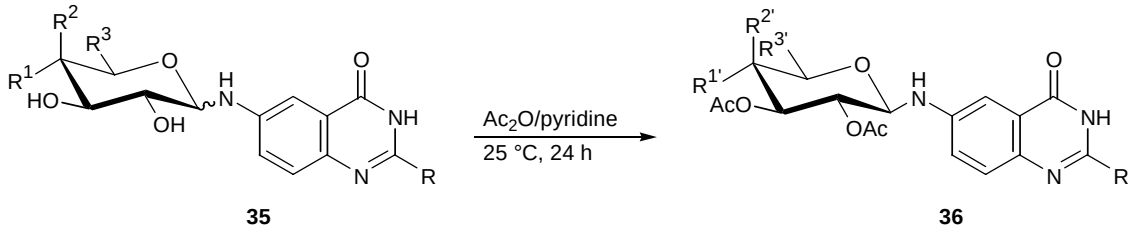
Scheme 18

Table 8: Synthesis of *N*-D-glycopyranosylamines (**35**) according to Scheme 18

Product	R	R^1	R^2	R^3	Yield (%)	α:β
35a	H	OH	H	CH_2OH	68	2:5
35b	H	H	OH	CH_2OH	70	1:3
35c	H	H	OH	H	70	1:4
35d	Et	OH	H	CH_2OH	72	1:4
35e	Et	H	OH	CH_2OH	72	1:3
35f	Et	H	OH	H	66	1:4
35g	Ph	OH	H	CH_2OH	73	1:3
35h	Ph	H	OH	CH_2OH	83	1:3
35i	Ph	H	OH	H	87	1:5

Compounds (**35**) were screened for the *in-vitro* antimicrobial activities against *Escherichia coli* 1357 and *Staphylococcus aureus* 1352 as well as antifungal activities against *Candida albicans*, *Aspergillus fumigatus* and *Saccharomyces cerevisiae*. Compounds (**35g-i**) showed the maximal effect against the tested organisms.[114]

Acetylation of *N*-glycopyranosylamines (**35a,b,g-i**) with acetic anhydride in anhydrous pyridine at room temperature gave the corresponding 6-[*N*-(per-*O*-acetyl-β-D-glycopyranosyl)]aminoquinazolin-4(3*H*)-ones (**36**) (Scheme 19) in only moderate yields (Table 9).[113,114] It was found that acetylation took place on hydroxyl groups of sugar moieties without affecting the NH residues.



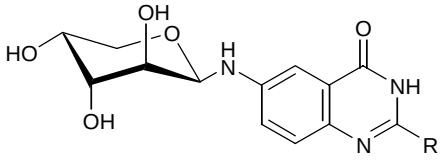
35 36

Scheme 19

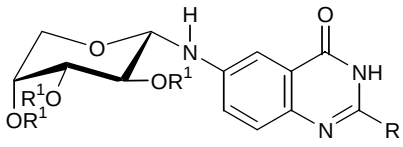
Table 9: Synthesis of *N*-β-D-glycopyranosyl acetates (**36**) according to Scheme 19

Product	R	$R^{1'}$	$R^{2'}$	$R^{3'}$	Yield (%)
36a	H	OAc	H	CH_2OAc	55
36b	H	H	OAc	CH_2OAc	53
36c	Ph	OAc	H	CH_2OAc	45
36d	Ph	H	OAc	CH_2OAc	38
36e	Ph	H	OAc	H	39

β-Selective glycosidation of **34a** (R = H) with D-arabinose (**1f**) in methanol in the presence of a few drops of glacial acetic acid as a catalyst under reflux conditions for 2 h gave the corresponding *N*-β-D-arabinoside (**37**) in 65% yield.[113] The NMR spectra of compound (**37**) showed that the anomeric proton resonated as a broad signal at δ 4.86, while C1′ resonated as a doublet at δ 85.2. These values are consistent with the β-configuration and $^4C1$(D) conformation. However, reactions of **34b** and **34c** with D-arabinose in boiling methanol in the presence of a few drops of glacial acetic acid for 2 h gave the corresponding *N*-α-D-arabinopyranosides (**38a)** and (**38b**) in 67 and 86% yields, respectively (Table 10).[113,114]



37 (65%)



38a,b, 39

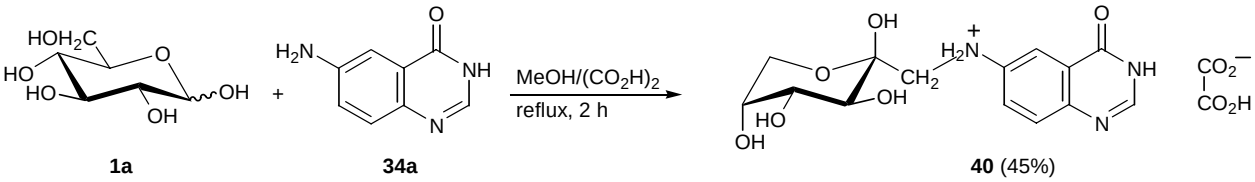
Table 10: Synthesis of *N*-α-D-arabinopyranosides (**38a,b**) and (**39**)

Product	R	R^1	Yield (%)
38a	Et	H	67
38b	Ph	H	86
39	Ph	Ac	42

Acetylation of **38b** using anhydrous acetic anhydride in dry pyridine at room temperature for 24 h afforded the corresponding acetyl derivative (**39**) in 42% yield.[114] The α-anomers with $^1C4$(D) conformation for compounds (**38**) and (**39**) appeared to be thermodynamically more stable than the corresponding α-anomers with $^4C1$(D) conformation.[114]

Reaction of **34a** with D-glucose (**1a**) in methanol in the presence of oxalic acid under reflux conditions

afforded Amadori rearrangement product (**40**) (Scheme 20) in 45% yield.[113] Product (**40**) was also obtained from the reaction of **35** with oxalic acid under reflux conditions in methanol.

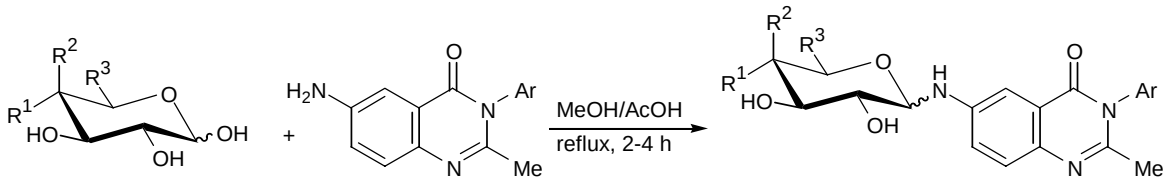


1a **34a** **40** (45%)

Scheme 20

2.7. *N*-Glycopyranosylamines of 6-amino-3-aryl-2-methylquinazolin-4(3*H*)-ones

Reactions of 6-amino-3-aryl-2-methylquinazolin-4(3*H*)-ones (**41**) with D-glucose, D-galactose and D-xylose (**1**) in methanol in the presence of a catalytic amount of glacial acetic acid under reflux conditions afforded the corresponding 3-aryl-2-methyl-6-[*N*-(D-glycopyranosyl)]aminoquinazolin-4(3*H*)-ones (**42**) as mixtures of α- and β-anomers (Scheme 21) in 50-75% yields (Table 11).[115] The NMR spectra confirmed that the β-anomer was the predominating anomer with $^4C1$(D) conformation.



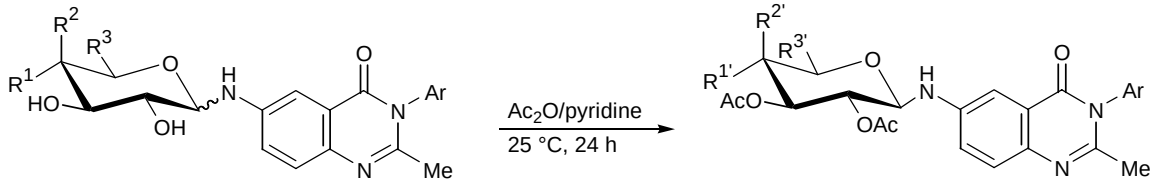
1 **41** **42**

Scheme 21

Table 11: Synthesis of *N*-glycopyranosylamines (**42**) according to Scheme 21

Product	Ar	R^1	R^2	R^3	Yield (%)	α:β
42a	C_6H_5	OH	H	CH_2OH	65	1:3
42b	4-MeC_6H_4	OH	H	CH_2OH	50	1:3
42c	4-$MeOC_6H_4$	OH	H	CH_2OH	60	1:3
42d	C_6H_5	H	OH	CH_2OH	70	1:4
42e	4-MeC_6H_4	H	OH	CH_2OH	59	1:4
42f	4-$MeOC_6H_4$	H	OH	CH_2OH	75	1:3
42g	C_6H_5	OH	H	H	55	1:4
42h	4-MeC_6H_4	OH	H	H	68	1:4
42i	4-$MeOC_6H_4$	OH	H	H	53	1:4

Acetylation of *N*-D-glycopyranosylamines **(42)** using acetic anhydride in pyridine gave the corresponding 3-aryl-2-methyl-6-[*N*-(per-*O*-acetyl-β-D-glycopyranosyl)]aminoquinazolin-4(3*H*)-ones (**43**) (Scheme 22) in good yields (Table 12).[115] The acetylation took place on hydroxyl groups of sugar moieties without affecting NH residues.



42 **43**

Scheme 22

Table 12: Synthesis of β-D-glycopyranosylamines (**43**) according to Scheme 22

Product	Ar	$R^{1'}$	$R^{2'}$	$R^{3'}$	Yield (%)
43a	C_6H_5	OAc	H	CH_2OAc	70
43b	4-MeC_6H_4	OAc	H	CH_2OAc	76
43c	4-$MeoC_6H_4$	OAc	H	CH_2OAc	80
43d	C_6H_5	H	OAc	CH_2OAc	80
43e	4-MeC_6H_4	H	OAc	CH_2OAc	86
43f	4-$MeOC_6H_4$	H	OAc	CH_2OAc	89
43g	C_6H_5	OAc	H	H	70
43h	4-MeC_6H_4	OAc	H	H	74
43i	4-$MeOC_6H_4$	OAc	H	H	69

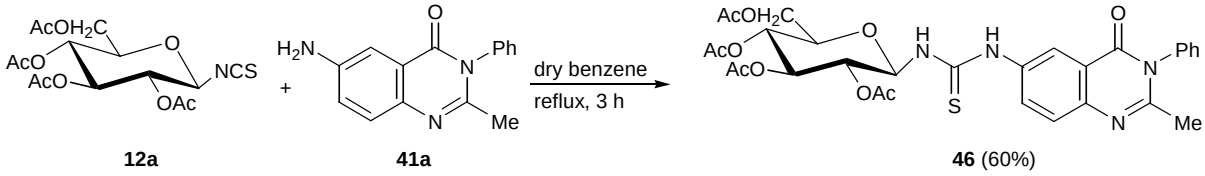
On the other hand, reactions of **41** with L-arabinose (**1e**) in methanol in the presence of a catalytic amount of glacial acetic acid under reflux conditions gave 3-aryl-2-methyl-6-[*N*-(L-arabinopyranosyl)]amino-quinazolin-4(3*H*)-ones (**44**) in 60-67% yields (Table 13).[115] The NMR spectra showed that the α-anomer was the predominating anomer with $^4C1$(L) conformation. Acetylation of **44** using acetic anhydride in pyridine at room temperature afforded the corresponding 3-aryl-2-methyl-6-[*N*-(tri-*O*-acetyl-α-L-arabino-pyranosyl)]aminoquinazolin-4(3*H*)-ones (**45**) in 83-89% yields (Table 13).[115]

44 **45**

Table 13: Synthesis of L-arabinopyranosylamines (**44**) and (**45**)

Product	Ar	Yield (%)
44a	C_6H_5	60
44b	4-MeC_6H_4	67
44c	4-$MeOC_6H_4$	63
45a	C_6H_5	80
45b	4-MeC_6H_4	83
45c	4-$MeOC_6H_4$	89

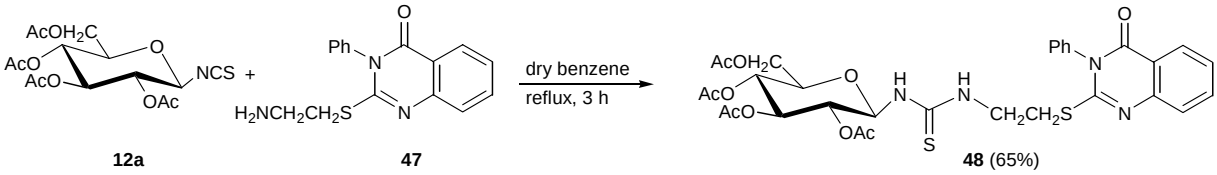
Treatment of 6-amino-2-methyl-3-phenylquinazolin-4(3*H*)-one (**41a**) with **12a** in dry benzene under reflux gave *N*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[2-methyl-3-phenylquinazolin-4(3*H*)-one-3-yl]thiourea (**46**) in 60% yield (Scheme 23).[116]



Scheme 23

2.8. *N*-Glucopyranosylthiourea of 2-(2-aminoethylthio)- 3-phenylquinazolin-4(3*H*)-one

Reaction of 2-(2-aminoethylthio)-3-phenylquinazolin-4(3*H*)-one (**47**) with **12a** in dry benzene gave the corresponding *N*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-[2-(3-phenylquinazolin-4(3*H*)-one-2-yl)thioethyl]thiourea (**48**) in 65% yield (Scheme 24).[116]



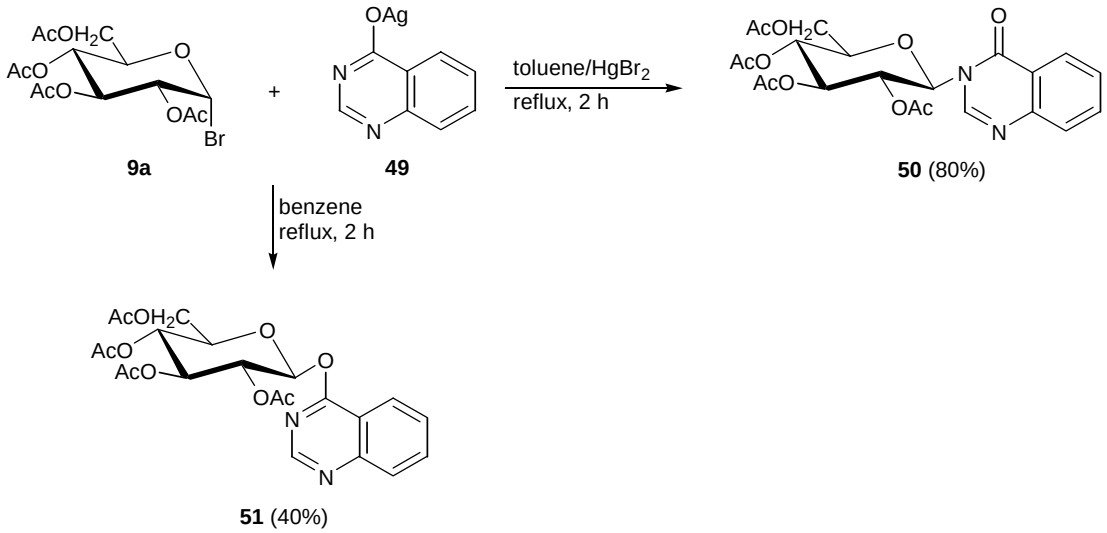
Scheme 24

3. *N*-GLYCOSIDES OF QUINAZOLIN-4(3*H*)-ONES

3.1. *N*-Glycopyranosides of quinazolin-4(3*H*)-one

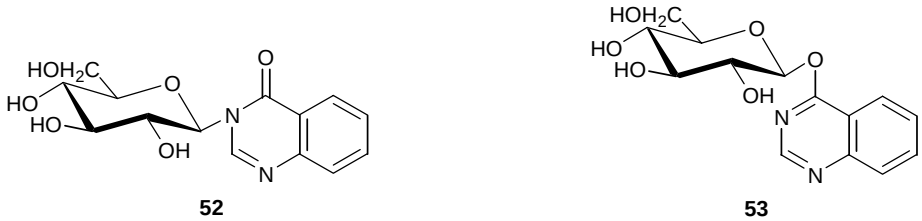
Reaction of the silver salt of quinazolin-4(3*H*)-one (**49**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl

bromide (**9a**) in toluene in the presence of $HgBr_2$ afforded the corresponding *N*-glucopyranoside (**50**) in 80% yield (Scheme 25).[117] However, the *O*-glucopyranoside (**51**) was obtained when benzene was used as a solvent (Scheme 25). Reaction of **9a** with quinazolin-2(1*H*)-one in acetone gave only the corresponding *O*-glucopyranoside in poor yield.[117]



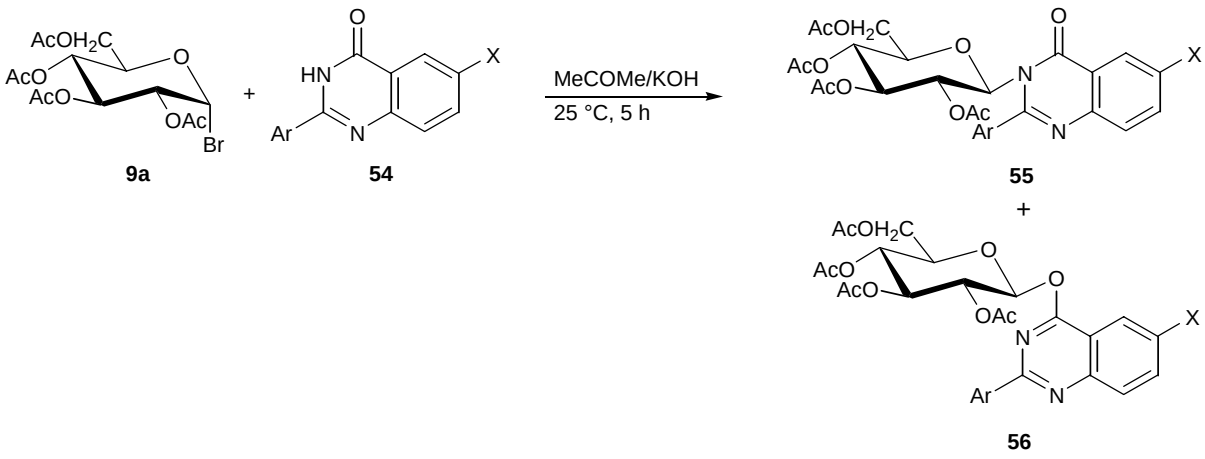
Scheme 25

Deacetylation of **50** and **51** using dilute sodium methoxide at room temperature afforded the corresponding *N*-glucopyranoside (**52**) and *O*-glucopyranoside (**53**), respectively in moderate yields.[117]



3.2. *N*-Glycopyranosides of 2-arylquinazolin-4(3*H*)-ones

Reactions of 6-substituted 2-arylquinazolin-4(3*H*)-ones (**54**) with **9a** in acetone in the presence of potassium hydroxide produced 2-aryl-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glycopyranosyl)quinazolin-4(3*H*)-ones (**55**) in fair yields together with 2-aryl-4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glycopyranosyloxo)-quinazolines (**56**) (Scheme 26) in poor yields (Table 14).[118]



Scheme 26

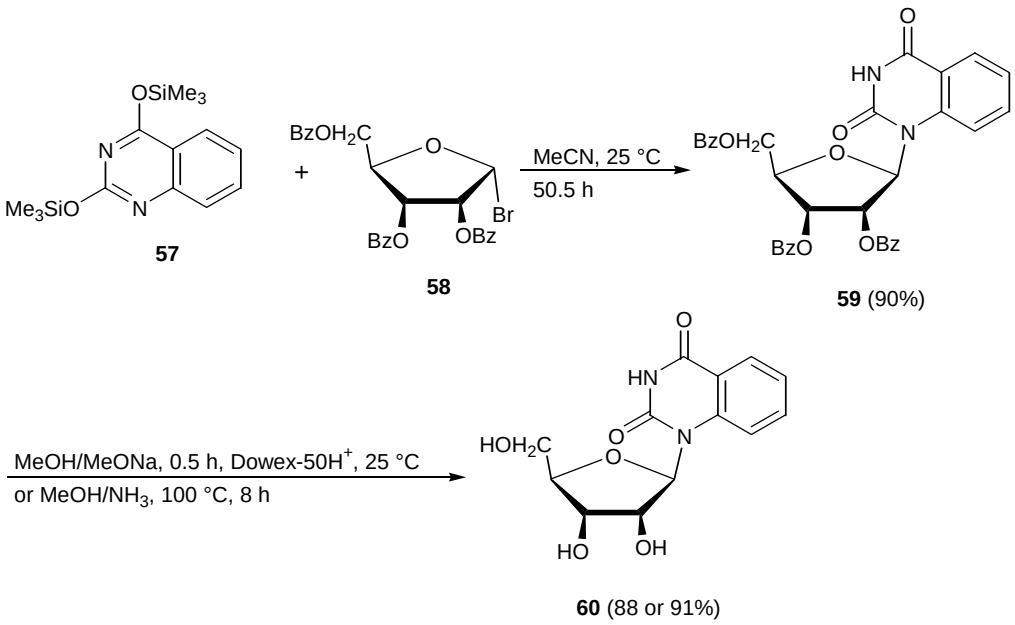
Table 14: Synthesis of *N*-glucosides (**55**) and *O*-glucosides (**56**) according to Scheme 26

Product	Ar	X	Yield (%)
55a	Ph	H	65
55b	Ph	Br	73
55c	4-ClC_6H_4	Br	68
55d	4-MeC_6H_4	Br	70
55e	4-$NO_2C_6H_4$	H	72
56a	Ph	H	12
56b	Ph	Br	13
56c	4-ClC_6H_4	Br	15
56d	4-MeC_6H_4	Br	15
56e	4-$NO_2C_6H_4$	H	16

Deacetylation of glucosides (**55**) and (**56**) using ammonia, hydrochloric acid and sodium hydroxide were attempted. However, in all cases, compounds (**54**) were obtained by cleavage of either the *N*-sugar or the *O*-sugar bonds.[118]

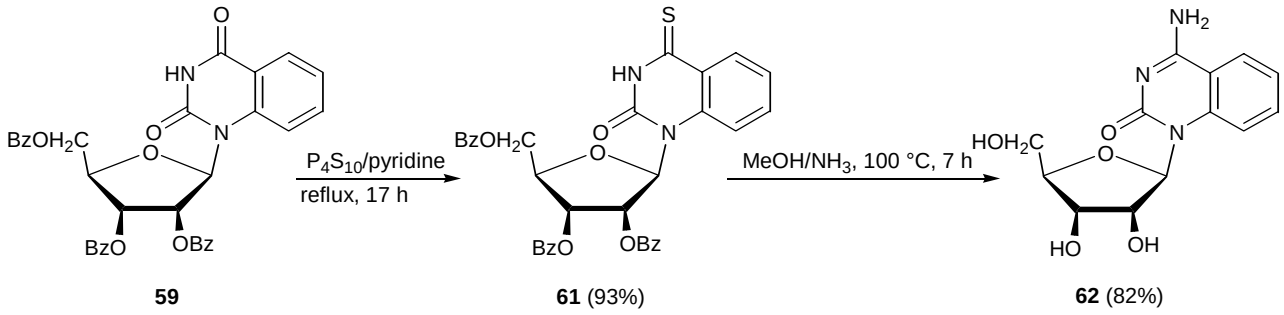
3.3. *N*-Glycofuranosides of quinazoline-2,4(1*H*,3*H*)-dione

Treatment of 2,4-bis(trimethylsilyloxy)quinazoline (**57**) with 2,3,5-tri-*O*-benzoylribofuranosyl bromide (**58**) in dry acetonitrile at room temperature gave 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)quinazoline-2,4(1*H*,3*H*)-dione (**59**) in 90% yield (Scheme 27).[119] Debenzoylation of **59** with sodium methoxide or methanolic ammonia gave 1-(β-D-ribofuranosyl)quinazoline-2,4(1*H*,3*H*)-dione (**60**) in the yield of 88 or 91%, respectively (Scheme 27).[119]



Scheme 27

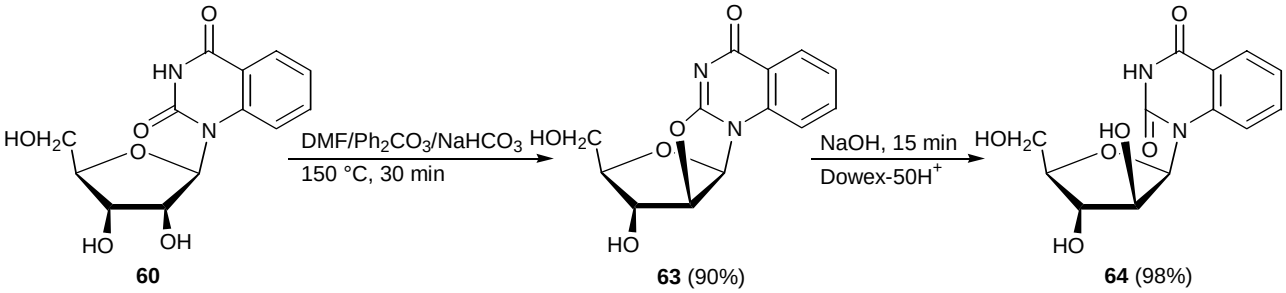
Treatment of **59** with phosphorus pentasulfide provided the corresponding 4-thione derivative (**61**) in 93% yield which upon treatment with methanolic ammonia at 100 °C gave 4-amino-1-(β-D-ribo-furanosyl)quinazolin-2(1*H*)-one (**62**) in 82% yield (Scheme 28).[119] Compound (**62**) could also obtained in 50% yield by treatment of compound (**59**) with phosphorus oxyxcloride and *N*,*N*-diethylaniline for 10 minutes followed by treatment with methanolic ammonia at 100 °C for 7 h.[119]



Scheme 28

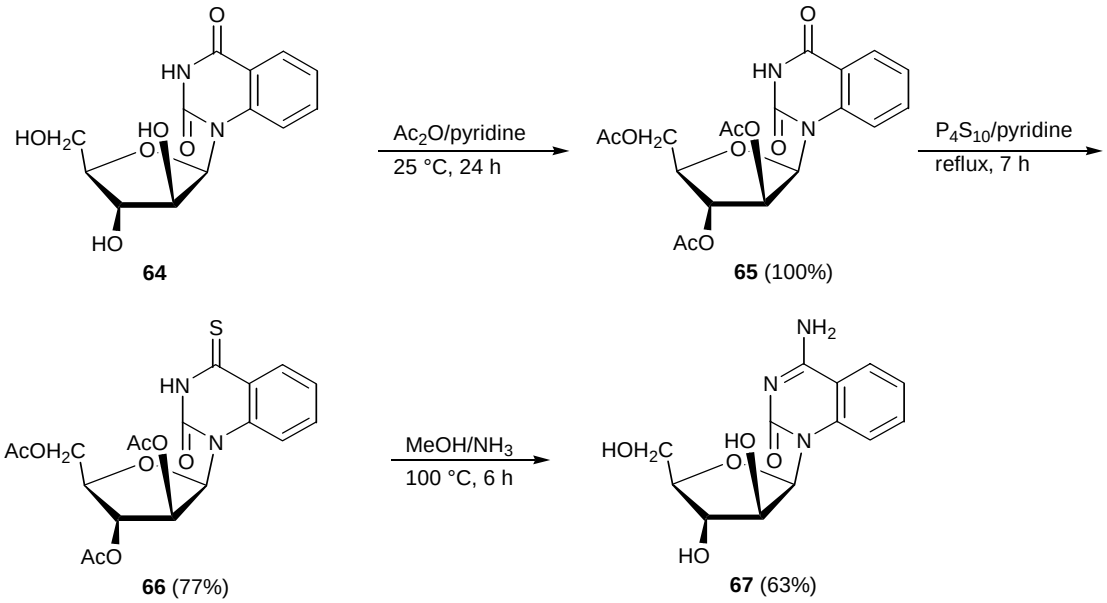
1-(β-D-Arabinofuranosyl)quinazoline-2,4(1*H*,3*H*)-dione (**64**) was prepared in two steps from compound (**60**) in which the method of Nichol and Hampton[120] for inversion of the 2′-hydroxyl group was employed. Treatment of **60** with diphenyl carbonate and sodium hydrogencarbonate in *N*,*N*-dimethylformamide

afforded **63** in 90% yield (Scheme 28).[119] Treatment of **63** with dilute sodium hydroxide in a steam bath gave **64** in quantitative yield (Scheme 29).[119]



Scheme 29

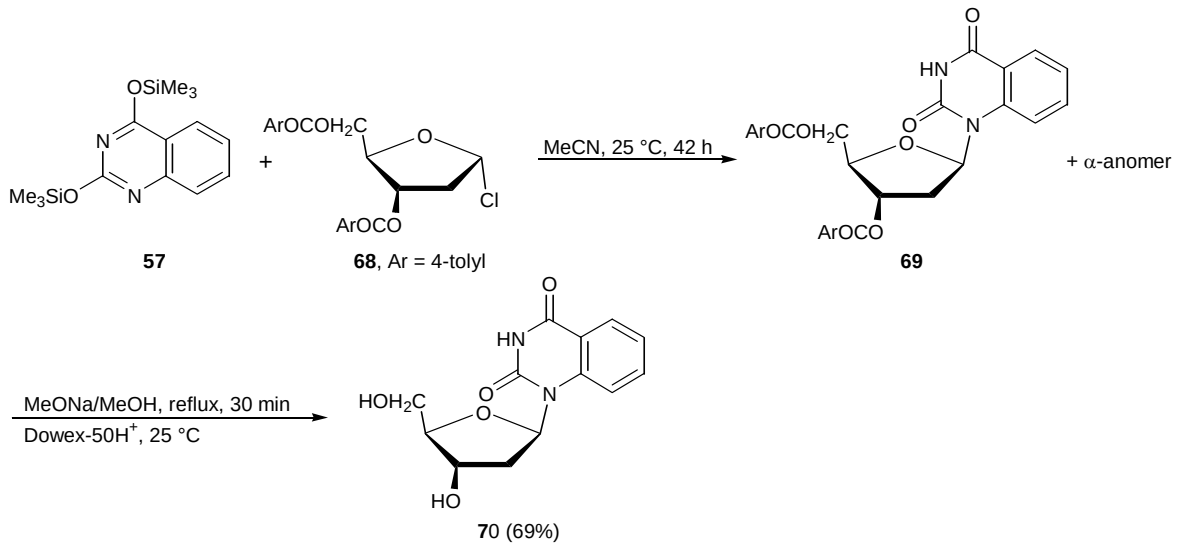
Acetylation of **64** gave a quantitative yield of the corresponding acetyl derivative (**65**), which on treatment with phosphorus pentasulfide in pyridine gave the corresponding 4-thione derivative (**66**) in 77% yield (Scheme 30).[119] Treatment of **66** with methanolic ammonia at 100 °C gave 4-amino-1-(β-D-arabinofuranosyl)quinazolin-2(1*H*)-one (**67**) in 63% yield (Scheme 30).[119]



Scheme 30

Treatment of **57** with 3,5-di-*O*-(4-methylbenzoyl)-2-deoxyribofuranosyl chloride (**68**) in acetonitrile gave an anomeric mixture of glycosides which separated on an alumina column.[119] 1-(3′,5′-Di-*O*-(4-methylbenzoyl)-β-D-2′-deoxyribofuranosyl)quinazoline-2,4(1*H*,3*H*)-dione (**69**) was obtained in 25%

yield along with 35% of mixed anomers (Scheme 31).[119] Deblocking **69** with sodium methoxide in methanol under reflux conditions gave 1-(2′-deoxy-β-D-ribofuranosyl)quinazoline-2,4(1*H*,3*H*)-dione (**70**) in 69% yield (Scheme 31).[119]

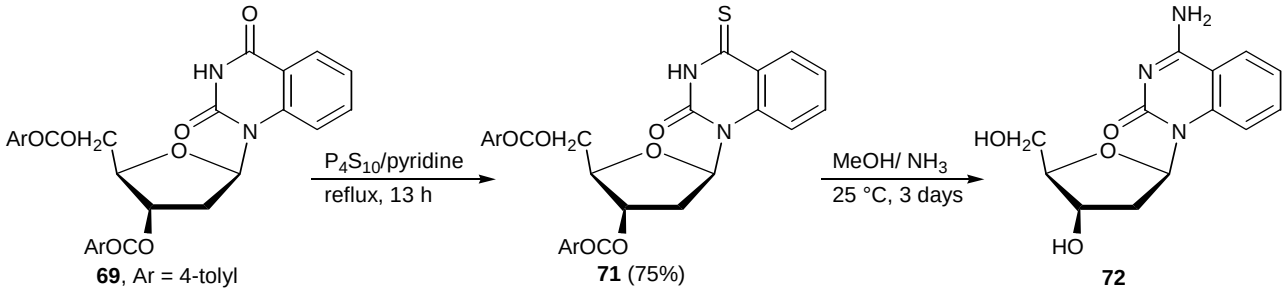


57 **68**, Ar = 4-tolyl **69**

70 (69%)

Scheme 31

Treatment of **69** with phosphorus pentasulfide in pyridine gave the corresponding 4-thione derivative (**71**) in 75% yield which in turn gave 4-amino-1-(2′-deoxy-β-D-ribofuranosyl)quinazolin-2(1*H*)-one (**72**) on treatment with methanolic ammonia (Scheme 32).[119]



69, Ar = 4-tolyl **71** (75%) **72**

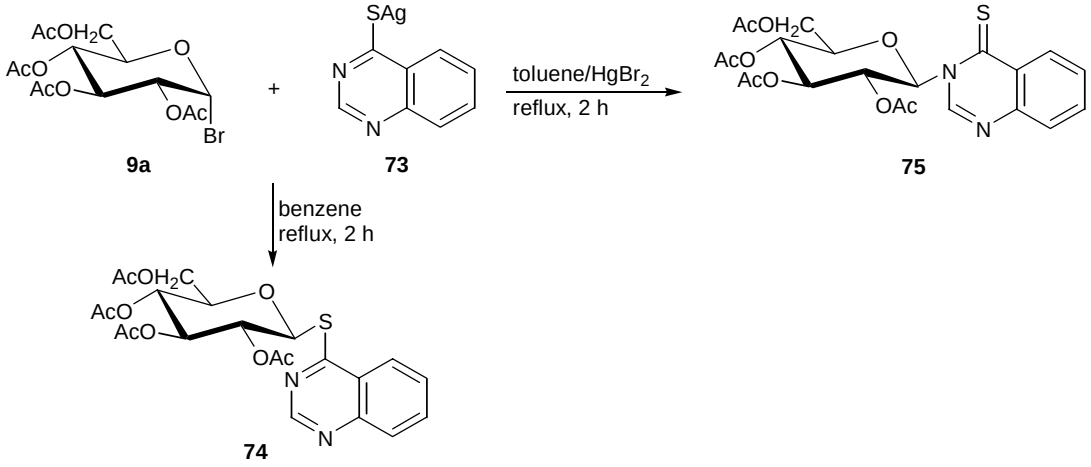
Scheme 32

4. *S*-GLYCOPYRANOSIDES OF QUINAZOLINETHIONES

4.1. *S*-Glucopyranosides of quinazoline-4-thione and quinazoline–2-thione

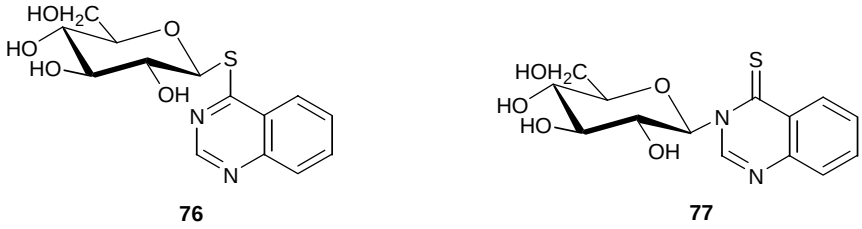
Reaction of the silver salt of quinazoline-4-thione (**73**) with **9a** in benzene gave 4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylthio)quinazolines (**74**), while afforded the corresponding *N*-glucopyranoside

(**75**) in toluene as a solvent (Scheme 33).[117]

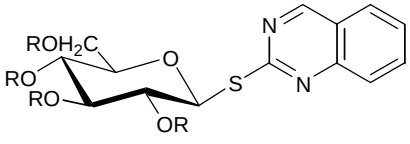


Scheme 33

Deacetylation of **74** and **75** using sodium methoxide at room temperature afforded the corresponding *S*-glucopyranoside (**76**) and *N*-glucopyranoside (**77**), respectively in good yields.[117]



However, reaction of **9a** with quinazoline-2-thione in acetone in the presence of potassium hydroxide at room temperature gave only a 38% yield of the corresponding *S*-glucopyranoside acetate (**78**), which was deacetylated to give the corresponding *S*-glucopyranoside (**79**) in 60% yield.[117]

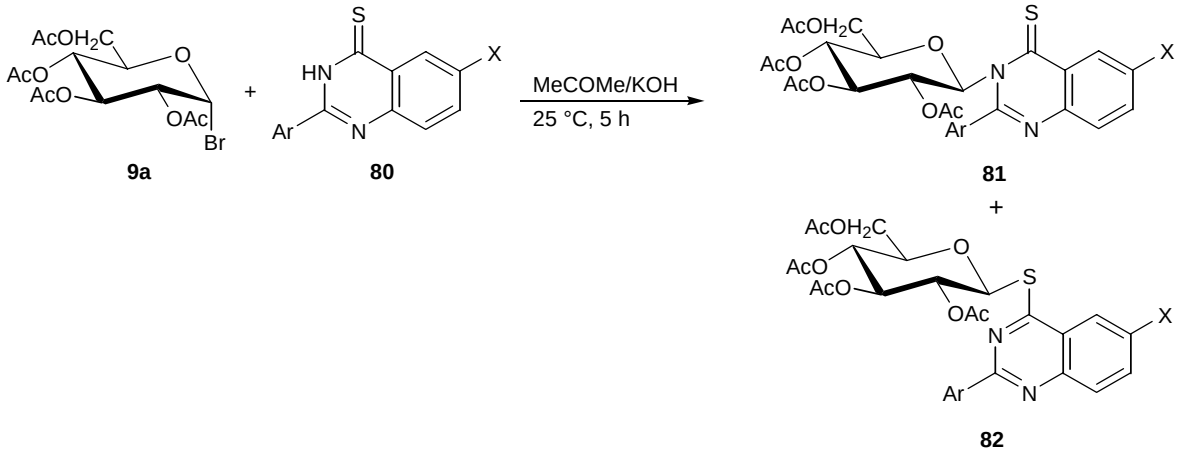


78, R =Ac (38%)
79, R = H (60%)

4.2. *S*-Glycopyranosides of 2-arylquinazoline-4-thiones

Reactions of 6-substituted 2-arylquinazoline-4-thiones (**80**) with **9a** in acetone in the presence of potassium hydroxide produced 2-aryl-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glycopyranosyl)quinazoline-4-

thiones (**81**) in fair yields together with 2-aryl-4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glycopyranosylthio)-quinazolines (**82**) (Scheme 34) in poor yields (Table 15).[118]

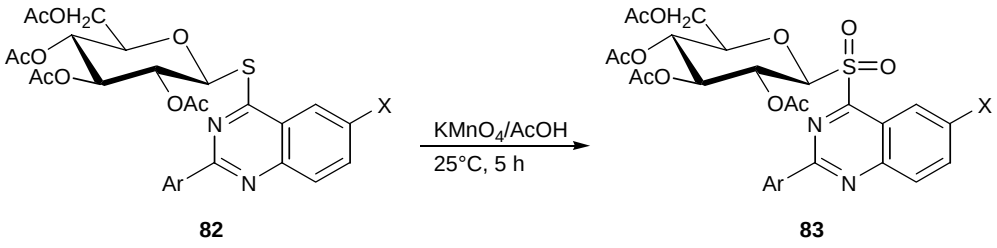


Scheme 34

Table 15: Synthesis of *N*-glucosides (**81**) and *S*-glucosides (**82**) according to Scheme 34

Product	Ar	X	Yield (%)
81a	Ph	H	63
81b	Ph	Br	60
81c	4-ClC_6H_4	Br	67
81d	4-MeC_6H_4	Br	56
81e	4-$NO_2C_6H_4$	H	63
82a	Ph	H	10
82b	Ph	Br	12
82c	4-ClC_6H_4	Br	16
82d	4-MeC_6H_4	Br	18
82e	4-$NO_2C_6H_4$	H	10

The *S*-glucopyranosides (**82**) were oxidised using potassium permanganate in acetic acid at room temperature to give the corresponding sulfones (**83**) (Scheme 35) in good yields (Table 16).[118]



Scheme 35

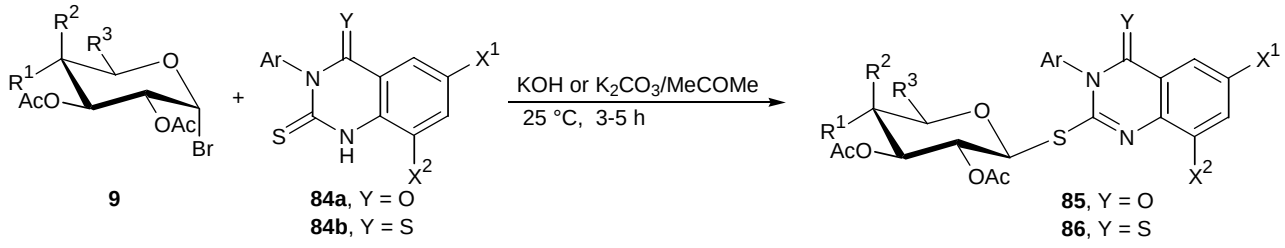
Table 16: Synthesis of sulfones (**83**) according to Scheme 35

Product	Ar	X	Yield (%)
83a	Ph	H	85
83b	Ph	Br	88
83c	4-ClC_6H_4	Br	82
83d	4-MeC_6H_4	Br	75
83e	4-$NO_2C_6H_4$	H	78

Attempts to deacetylate the glucopyranosides (**81**) and (**82**) with ammonia, hydrochloric acid or sodium hydroxide was not successful.[118] In all cases, quinazoline-4-thiones (**80**) are obtained by cleavage of either the *N*-sugar or the *S*-sugar bonds.[118]

4.3. *S*-Glycosides of 3-aryl-2-thioquinazolin-4(3*H*)-ones and 3-arylquinazoline-4(3*H*)-dithiones

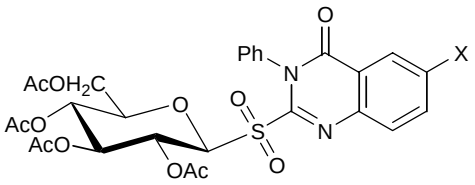
Reactions of 3-aryl-2-thioquinazolin-4(3*H*)-ones (**84a**) and 3-arylquinazoline-2,4-dithione (**84b**) with per-*O*-acetyl-β-D-glycopyranosyl bromides (**9**) in acetone in the presence of potassium hydroxide or potassium carbonate afforded 3-aryl-2-(per-*O*-acetyl-β-D-glycopyranosylthio)quinazolin-4(3*H*)-ones (**85**) and 3-aryl-2-(per-*O*-acetyl-β-D-glycopyranosylthio)quinazoline-4-thiones (**86**), respectively (Scheme 36) in the yields of 16-86% (Table 17).[121]



9 **84a**, Y = O; **84b**, Y = S → **85**, Y = O; **86**, Y = S

Scheme 36

Oxidation of **85a** and **85b** with potassium permanganate in acetic acid at room temperature for 30 min followed by reflux for 5 min gave the corresponding sulfones (**87a**) and (**87b**) in 62 and 60% yields, respectively.[121] Also, oxidation of **85a** and **85b** was carried out using hydrogen peroxide in acetic acid at room temperature for 12 h to give sulfones (**87a**) and (**87b**) in 50 and 53% yields, respectively.[121]



87a, X = H (50-62%)
87b, X = Br (53-60%)

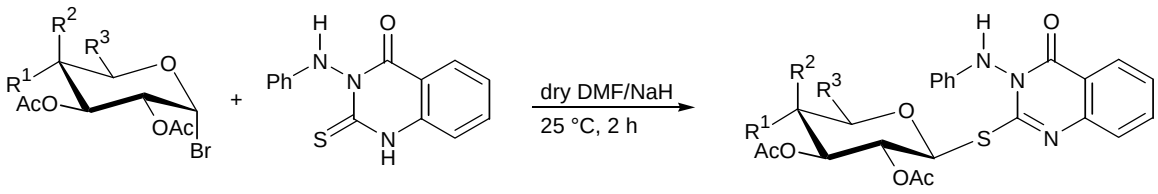
Table 17: Synthesis of *S*-glycopyranosides (**85**) and (**86**) according to Scheme 36

Product	Ar	X^1	X^2	Y	R^1	R^2	R^3	Yield (%)
85a	Ph	H	H	O	OAc	H	CH_2OH	51
85b	Ph	Br	H	O	OAc	H	CH_2OH	80
85c	4-MeC_6H_4	H	H	O	OAc	H	CH_2OH	86
85d	Ph	Br	Br	O	OAc	H	CH_2OH	43
85e	Ph	H	H	O	H	OAc	CH_2OH	45
85f	Ph	Br	H	O	H	OAc	CH_2OH	30
85g	4-MeC_6H_4	H	H	O	H	OAc	CH_2OH	65
85h	Ph	H	H	O	OAc	H	H	60
85i	Ph	Br	H	O	OAc	H	H	30
85j	4-MeC_6H_4	H	H	O	OAc	H	H	45
85k	Ph	H	H	O	H	OAc	H	25
85l	Ph	Br	H	O	H	OAc	H	16
86a	Ph	H	H	S	OAc	H	CH_2OH	32
86b	Ph	Br	H	S	OAc	H	CH_2OH	28
86c	Ph	H	H	S	H	OAc	CH_2OH	60
86d	Ph	H	H	S	OAc	H	H	55
86e	Ph	H	H	S	H	OAc	H	35

The anticarcinogenic activities of compounds (**85-87**) against the percentage growth of a wide variety of cancer cells as well as Human Immunodeficiency Virus (HIV) were investigated under different concentrations. Some of these compounds were found to be slightly active against different types of tumor, although none of these compounds showed HIV activity.

4.4. *S*-Glycopyranosides of 3-phenylamino-2-thioquinazolin-4(3*H*)-one

Reactions of 3-phenylamino-2-thioquinazolin-4(3*H*)-one (**88**) with per-*O*-acetyl-β-D-glycopyranosyl bromides (**9**) in dry dimethylformamide in the presence of sodium hydride at room temperature gave the corresponding 3-phenylamino-2-(per-*O*-acetyl-β-D-glycopyranosylthio)quinazolin-4(3*H*)-ones (**89**) in 58-64% yields (Scheme 37).[122] The results are summarized in Table 18.



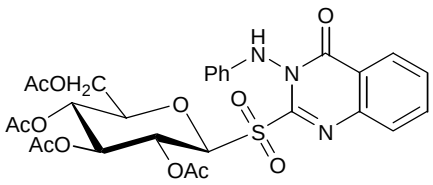
9 **88** **89**

Scheme 37

Table 18: Synthesis of *S*-glycopyranosides (**89**) according to Scheme 37

Product	R^1	R^2	R^3	Yield (%)
89a	OAc	H	CH_2OAc	64
89b	H	OAc	CH_2OAc	58
89c	OAc	H	H	60

Oxidation of **89a** with hydrogen peroxide in acetic acid at room temperature for 6 h gave the corresponding sulfone (**90**) in 65% yield.[122]



90 (65%)

Compounds (**89**) and (**90**) were screened for the *in-vitro* antimicrobial activities against *Staphylococcus aureus* and *Escherichia coli* as well as antifungal activity against *Candida albicans*. Compounds (**89c**) and (**90**) were found to be active and showed strong activities against *S. aureus*.[122]

5. CONCLUSION

Syntheses of glycosides containing quinazolin-4(3*H*)-one ring are simple and practical providing various types of glycosides including *N*-glycosylamines, *N*- and *S*-glycosides. These simple procedures should be beneficial for the synthesis of analogues that might possess potentially useful pharmacological properties.

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