

HETEROCYCLES, Vol. 65, No. 12, 2005, pp. 3007 - 3041

Received, 25th July, 2005, Accepted, 20th September, 2005, Published online, 22nd September, 2005

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

Gamal A. El-Hiti*^a and Mohamed F. Abdel-Megeed^b

^a Centre for Clean Chemistry, Department of Chemistry, University of Wales Swansea, Singleton Park, Swansea SA2 8PP, UK;

e-mail: g.a.el-hiti@swansea.ac.uk

^b Department of Chemistry, Faculty of Science, Tanta University, Tanta 31527, Egypt

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 deacetylated 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
2. *N*-GLYCOPYRANOSYLAMINES OF AMINOQUINAZOLIN-4(3*H*)-ONES
 - 2.1. *N*-Glycopyranosylamines of 3-amino-2-arylquinazolin-4(3*H*)-ones
 - 2.2. *N*-Glycopyranosylamines of 3-aminoquinazoline-2,4(1*H*,3*H*)-dione
 - 2.3. *N*-Glycopyranosylamines of 3-(4-aminophenyl)- and 3-(2-aminophenyl)- 2-methylquinazolin-4(3*H*)-ones
 - 2.4. *N*-Glycopyranosylamines of 3-(4-aminophenyl)-2-thioquinazolin-4(3*H*)-ones
 - 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
 - 2.6. *N*-Glycopyranosylamines of 6-aminoquinazolin-4(3*H*)-ones
 - 2.7. *N*-Glycopyranosylamines of 6-amino-3-aryl-2-methylquinazolin-4(3*H*)-ones
 - 2.8. *N*-Glucopyranosylthiourea of 2-(2-aminoethylthio)-3-phenylquinazolin-4(3*H*)-one

3. *N*-GLYCOPYRANOSIDES OF QUINAZOLIN-4(3*H*)-ONES
 - 3.1. *N*-Glycopyranosides of quinazolin-4(3*H*)-one
 - 3.2. *N*-Glycopyranosides of 2-arylquinazolin-4(3*H*)-ones
 - 3.3. *N*-Glycofuranosides of quinazoline-2,4(1*H*,3*H*)-dione
4. *S*-GLYCOPYRANOSIDES OF QUINAZOLINETHIONES
 - 4.1. *S*-Glucopyranosides of quinazoline-4-thione and quinazoline-2-thione
 - 4.2. *S*-Glycopyranosides of 2-arylquinazoline-4-thiones
 - 4.3. *S*-Glycopyranosides of 3-aryl-2-thioquinazolin-4(3*H*)-ones and 3-arylquinazoline-2,4-dithiones
 - 4.4. *S*-Glycopyranosides of 3-phenylamino-2-thioquinazolin-4(3*H*)-one
5. CONCLUSION
6. REFERENCES

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 glycosides⁹⁻²⁷ 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

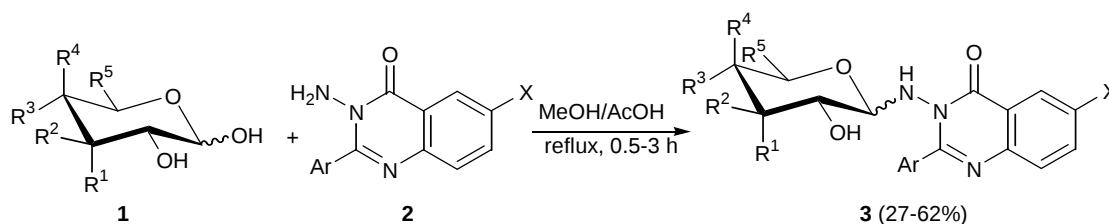
published on the synthesis of *N*-glycosyl amines, *N*- and *S*-glycosides containing quinazolin-4(3*H*)-one ring system.

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}



Scheme 1

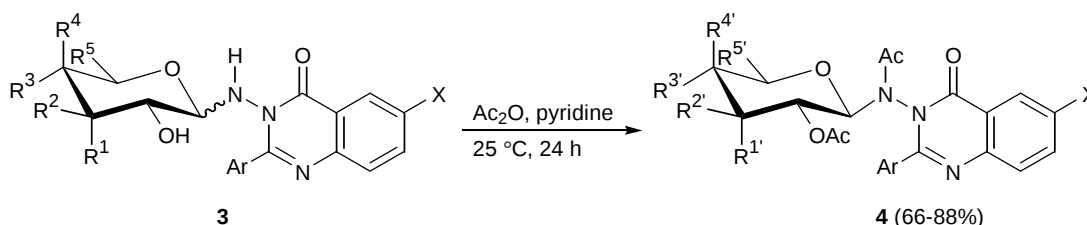
As expected, in solution, the *N*-glycopyranosylamines (**3**) were mixtures of α - and β -anomers in unequal

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 ${}^4C_1(D)$ 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 (%)	$\alpha:\beta$
3a	Ph	H	H	OH	OH	H	CH ₂ OH	27	1:4
3b	Ph	Br	H	OH	OH	H	CH ₂ OH	60	1:4
3c	Ph	H	H	OH	H	OH	CH ₂ OH	40	1:3
3d	Ph	Br	H	OH	H	OH	CH ₂ OH	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 ₆ H ₄	H	H	OH	OH	H	CH ₂ OH	50	1:3
3i	4-BrC ₆ H ₄	H	H	OH	OH	H	CH ₂ OH	62	1:4
3j	4-MeC ₆ H ₄	H	H	OH	OH	H	CH ₂ OH	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}



Scheme 2

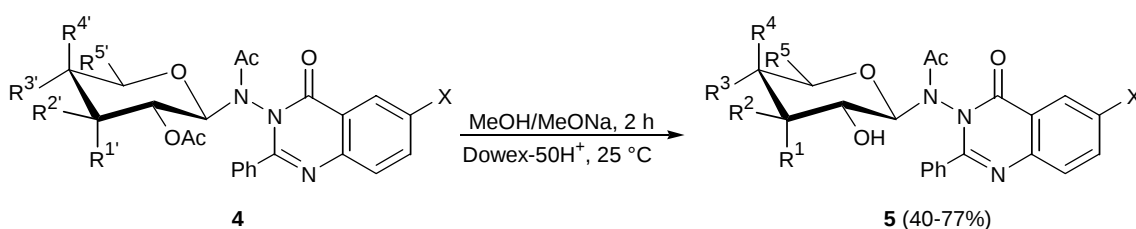
The NMR spectra verified the β -configuration and ${}^4C_1(D)$ conformation for compounds (**4**). The ambient temperature NMR spectra of compounds (**4**) showed the presence of two (*exo*- and *endo*-) sterically hindered rotamers due to hindered rotation about the N-N bond.^{101,102} The barriers 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 ₂ OAc	70	1:3
4b	Ph	Br	H	OAc	OAc	H	CH ₂ OAc	75	1:3
4c	Ph	H	H	OAc	H	OAc	CH ₂ OAc	80	1:4
4d	Ph	Br	H	OAc	H	OAc	CH ₂ OAc	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 ₆ H ₄	H	H	OAc	OAc	H	CH ₂ OAc	72	1:3
4i	4-BrC ₆ H ₄	H	H	OAc	OAc	H	CH ₂ OAc	88	1:3
4j	4-MeC ₆ H ₄	H	H	OAc	OAc	H	CH ₂ OAc	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.



Scheme 3

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

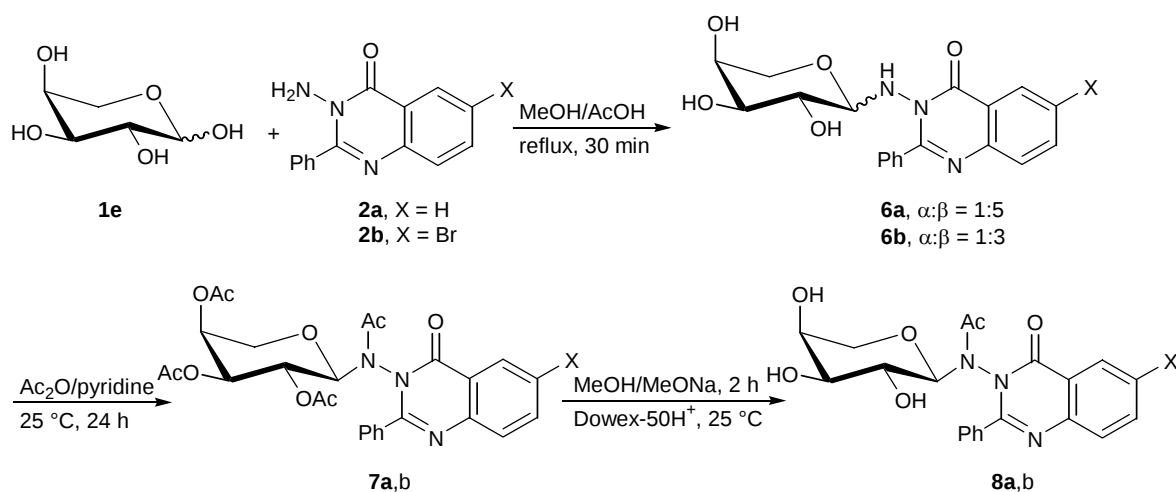
Product	X	R ¹	R ²	R ³	R ⁴	R ⁵	Yield (%)	exo:endo
5a	H	H	OH	OH	H	CH ₂ OH	40	1:4
5b	H	H	OH	H	OH	CH ₂ OH	40	1:4
5f	H	OH	H	OH	H	H	40	1:4
5g	Br	H	OH	OH	H	CH ₂ OH	46	1:3
5h	Br	H	OH	H	OH	CH ₂ OH	52	1:3
5i	Br	H	OH	OH	H	H	77	1:5
5j	Br	OH	H	OH	H	H	52	1:5

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 ^1H -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}

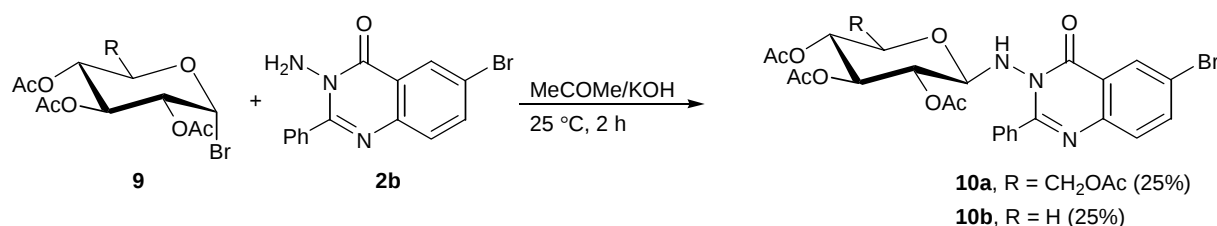
The NMR spectra of compounds (**6a,b**) verified the α -configuration and $^4\text{C}_1(\text{L})$ conformation of the pyranoside structure was the predominating species.



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 $^1\text{C}_4(\text{L})$ 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 ^1H -NMR signals of the two rotamers were coalesced to one set of signals at higher temperature.

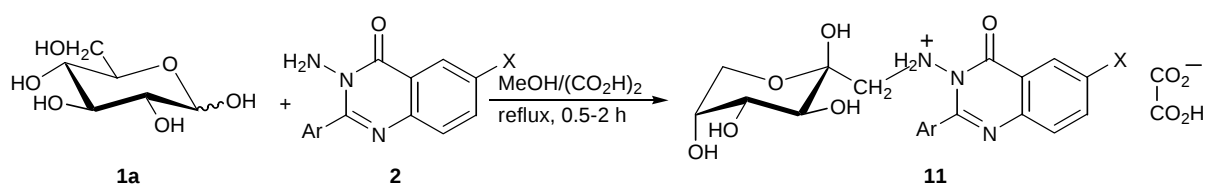
The anticarcinogenic activities of compounds (**3-8**) against the percentage growth of a wide variety of cancer cells were investigated under different concentrations. The bromo derivatives (**3b**, **3g**, **3j**, **5b** and **5d**) showed the maximum measured effect against leukaemia/lymphoma cancer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



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

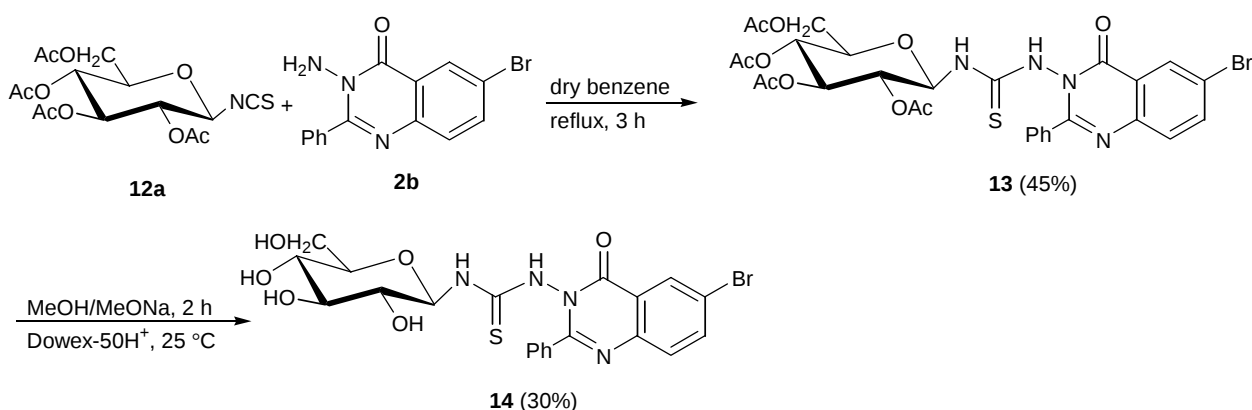


Scheme 6

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 ₆ H ₄	H	58
11d	2-ClC ₆ H ₄	Br	65
11e	3-ClC ₆ H ₄	H	52
11f	4-MeC ₆ H ₄	H	32

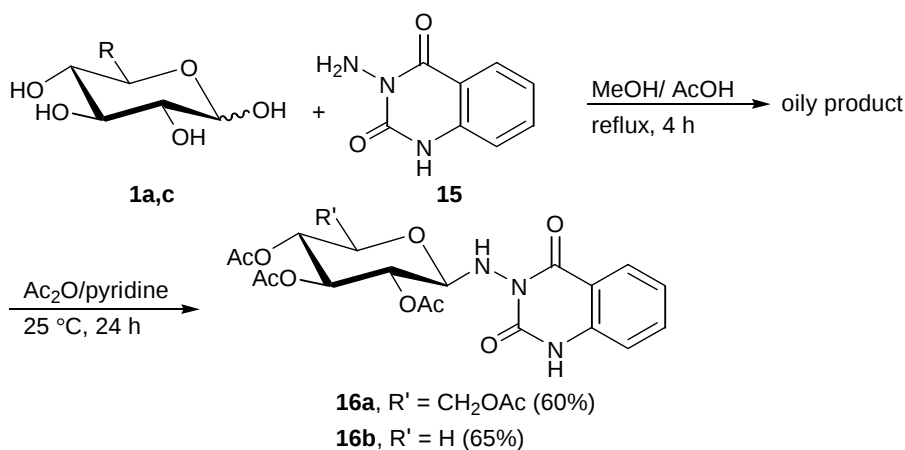
Reaction of 3-amino-2-phenylquinazolin-4(3*H*)-one (**2a**) with 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl isothiocyanate (**12a**) in dry benzene under reflux conditions gave *N*-(2',3',4',6'-tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-[2-phenylquinazolin-4(3*H*)-one-3-yl]thiourea (**13**) in 45%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



Scheme 7

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

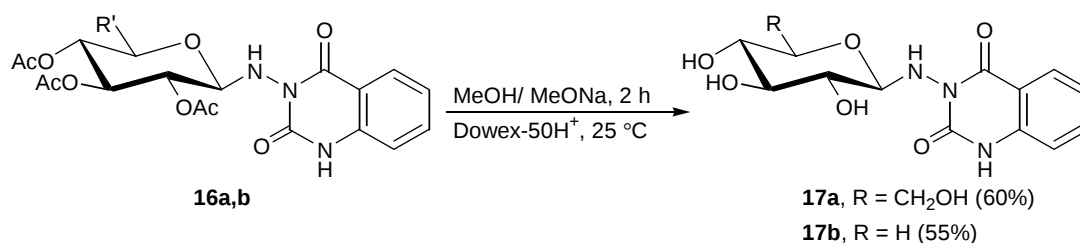
Reactions of 3-aminoquinazoline-2,4(1*H*,3*H*)-dione (**15**) with D-glucose (**1a**) and D-xylose (**1c**) in boiling methanol in the presence of a few drops of glacial acetic acid as a catalyst for 4 h, followed by solvent evaporation, gave oily materials.¹¹⁰ However, these oily products were purified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



Scheme 8

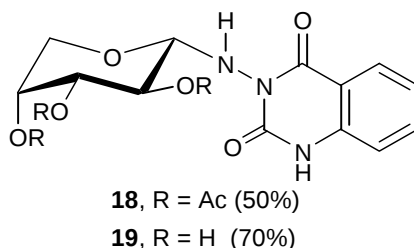
3-[*N*-(tetra-*O*-Acetyl- β -D-glucopyranosyl)]aminoquinazoline-2,4-(1*H*,3*H*)-dione (**16a**) and 3-[*N*-(tri-*O*-acetyl- β -D-xylopyranosyl)]aminoquinazoline-2,4-(1*H*,3*H*)-dione (**16b**) were obtained in 60 and 65% yields, respectively (Scheme 8).¹¹⁰ The acetylation took place on the sugar hydroxyl 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**).

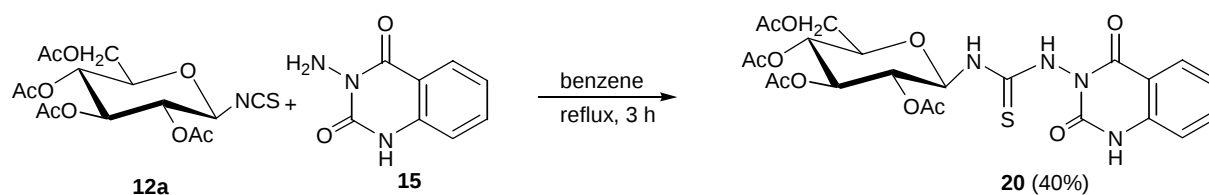


Scheme 9

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.



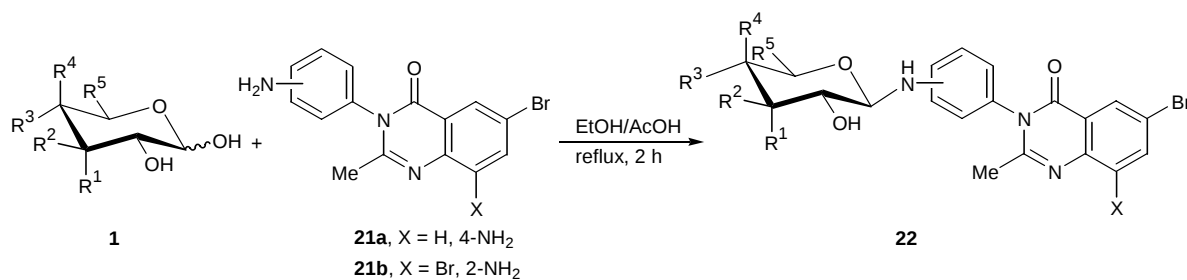
It was found that reaction of **15** with 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl isothiocyanate (**12a**) in dry benzene under reflux conditions gave *N*-(2',3',4',6'-tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-[quinazolin-2,4(1*H*,3*H*)-dione-3-yl]thiourea (**20**) in 40% yield (Scheme 10).¹⁰⁹



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 ¹H-NMR spectra of **22** showed that *J*(1,2) was approximately 8 Hz, which consistent with the β-configuration and ⁴C₁(D) conformation.

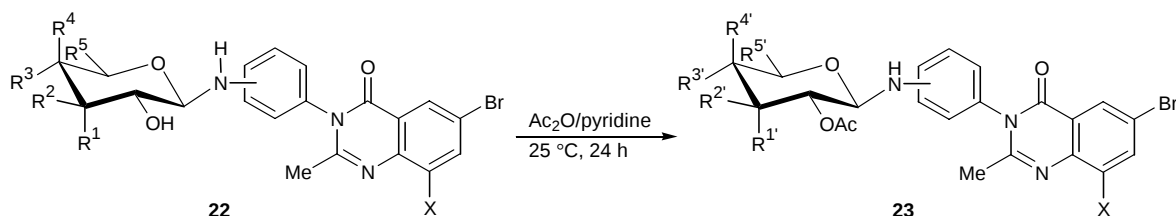


Scheme 11

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 ₂ OH	72
22b	4	H	H	OH	H	OH	CH ₂ OH	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 ₂ OH	52
22f	2	Br	H	OH	H	OH	CH ₂ OH	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.

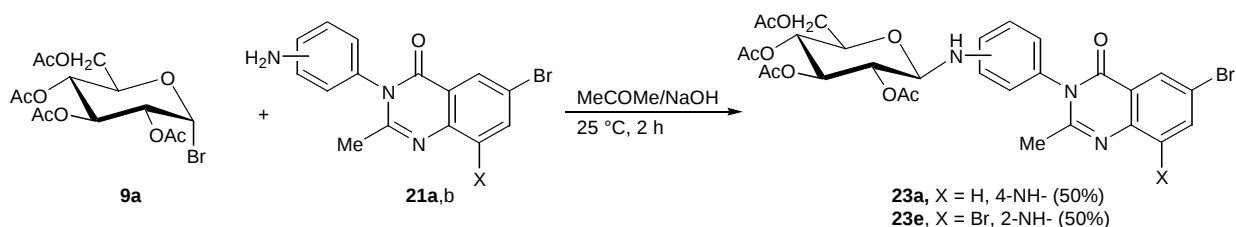


Scheme 12

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 ₂ OAc	85
23b	4	H	H	OAc	H	OAc	CH ₂ OAc	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 ₂ OAc	85
23f	2	Br	H	OAc	H	OAc	CH ₂ OAc	82
23g	2	Br	H	OAc	OAc	H	H	82
23h	2	Br	OAc	H	OAc	H	H	80

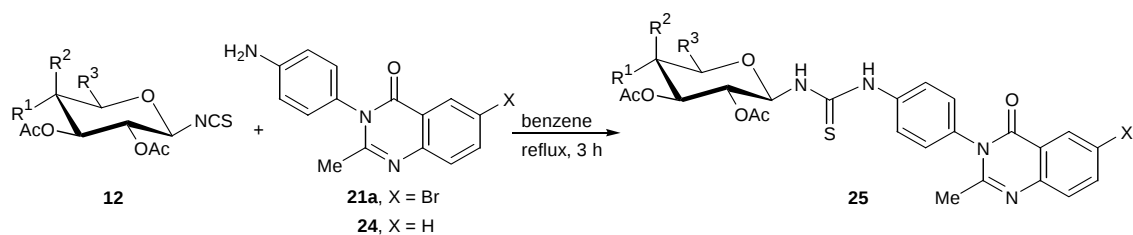
Deacetylation of **23** gave back the corresponding *N*- β -D-glycopyranosylamines (**22**).¹¹¹ Compounds (**23a**) and (**23e**) were also obtained in 50% yields from the direct reactions of **21a** and **21b** with 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl bromide (**9a**) (Scheme 13).¹¹¹



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

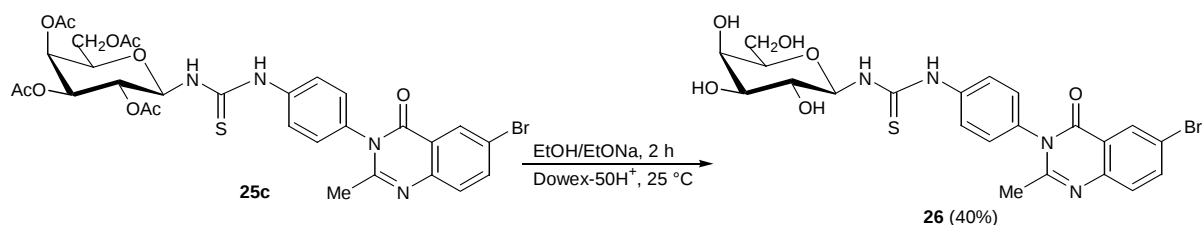


Scheme 14

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 ₂ OAc	60
25b	Br	OAc	H	CH ₂ OAc	70
25c	Br	H	OAc	CH ₂ OAc	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

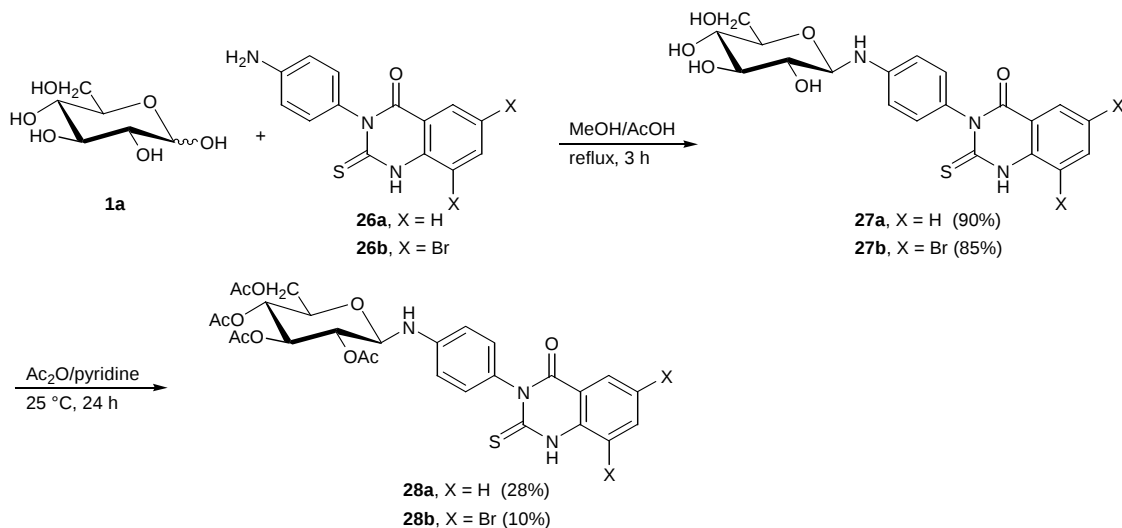


Scheme 15

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-

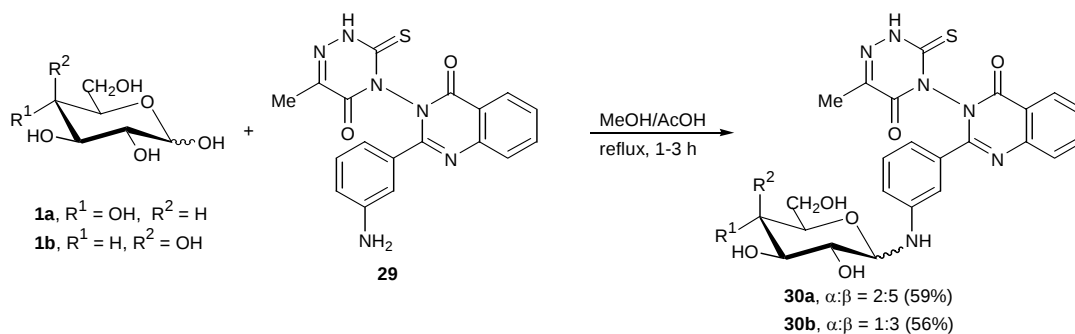
glucopyranosyl)]aminophenyl-2-thioquinazolin-4(3*H*)-one (**28a**) and 6,8-dibromo-3-[4-*N*-(2',3',4',6'-tetra-*O*-acetyl- β -D-glucopyranosyl)]aminophenyl-2-thioquinazolin-4(3*H*)-one (**28b**) (Scheme 16).¹¹² A series of experiments was conducted under different reaction conditions in order to improve 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

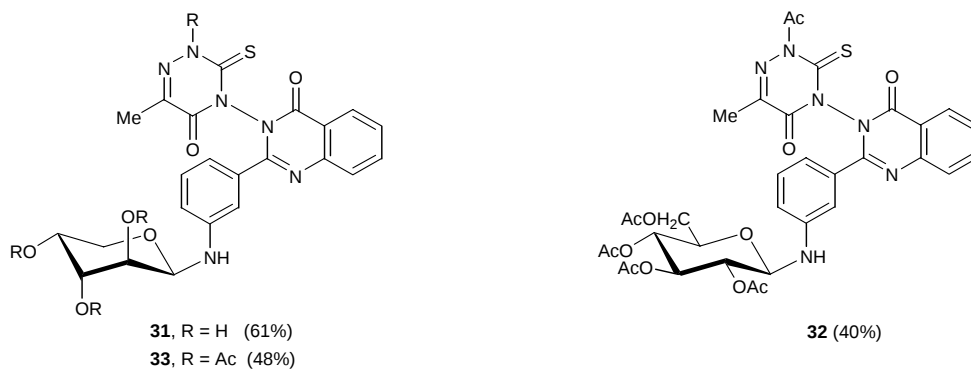
Reactions of 2-(3-aminophenyl)-3-[6-methyl-5(4*H*)-3-thio-1,2,4-triazin-4-yl]quinazolin-4(3*H*)-one (**29**) with D-glucose (**1a**) and D-galactose (**1b**) in methanol under reflux conditions gave the corresponding *N*-glycopyranosylamines (**30a**) and (**30b**) as α - and β -anomeric mixtures in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



Scheme 17

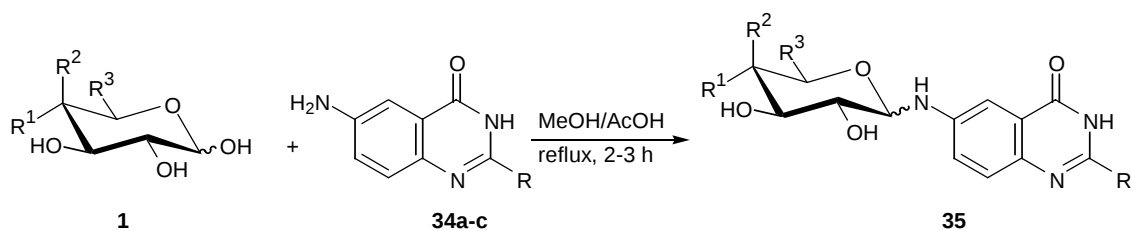
The anticarcinogenic activities of compounds (**30**) against the percentage growth of a wide variety of cancer cells were investigated under different concentrations. However, none of these compounds showed significant anti-cancer activity.¹¹³

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 ¹H-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 ¹³C-NMR spectrum. These values are consistent with the β -configuration and ⁴C₁(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.



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}



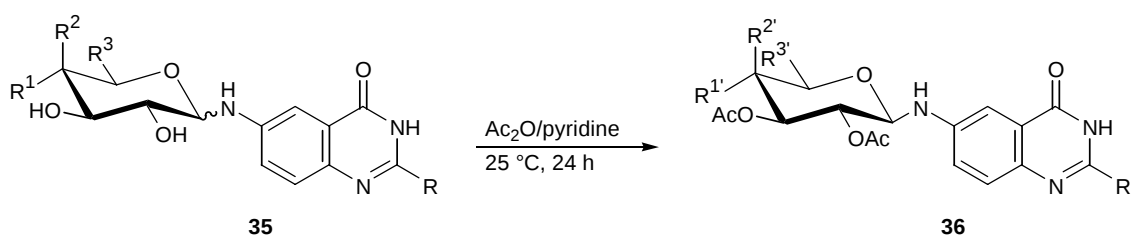
Scheme 18

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 ₂ OH	68	2:5
35b	H	H	OH	CH ₂ OH	70	1:3
35c	H	H	OH	H	70	1:4
35d	Et	OH	H	CH ₂ OH	72	1:4
35e	Et	H	OH	CH ₂ OH	72	1:3
35f	Et	H	OH	H	66	1:4
35g	Ph	OH	H	CH ₂ OH	73	1:3
35h	Ph	H	OH	CH ₂ OH	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.

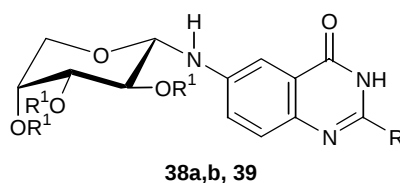
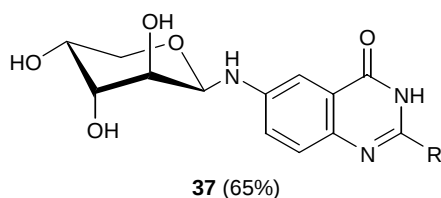


Scheme 19

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 ₂ OAc	55
36b	H	H	OAc	CH ₂ OAc	53
36c	Ph	OAc	H	CH ₂ OAc	45
36d	Ph	H	OAc	CH ₂ OAc	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}

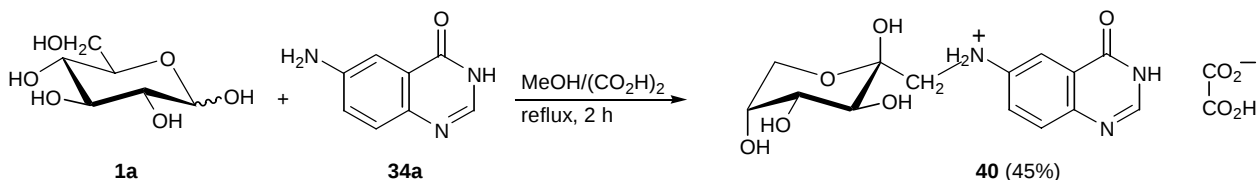
Table 10: Synthesis of *N*-α-D-arabinopyranosides (**38a,b**) and (**39**)

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

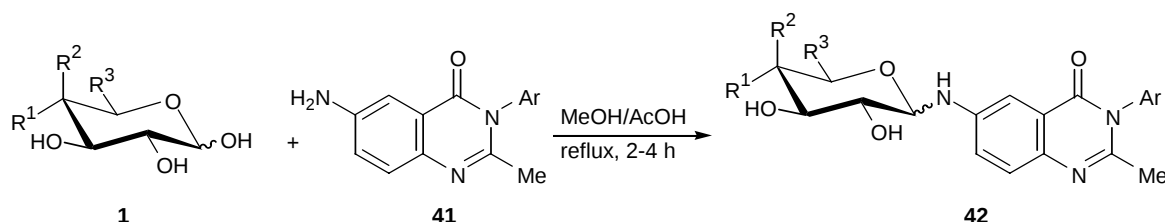
afforded Amadori rearrangement product (**40**) (Scheme 20) in 45% yield.¹¹³ Product (**40**) was also obtained from the reaction of **35** with oxalic acid under reflux conditions in methanol.



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.

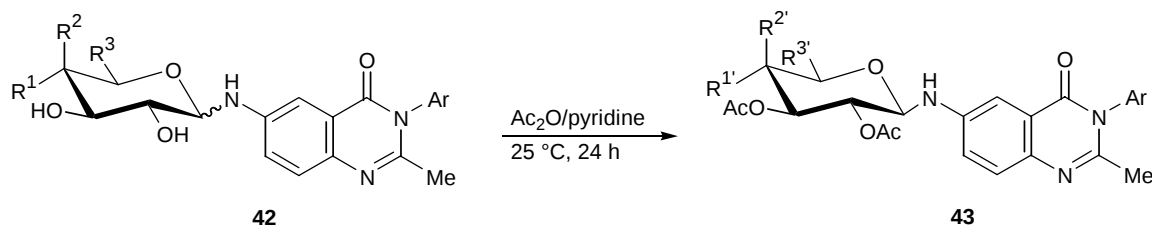


Scheme 21

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

Product	Ar	R ¹	R ²	R ³	Yield (%)	α : β
42a	C ₆ H ₅	OH	H	CH ₂ OH	65	1:3
42b	4-MeC ₆ H ₄	OH	H	CH ₂ OH	50	1:3
42c	4-MeOC ₆ H ₄	OH	H	CH ₂ OH	60	1:3
42d	C ₆ H ₅	H	OH	CH ₂ OH	70	1:4
42e	4-MeC ₆ H ₄	H	OH	CH ₂ OH	59	1:4
42f	4-MeOC ₆ H ₄	H	OH	CH ₂ OH	75	1:3
42g	C ₆ H ₅	OH	H	H	55	1:4
42h	4-MeC ₆ H ₄	OH	H	H	68	1:4
42i	4-MeOC ₆ H 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.



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 ₆ H ₅	OAc	H	CH ₂ OAc	70
43b	4-MeC ₆ H ₄	OAc	H	CH ₂ OAc	76
43c	4-MeoC ₆ H ₄	OAc	H	CH ₂ OAc	80
43d	C ₆ H ₅	H	OAc	CH ₂ OAc	80
43e	4-MeC ₆ H ₄	H	OAc	CH ₂ OAc	86
43f	4-MeOC ₆ H ₄	H	OAc	CH ₂ OAc	89
43g	C ₆ H ₅	OAc	H	H	70
43h	4-MeC ₆ H ₄	OAc	H	H	74
43i	4-MeOC ₆ H 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)]aminoquinazolin-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-arabinopyranosyl)]aminoquinazolin-4(3*H*)-ones (**45**) in 83-89% yields (Table 13).¹¹⁵

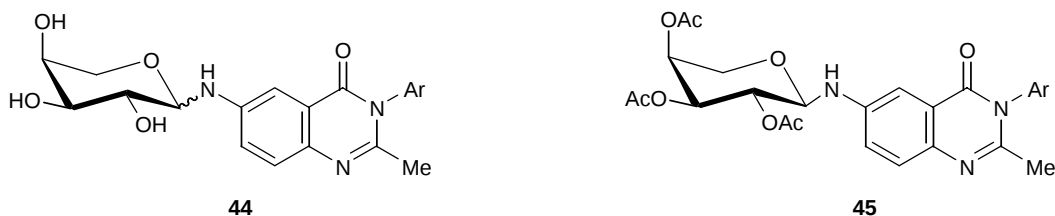
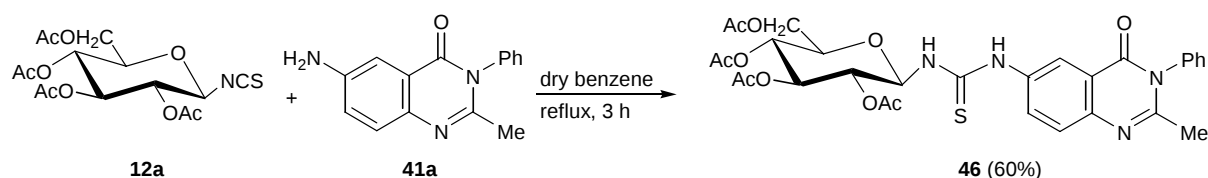


Table 13: Synthesis of L-arabinopyranosylamines (**44**) and (**45**)

Product	Ar	Yield (%)
44a	C ₆ H ₅	60
44b	4-MeC ₆ H ₄	67
44c	4-MeOC ₆ H ₄	63
45a	C ₆ H ₅	80
45b	4-MeC ₆ H ₄	83
45c	4-MeOC ₆ H ₄	89

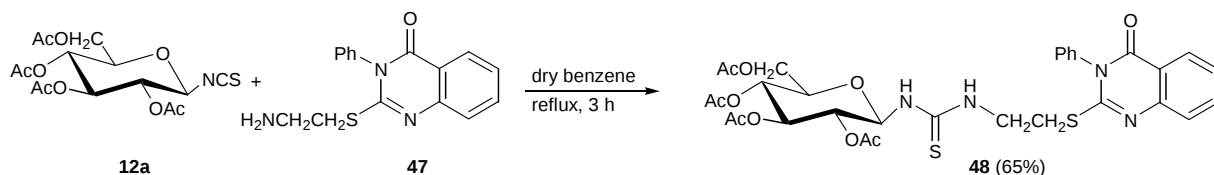
Treatment of 6-amino-2-methyl-3-phenylquinazolin-4(3*H*)-one (**41a**) with **12a** in dry benzene under reflux gave *N*-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*-[2-methyl-3-phenylquinazolin-4(3*H*)-one-3-yl]thiourea (**46**) in 60% yield (Scheme 23).¹¹⁶



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



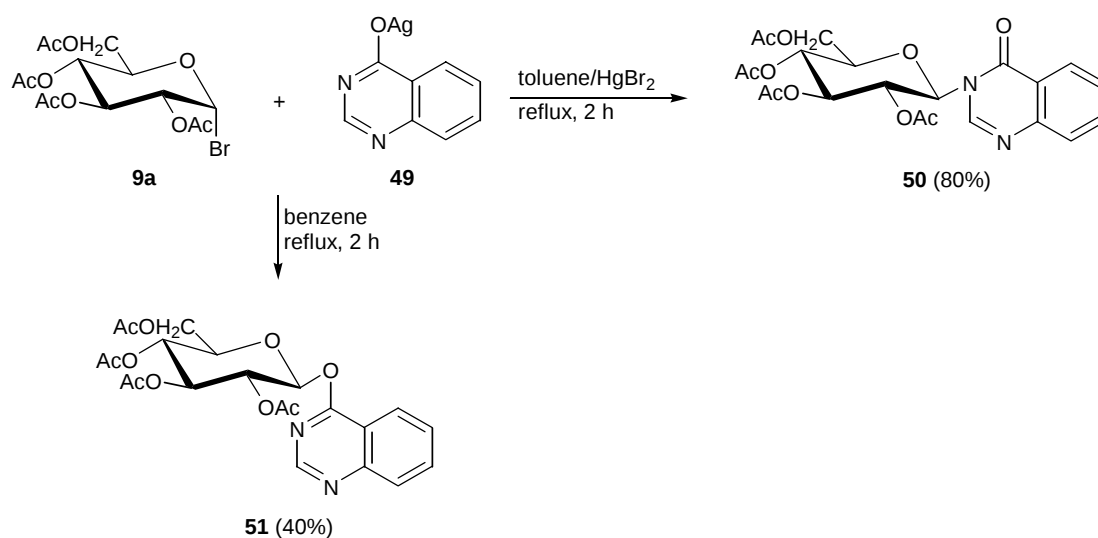
Scheme 24

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

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

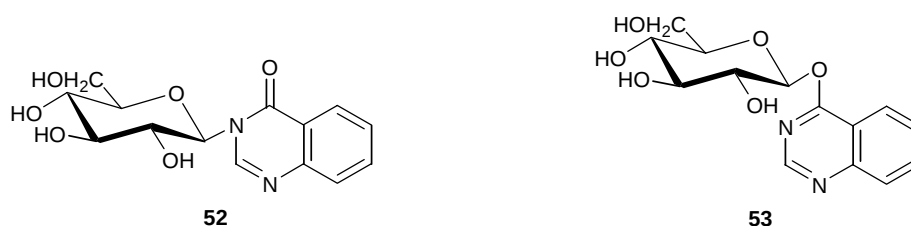
Reaction of the silver salt of quinazolin-4(3*H*)-one (**49**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl

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



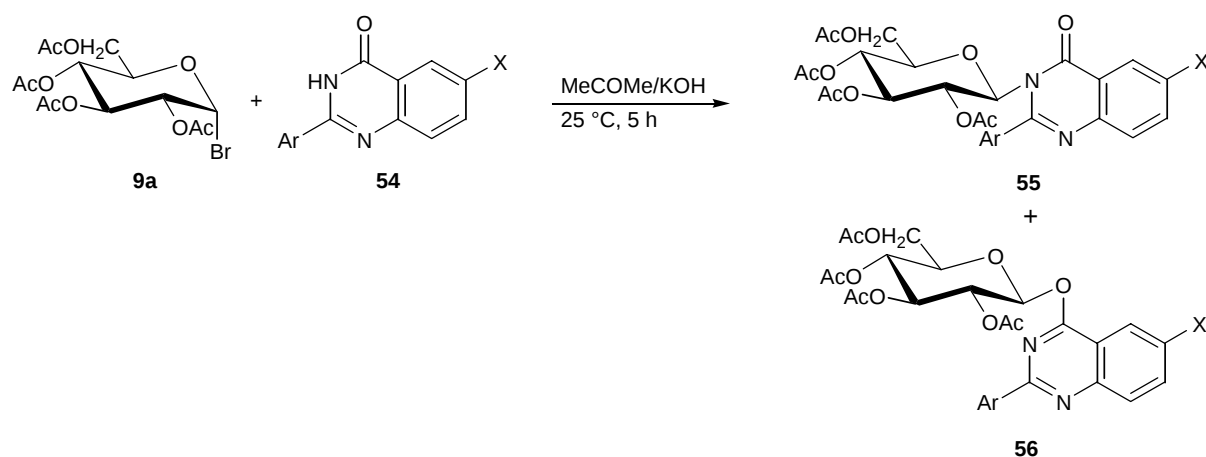
Scheme 25

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-glycopyranosyloxy)-quinazolines (**56**) (Scheme 26) in poor yields (Table 14).¹¹⁸



Scheme 26

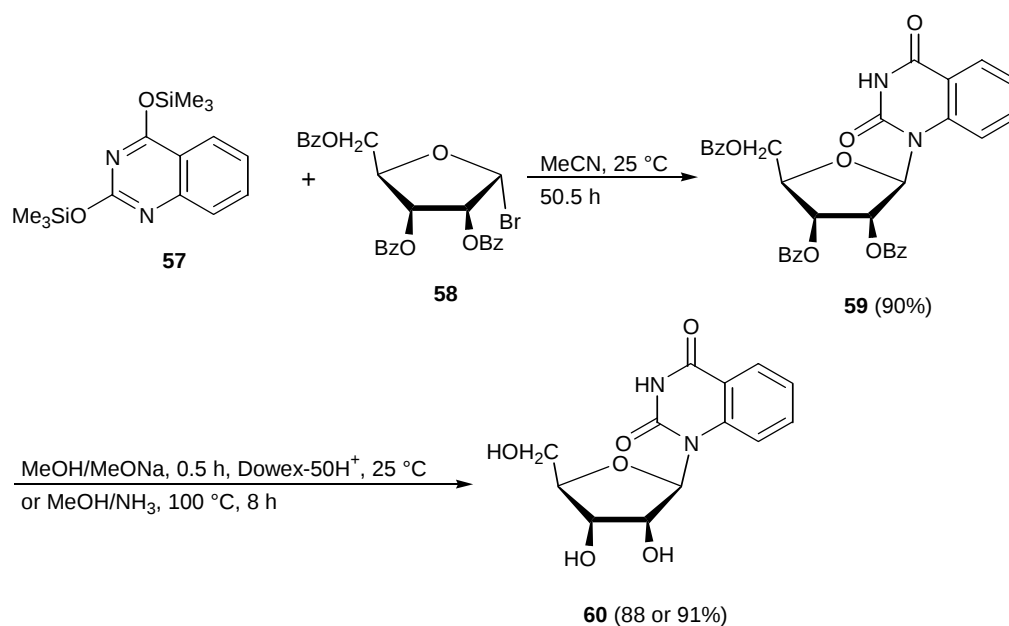
Table 14: Synthesis of *N*-glucosides (**55**) and *O*-glucosides (**56**) according to Scheme 26

Product	Ar	X	Yield (%)
55a	Ph	H	65
55b	Ph	Br	73
55c	4-ClC ₆ H ₄	Br	68
55d	4-MeC ₆ H ₄	Br	70
55e	4-NO ₂ C ₆ H ₄	H	72
56a	Ph	H	12
56b	Ph	Br	13
56c	4-ClC ₆ H ₄	Br	15
56d	4-MeC ₆ H ₄	Br	15
56e	4-NO ₂ C ₆ H 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

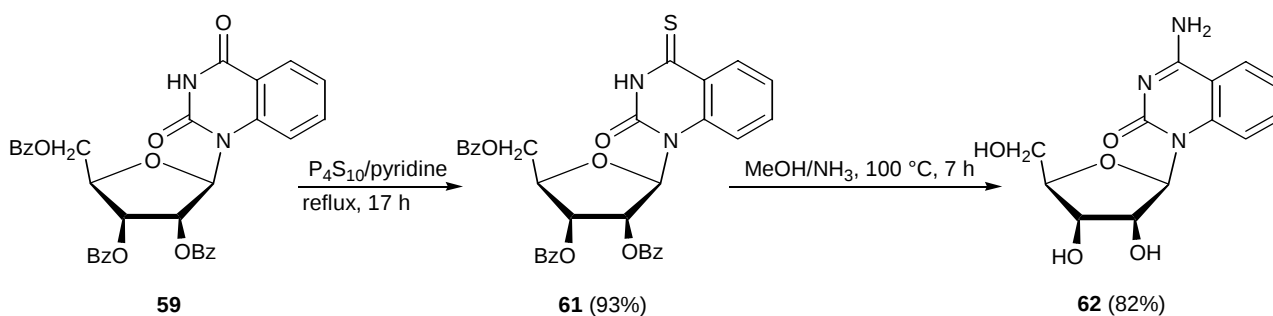
3.3. *N*-Glycofuranosides of quinazoline-2,4(1*H*,3*H*)-dione

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

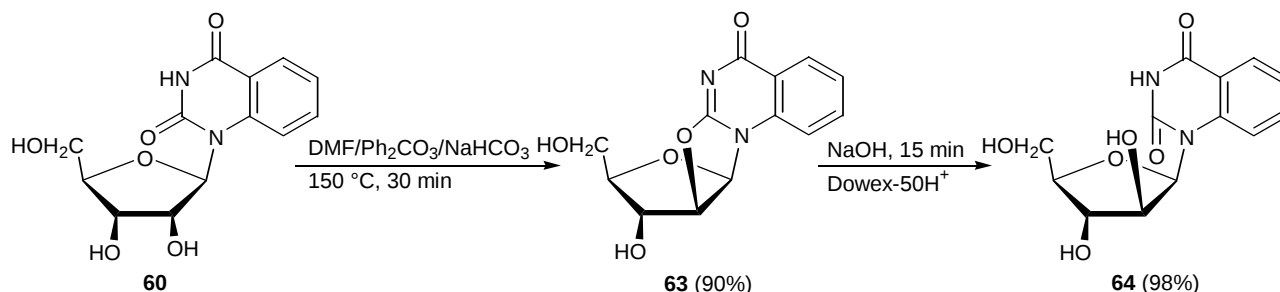
Treatment of **59** with phosphorus pentasulfide provided the corresponding 4-thione derivative (**61**) in 93% yield which upon treatment with methanolic ammonia at 100 °C gave 4-amino-1-(β-D-ribofuranosyl)quinazolin-2(1H)-one (**62**) in 82% yield (Scheme 28).¹¹⁹ Compound (**62**) could also be obtained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



Scheme 28

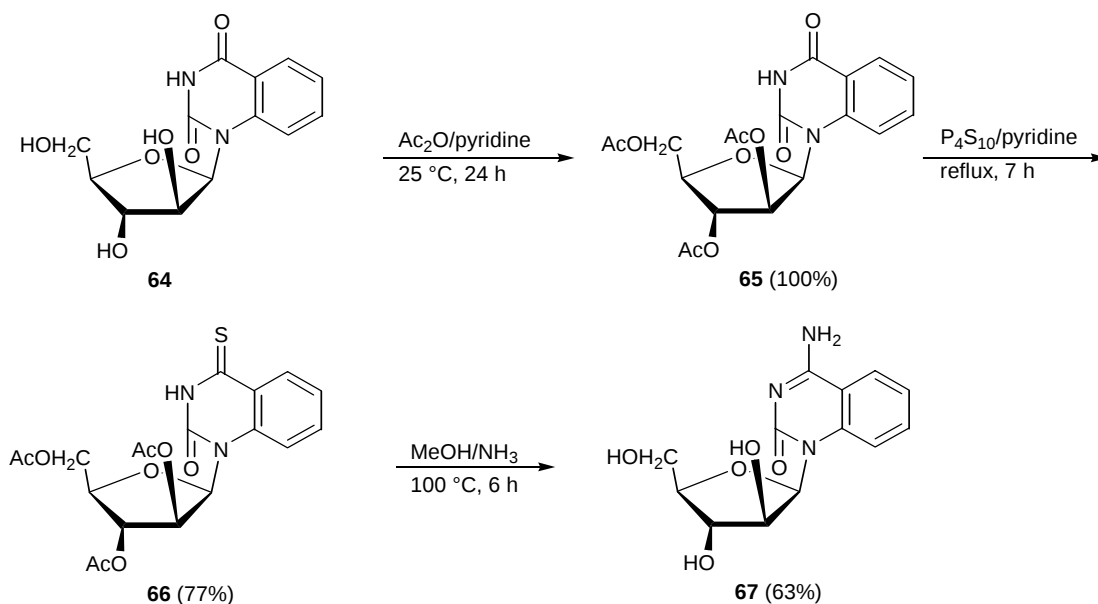
1-(β-D-Arabinofuranosyl)quinazoline-2,4(1H,3H)-dione (**64**) was prepared in two steps from compound (**60**) in which the method of Nichol and Hampton¹²⁰ for inversion of the 2'-hydroxyl group was employed. Treatment of **60** with diphenyl carbonate and sodium hydrogencarbonate in *N,N*-dimethylformamide

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

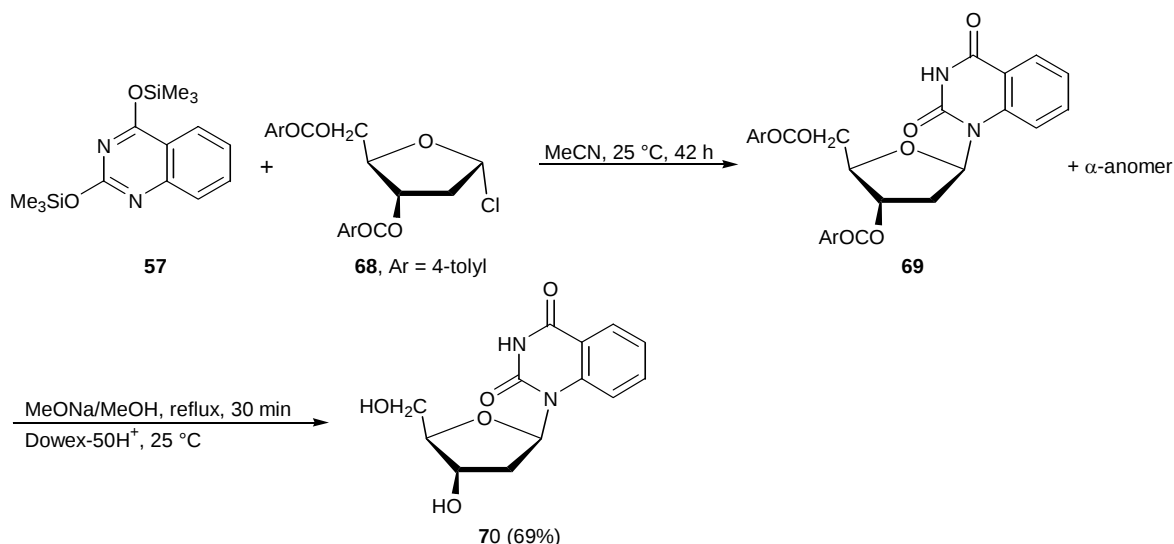
Acetylation of **64** gave a quantitative yield of the corresponding acetyl derivative (**65**), which on treatment with phosphorus pentasulfide in pyridine gave the corresponding 4-thione derivative (**66**) in 77% yield (Scheme 30).¹¹⁹ Treatment of **66** with methanolic ammonia at 100 °C gave 4-amino-1-(β-D-arabinofuranosyl)quinazolin-2(1*H*)-one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



Scheme 30

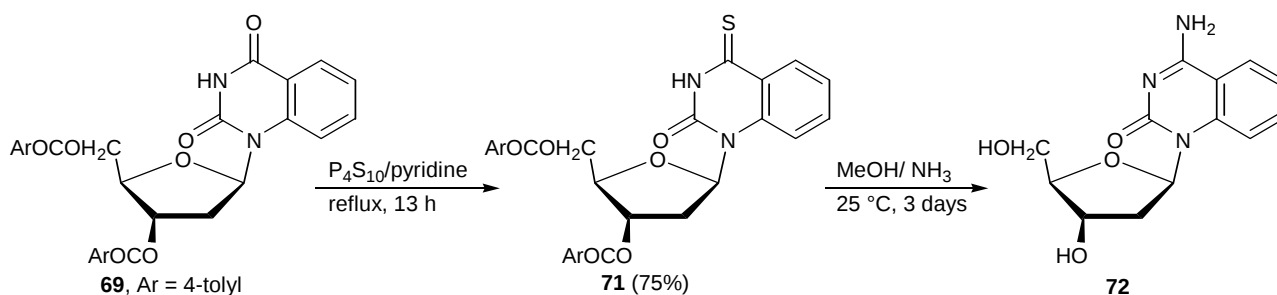
Treatment of **57** with 3,5-di-*O*-(4-methylbenzoyl)-2-deoxyribofuranosyl chloride (**68**) in acetonitrile gave an anomeric mixture of glycosides which separated on an alumina column.¹¹⁹ 1-(3',5'-Di-*O*-(4-methylbenzoyl)-β-D-2'-deoxyribofuranosyl)quinazoline-2,4(1*H*,3*H*)-dione (**69**) was obtained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



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



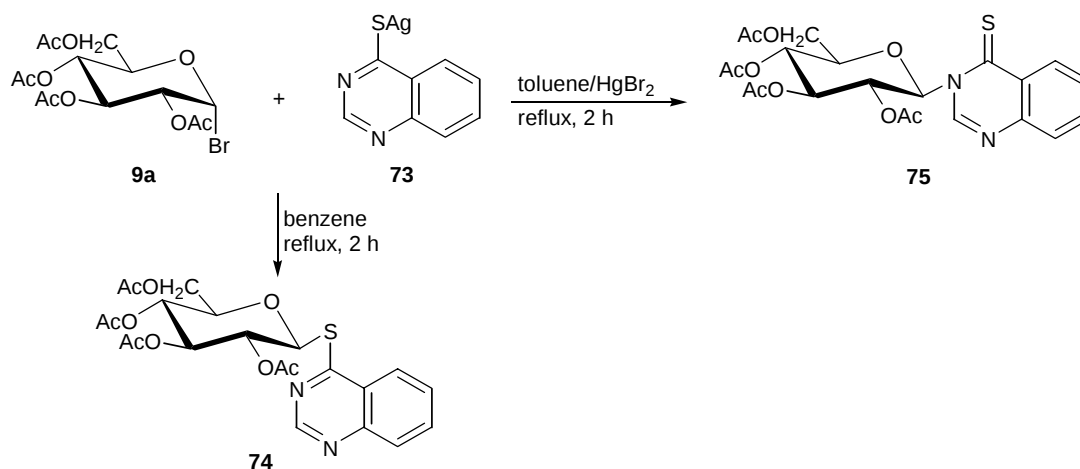
Scheme 32

4. S-GLYCOPYRANOSIDES OF QUINAZOLINETHIONES

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

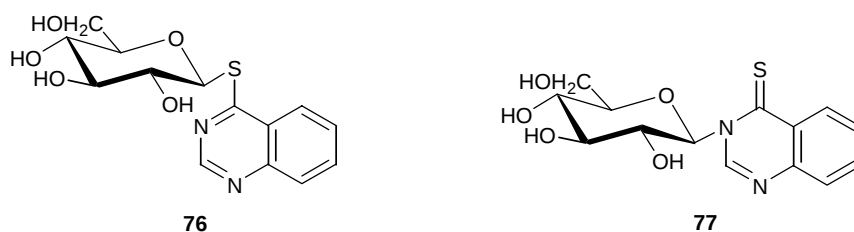
Reaction of the silver salt of quinazoline-4-thione (**73**) with **9a** in benzene gave 4-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosylthio)quinazolines (**74**), while afforded the corresponding *N*-glucopyranoside

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

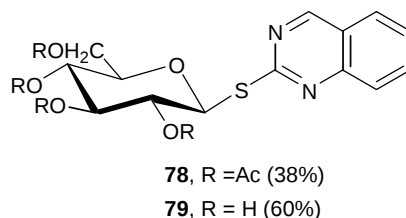


Scheme 33

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



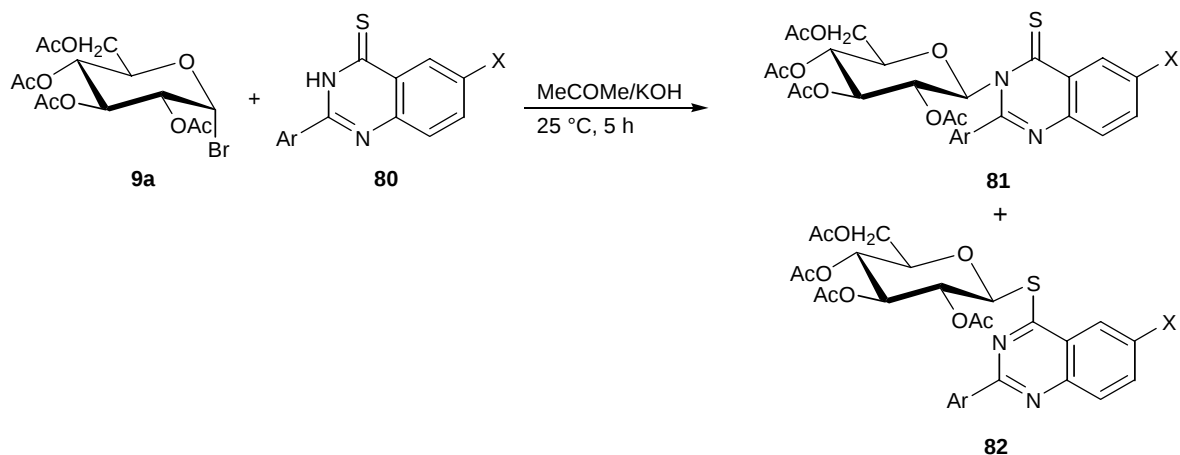
However, reaction of **9a** with quinazoline-2-thione in acetone in the presence of potassium hydroxide at room temperature gave only a 38% yield of the corresponding *S*-glucopyranoside acetate (**78**), which was deacetylated to give the corresponding *S*-glucopyranoside (**79**) in 60% yield.¹¹⁷



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-glucopyranosyl)quinazoline-4-

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

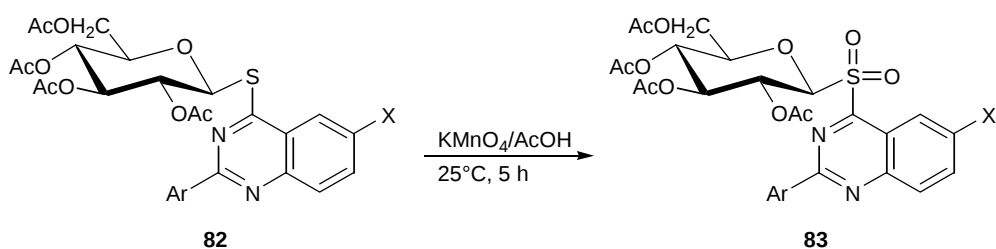


Scheme 34

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 ₆ H ₄	Br	67
81d	4-MeC ₆ H ₄	Br	56
81e	4-NO ₂ C ₆ H ₄	H	63
82a	Ph	H	10
82b	Ph	Br	12
82c	4-ClC ₆ H ₄	Br	16
82d	4-MeC ₆ H ₄	Br	18
82e	4-NO ₂ C ₆ H 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

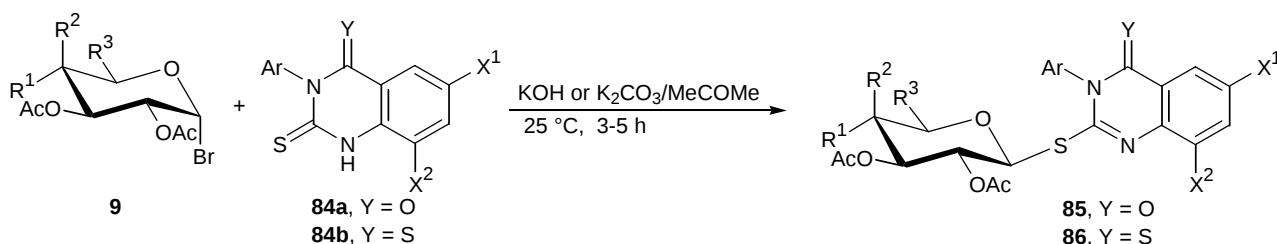
Table 16: Synthesis of sulfones (**83**) according to Scheme 35

Product	Ar	X	Yield (%)
83a	Ph	H	85
83b	Ph	Br	88
83c	4-ClC ₆ H ₄	Br	82
83d	4-MeC ₆ H ₄	Br	75
83e	4-NO ₂ C ₆ H 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

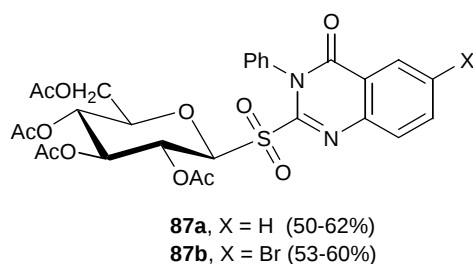
4.3. S-Glycosides of 3-aryl-2-thioquinazolin-4(3*H*)-ones and 3-arylquinazoline-4(3*H*)-dithiones

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



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

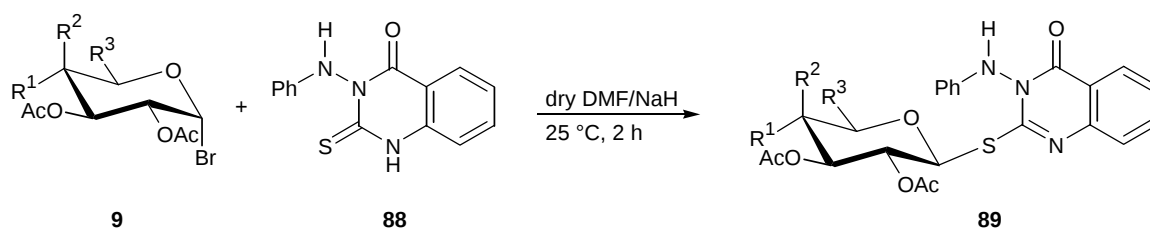
Table 17: Synthesis of *S*-glycopyranosides (**85**) and (**86**) according to Scheme 36

Product	Ar	X ¹	X ²	Y	R ¹	R ²	R ³	Yield (%)
85a	Ph	H	H	O	OAc	H	CH ₂ OH	51
85b	Ph	Br	H	O	OAc	H	CH ₂ OH	80
85c	4-MeC ₆ H ₄	H	H	O	OAc	H	CH ₂ OH	86
85d	Ph	Br	Br	O	OAc	H	CH ₂ OH	43
85e	Ph	H	H	O	H	OAc	CH ₂ OH	45
85f	Ph	Br	H	O	H	OAc	CH ₂ OH	30
85g	4-MeC ₆ H ₄	H	H	O	H	OAc	CH ₂ OH	65
85h	Ph	H	H	O	OAc	H	H	60
85i	Ph	Br	H	O	OAc	H	H	30
85j	4-MeC ₆ H 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 ₂ OH	32
86b	Ph	Br	H	S	OAc	H	CH ₂ OH	28
86c	Ph	H	H	S	H	OAc	CH ₂ OH	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.

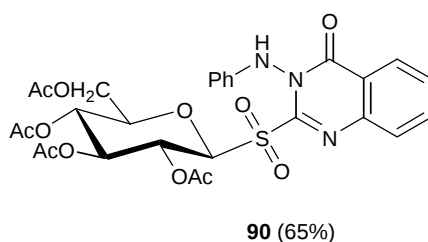


Scheme 37

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

Product	R ¹	R ²	R ³	Yield (%)
89a	OAc	H	CH ₂ OAc	64
89b	H	OAc	CH ₂ OAc	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



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.

ACKNOWLEDGMENTS

G A El-Hiti thanks Professor Keith Smith, Centre for Clean Chemistry, Chemistry Department,

University of Wales Swansea, UK for his revision and the Royal Society of Chemistry for an international author grant.

6. REFERENCES

1. J. C. Briggs, A. H. Haines, and R. J. K. Taylor, *J. Chem. Soc., Perkin. Trans. 1*, 1995, 27.
2. L. E. Fellows and R. J. Nash, *Sci. Prog.*, 1990, **74**, 245.
3. P. S. Liu, *J. Org. Chem.*, 1987, **52**, 4717.
4. M. J. Humphries, K. Matsumoto, S. L. White, R. J. Molyneux, and K. Olden, *Proc. Natl. Acad. Sci. USA*, 1986, **83**, 1752.
5. E. Truscheit, W. Frommer, B. June, L. Muller, D. D. Schmidt, and W. Wingender, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 744.
6. A. S. Tyms, D. L. Taylor, P. S. Sunkara, and M. S. Kang, *Design of Anti-Aids Drugs*, ed. by E. De Clercq, Amsterdam, 1990, pp. 257-318.
7. J. E. Baldwin, *Ber.*, 1989, **25**, 583.
8. G. B. Karlsson, T. D. Butters, R. A. Dwek, and F. M. Platt, *J. Biol. Chem.*, 1995, **268**, 570.
9. E. S. H. El-Ashry, N. Rashed, and E. S. I. Ibrahim, *Curr. Org. Synth.*, 2005, **2**, 175.
10. N. S. A. M. Khalil, *Nucleosides, Nucleotides Nucleic Acids*, 2005, **24**, 111.
11. O. M. E. D. Awad, W. E. Attia, and E. S. H. El-Ashry, *Carbohydr. Res.*, 2004, **339**, 469.
12. S. Sinha, R. Srivastava, E. De Clercq, and R. K. Singh, *Nucleosides, Nucleotides Nucleic Acids*, 2004, **23**, 1815.
13. S. Kohgo, K. Yamada, K. Kitano, Y. Iwai, S. Sakata, N. Ashida, H. Hayakawa, D. Nameki, E. Kodama, M. Matsuoka, H. Mitsuya, and H. Ohri, *Nucleosides, Nucleotides Nucleic Acids*, 2004, **23**, 671.
14. N. A. Al-Masoudi and Y. A. Al-Soud, *J. Carbohydr. Chem.*, 2004, **23**, 111.
15. I. M. Abdou, A. M. Saleh, and H. F. Zohdi, *Molecules*, 2004, **9**, 109.
16. A. Z. Haikal, E. S. H. El-Ashry, and J. Banoub, *Carbohydr. Res.*, 2003, **338**, 2291.
17. M. A. Saleh and M. F. Abdel-Megeed, *J. Carbohydr. Chem.*, 2003, **22**, 79.
18. A. A. H. Abdel-Rahman and E. S. H. El-Ashry, *Synlett*, 2002, 2043.
19. M. A. Saleh, *Sulfur Lett.*, 2002, **25**, 235.
20. G. H. Elgemeie, A.-F. Z. Heikel, and M. A. Ahmed, *Nucleosides, Nucleotides Nucleic Acids*, 2002, **21**, 411.
21. M. A. Saleh, *Nucleosides, Nucleotides Nucleic Acids*, 2002, **21**, 401.
22. G. H. Elgemeie and E. A. Kamal, *Nucleosides, Nucleotides Nucleic Acids*, 2002, **21**, 287.
23. A. M. E. Attia, *Nucleosides, Nucleotides Nucleic Acids*, 2002, **21**, 207.

24. I. M. Abdou, A. M. Attia, and L. Strekowski, *Nucleosides, Nucleotides Nucleic Acids*, 2002, **21**, 15.
25. K. Benakli, C. Zha, and R. J. Kerns, *J. Am. Chem. Soc.*, 2001, **123**, 9461.
26. L. Strekowski, I. M. Abdou, A. M. E. Attia, and S. E. Patterson, *Tetrahderon Lett.*, 2000, **41**, 4757.
27. I. M. Abdou and L. Strekowski, *Tetrahderon*, 2000, **56**, 8631.
28. A. Gomtsyan, E. K. Bayburt, R. G. Schmidt, G. Z. Zheng, R. J. Perner, S. Didomenico, J. R. Koenig, S. Turner, T. Jinkerson, I. Drizin, S. M. Hannick, B. S. Macri, H. A. McDonald, P. Honore, C. T. Wismer, K. C. Marsh, J. Wetter, K. D. Stewart, T. Oie, M. F. Jarvis, C. S. Surowy, C. R. Faltynek, and C.-H. Lee, *J. Med. Chem.*, 2005, **48**, 744.
29. K. Matsuno, J. Ushiki, T. Seishi, M. Ichimura, N. A. Giese, J.-C. Yu, S. Takahashi, S. Oda, and Y. Nomoto, *J. Med. Chem.*, 2003, **46**, 4910.
30. N.-h. Ho, R. S. Harapanhalli, B. A. Dahman, K. Chen, K. Wang, S. J. Adelstein, and A. I. Kassis, *Bioconjugate Chem.*, 2002, **13**, 357.
31. K. Matsuno, M. Ichimura, T. Nakajima, K. Tahara, S. Fujiwara, H. Kase, J. Ushiki, N. A. Giese, A. Pandey, R. M. Scarborough, N. A. Lokker, J.-C. Yu, J. Irie, E. Tsukuda, S.-I. Ide, S. Oda, and Y. Nomoto, *J. Med. Chem.*, 2002, **45**, 3057.
32. H.-R. Tsou, N. Mamuya, B. D. Johnson, M. F. Reich, B. C. Gruber, F. Ye, R. Nilakantan, R. Shen, C. Discafani, R. DeBlanc, R. Davis, F. E. Koehn, L. M. Greenberger, Y.-F. Wang, and Wissner, A. *J. Med. Chem.*, 2001, **44**, 2719.
33. M.-J. Hour, L.-J. Huang, S.-C. Kuo, Y. Xia, K. Bastow, Y. Nakanishi, E. Hamel, and K.-H. Lee, *J. Med. Chem.*, 2000, **43**, 4479.
34. H. Valette, F. Dolle, I. Guenther, S. Demphel, C. Rasetti, F. Hinnen, C. Fuseau, and C. Crouzel, *Nucl. Med. Bio.*, 1999, **26**, 105.
35. D. J. Baek, Y. K. Park, H. I. Heo, M. H. Lee, Z. Y. Yang, and M. H. Choi, *Biorg. Med. Chem. Lett.*, 1998, **8**, 3287.
36. S. Johnne, *The Alkaloids, Chemistry and Pharmacology*, vol. 29, ed. by A. Brossi, Orlando, Academic Press, 1986, p. 99.
37. M. Abou Kull, *Zhonghua Yaoxue Zazhi*, 1993, **45**, 109 (*Chem. Abstr.*, 1994, **120**, 54518).
38. F. A. Ashour, A. H. Yousry, and A. F. Hamouda, *Alex. J. Pharm. Sci.*, 1993, **7**, 127.
39. P. B. Trivedi, N. K. Undavia, A. M. Dave, K. N. Bhatt, and N. C. Desai, *Indian J. Chem.*, 1993, **32B**, 497.
40. P. Mishra, P. N. Gupta, and A. K. Shakya, *J. Indian Chem. Soc.*, 1991, **68**, 618.
41. A. M. Farghaly, A. Mohsen, M. E. Omar, M. A. Khalil, and M. A. Gaber, *Farmaco*, 1990, **45**,

- 431.
42. Y. D. Kulkarni and A. Rowhani, *J. Indian Chem. Soc.*, 1990, **67**, 46.
43. L. N. Vostrova, M. V. Grenaderova, V. S. Nedzvetsky, I. P. Konup, E. K. Andreyeva, and A. E. Bondar, *Khim.-Farm. Zh.*, 1989, **23**, 584 (*Chem. Abstr.*, 1990, **112**, 55758).
44. G. Honda, M. Tabata, and M. Tsuda, *Planta Med.*, 1979, **37**, 172.
45. N. Singhal, I. S. Gupta, and P. C. Bansal, *J. Indian Chem. Soc.*, 1984, **61**, 690.
46. S. John, *Pharmazie*, 1981, **36**, 583.
47. W. Baker and L. A. Mitscher, *PCT Int Appl WO*, 1995, 9153,807 (*Chem. Abstr.*, 1995, **123**, 256757).
48. M. F. El-Zohry, A. N. Abd El Hamed, F. A. Omar, and M. A. Abd-Alla, *J. Chem. Technol. Biotechnol.*, 1992, **53**, 329.
49. S. A. H. El-Feky and Z. K. Abd El-Samii, *J. Chem. Technol. Biotechnol.*, 1991, **51**, 61.
50. S. John, *Prog. Drug Res.*, 1982, **26**, 259.
51. G. E. Hardtmann and H. Ott, *US Patent*, 1969, 3,470,182 (*Chem. Abstr.*, 1970, **72**, 90502).
52. A. A. M. Abdel-Alim, A. N. A. El-Shorbagi, M. A. El-Gendy, and H. A. H. El-Shareif, *Collect. Czech. Chem. Commun.*, 1993, **58**, 163.
53. A. I. Mikhalev, M. E. Konshin, O. A. Yanborisova, A. S. Zaks, and V. V. Yushkov, *Khim-Farm. Zh.*, 1991, **25**, 37 (*Chem. Abstr.*, 1991, **115**, 279955).
54. S. Malhotra, S. K. Koul, S. Singh, G. B. Singh, and K. L. Dhar, *Indian J. Chem.*, 1989, **28B**, 100.
55. J. Bartroli, E. Turmo, M. Alguero, E. Boncompte, M. L. Vericat, L. Conte, J. Ramis, M. Merlos, J. GarciaRafanell, and J. Forn, *J. Med. Chem.*, 1998, **41**, 1869.
56. S. Andreae, E. Schmitz, *Ger (Eas) DD*, 1991, 289,525 (*Chem. Abstr.*, 1991, **115**, 232271).
57. G. K. Smith, D. S. Duch, R. Ferone, and A. Koch, *PCT Int Appl WO*, 1994, 14,448 (*Chem. Abstr.*, 1994, **121**, 230789).
58. N. V. Harris, C. Smith, and K. Bowden, *J. Med. Chem.*, 1990, **33**, 434.
59. V. J. Ram, R. C. Srimal, D. S. Kushwaha, and L. Mishra, *J. Prakt. Chem.*, 1990, **332**, 629.
60. K. A. M. Abou-Zeid, K. M. Youssef, F. M. Amine, S. Botros, and Z. Isaac, *Egypt. J. Pharm. Sci.*, 1989, **30**, 429.
61. N. Tiwari, B. Dwivedi, and Nizamuddin, *Nippon Noyaku Gakkaishi*, 1990, **15**, 357 (*Chem. Abstr.*, 1991, **114**, 143356).
62. R. J. Alaimo, *US Patent*, 1976, 3,997,538 (*Chem. Abstr.*, 1977, **86**, 121366).
63. E. F. Harrison and A. A. Larsen, *US Patent*, 1971, 3,560,619 (*Chem. Abstr.*, 1971, **75**, 5929).
64. H. Gysin and E. Knusli, *Ger Patent*, 1958, 1,035,398 (*Chem. Abstr.*, 1960, **54**, 25543).
65. J. D. Jones, *PCT Int Appl WO*, 1992, 15,569 (*Chem. Abstr.*, 1992, **118**, 22253).

66. L. Korzycka, A. Szadowska, and W. Pakulska, *Pharmazie*, 1994, **49**, 815.
67. R. Schlecker, H. J. Treiber, B. Behl, and H. P. Hofmann, *Ger Offen DE*, 1994, 4,241,563 (*Chem. Abstr.*, 1994, **121**, 230787).
68. R. K. Saksena and M. A. Khan, *Indian J. Chem.*, 1989, **28B**, 443.
69. J. Tani, Y. Yamada, T. Oine, T. Ochiai, R. Ishida, and I. Inoue, *J. Med. Chem.*, 1979, **22**, 95.
70. A. J. Barker, *Eur Patent*, 1995, 635,498 (*Chem. Abstr.*, 1995, **122**, 214099).
71. J. B. Jiang, D. P. Hesson, B. A. Dusak, D. L. Dexter, G. J. Kang, and E. Hamel, *J. Med. Chem.*, 1990, **33**, 1721.
72. S. F. Bricher, W. C. Lumma, M. E. Goldman, T. A. Lyle, J. R. Huff, L. S. Payne, M. L. Quesada, S. D. Young, and W. M. Sanders, *Eur Patent*, 1993, 530,994 (*Chem. Abstr.*, 1994, **120**, 30778).
73. K. Smith, G. A. El-Hiti, and A. S. Hegazy, *Synthesis*, 2005, in press.
74. K. Smith, G. A. El-Hiti, and A. S. Hegazy, *J. Sulfur Chem.*, **26**, 2005, 121.
75. K. Smith, G. A. El-Hiti, and M. F. Abdel-Megeed, *Synthesis*, 2004, 2121.
76. G. A. El-Hiti, *Synthesis* 2004, 363.
77. G. A. El-Hiti, *Monatsh. Chem.*, 2004, **135**, 323.
78. K. Smith, G. A. El-Hiti, and M. F. Abdel-Megeed, *Russ. J. Org. Chem.*, **39**, 2003, 430.
79. G. A. El-Hiti, M. F. Abdel-Megeed, and Y. A.-G. Mahmoud, *Indian J. Chem.*, 2000, **39B**, 368.
80. G. A. El-Hiti, *Heterocycles*, 2000, **53**, 1839.
81. M. F. Abdel-Megeed, G. A. El-Hiti, M. A. Saleh, M. A. Abdo, and S. E. Awadallah, *Rev. Roum. Chim.*, 1999, **44**, 67.
82. M. A. Abdo, I. F. Zeid, G. A. El-Hiti, and O. E. Mahmoud, *Indian J. Chem.*, 1999, **38B**, 850.
83. K. Smith, G. A. El-Hiti, M. F. Abdel-Megeed, and M. A. Abdo, *Collect. Czech. Chem. Commun.*, 1999, **64**, 515.
84. G. A. El-Hiti, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 2209.
85. K. Smith, G. A. El-Hiti, M. F. Abdel-Megeed, and M. A. Abdo, *J. Org. Chem.*, 1996, **61**, 656.
86. K. Smith, G. A. El-Hiti, M. F. Abdel-Megeed, and M. A. Abdo, *J. Org. Chem.*, 1996, **61**, 647.
87. K. Smith, G. A. El-Hiti, M. A. Abdo and M. F. Abdel-Megeed, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1029.48.
88. M. F. Abdel-Megeed, Y. L. Aly, M. A. Saleh, I. M. Abdo, G. A. El-Hiti, and K. Smith, *Sulfur Lett.*, 1995, **19**, 129.
89. H. Schiff, *Ann. Pharm*, 1870, **154**, 30.
90. H. Schiff, *Ann. Pharm.*, 1866, **140**, 123.
91. B. Sorokin, *Ber.*, 1886, **19**, 513.
92. B. Sorokin, *J. Chem. Soc.*, 1886, **50**, 526.

93. J. C. Irvine and R. Gilmour, *J. Chem. Soc.*, 1909, 1545.
94. J. C. Irvine and R. Gilmour, *J. Chem. Soc.*, 1909, 95.
95. J. C. Irvine and R. Gilmour, *J. Chem. Soc.*, 1908, 1429.
96. G. P. Ellis and J. Honeyman, *Adv. Carbohydr. Chem.*, 1955, **10**, 95.
97. G. P. Ellis and J. Honeyman, *J. Chem. Soc.*, 1952, 1490.
98. E. Mitts and R. M. Hixon, *J. Am. Chem. Soc.*, 1944, **66**, 483.
99. M. A. Abdo, M. F. Abdel-Megeed, M. A. Saleh, and G. A. El-Hiti, *Polish J. Chem.*, 1995, **69**, 583.
100. M. F. Abdel-Megeed, M. A. Saleh, M. A. Abdo, and G. A. El-Hiti, *Collect. Czech. Chem. Commun.*, 1995, **60**, 1016.
101. M. A. Salekh, L. S. Krasavina, M. M. Vigdrochik, K. F. Turchin, E. F. Kulechoua, and N. N. Suorov, *Zh. Org. Khim.*, 1989, **25**, 2613 (*Chem. Abstr.*, 1990, **113**, 115694).
102. W. E. Stewart and T. H. Siddall, *Chem. Rev.*, 1970, **70**, 517.
103. G. A. El-Hiti, *Spectrosc. Lett.*, 1999, **32**, 671.
104. R. S. Atkinson, E. Barker, C. J. Price, and D. R. Russell, *J. Chem. Soc., Chem. Commun.*, 1994, 1159.
105. G. Zemplén and E. Pascu, *Ber.*, 1929, **62**, 1613.
106. M. A. Saleh, *Rev. Roum. Chim.*, 1994, **39**, 659.
107. M. A. Saleh, M. A. Abdo, M. F. Abdel-Megeed, and G. A. El-Hiti, *Indian J. Chem.*, 1996, **35B**, 147.
108. L. Mester and M. Mester, *J. Carbohydr. Nucleos. Nucleot.*, 1975, **2**, 141.
109. M. A. Saleh, M. F. Abdel-Megeed, M. A. Abdo, and A. M. Shokr, *Nucleosides, Nucleotides Nucleic Acids*, 2002, **21**, 93.
110. A. M. Shokr, Ph D thesis, 1999, Tanta University, Tanta, Egypt.
111. M. F. Abdel-Megeed, G. A. El-Hiti, M. A. Abdo, and M. A. Saleh, *Rev. Roum. Chim.*, 2000, **45**, 545.
112. G. A. El-Hiti, M. F. Abdel-Megeed, and T. M. Zied, *Indian J. Chem.*, 2002, **41B**, 1519.
113. N. R. El-Brollosy, M. F. Abdel-Megeed, G. A. El-Hiti, and A. R. Genady, *Afinidad*, 2003, **60**, 199.
114. T. M. Ayad, Ph D thesis, 2002, Tanta University, Tanta, Egypt.
115. M. A. Saleh, Y. A. Abbas, F. A. Abdel-Hai, and S. A. Youssef, *Nucleosides, Nucleotides Nucleic Acids*, 2001, **20**, 1891.
116. S. A. Youssef, M. Sc. Thesis, 1996, Tanta University, Tanta, Egypt.
117. G. Wagner and F. Süß, *Pharmazie*, 1969, **24**, 35.

118. M. F. Abdel-Megeed and M. A. H. Saleh, *Sulfur Lett.*, 1987, **6**, 115.
119. M. G. Stout and R. K. Robins, *J. Org. Chem.*, 1968, **33**, 1219.
120. A. Hampton and A. W. Nichol, *Biochemistry*, 1966, **5**, 2076.
121. M. F. Abdel-Megeed, M. A. Saleh, Y. L. Aly, and I. M. Abdou, *Nucleosides, Nucleotides*, 1995, **14**, 1985.
122. M. A. Saleh, Y. A. Hafez, F. E. Abdel-Hay, and W. I. Gad, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 411.