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Synthesis, molecular modeling and anti-cancer evaluation of a series of quinazoline derivatives

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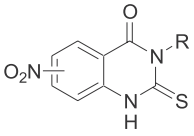
ABSTRACT

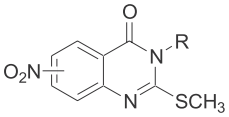
Quinazolines were surveyed as biologically relevant moieties against different cancer cell lines, so in the present study, we analyzed novel derivatives as target-oriented chemotherapeutic anti-cancer drugs. A series of 3-substituted 2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones **4a-e** were synthesized *via* the reaction of 2-aminobenzoic acid (**1**) with isothiocyanate derivatives **2a-e**. S-alkylation and *S*-glycosylation were carried *via* the reaction of **4a-e** with alkyl halides and α-glycopyranosyl bromides **7a,b** under anhydrous alkaline and glycoside conditions, respectively. The *S*-alkylated and *S*-glycosylated structures, and not that of the *N*-alkylated and *N*-glycosylated isomers, have been selected for the products. Conformational analysis has been studied by homo- and heteronuclear two-dimensional NMR methods (DQF-COSY, HMQC, and HMBC). The *S* site of alkylation and glycosylation were determined from the ^{1}H, ^{13}C heteronuclear multiple-quantum coherence (HMQC) experiments. All derivatives were subjected to molecular docking calculations, which selected some derivatives (**5n**, **8c**, **8g**, **9c,** and **9a)** as promising ones based on their excellent binding affinities towards the EGFR tyrosine kinase molecular target. The *in vitro* cytotoxic activity against MCF-7 and HepG2 cell lines showed effective anti-proliferative activity of the analyzed derivatives with lower IC_{50} values especially **9a** with IC_{50} = 2.09 and 2.08 μM against MCF-7 and HepG2, respectively, and their treatments were safe against the normal cell line Gingival mesenchymal stem cells (GMSC). Moreover, RT-PCR reaction investigated the apoptotic pathway for the compound **9a**, which activated the P53 genes and its related genes. So, further work is recommended for developing it as a chemotherapeutic drug.

1. Introduction

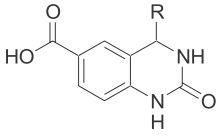
Quinazolines are considered to be an important chemical scaffold of various physiological significance and pharmaceutical utility. They possess a variety of biological effects including antihypertensive [1,2], antimicrobial [3,4], antihyperlipidemic [5,6], anti-inflammatory [7,8] and anticonvulsant [9–13] activities. Moreover, many quinazolines contributed to the quest for an ultimate antitumor chemotherapeutic agent [14–18]. It was reported that 2-thioxo-3-substituted quinazolinones (**I**) [19] and their *S*-methyl thioether counterparts (**II**), in addition to the 6-substituted quinazolinone derivatives (**III**) showed promising antitumor potency [20]. As the first part of this study, we at this moment report the synthesis and spectroscopy of a new series of *S*-alkylated bearing 3-substituted-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones bases as potential antiviral and antitumor activities (Scheme 1).



I, R = Et, Ph, Bn



II, R = Et, Ph, Bn



III, R = H, Ph

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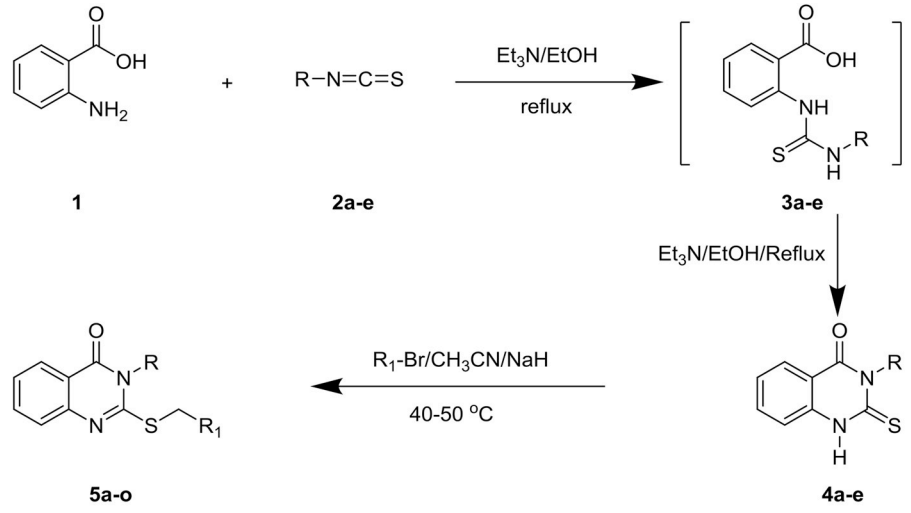
Moreover, nucleoside analogs constitute an important class of therapeutic agents in the treatment of cancers and viral infections [21,22]. The mode of action of these derivatives is based upon their intracellular conversation to their phosphorylated forms (nucleotides), which can interact with different cell biosynthesis. During the last decades, intensive research was dedicated to the discovery of more effective, selective, and non-toxic new nucleoside derivatives [23–26]. Glycosides of structurally similar heterocyclic systems have been reported before [27–30]. In continuation of our work on the synthesis of novel nucleosides as potential antiviral, antitumor agents and keeping in mind the biological significance of 2-thioxo-quinazolin-4-ones [31–37]. As the second part of this study, we at this moment report the synthesis and spectroscopy of a new series of *S*-glycosylated bearing 3-substituded-2-thioxo-2,3-dihydro-1*H*-benzo [g]-quinazolin-4-onebases as potential antiviral and antitumor activities (Scheme 2). This is the first time to prepare S-glycosides of 3-substituted-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones *via* new synthetic strategies. The previous studies of Abdel-Megeed et al. [38] and El-Barbary et al. [39] succeeded to prepare S-glycosides of 3-substituted 2-thioxoquinazolin-4-one derivatives, and they did not succeed to get the corresponding deprotected S-glycosides of 3- substituted 2-thioxoquinazolin-4-one derivatives.

2. Results and discussion

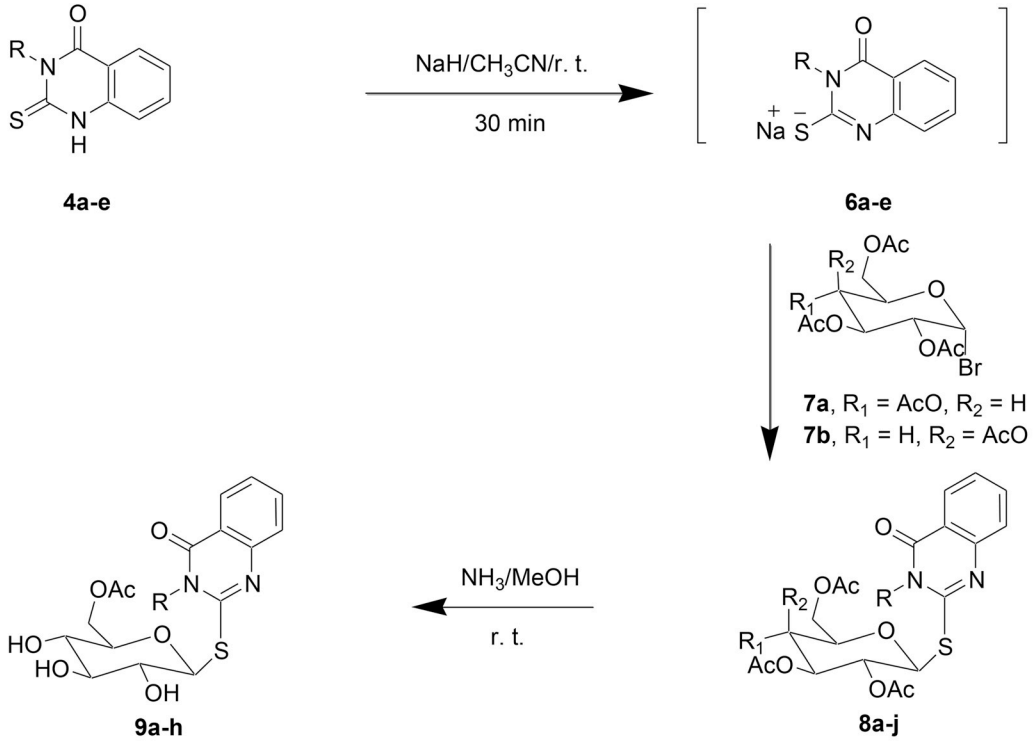
2.1. Chemistry

3-Substituted 2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones **4a–e** were synthesized by one-pot-reaction of 2-aminobenzoic carboxylic acid (**1**) and the appropriate alkyl/aryl isothiocyanates **2a–e** in refluxing absolute ethanol in the presence of triethylamine as a base catalyst. Compounds **4a–e** were then reacted with the appropriate alkyl halides namely ethyl bromide, ethyl bromoacetate and finally 1-chloro-2-methoxyethaneto yield the corresponding 3-substituted2-alkylsulfanyl-2,3-dihydro-1*H*-quinazolin-4-ones **5a-e**, 3-substituted4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl-acetic acid ethyl esters **5f-j**, 3-substituted2-ethoxy-methyl-sulfanyl-2,3-dihydro-1*H*-quinazolin-4-ones **5k-o**, respectively (Scheme 1). The structures of **4a-e** and **5a-o** were established and confirmed by elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR, and MS). The IR absorption spectra of **4a–e** were characterized the presence of a signal for NH group at ν_{max} 3176-3247 cm^{-1} and the presence of a signal for the thiocarbonyl group at ν_{max}1262-1300 cm^{-1}. While the IR absorption spectra of **5a–o** were characterized by the absence of signals for NH and C=S groups. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **4b** showed a triplet at δ_H1.23 ppm (J = 6.50 Hz) assigned to the methyl proton, a quartet at 4.46 ppm (J = 7.0 Hz) assigned to the methylene proton, a triplet at δ_H 7.33 ppm (J = 7.50 Hz) assigned to 6-H, a doublet at δ_H 7.39 ppm (J = 8.50 Hz) assigned to 8-H, a singlet at δ_H 7.74 ppm assigned to 7-H, a doublet at δ_H7.90 ppm (J = 7.50 Hz) assigned to 5-H and a singlet at δ_H 13.00 ppm assigned to NH. This agrees with the ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of 3-(4-methoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one [40], whose NH appears at δ_H 13.02 ppm. The ^{13}C NMR (500 MHz, DMSO-d_6) spectrum of **4d** showed a singlet at δ_C160.27 ppm and 176.58 ppm assigned to the carbonyl group at C-4 and the thiocarbonyl group at C-2, respectively. These data are also in agreement with the ^{13}C NMR (300 MHz, DMSO-d_6) spectrum of 3-(4-methoxyphenyl)-2-thioxo-2,3-dihydro-quinazolin-4(1*H*)-one [40] since the carbonyl at C-4 appears at δ_c 160.40 ppm and the thiocarbonyl group at



2-5	R	R_1	2-5	R	R_1
a	CH_3	CH_3	**i**	C_6H_5	CH_3CH_2OCO
b	CH_3CH_2	CH_3	**j**	4-$CH_3OC_6H_4$	CH_3CH_2OCO
c	CH_2=$CHCH_2$	CH_3	**k**	CH_3	CH_3OCH_2
d	C_6H_5	CH_3	**l**	CH_3CH_2	CH_3OCH_2
e	4-$CH_3OC_6H_4$	CH_3	**m**	CH_2=$CHCH_2$	CH_3OCH_2
f	CH_3	CH_3CH_2OCO	**n**	C_6H_5	CH_3OCH_2
g	CH_3CH_2	CH_3CH_2OCO	**o**	4-$CH_3OC_6H_4$	CH_3OCH_2
h	CH_2=$CHCH_2$	CH_3CH_2OCO			

Scheme 1. Synthesis of the target compounds **4a-e** and **5a-o**.



4-8	R	R_1	R_2	9	R	R_1	R_2
a	CH_3	CH_3CO	H	**a**	CH_3	OH	H
b	CH_3CH_2	CH_3CO	H	**b**	CH_3CH_2	OH	H
c	CH_2=$CHCH_2$	CH_3CO	H	**c**	CH_2=$CHCH_2$	OH	H
d	C_6H_5	CH_3CO	H	**d**	C_6H_5	OH	H
e	4-$CH_3OC_6H_4$	CH_3CO	H	**e**	4-$CH_3OC_6H_4$	OH	H
f	CH_3	H	CH_3CO	**f**	CH_3CH_2	H	OH
g	CH_3CH_2	H	CH_3CO	**g**	CH_2=$CHCH_2$	H	OH
h	CH_2=$CHCH_2$	H	CH_3CO	**h**	C_6H_5	H	OH
i	C_6H_5	H	CH_3CO				
j	4-$CH_3OC_6H_4$	H	CH_3CO				

Scheme 2. Synthesis of the target compounds **8a-j** and **9a-h**.

C-2 appears at δ_C 176.80 ppm. Furthermore, data from the elemental analyses have been found to conform to the assigned structure. Also, the molecular ion recorded in the mass spectrum is also in agreement with the molecular weight of the compound. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **5k** showed a singlet at 3.31 ppm assigned to N_3CH_3, a singlet at 3.43 ppm assigned to OCH_3, a triplet at δ_H 3.59 ppm (J = 6.25 Hz) assigned to SCH 2, a singlet at 3.67 ppm assigned to OCH_3, a triplet at 3.64 ppm (J = 6.25 Hz) assigned to the OCH_2, a triplet at δ_H 7.38 ppm (J = 7.25 Hz) assigned to 6-H, a doublet at 7.45 ppm (J = 7.00 Hz) assigned to 8-H, a triplet at δ_H 7.71 ppm (J = 6.50 Hz) assigned to 7-H and a doublet at δ_H 8.06 ppm assigned to 5-H. The ^{13}C NMR (500 MHz, DMSO-d_6) spectrum of **5k** showed a singlet at δ_C 157.20 ppm and 162.10 ppm assigned to –N=C–S– at C-2 and the carbonyl group at C-4, respectively, indicated that the site of the alkylation is the sulfur atom rather than the nitrogen atom. These data are also in agreement with the ^{13}C NMR (300 MHz, DMSO-d_6) spectrum of 3-ethyl-2-[2-(4-methoxyphenyl)-2-oxo-ethylthio]quinazolin-4(3*H*)-one [32], since –N=C–S– at C-2 appears at δ_c 153.40 ppm, and the carbonyl group at C-4 appears at δ_C 160.60 ppm.

The key intermediates for the synthesis of cyclic thioglycosides are shown in Scheme 2. Analogously, Treatment of **3a-f** with 1.1 equivalents of NaH in anhydrous acetonitrile furnished the sodium salts of 2-thioxo-4-thiazolidinones **6a-e**, which in turn were treated with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**7a**) or 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**7b**) to afford the *S*-glycosylated nucleosides **8a–j** in good yields (54–91%), (Scheme 2). Thin layer chromatography (CH_2Cl_2/MeOH, 98:2) indicated the formation of pure compounds. The structures of the S-glycoside **8a–j** were confirmed by elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR). The ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **8a** as an example, showed the anomeric proton of the glucose moiety as a doublet at δ5.99 ppm with a coupling constant $^2J_{1',2'}$ = 10.50 Hz indicating β-configuration of the anomeric center. The other protons of the glucopyranose ring resonated at δ3.98–5.42 ppm, while the four acetoxy groups appeared as four singlets at δ1.92–2.00 ppm. The ^{13}C NMR (500 MHz, $CDCl_3$) revealed the absence of the thione carbon atom at about 175.85 ppm and the resonance of –N=C–N– carbon atom (C-2) at δ153.04 ppm was indicated to the chemical shift of the corresponding carbon atom (Fig. 1).

The signals at δ, 169.00, 170.00, 171.00 ppm were due to the four acetoxy carbonyl atoms (4C=O), and the six signals at δ 61.97, 68.40, 68.80, 74.09, 76.46, 82.29 ppm were assigned to C-6′,C-2, C-3′, C-4′, C-5′, and C-1′, respectively. Moreover, the IR spectra of compounds **8a-j** revealed the absence of the stretching signal of a thione group. These

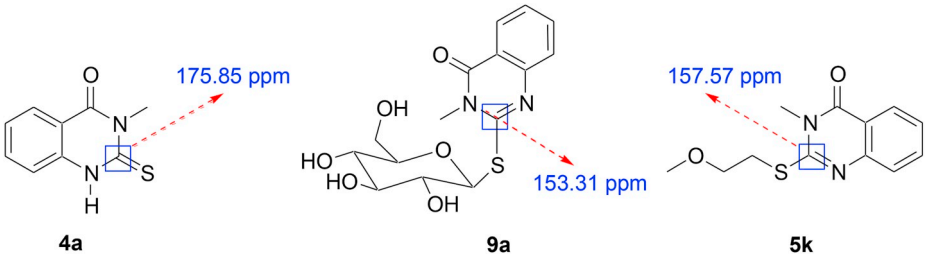


Fig. 1. The chemical shift of the corresponding carbon atom at position 2 in **4a**, **9a,** and **5k**.

data are also in agreement with the ^{13}C NMR (DMSO-d_6) spectrum of 7-(4-chlorophenyl)-5-phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylthio)pyrido [2,3-*d*]pyrimidine-4-one [34] since the carbonyl at C-4 appears at δ_C163.20 ppm and –N═C–N– carbon atom (C-2) appears at δ_C152.20.8 ppm, indicating the presence of S-glycosylation.

Removal of the acetyl groups from the glycon moiety of **8a-e** and **8g-j** with a saturated 5% NH_3/MeOH solution at room temperature furnished the corresponding free nucleosides **9a-e** and **9f-h**, respectively (Scheme 2). The structures of **9a** were confirmed by their spectroscopic and mass spectral data. The mass spectrum of **9a** showed a molecular ion peak at *m/z* = 354, while the ^{1}H NMR spectrum showed a doublet at δ_H 5.50 with $J_{1',2'}$ = 12.00 Hz, corresponding to the 1′-H and indicating a β-configuration. C-2 of **9a** resonated at δ_C153.31 ppm, establishing the S-glycosylation. Furthermore, the heteronuclear spectra (HMQC, DFQ-COSY) of **9a-h** no such correlation was shown between C-8a and 1′-H, which is an indication of the S-glycosylation. The nucleoside bases **4** can be utilized as starting materials for the synthesis of other carbohydrate derivatives as deoxy, amino and azido nucleosides.

2.2. Molecular docking studies

All synthesized derivatives were subjected to molecular docking studies, in which their binding affinities were studied as EGFR activity. Molecular docking calculations concluded that among the docked derivatives, only some of them had nearly the same binding mode of interactions as the co-crystallized ligand inside the receptor binding site. In this part, the ligand-receptor interactions for the promising compounds which have the same EGFR activity were provided.

Table 1 and Fig. 2, summarize the ligand-receptor interactions inside the 1M17 binding site to compare the overall interactions of the docked compounds with that made by the co-crystallized ligand. From this comparison, we concluded that **5n**, **8c**, **8g**, **9c** and especially **9a** might have the same EGFR activity as the co-crystallized ligand where they form the same interactions with **Met 769** which is the key amino acid interactions for the EGFR activity Fig. 2A. So, these derivatives were worthy of being further tested against different cancer cell lines to collect an overview of their biological activity.

2.3. In vitro cytotoxic activity

Anti-cancer activity of the promising derivatives **5n, 8c, 8g, 9c,** and **9a** was tested against breast (MCF-7), liver (HepG2) cell lines by measuring the percentage of cell survival against their serial dilutions (0.01, 0.1, 1, 10, and 100 μM). Moreover, they were screened against the GMSC as normal cell line to test their safety.

As shown in Fig. 3, the percentage of cell survival relative to control decreases with increasing concentrations proving their cytotoxic activities. It decreased in a dose-response curve that means with increasing concentrations percentage of cell survival decreased, except in some treatments due to some variation in the biological behavior of cells. Moreover, some of the analyzed compounds exhibited a substantial decrease in the percentage of cell survival than the standard drug itself. For the cytotoxic activity against the normal GMSC cells, it was found that the treatment of the compounds was safe (non-toxic) because there was a slight decrease in the percentage of cell survival. These results proved the safety of the treatments of the compounds towards noncancerous cells.

In the present study, we conclude the incorporation of sugar portion to the nucleus, enhanced the cytotoxic activity against the MCF-7 and HepG2 cell lines by having lower IC_{50} values, as shown in Table 2. Although both compounds **9a** and **9c** have near IC_{50} values (**2.09** and **2.04 μM**, respectively) against HepG2 cells, **9a** was considered as the lead compound in our study according to the molecular docking results. It has a higher binding affinity towards the EGFR tyrosine kinase receptor because it forms larger number of hydrogen bonds with the key amino acid residue **Met 769** compared to other derivatives, so it was selected for further testing as the molecular mode of action. An attempt to study the structure-activity relationship using the molecular docking tool for elucidation the binding interactions of the nucleosides which might justify their higher potency.

2.4. Apoptotic assay

Based on the high binding affinity of the analyzed derivatives especially compound **9a** towards EGFR tyrosine kinase receptor through the molecular modeling analysis, and the significant cytotoxic activity of **9a** (IC_{50} = 2.09 μM), it was thought worthwhile to further investigate its effect on induction of apoptosis in HepG2 cancer cells for investigation the apoptotic pathway. HepG2 cells were treated with 50 μM of the compound for 48 h after this RNA was extracted, cDNA was synthesized, and RT-PCR reaction was made to follow the mRNA expression of apoptosis-related genes; pro-apoptotic P53, MDM2, PUMA and Bax in the **9a**-treated HepG2 cells. It is well known that the upregulation of the pro-apoptotic genes is a sign for the modulation of cell death.

As shown in Fig. 4, Compound **9a** significantly activated the level of P53 gene (with a maximum increase of ≈3.1-fold, $P \leq 0.001$). The compound was able to significantly increase the mRNA levels of all the p53 target genes: PUMA (with a maximum increase of ≈8.03-fold, $P \leq 0.001$), and MDM2 (with a maximum increase of ≈2.6-fold, $P \leq 0.05$). Then, the expression of another gene that is correlated to p53 reactivation was investigated. The expression of the pro-apoptotic "multi-domain" Bcl-2 family member BAX was assessed by RT-PCR analysis. As expected, the compound treatment of the HepG2 cells caused a significant increase in BAX (maximum increase of ≈1.9-fold, $P \leq 0.05$). The results are in accordance with the proposed apoptotic pathway for anti-cancer activity.

3. Experimental

3.1. General procedures

All melting points were taken on the Electrothermal IA 9100 series digital melting point apparatus. Microanalytical data (in accord with the calculated values) were performed by Vario, Elementar apparatus (Shimadzu). The IR spectra (KBr) were recorded on a Perkin–Elmer 1650 spectrometer (USA). ^{1}H NMR and ^{13}C NMR spectra were

Table 1
Summarized Ligand-receptor interactions of promising compounds compared to the original ligand.

Molecular target (PDB code)	Original ligand			Docked compounds		
	Co-crystallized ligand	Hydrogen bond No.	Vander Waals interaction[a]	Compound No.	Hydrogen bond No.	Vander Waals interaction[a]
1M17	**4-anilinoquinazolinelerlotinib**	One hydrogen bond with **Met 769**	Leu 820, Leu 768, Gly 772 and Leu 694	**5n**	Two hydrogen bonds with **Met 769** and Thr 830	–
				8c	Two hydrogen bonds with **Met 769** and Lys 721	–
				8g	One hydrogen bond with **Met 769**	–
				9c	Seven hydrogen bonds with Asp 831, Lys 721, Glu 738, Thr 830, and **Met 769**	
				9a	Three hydrogen bonds. Two of which with **Met 769** and Lys 721	Phe 699

[a] Vander Waals interactions are lipophilic interactions arene-arene interactions or arene-cation interactions.

determined on a JEOL ECA-500. Chemical shifts were expressed in ppm relative to $SiMe_4$ as internal standards and DMSO-$d_6$or $CDCl_3$ or CD_3OD as a solvent. Mass spectra were recorded on70 eV EI Ms-QP 1000 EX (Shimadzu).

3.2. Synthesis

3-Substituted 2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones (4a-e).

To a mixture of 2-aminobenzoic acid (**1**) (1.37 g, 10 mmol), anhydrous triethylamine (2.00 mL, 22.22 mmol) and anhydrous ethanol (50 mL) was added the appropriate alkyl/aryl isothiocyanates **2a–e** (11 mmol). The mixture was refluxed until the starting material was consumed (4 h; TLC, ethyl acetate/methanol, 99.9:0.1) and cooled at room temperature. The reaction mixture was diluted with water and neutralized with diluted hydrochloric acid. The solid separated was collected by filtration and recrystallized from ethanol to give the products **4a-e** in quantitative yields.

3-Methyl-2-thioxo-2,3-dihydroquinazolin-4(*1H*)-one (4a):Yield:1.75 g (91%), mp: 244–246 °C (270–272 °C [41]). MS:*m/z*: 192 (M^+, 100%). Calculated for $C_9H_8N_2OS$ (192.24): C, 56.23; H, 4.19; N, 14.57. Found: C, 56.02; H, 4.38; N, 14.26. IR (KBr): ν 3176 (NH), 1622 (C═O), 1289 (C═S) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.60 (3H, s, CH_3), 7.33(1H, t, J = 7.50 Hz, H-6), 7.39(1H, d, J = 8.50 Hz, H-8), 7.74 (1H, t, J = 7.50 Hz, H-7), 7.94 (1H, d, J = 8.00 Hz, H-5), 12.80 (1H, s, NH).^{13}C NMR (500 MHz, DMSO-d_6): δ = 33.70 (CH_3), 115.76 (C-6), 116.07 (C-8), 124.28 (C-5), 127.70 (C-7), 135.76 (C-4a), 139.55 (C-8a), 160.08 (C-4), 175.85 (C-2).

3-Ethyl-2-thioxo-2,3-dihydroquinazolin-4(H)-one (4b): Yield:1.76 g (85%), mp: 246–248 °C (290–291 °C [42]). MS:*m/z*: 206 (M^+, 84%). Calculated for $C_{10}H_{10}N_2OS$ (206.27): C, 58.23; H, 4.89; N, 13.58. Found: C, 58.12; H, 4.98; N, 13.37. IR (KBr): ν 3247 (NH), 1651 (C═O), 1285 (C═S) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.23 (3H, t, J = 6.50.00 Hz, CH_3), 4.46 (2H, q, J = 7.00 Hz, CH_2), 7.33 (1H, t, J = 7.50 Hz, H-6), 7.39 (1H, d, J = 8.50 Hz, H-8), 7.74 (1H, t, J = 7.25 Hz, H-7), 7.90 (1H, d, J = 7.50 Hz, H-5), 13.00 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 12.40 ($CH_2\mathit{CH_3}$), 41.45 ($\mathit{CH_2}CH_3$), 116.02 (C-6), 116.06 (C-8), 124.90 (C-5), 127.67 (C-7), 135.84 (C-4a), 139.52 (C-8a), 159.49 (C-4), 175.30 (C-2).

3-Allyl-2-thioxo-2,3-dihydroquinazolin-4(*1H*)-one (4c):Yield: 1.82 g (83%), mp: 184–186 °C (180–182 °C [42]). MS:*m/z*: 218 (M^+, 7%). Calculated for $C_{11}H_{10}N_2OS$ (218.28): C, 60.53; H, 4.62; N, 12.83. Found: C, 60.38; H, 4.84; N, 12.60. IR (KBr): ν 3159 (NH), 1654 (C═O), 1262 (C═S) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.03 (2H, d, J = 4.85 Hz, H-1_{allyl}), 5.15 (1H, m, H-3_{allyl}), 5.91 (1H, m, H-2_{allyl}),7.30 (1H, t, J = 7.25 Hz, H-6), 7.38 (1H, d, J = 8.50 Hz, H-8), 7.71 (1H, t, J = 7.00 Hz, H-7), 7.90 (1H, d, J = 7.50 Hz, H-5), 12.80 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 48.03 (C_1-allyl), 115.88 (C_3-allyl), 116.61 (C-6), 117.61 (C-8), 124.84 (C-5), 127.69 (C-7), 132.29 (C_2-allyl), 135.83 (C-4a), 139.62(C-8a), 159.45(C-4), 175.54 (C-2).

3-Phenyl-2-thioxo-2,3-dihydroquinazolin-4(*1H*)-one (4d): Yield:2.23 g (88%), mp: 290–292 °C (160–165 °C, 305–307 °C [43–45], 300–320 °C [46]). MS:*m/z*: 254 (M^+, 53%). Calculated for $C_{14}H_{10}N_2OS$ (254.31): C, 66.12; H, 3.96; N, 11.02. Found: C, 65.87; H, 4.05; N, 10.78. IR (KBr): ν 3214 (NH), 1662 (C═O), 1289 (C═S) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.28 (2H, d, J = 7.50 Hz, H-2′, H-6′), 7.30 (1H, t, J = 7.50 Hz, H-6), 7.41 (1H, d, J = 7.50 Hz, H-8), 7.47 (3H, m, H-4′, H-3′,H-5′), 7.78 (1H, t, J = 7.50 Hz, H-7), 7.95 (1H, d, J = 7.50 Hz, H-5), 13.00 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 116.18 (C-6), 116.66 (C-8), 124.78 (C-5), 127.88 (C-7), 128.56(C-4′), 129.35(C-2′, C-6′), 129.48 (C-3′, C-5′), 136.03 (C-1′), 139.78 (C-4a), 140.096 (C-8a), 160.27 (C-4), 176.58 (C-2).

3-(4-Methoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(*1H*)-one (4e): Yield 2.32 g (82%), mp: 240–242 °C, (178–280 °C [47]). MS:*m/z*: 284 (M^+, 5%). Calculated for $C_{15}H_{12}N_2O_2S$ (284.33): C, 63.36; H, 4.25; N, 9.85. Found: C, 63.14; H, 4.42; N, 9.63. IR (KBr): ν 3243

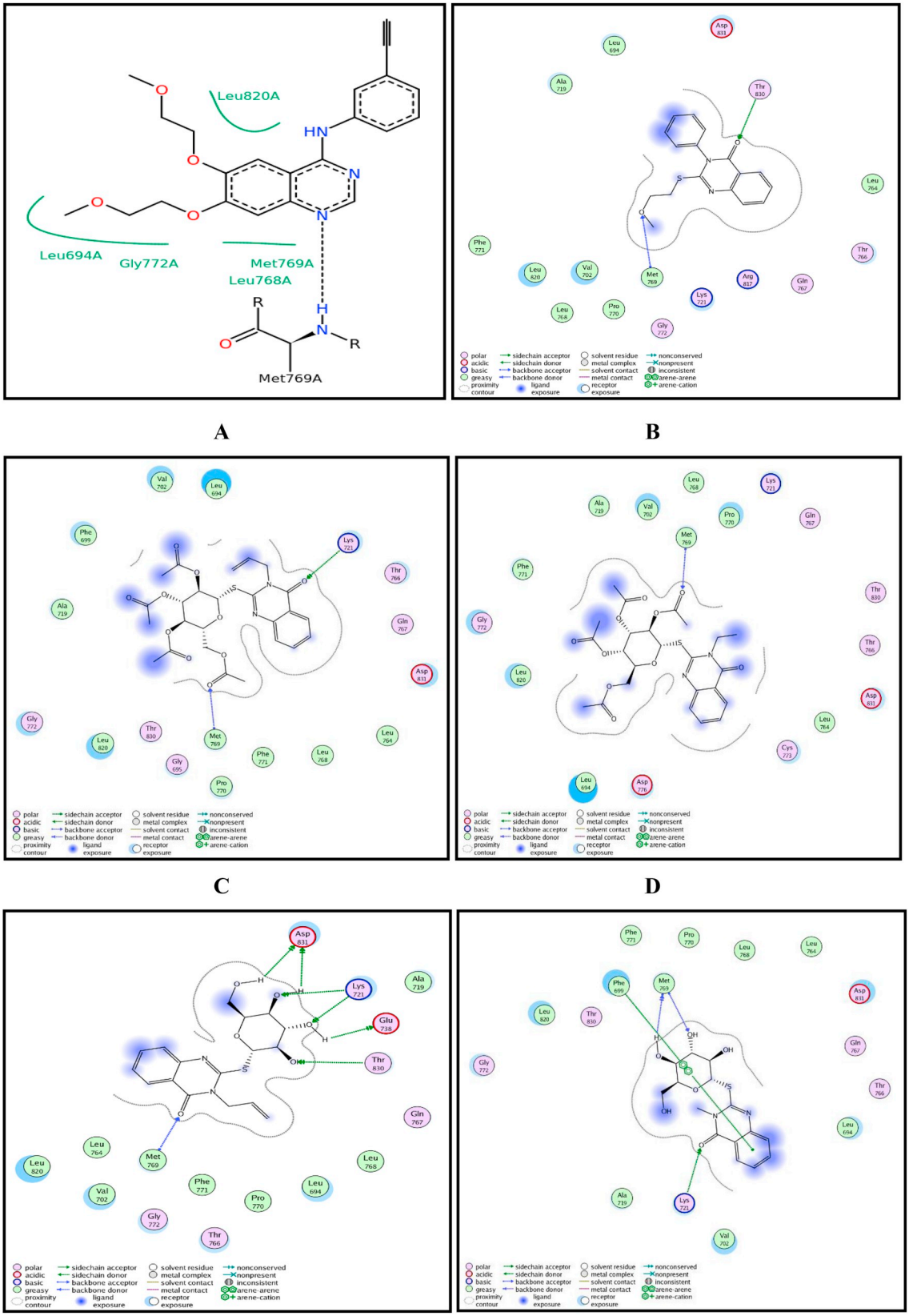


Fig. 2. Binding modes of the co-crystallized ligand **(A)** and the docked compounds **5n**, **8c**, **8g**, **9c** and **9a** (**B–F**), receptively, and their molecular interactions to the 1M17 binding site.

(NH), 1661 (C═O), 1300 (C═S) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.81 (3H, s, OCH_3), 7.00 (2H, d, J = 8.50 Hz, H-3′, H-5′), 7.16 (2H, d, J = 7.00 Hz, H-2′, H-6′), 7.31 (1H, t, J = 7.50 Hz, H-6), 7.42 (1H, d, J = 8.00 Hz, H-8), 7.74 (1H, t, J = 7.50 Hz, H-7), 7.93 (1H, d, J = 7.50 Hz, H-5), 12.80 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 55.75 (OCH_3), 114.51 (C-2′, C-6′), 116.82 (C-6), 116.91 (C-8),

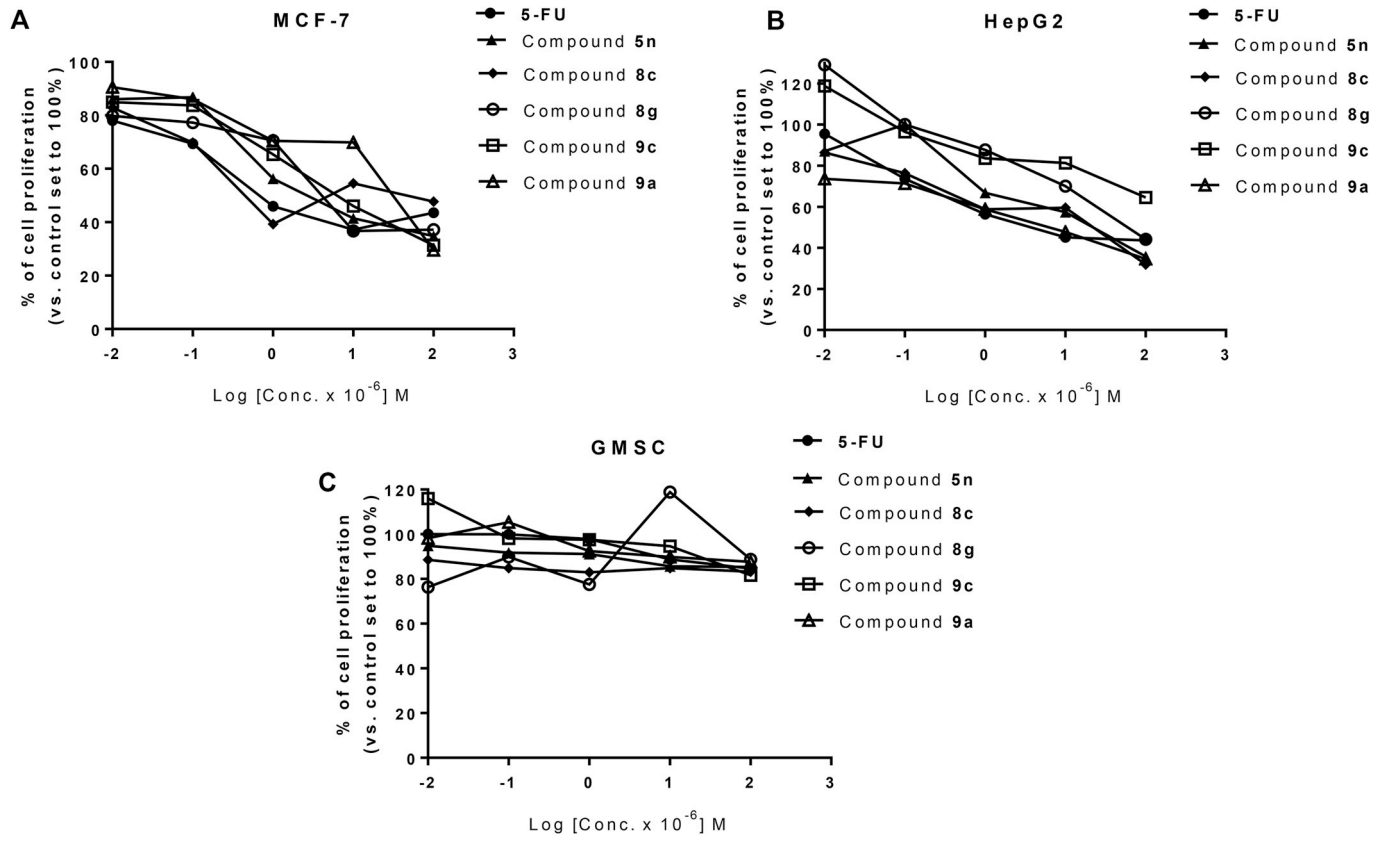


Fig. 3. Cytotoxic activity of the analyzed compounds against breast (MCF-7), liver (HepG2) cell lines, and normal cell line (GMSC).

Table 2
Summarized IC_{50} for the activity of the analyzed compounds against the MCF-7 and HepG2 cell lines.

	IC_{50} (μM)		
	MCF-7	HepG2	GMSC
5-FU	4.23	4.43	> 50
5n	8.96	1.52	> 50
8c	5.93	3.79	> 50
8 g	2.42	1.17	ND
9c	2.04	2.09	> 50
9a	2.09	2.08	> 50

ND = Not Determined.

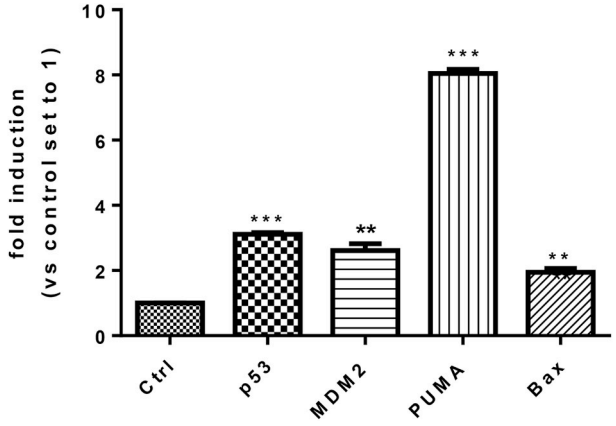


Fig. 4. RT-PCR analysis of the p53 mRNA and p53-related genes was performed after the HepG2 cells were treated with Compound **9a** (50 μM) for 48 h. Signs of * and *** mean values are significantly ($P \leq 0.05$) and highly significant ($P \leq 0.001$) different using unpaired *t*-test (GraphPad Prism).

124.38 (C-5), 127.78 (C-7), 128.56 (C-3′, C-5′), 130.45(C-1′), 132.75 (C-4a), 135.75 (C-8a), 140.99 (C-4′), 160.68 (C-4), 176.90 (C-2).

3-Substituded 2-ethylsulfanyl-2,3-dihydroquinazolin-4(H)-ones (5a-e): A mixture of 3-substituded-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones (**4a-e**) (1 mmol), anhydrous acetonitrile (10 mL) and sodium hydride (45 mg, 80%) was stirred at room temperature for ½ hour. Ethyl bromide (0.22 g, 2 mmol) was added to the mixture with stirring at 40–50 °C until the starting material was consumed (8 h; TLC, ethyl acetate/hexane, 30:70) and cooled at room temperature. Then solvent was removed under reduced pressure and the residue was treated with cold water. The solid separated was collected by filtration and recrystallized from ethanol to give the products **5a-e** in quantitative yields.

3-Methyl-2-ethylsulfanyl-2,3-dihydroquinazolin-4(*1H*)-one (5a): Yield: 0.21 g (95%), mp: 65–67 °C. MS: *m/z*: 220 (M^+, 1%). Calculated for $C_{11}H_{12}N_2OS$ (220.29): C, 59.97; H, 5.49; N, 12.72. Found: C, 60.14; H, 5.60; N, 12.38. IR (KBr): ν 1685 (C═O) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.37 (3H, t, J = 6.75 Hz, SCH_2CH_3), 3.27 (2H, q, J = 7.00 Hz, SCH_2CH_3), 3.48 (3H, s, N_3–CH_3), 7.42 (1H, t, J = 7.50 Hz, H-6), 7.52 (1H, d, J = 8.00 Hz, H-8), 7.76 (1H, t, J = 7.50 Hz, H-7), 8.06 (1H, d, J = 7.50 Hz, H-5).^{13}C NMR (500 MHz, DMSO-d_6): δ = 14.37 (SCH_2CH_3), 26.37 (SCH_2CH_3), 26.37 (N_3–CH_3), 119.04 (C-6), 126.29 (C-8), 126.70 (C-5), 126.83 (C-7), 134.93 (C-4a), 147.39 (C-8a), 157.57 (C-2), 161.21 (C-4).

3-Ethyl-2-ethylsulfanyl-2,3-dihydroquinazolin-4(H)-one (5b): Yield: 0.23 g (62%), mp: 37–39 °C [173–174 °C [41]]. MS: *m/z*: 234 (M^+, 100%). Calculated for $C_{12}H_{14}N_2OS$ (234.32): C, 61.51; H, 6.02; N, 11.96. Found: C, 61.34; H, 6.44; N, 11.67. IR (KBr): ν 1679 (C═O) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.25 (3H, t, J = 7.00 Hz, SCH_2CH_3), 1.37 (3H, t, J = 7.25 Hz, NCH_2CH_3), 3.27 (2H, q, J = 7.25 Hz, SCH_2CH_3), 4.07 (2H, q, J = 6.75 Hz, NCH_2CH_3), 7.43 (1H,

t, J = 7.50 Hz, H-6), 7.51 (1H, d, J = 8.00 Hz, H-8), 7.76 (1H, t, J = 7.50 Hz, H-7), 8.06 (1H, d, J = 7.50 Hz, H-5). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 13.43 ($SCH_2\mathit{CH_3}$), 14.14 ($N_3CH_2\mathit{CH_3}$), 26.33 ($S\mathit{CH_2}CH_3$), 39.57 ($N_3\mathit{CH_2}CH_3$), 119.29 (C-6), 126.20 (C-8), 126.33 (C-5), 126.77 (C-7), 135.02 (C-4a), 147.39 (C-8a), 156.68 (C-2), 160.82 (C-4).

3-Allyl-2-ethylsulfanyl-2,3-dihydroquinazolin-4(*1H*)-one (5c): Yield: 0.22 g (89%), pale yellow oil. MS: *m/z*: 246 (M^+, 20%). Calculated for $C_{13}H_{14}N_2OS$ (246.33): C, 63.39; H, 5.73; N, 11.37. Found: C, 63.05; H, 5.96; N, 11.11. IR (KBr): ν 1676 (C═O) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.48 (t, J = 6.75 Hz, $SCH_2\mathit{CH_3}$), 3.35 (2H, q, J = 7.25 Hz, $S\mathit{CH_2}CH_3$), 4.80 (2H, d, J = 4.85 Hz, H-1_{allyl}), 5.27 (2H, m, H-3_{allyl}), 6.02 (1H, m, H-2_{allyl}), 7.41 (1H, t, J = 7.50 Hz, H-6), 7.50 (1H, d, J = 8.00 Hz, H-8), 7.77 (1H, t, J = 7.50 Hz, H-7), 8.04 (1H, d, J = 7.50 Hz, H-5). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 14.02 ($SCH_2\mathit{CH_3}$), 26.72 ($S\mathit{CH_2}CH_3$), 46.37 (C-1_{allyl}), 118.23 (C-3_{allyl}), 118.84 (C-6), 126.25 (C-8), 126.36 (C-5), 126.78 (C-7), 131.32 (C-2_{allyl}), 135.06 (C-4a), 147.38 (C-8a), 156.69 (C-2), 160.87 (C-4).

3-Phenyl-2-ethylsulfanyl-2,3-dihydroquinazolin-4(*1H*)-one (5d): Yield: 0.27 g (96%), mp: 96–98 °C. MS: *m/z*: 282 (M^+, 6%). Calculated for $C_{16}H_{14}N_2OS$ (282.36): C, 68.06; H, 5.00; N, 9.92. Found: C, 67.85; H, 5.18; N, 9.78. IR (KBr): ν 1662 (C═O) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.27 (t, J = 7.25 Hz, $SCH_2\mathit{CH_3}$), 3.12 (2H, q, J = 7.25 Hz, $S\mathit{CH_2}CH_3$),7.08 (2H, d, J = 8.50 Hz, H-2′, H-6′), 7.34 (1H, t, J = 8.50 Hz, H-6), 7.46 (3H, m, H-3′, H-4′, H-5′), 7.60 (1H, d, J = 8.00 Hz, H-8), 7.82 (1H, t, J = 7.50 Hz, H-7), 8.07 (1H, d, J = 7.50 Hz, H-5). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 14.23 ($SCH_2\mathit{CH_3}$), 26.76 ($S\mathit{CH_2}CH_3$), 120.01 (C-6), 126.31 (C-8), 126.51 (C-5), 127.00 (C-7), 129.86 (C-4′), 129.88 (C-2′, C-6′), 130.19 (C-3′, C-5′), 135.34 (C-1′), 136.49 (C-4a), 147.80 (C-8a), 157.82 (C-2), 161.23 (C-4).

3-(4-Methoxyphenyl)-2-ethylsulfanyl-2,3-dihydroquinazolin-4(*1H*)-one (5e): Yield: 0.25 g (80%), mp: 142–144 °C. MS: *m/z*: 312 (M^+, 6%). Calculated for $C_{17}H_{16}N_2O_2S$ (312.39): C, 65.36; H, 5.16; N, 8.97. Found: C, 65.17; H, 5.30; N, 8.01. IR (KBr): ν 1685 (C═O) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.27 (t, J = 7.25 Hz, $SCH_2\mathit{CH_3}$), 3.10 (2H, q, J = 7.25 Hz, $S\mathit{CH_2}CH_3$), 3.84 (1H, s, $O\mathit{CH_3}$), 7.42(2H, d, J = 7.00 Hz, H-2′, H-6′), 7.43 (1H, t, J = 7.50 Hz, H-6), 7.48 (2H, d, J = 7.00 Hz, H-3′, H-5′), 7.60 (1H, d, J = 7.50 Hz, H-8), 7.80 (1H, t, J = 7.00 Hz, H-7), 8.06 (1H, d, J = 7.50 Hz, H-5). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 14.19 ($SCH_2\mathit{CH_3}$), 26.73 ($S\mathit{CH_2}CH_3$), 55.93 ($O\mathit{CH_3}$), 115.04 (C-2′, C-6′), 120.01 (C-6), 126.22 (C-8), 126.48 (C-5), 127.03 (C-7), 128.91 (C-3′, C-5′), 131.04 (C-1′), 135.24 (C-4a), 147.85 (C-8a), 158.53 (C-2), 160.45 (C-4′), 161.42 (C-4).

(3-Substituded 4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)-acetic acid ethyl esters (5f-j):

A mixture of **4a-e** (1 mmol), anhydrous acetonitrile (10 mL) and sodium hydride (45 mg, 80%) was stirred at room temperature for ½ hour. Ethylbromoacetate (0.33 g, 2 mmol) was added to the mixture with stirring at 40–50 °C until the starting material was consumed (8 h; TLC, ethyl acetate/hexane, 30:70) and cooled at room temperature. The solvent was removed under reduced pressure and the residue was treated with cold water. The solid separated was collected by filtration and recrystallized from ethanol to give the products **5f-j** in quantitative yields.

(3-Methyl-4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)-acetic acid ethyl ester (5f): Yield: 0.17 g (61%), mp: 70–72 °C. MS: *m/z*: 278 (M^+, 18%). Calculated for $C_{13}H_{14}N_2O_3S$ (278.33): C, 56.10; H, 5.07; N, 10.06. Found: C, 55.95; H, 5.35; N, 9.87. IR (KBr): ν 1733 (COO), 1674 (C═O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (3H, t, J = 7.00 Hz, $OCH_2\mathit{CH_3}$), 3.64 (3H, s, N_3–CH_3), 4.04 (2H, s, $S\mathit{CH_2}$COO), 4.26 (2H, t, J = 7.25 Hz, $O\mathit{CH_2}CH_3$), 7.37 (1H, t, J = 7.00 Hz, H-6), 7.49 (1H, d, J = 8.00 Hz, H-8), 7.67 (1H, t, J = 6.75 Hz, H-7), 8.21 (1H, d, J = 7.00 Hz, H-5). ^{13}C NMR (DMSO-d_6): δ = 14.25 ($OCH_2\mathit{CH_3}$), 30.36 (N_3–CH_3), 34.54 ($S\mathit{CH_2}$COO), 61.92 ($O\mathit{CH_2}CH_3$), 119.15 (C-6), 125.85 (C-8), 125.99 (C-5), 126.98 (C-7), 134.24 (C-4a), 147.15 (C-8a), 155.50 (C-2), 161.70 (C-4), 168.50 (COO).

(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)-acetic acid ethyl ester (5g): Yield: 0.20 g (83%), mp: 64–66 °C. MS: *m/z*: 292 (M^+, 4%). Calculated for $C_{14}H_{16}N_2O_3S$ (292.35): C, 57.52; H, 5.52; N, 9.58. Found: C, 57.35; H, 5.58; N, 9.26. IR (KBr): ν 1738 (COO), 1684 (C═O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (3H, t, J = 7.25 Hz, $N_3CH_2\mathit{CH_3}$), 1.43 (3H, t, J = 7.00 Hz, $OCH_2\mathit{CH_3}$), 4.05 (2H, s, $S\mathit{CH_2}$COO), 4.25 (4H, m, N_3–$\mathit{CH_2}$, $O\mathit{CH_2}CH_3$), 7.39 (1H, t, J = 7.25 Hz, H-6), 7.40 (1H, d, J = 8.00 Hz, H-8), 7.68 (1H, d, J = 6.75 Hz, H-7), 8.22 (1H, d, J = 7.00 Hz, H-5). ^{13}C NMR (500 MHz,$CDCl_3$): δ = 13.29 ($N_3CH_2\mathit{CH_3}$), 14.25 ($OCH_2\mathit{CH_3}$), 34.48 ($S\mathit{CH_2}$COO), 39.95 ($N_3\mathit{CH_2}CH_3$), 61.89 ($O\mathit{CH_2}CH_3$), 119.50 (C-6), 125.86 (C-8), 125.99 (C-5), 126.93 (C-7), 134.23 (C-4a), 147.19 (C-8a), 154.80 (C-2), 161.40 (C-4), 168.60 (COO).

(3-Allyl-4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)-acetic acid ethyl ester (5h): Yield: 0.30 g (86%), mp: 52–54 °C. MS: *m/z*: 304 (M^+, 0.01%). Calculated for $C_{15}H_{16}N_2O_3S$ (304.37): C, 59.19; H, 5.30; N, 9.20. Found: C, 59.01; H, 5.49; N, 8.88. IR (KBr): ν 1743 (COO), 1685 (C═O) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.21 (3H, t, J = 7.00 Hz, $OCH_2\mathit{CH_3}$), 4.12 (6H, s, $S\mathit{CH_2}$COO), 4.15 (2H, q, J = 7.75 Hz, $O\mathit{CH_2}CH_3$), 4.70 (2H, d,J = 7.75 Hz, $N\mathit{CH_2}CH{=}CH_2$), 5.20 (2H, m, $NCH_2CH{=}\mathit{CH_2}$), 5.93 (1H, m, $NCH_2\mathit{CH}{=}CH_2$), 7.42 (1H, t, J = 7.25 Hz, H-6), 7.46 (1H, d, J = 8.00 Hz, H-8), 7.79 (1H, d, J = 7.25 Hz, H-7), 8.07 (1H, d, J = 7.50 Hz, H-5). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 14.59 ($OCH_2\mathit{CH_3}$), 34.53 ($S\mathit{CH_2}$COO), 46.34 (C-1_{allyl}), 61.55 ($O\mathit{CH_2}CH_3$), 118.40(C-3_{allyl}), 119.11 (C-6), 126.20 (C-8), 126.57 (C-5), 126.98 (C-7), 131.70 (C-2_{allyl}), 135.30 (C-4a), 147.06 (C-8a), 156.40 (C-2), 160.40 (C-4), 168.70 (COO).

(3-Phenyl-4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)-acetic acid ethyl ester (5i): Yield: 0.30 g (94%), mp: 98–100 °C. MS: *m/z*: 340 (M^+, 14%). Calculated for $C_{18}H_{16}N_2O_3S$ (390.46): C, 63.51; H, 4.74; N, 8.23. Found: C, C, 63.23; H, 4.92; N, 8.07. IR (KBr): ν 1739 (COO), 1694 (C═O) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.22 (3H, t, J = 7.00 Hz, $OCH_2\mathit{CH_3}$), 3.98 (2H, s, $S\mathit{CH_2}$COO), 4.10 (2H, q, J = 6.75 Hz, $O\mathit{CH_2}CH_3$), 7.48 (4H, m, H-2′, H-6′, H-6, H-8), 7.59 (3H, m, H-4′, H-3′, H-5′), 7.84 (1H, t, J = 7.00 Hz, H-7), 8.09 (1H, d, J = 7.50 Hz, H-5). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 14.60 ($OCH_2\mathit{CH_3}$), 34.88 ($S\mathit{CH_2}$COO), 61.50 ($O\mathit{CH_2}CH_3$), 119.96 (C-6), 126.36 (C-8), 126.61 (C-5), 127.09 (C-7), 129.84 (C-4′), 130.05 (C-2′, C-6′), 130.52 (C-3′, C-5′), 135.47 (C-1′), 136.16(C-4a), 147.49 (C-8a), 157.00 (C-2), 161.00 (C-4), 168.80 (COO).

(3-(4-Methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)-acetic acid ethyl ester (5j): Yield: 0.34 g (65.50%), mp: 138–140 °C. MS: *m/z*: 370 (M^+, 23%). Calculated for $C_{19}H_{18}N_2O_4S$ (390.46): C, 61.61; H, 4.90; N, 7.56. Found: C, C, 72.61; H, 4.98; N, 7.43. IR (KBr): ν 1735 (COO), 1687 (C═O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (3H, t, J = 6.50 Hz, $OCH_2\mathit{CH_3}$), 3.91 (2H, s, $S\mathit{CH_2}$COO), 4.24 (2H, q, J = 7.00 Hz, $O\mathit{CH_2}CH_3$), 7.07 (2H, d, J = 8.00 Hz, H-2′, H-6′), 7.29 (2H, d, J = 8.50 Hz, H-3′, H-5′), 7.43 (1H, t, J = 6.70 Hz, H-6), 7.56 (1H, d, J = 7.50 Hz, H-8), 7.73 (1H, t, J = 8.50 Hz, H-7), 8.24(1H, d, J = 6.50 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 14.28 ($OCH_2\mathit{CH_3}$), 35.00 ($S\mathit{CH_2}$COO), 61.77 ($O\mathit{CH_2}CH_3$), 115.04 (C-2′, C-6′), 119.90 (C-6), 126.01 (C-8), 126.20 (C-5), 127.30 (C-7), 128.01 (C-3′, C-5′), 130.04 (C-1′), 134.06 (C-4a), 147.56 (C-8a), 156.66 (C-2), 160.70 (C-4′), 161.90 (C-4), 168.70 (COO).

3-Substituded 2-ethoxymethylsulfanyl-2,3-dihydro-1*H*-quinazolin-4-ones (5k-o):

A mixture of **4a-e** (5 mmol), anhydrous dimethylformamide (10 mL) and potassium carbonate (0.83 g, 6 mmol) was stirred at room temperature for ½ hour.1-Chloro-2-rmethoxyethane (0.54 g, 6 mmol) was added to the mixture with stirring 90–100 °C until the starting material was consumed (2 h; TLC, ethyl acetate/hexane, 50:50) and cooled at room temperature. The mixture was poured into cold water and the separated was collected by filtration and recrystallized from cyclohexane to give the products **5k-o** in quantitative yields.

3-Methyl-2-ethoxymethylsulfanyl-2,3-dihydroquinazolin-

4(1H)-one (5k): Yield: 1.00 g (80%), mp: 40–42 °C. MS: *m/z*: 250 (M^+, 1%). Calculated for $C_{12}H_{14}N_2O_2S$ (250.32): C, 57.58; H, 5.64; N, 11.19. Found: C, C, 57.39; H, 5.58; N, 11.04. IR (KBr): ν 1675 (C=O) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.31 (3H, s, N_3CH_3), 3.43 (3H, s, OCH_3), 3.43 (2H, t, J = 5.25 Hz, SCH 2), 3.64 (2H, t, J = 6.25 Hz, OCH_2), 7.38 (1H, t, J = 7.25 Hz, H-6), 7.45 (1H, d, J = 7.00 Hz, H-8), 7.71 (1H, t, J = 6.50 Hz, H-7), 8.06 (1H, d, J = 6.00 Hz, H-5). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 30.42 (SCH 2), 31.42 (N_3CH_3), 58.38 (OCH_3), 70.26 (OCH_2), 118.98 (C-6), 126.03 (C-8), 126.04 (C-7), 126.77 (C-5), 134.79 (C-4a), 141.17 (C-8a), 157.20 (C-2), 162.10 (C-4).

3-Ethyl-2-ethoxymethylsulfanyl-2,3-dihydroquinazolin-4(*1H*)-one (5l): Yield: 1.06 g (80%), mp: 38–40 °C. MS: *m/z*: 264 (M^+, 1.6%). Calculated for $C_{13}H_{16}N_2O_2S$ (264.34): C, 59.07; H, 6.10; N, 10.60. Found: C, 58.76; H, 6.35; N, 10.48. IR (KBr): ν 1680 (C=O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (3H, t, J = 6.25 Hz, $N_3CH_2CH_3$), 3.52 (2H, q, J = 6.25 Hz, $N_3CH_2CH_3$), 3.44 (3H, s, OCH_3), 3.75 (2H, t, J = 5.50 Hz, SCH 2), 4.22 (2H, t, J = 6.50 Hz, OCH_2), 7.37(1H, t, J = 7.00 Hz, H-6), 7.39(1H, d, J = 7.50 Hz, H-8), 7.66 (1H, t, J = 6.50 Hz, H-7), 8.21(1H, d, J = 7.50 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 13.30 ($N_3CH_2CH_3$), 31.48 (SCH 2), 39.70 ($N_3CH_2CH_3$), 58.81 (OCH_3), 70.70 (OCH_2), 119.47 (C-6), 125.58 (C-8), 125.99 (C-5), 126.90 (C-7), 134.14 (C-4a), 147.40 (C-8a), 159.90 (C-2), 161.50 (C-4).

3-Allyl-2-ethoxymethylsulfanyl-2,3-dihydroquinazolin-4(*1H*)-one (5m): Yield:1.00 g (72%), mp: 40–42 °C.MS: *m/z*: 376 (M^+, 1.2%). Calculated for $C_{14}H_{16}N_2O_2S$ (326.41): C, 60.85; H, 5.84; N, 10.14. Found: C, 60.64; H, 5.99; N, 10.00. IR (KBr): ν 1683 (C=O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.44 (3H, s, OCH_3), 3.50 (2H, t, J = 6.00 Hz, SCH 2), 3.70 (2H, t, J = 5.00 Hz, OCH_2), 4.80 (2H, d, J = 5.00 Hz, $N_3CH_2CH{=}CH_2$), 5.28 (2H, m, $N_3CH_2CH{=}CH_2$), 5.96 (1H, m, $N_3CH_2CH{=}CH_2$), 7.40 (1H, t, J = 7.00 Hz, H-6), 7.55 (1H, d, J = 7.50 Hz, H-8), 7.68 (1H, t, J = 7.00 Hz, H-7), 8.23 (1H, d, J = 7.00 Hz, H-5).^{13}C NMR (500 MHz, $CDCl_3$): δ = 31.64(SCH 2), 46.25 (N_3–$CH_2CH{=}CH_2$), 58.85 (OCH_3), 70.64 (OCH_2), 118.56 (N_3–$CH_2CH{=}CH_2$), 119.32 (C-6), 125.70 (C-8), 126.03 (C-5), 127.00 (C-7), 130.82 (N_3–$CH_2CH{=}CH_2$), 134.32 (C-4a), 147.32 (C-8a), 156.10 (C-2), 161.50 (C-4).

3-Phenyl-2-ethoxymethylsulfanyl-2,3-dihydroquinazolin-4(*1H*)-one (5n): Yield:1.40.00 g (90%), mp: 96–98 °C. MS: *m/z*: 312 (M^+, 1%). Calculated for $C_{17}H_{16}N_2O_2S$ (312.39): C, 65.36; H, 5.16; N, 8.97. Found: C, 65.07; H, 5.35; N, 8.71. IR (KBr): ν 1689 (C=O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.40(3H, s, OCH_3), 3.44 (2H, t, J = 6.30 Hz, SCH 2), 3.70 (2H, q, J = 6.30 Hz, OCH_2), 7.34 (2H, d, J = 7.50 Hz, H-2′, H-6′), 7.43 (1H, t, J = 7.50 Hz, H-6), 7.56 (3H, m, H-3′, H-4′, H-5′), 7.67 (1H, d, J = 8.00 Hz, H-8), 7.75 (1H, t, J = 8.00 Hz, H-7), 8.20 (1H, d, J = 7.50 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 32.01 (SCH 2), 58.76 (OCH_3), 70.58 (OCH_2), 125.94 (C-6), 126.13 (C-8), 127.31 (C-5), 129.17 (C-7), 129.17 (C-4′), 129.75 (C-2′, C-6′), 130.01 (C-3′, C-5′), 134.71 (C-1′), 135.81 (C-4a), 147.58 (C-8a), 157.20 (C-2), 161.80 (C-4).

3-(4-Methoxyphenyl)-2-ethoxymethylsulfanyl-2,3-dihydroquinazolin-4(*1H*)-one (5o): Yield: 1.19 g (70%), mp: 112–114 °C. MS: *m/z*: 342 (M^+, 1%). Calculated for $C_{18}H_{18}N_2O_3S$ (342.41): C, 63.14; H, 5.30; N, 8.18. Found: C, 62.90; H, 5.48; N, 8.02. IR (KBr): ν 1690 (C=O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.40 (3H, s, OCH_3), 3.50 (2H, t, J = 6.00 Hz, SCH 2), 3.70 (2H, q, J = 6.00 Hz, OCH_2), 3.90 (3H, s, OCH_3), 7.05 (2H, d, J = 9.00 Hz, H-2′, H-6′), 7.24 (2H, d, J = 9.00 Hz, H-3′, H-5′), 7.41 (1H, t, J = 7.00 Hz, H-6), 7.63 (1H, d, J = 7.50 Hz, H-8), 7.74 (1H, t, J = 7.00 Hz, H-7), 8.25 (1H, d, J = 7.00 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 31.92 (SCH 2), 58.71 (OCH_3), 70.65 (OCH_2), 114.95 (C-2′, C-6′), 119.90 (C-6), 125.76 (C-8), 126.20 (C-5), 127.30 (C-7), 128.30 (C-3′, C-5′), 130.26 (C-1′), 134.54 (C-4a), 147.79 (C-8a), 160.10 (C-2), 160.70 (C-4′), 162.10 (C-4).

3-Substituded 2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylsulfanyl)-2,3-dihydroquin-azolin-4(*1H*)-ones (8a-j):

The nucleoside bases **4a-e** (5 mmol) was suspended in anhydrous acetonitrile (25 mL) at room temperature. To this suspension was added NaH (80% in mineral oil, 0.15 g, 5 mmol), and the mixture was stirred at room temperature for ½ hour. 2′,3′,4′,6′-Tetra-*O*-acetyl-α-D-glycopyranosyl bromides (**7a,b**, 2.66 g, 5.50 mmol) was added, and the mixture was stirred at room temperature for 12 h until the starting material was consumed (TLC, CH_2Cl_2/MeOH, 98:2). The solvent was removed under reduced pressure and then treated with water. The solid separated was collected by filtration and recrystallized from ethanol to give the products **8a-j** in quantitative yields.

3-Methyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylsulfanyl)-2,3-dihydroquinazol-in-4(*1H*)-one (8a): Yield: 2.00 g (77%), mp: 158–162 °C. MS: *m/z*: 522 (M^+, 1%). Calculated for $C_{23}H_{26}N_2O_{10}S$ (522.53): C, 52.87; H, 5.02; N, 5.36. Found: C, 52.59; H, 5.32; N, 5.17. IR (KBr): ν 1755 (C=O), 1698 (C=O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92 (3H, s, Ac), 1.98 (3H, s, Ac), 2.00 (3H, s, Ac), 2.06 (3H, s, Ac), 3.57 (3H, s, N_3CH_3), 3.98 (1H, m, H-6′), 4.25 (2H, m, H-5′, H-6″), 5.15 (1H, t, J = 9.50 Hz, 4′-H), 5.31 (1H, t, J = 10.00 Hz, 2′-H), 5.42 (1H, t, J = 9.00 Hz, 3′-H), 5.99 (1H, d, $^2J_{1',2'}$ = 10.50 Hz, 1′-H), 7.41 (1H, t, J = 7.00 Hz, H-6), 7.53 (1H, d, J = 7.50 Hz, H-8), 7.71 (1H, t, J = 6.75 Hz, H-7), 8.22 (1H, d, J = 7.00 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 20.57 (4Ac), 30.39 (N_3CH_3), 61.97 (C-6′), 68.40 (C-2′), 68.80 (C-3′), 74.09 (C-4′), 76.46 (C-5′), 82.29 (C-1′), 119.52 (C-6), 126.25 (C-5, C-8), 127.03 (C-7), 134.51 (C-4a), 147.10 (C-8a), 153.04 (C-2), 161.30 (C-4), 169.00, 170.00, 171.00 (4Ac).

3-Ethyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylsulfanyl)-2,3-dihydroquinazolin-4(*1H*)-one (8b): Yield: 1.90 g (71%), mp: 87–89 °C. MS: *m/z*: 536 (M^+, 0.5%). Calculated for $C_{24}H_{28}N_2O_{10}S$ (536.55): C, 53.72; H, 5.26; N, 5.22. Found: C, 53.64; H, 5.70; N, 5.03. IR (KBr): ν 1751 (C=O), 1694 (C=O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90 (3H, s, Ac), 1.98 (3H, s, Ac), 2.05 (3H, s, Ac), 2.07 (3H, s, Ac), 1.35 (3H, t, J = 7.00 Hz, $N_3CH_2CH_3$), 3.90 (1H, m, H-6′), 4.20 (2H, m, H-5′, H-6″), 4.60 (2H, q, J = 7.00 Hz, $N_3CH_2CH_3$), 5.16 (1H, t, J = 9.00 Hz, 4′-H), 5.31 (1H, t, J = 9.50 Hz, 2′-H), 5.42 (1H, t, J = 8.50 Hz, 3′-H), 5.98 (1H, d, $^2J_{1',2'}$ = 10.00 Hz, 1′-H), 7.13 (1H, t, J = 7.00 Hz, H-6), 7.31 (1H, d, J = 8.50 Hz, H-8), 7.52 (1H, t, J = 7.00 Hz, H-7), 7.70 (1H, d, J = 8.00 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 13.37 ($N_3CH_2CH_3$), 20.58 (4Ac), 39.89 ($N_3CH_2CH_3$), 62.00 (C-6′), 68.40 (C-2′), 68.91 (C-3′), 74.13 (C-4′), 76.47 (C-5′), 82.58 (C-1′), 119.79 (C-6), 124.80 (C-5), 126.22 (C-5, C-8), 127.83 (C-7), 134.32 (C-4a), 147.09 (C-8a), 150.00 (C-2), 161.30 (C-4), 169.49, 170.07, 170.56 (4Ac).

3-Allyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylsulfanyl)-2,3-dihydroquinazolin-4(*1H*)-one (8c): Yield: 1.89 g (70%), mp: 108–110 °C. MS: *m/z*: 548 (M^+, 0%). Calculated for $C_{25}H_{28}N_2O_{10}S$ (548.56): C, 54.74; H, 5.14; N, 5.11. Found: C, 54.52; H, 5.27; N, 4.88. IR (KBr): ν 1751 (C=O), 1694 (C=O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.94 (3H, s, Ac), 1.97 (3H, s, Ac), 2.04 (3H, s, Ac), 2.06 (3H, s, Ac), 3.98 (1H, m, H-6′), 4.25 (2H, m, H-5′, H-6″), 4.63 (2H, dd, J = 5.50, 11.50 Hz, H-1$_{allyl}$), 4.80 (2H, dd, J = 5.50, 11.50 Hz, H-3$_{allyl}$), 5.15 (1H, t, J = 9.50 Hz, 4′-H), 5.27 (1H, t, J = 9.50 Hz, 2′-H), 5.41 (1H, t, J = 8.50 Hz, 3′-H), 5.90 (1H, m, H-2$_{allyl}$), 5.96 (1H, d, $^2J_{1',2'}$ = 10.00 Hz, 1′-H), 7.42 (1H, t, J = 7.00 Hz, H-6), 7.54 (1H, d, J = 8.50 Hz, H-8), 7.73 (1H, t, J = 7.00 Hz, H-7), 8.20 (1H, d, J = 8.00 Hz, H-5).^{13}C NMR (500 MHz, $CDCl_3$): δ = 20.55 (4Ac), 46.31 (C-1$_{allyl}$), 61.98 (C-6′), 68.38 (C-2′), 68.87 (C-3′), 74.07 (C-4′), 76.47 (C-5′), 82.71 (C-1′), 118.93 (C-3$_{allyl}$), 119.68 (C-6), 126.27 (C-8), 126.34 (C-5), 127.17 (C-7), 130.46 (C-2$_{allyl}$), 134.48 (C-4a), 147.09 (C-8a), 153.02 (C-2), 161.28 (C-4), 169.42, 170.06, 170.52 (4Ac).

3-Phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylsulfanyl)-2,3-dihydroquinazol-in-4(*1H*)-one (8d): Yield: 2.67 g, mp: 122–124 °C (140–141 °C [38]). MS: *m/z*: 584.60 (M^+, 2%). Calculated for $C_{28}H_{28}N_2O_{10}S$ (584.66): C, 57.53; H, 4.83; N, 4.79. Found: C, 57.35; H, 5.01; N, 4.55. IR (KBr): ν 1745 (C=O), 1694 (C=O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.97 (3H, s, Ac), 1.98 (3H, s, Ac), 2.00 (3H, s, Ac), 2.06 (3H, s, Ac), 3.90–4.60 (3H, m, H-5′, H-6′, H-6′),

5.11 (2H, m, H-2′, 4′-H), 5.37 (1H, t, J = 9.00 Hz, 3′-H), 5.87 (1H, d, $^{2}J_{1',2'}$ = 10.50 Hz, 1′-H), 7.28 (1H, t, J = 7.50 Hz, H-6), 7.42 (2H, d, J = 7.50 Hz, H-2′, H-6′), 7.55 (1H, d, J = 7.50 Hz, H-8), 7.78 (4H, m, H-3′, H-4′, H-5′, H-7), 8.26 (1H, d, J = 7.50 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 20.56 (4Ac), 61.97 (C-6′), 68.28 (C-2′), 68.87 (C-3′), 74.22 (C-4′), 76.42 (C-5′), 82.43 (C-1′), 120.20 (C-6), 126.45 (C-8), 127.39 (C-5), 128.77 (C-7), 129.36 (C-4′), 129.77 (C-2′, C-6′), 129.88 (C-3′, C-5′), 130.41 (C-1′), 134.75 (C-4a), 147.43 (C-8a), 153.96 (C-2), 161.65 (C-4), 169.14, 169.37, 170.11, 170.58 (4Ac).

3-(4-Methoxyphenyl)-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylsulfanyl)-2,3-dihy-droquinazolin-4(*1H*)-one (8e): Yield: 1.66 g (54%), mp: 152–154 °C. MS: *m/z*: 614 (M^+, 1%). Calculated for $C_{29}H_{30}N_2O_{11}S$ (614.62): C, 56.67; H, 4.92; N, 4.56. Found: C, 56.52; H, 5.18; N, 4.39. IR (KBr): ν 1742 (C═O), 1699 (C═O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.98 (3H, s, Ac), 1.99 (3H, s, Ac), 2.00 (3H, s, Ac), 2.05 (3H, s, Ac), 3.88 (3H, s, OCH_3), 3.96–4.26 (3H, m, H-5′, H-6′, H-6′), 5.13 (2H, d, J = 9.00 Hz, H-2′, 4′-H), 5.36 (1H, t, J = 9.00 Hz, 3′-H), 5.85 (1H, d, $^{2}J_{1',2'}$ = 10.50 Hz, 1′-H), 7.02 (2H, d, J = 6.50 Hz, H-3′, H-5′), 7.13 (1H, t, J = 7.50 Hz, H-6), 7.27 (1H, d, J = 7.50 Hz, H-8), 7.52 (2H, d, J = 6.50 Hz, H-2′, H-6′), 7.76 (4H, t, J = 7.50 Hz, H-7), 8.26 (1H, d, J = 7.50 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 20.55 (4Ac), 61.98 (C-6′), 68.31 (C-2′), 68.89 (C-3′), 74.22 (C-4′), 76.41 (C-5′), 82.43 (C-1′), 114.91 (C-3′, C-5′), 115.24 (C-6), 126.17 (C-8), 126.36 (C-5), 127.39 (C-7), 129.89 (C-2′, C-6′), 130.47 (C-1′), 134.67 (C-4a), 147.43 (C-8a), 154.62 (C-2), 160.70 (C-4′), 161.90 (C-4), 169.17, 169.37, 170.11, 170.56 (4Ac).

3-Methyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosylsulfanyl)-2,3-dihydroquinaz-olin-4(*1H*)-ones (8f). Yield: 2.08 g (79%), mp: 159–161 °C. MS: *m/z*: 522 (M^+, 0.4%). Calculated for $C_{23}H_{26}N_2O_{10}S$ (522.53): C, 52.87; H, 5.02; N, 5.36. Found: C, 52.50; H, 5.16; N, 5.13. IR (KBr): ν 1746 (C═O), 1672 (C═O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.91 (3H, s, Ac), 1.94 (3H, s, Ac), 1.98 (3H, s, Ac), 2.02 (3H, s, Ac), 3.60 (3H, s, N_3CH_3), 4.10 (1H, m, H-6′), 4.23 (2H, m, H-5′, H-6″), 5.28 (1H, dd, J = 3.25, 9.50 Hz, 4′-H), 5.50 (1H, t, J = 10.00 Hz, 2′-H), 5.52 (1H, t, J = 9.00 Hz, 3′-H), 6.00 (1H, d, $^{2}J_{1',2'}$ = 11.00 Hz, 1′-H), 7.40 (1H, t, J = 7.00 Hz, H-6), 7.58 (1H, d, J = 8.00 Hz, H-8), 7.74(1H, t, J = 7.00 Hz, H-7), 8.25 (1H, d, J = 8.00 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 20.60, 20.68, 20.70 (4Ac), 30.42 (N_3CH_3), 61.55 (C-6′), 66.18 (C-2′), 67.41 (C-3′), 72.07 (C-4′), 75.18 (C-5′), 82.75 (C-1′), 119.47 (C-6), 126.29 (C-5, C-8), 127.09 (C-7), 134.43 (C-4a), 147.07 (C-8a), 153.31 (C-2), 161.78 (C-4), 169.79, 169.96, 170.23, 170.42 (4Ac).

3-Ethyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosylsulfanyl)-2,3-dihydroquinazol-in-4(*1H*)-one (8g). Yield: 2.35 g (87%), mp: 164–166 °C. MS: *m/z*: 536 (M^+, 2%). Calculated for $C_{24}H_{28}N_2O_{10}S$ (536.55): C, 53.72; H, 5.26; N, 5.22. Found: C, 53.58; H, 5.73; N, 5.00. IR (KBr): ν 1748 (C═O), 1666 (C═O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92 (3H, s, Ac), 2.00 (3H, s, Ac), 2.15 (3H, s, Ac), 2.21 (3H, s, Ac), 1.37 (3H, t, J = 7.00 Hz, $N_3CH_2CH_3$), 4.10 (1H, m, H-6′), 4.22 (4H, m, $N_3CH_2CH_3$, H-5′, H-6″), 5.27 (1H, dd, J = 3.25, 9.50 Hz, 4′-H), 5.50 (1H, t, J = 10.50 Hz, 2′-H), 5.54 (1H, t, J = 9.00 Hz, 3′-H), 5.90 (1H, d, $^{2}J_{1',2'}$ = 11.00 Hz, 1′-H), 7.44 (1H, t, J = 7.00 Hz, H-6), 7.56 (1H, d, J = 8.00 Hz, H-8), 7.70 (1H, t, J = 7.00 Hz, H-7), 8.24 (1H, d, J = 8.00 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 13.42 ($N_3CH_2CH_3$), 20.61, 20.63, 20.70, 20.75 (4Ac), 39.89 ($N_3CH_2CH_3$), 61.49 (C-6′), 66.24 (C-2′), 67.39 (C-3′), 72.07 (C-4′), 75.14 (C-5′), 83.02 (C-1′), 119.76 (C-6), 126.28 (C-5, C-8), 127.01 (C-7), 134.40 (C-4a), 147.10 (C-8a), 152.73 (C-2), 161.40 (C-4), 169.80, 169.99, 170.25, 170.44 (4Ac).

3-Allyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosylsulfanyl)-2,3-dihydroquinazol-in-4(*1H*)-one (8h): Yield: 2.40 g (87%), mp: 146–148 °C. MS: *m/z*: 548 (M^+, 30%). Calculated for $C_{25}H_{28}N_2O_{10}S$ (548.56): C, 54.74; H, 5.14; N, 5.11. Found: C, 54.46; H, 5.18; N, 4.72. IR (KBr): ν 1745 (C═O), 1672 (C═O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.93 (3H, s, Ac), 1.98 (3H, s, Ac), 2.10 (3H, s, Ac), 2.20 (3H, s, Ac), 4.12 (1H, m, H-6′), 4.22 (2H, m, H-5′, H-6″), 4.67 (1H, dd, J = 5.50, 9.00 Hz, 4′-H), 4.85 (1H, dd, J = 3.00, 9.50 Hz, 2′-H), 5.28 (3H, m, 3′-H, H-2_{allyl}), 5.50 (2H, dt, J = 2.50, 10.50 Hz, H-1_{allyl}), 5.90 (1H, d, $^{2}J_{1',2'}$ = 11.00 Hz, 1′-H), 5.95 (2H, m, H-3_{allyl}), 7.45 (1H, t, J = 7.00 Hz, H-6), 7.59 (1H, d, J = 8.00 Hz, H-8), 7.70(1H, t, J = 7.00 Hz, H-7), 8.25 (1H, d, J = 8.00 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 20.61, 20.68 (4Ac), 46.31 (C-1_{allyl}), 61.47 (C-6′), 66.24 (C-2′), 67.38 (C-3′), 72.05 (C-4′), 75.15 (C-5′), 83.17 (C-1′), 118.96 (C-3_{allyl}), 119.60 (C-6), 126.34 (C-8), 127.16 (C-5, C-7), 130.47 (C-2_{allyl}), 134.55 (C-4a), 147.09 (C-8a), 153.07 (C-2), 161.38 (C-4), 169.72, 169.98, 170.23, 170.41 (4Ac).

3-Phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosylsulfanyl)-2,3-dihydroquinazo-lin-4(*1H*)-one (8i): Yield: 2.30 g, mp: 131–133 °C (145–147 °C [38]). MS: *m/z*: 584.60 (M^+, 2%). Calculated for $C_{28}H_{28}N_2O_{10}S$ (584.66): C, 57.53; H, 4.83; N, 4.79. Found: C, 57.40; H, 5.12; N, 4.68. IR (KBr): ν 1749 (C═O), 1694 (C═O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.98 (3H, s, Ac), 1.99 (3H, s, Ac), 2.01 (3H, s, Ac), 2.02 (3H, s, Ac), 4.16 (3H, m, H-5′, H-6′, H-6′), 5.20 (1H, dd, J = 3.25, 9.50 Hz, H-4′), 5.32 (1H, t, J = 10.50 Hz, 2′-H), 5.50 (1H, d, J = 10.50 Hz, 3′-H),5.90 (1H, d, $^{2}J_{1',2'}$ = 10.50 Hz, 1′-H), 7.28 (1H, t, J = 7.50 Hz, H-6), 7.42 (2H, d, J = 7.50 Hz, H-2′, H-6′), 7.56 (1H, d, J = 8.00 Hz, H-8), 7.60 (4H, m, H-3′, H-4′, H-5′), 7.80 (1H, t, J = 7.50 Hz, H-7), 8.40 (1H, d, J = 7.50 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 20.63 (4Ac), 61.43 (C-6′), 66.22 (C-2′), 67.36 (C-3′), 72.19 (C-4′), 75.05 (C-5′), 82.87 (C-1′), 124.90 (C-6), 126.48 (C-8), 127.38 (C-5), 128.77 (C-7), 129.36 (C-4′), 129.81 (C-2′, C-6′), 129.89 (C-3′, C-5′), 130.42 (C-1′), 134.81 (C-4a), 147.59 (C-8a), 152.00 (C-2), 162.00 (C-4), 169.10, 169.72, 170.42 (4Ac).

3-(4-Methoxyphenyl)-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosylsulfanyl)-2,3-dih-ydroquinazolin-4(*1H*)-one (8j): Yield: 1.30 g (42%), mp: 124–126 °C. MS: *m/z*: 614 (M^+, 0.5%). Calculated for $C_{29}H_{30}N_2O_{11}S$ (614.62): C, 56.67; H, 4.92; N, 4.56. Found: C, 56.48; H, 5.20; N, 4.36. IR (KBr): ν 1742 (C═O), 1699 (C═O) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92 (3H, s, Ac), 1.98 (3H, s, Ac), 2.00 (3H, s, Ac), 2.10 (3H, s, Ac), 3.80 (3H, s, OCH_3), 4.10 (3H, m, H-5′, H-6′, H-6′), 5.12 (1H, dd, J = 3.25, 9.50 Hz, 4′-H), 5.25 (1H, t, J = 10.50 Hz, 2′-H), 5.41 (1H, dd, J = 3.25, 9.50 Hz, 3′-H), 5.80 (1H, d, $^{2}J_{1',2'}$ = 10.50 Hz, 1′-H), 6.94 (2H, d, J = 8.00 Hz, H-3′, H-5′), 7.05 (1H, t, J = 9.00 Hz, H-6), 7.40 (1H, d, J = 8.00 Hz, H-8), 7.50 (2H, d, J = 9.00 Hz, H-2′, H-6′), 7.80 (4H, t, J = 7.50 Hz, H-7), 8.20 (1H, d, J = 8.00 Hz, H-5). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 20.66 (4Ac), 61.45 (C-6′), 66.24 (C-2′), 67.39 (C-3′), 72.23 (C-4′), 75.03 (C-5′), 82.87 (C-1′), 114.93 (C-3′, C-5′), 115.25 (C-6), 126.39 (C-8), 127.39 (C-5), 127.51 (C-7), 128.86 (C-2′, C-6′), 130.92 (C-1′), 134.74 (C-4a), 147.80 (C-8a), 154.62 (C-2), 157.20 (C-4′), 161.90 (C-4), 167.00, 169.00, 170.20 (4Ac).

3-Substituded 2-(β-D-glucopyranosylsulfanyl)-2,3-dihydroquinazolin-4(*1H*)-ones (9a-h):

The protected nucleosides **8a-e, g-i** (1 mmol) was stirred in saturated NH_3/MeOH (5%, 50 mL) at room temperature for 12 h until the starting material was consumed (TLC, ether petroleum ether, 90:10). The solvent was removed in *vacuo*, and the residue was chromatographed on silica gel with a gradient at 1–5% MeOH in CH_2Cl_2 to afford the deprotected nucleosides **9a-h** as a white solid.

3-Methyl-2-(β-D-glucopyranosylsulfanyl)-2,3-dihydroquinazolin-4(*1H*)-one (9a): Yield: 0.27 g (76%), mp: 186–188 °C. MS: *m/z*: 354 (M^+, 6%). Calculated for $C_{15}H_{18}N_2O_6S$ (354.09): C, 50.84; H, 5.12; N, 7.90. Found: C, 50.48; H, 5.40; N, 7.56. IR (KBr): ν 3412 (OH), 1658 (C═O) cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.26–3.52(9H, m, H-2′, H-3′, H-4′, H-5′, H-6′, H-6″, N_3CH_3),4.42 (1H, t, J = 5.00 Hz, 6′-OH), 5.12 (1H, d, J = 5.00 Hz, 4′-OH), 5.20 (1H, d, J = 3.60 Hz, 3′-OH), 5.50 (1H, d, $^{2}J_{1',2'}$ = 12.00 Hz, 1′-H), 5.53 (1H, d, J = 3.60 Hz, 2′-OH), 7.45 (1H, t, J = 7.00 Hz, H-6), 7.60 (1H, d, J = 8.00 Hz, H-8), 7.77 (1H, t, J = 7.00 Hz, H-7), 8.15 (1H, d, J = 7.00 Hz, H-5). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 30.69 (N_3CH_3)), 61.17 (C-6′), 70.13 (C-4′), 72.09 (C-2′), 79.06 (C-5′), 82.16 (C-3′), 85.50 (C-1′), 119.20 (C-6), 126.36 (C-8), 126.62 (C-5), 126.82 (C-7), 135.03 (C-4a), 147.29 (C-8a), 153.31 (C-2), 161.78 (C-4), 169.79, 169.96,

170.23, 170.42 (4Ac).

3-Ethyl-2-(β-D-glucopyranosylsulfanyl)-2,3-dihydroquinazolin-4(*1H*)-one (9b): Yield: 0.29 g (79%), mp: 204–206 °C. MS: *m/z*: 368 (M^+, 0.5%). Calculated for $C_{16}H_{20}N_2O_6S$ (368.41): C, 52.16; H, 5.47; N, 7.60. Found: C, 51.93; H, 5.75; N, 7.48. IR (KBr): ν 3400 (OH), 1662 (C═O) cm^{-1}.^{1}H NMR (500 MHz, CD_3OD-d_4): δ = 1.38 (3H, t, J = 7.00 Hz, $N_3CH_2CH_3$), 3.33 (2H, m, H-3′, H-4′), 3.40 (1H, m, H-5′), 3.50 (1H, t, J = 9.00 Hz, H-6′), 3.71 (1H, dd, J = 5.00, 9.00 Hz, H-6′), 3.86 (1H, d, J = 12.00 Hz, H-2′), 4.23 (1H, q, J = 7.00 Hz, $N_3CH_2CH_3$), 5.77 (1H, d, J = 10.00 Hz, H-1′), 7.45 (1H, t, J = 7.00 Hz, H-6), 7.60 (1H, d, J = 8.00 Hz, H-8), 7.70 (1H, t, J = 7.00 Hz, H-7), 8.15 (1H, d, J = 7.00 Hz, H-5).^{13}C NMR (500 MHz, CD_3OD-d_4): δ = 13.61 ($N_3CH_2CH_3$), 40.02 ($N_3CH_2CH_3$), 62.63 (C-6′), 71.25 (C-4′), 73.20 (C-2′), 80.11 (C-5′), 82.72 (C-3′), 86.61 (C-1′), 116.13 (C-6), 120.55 (C-8), 127.21 (C-5), 127.49 (C-7), 135.79 (C-4a), 148.83 (C-8a), 155.81 (C-2), 163.23 (C-4).

3-Allyl-2-(β-D-glucopyranosylsulfanyl)-2,3-dihydroquinazolin-4(*1H*)-one (9c): Yield: 0.26 g (65%), mp: 92–94 °C. MS: *m/z*: 380 (M^+, 0.5%). Calculated for $C_{17}H_{20}N_2O_6S$ (354.09): C, 53.67; H, 5.30; N, 7.36. Found: C, 53.50; H, 5.45; N, 7.17. IR (KBr): ν 3412 (OH), 1686 (C═O) cm^{-1}.^{1}H NMR (500 MHz, CD_3OD-d_4): δ = 3.33 (2H, m, H-3′, H-4′), 3.42 (1H, m, H-5′), 3.50 (1H, t, J = 9.00 Hz, H-6′), 3.68 (1H, dd, J = 5.00, 12.00 Hz, H-6″), 3.84 (1H, dd, J = 1.50, 12.00 Hz, H-2′), 4.83 (2H, m, H-1_{allyl}), 5.26 (2H, m, H-2_{allyl}), 5.76 (1H, d, J = 9.50 Hz, H-1′), 5.90 (2H, m, H-3_{allyl}), 7.47 (1H, t, J = 7.00 Hz, H-6), 7.62 (1H, d, J = 8.00 Hz, H-8), 7.79 (1H, t, J = 6.50 Hz, H-7), 8.17 (1H, d, J = 7.00 Hz, H-5).^{13}C NMR (500 MHz, CD_3OD-d_4): δ = 47.50 (C-1_{allyl}), 62.62 (C-6′), 71.23 (C-4′), 73.21 (C-2′), 80.10 (C-5′), 82.72 (C-3′), 86.77 (C-1′), 118.75 (C-3_{allyl}), 120.48 (C-6), 127.32 (C-8), 127.62 (C-5), 127.68 (C-7), 132.29 (C-2_{allyl}), 135.93 (C-4a), 148.84 (C-8a), 156.22 (C-2), 163.21 (C-4).

3-Phenyl-2-(β-D-glucopyranosylsulfanyl)-2,3-dihydroquinazolin-4(*1H*)-one (9d): Yield: 0.35 g (84%), mp: 106–108 °C. MS: *m/z*:416 (M^+, 2%). Calculated for $C_{20}H_{20}N_2O_6S$ (416.45): C, 57.68; H, 4.84; N, 6.73. Found: C, 57.43; H, 5.02; N, 6.56. IR (KBr): ν 3421 (OH), 1686 (C═O) cm^{-1}.^{1}H NMR (500 MHz, CD_3OD): δ = 3.18 (2H, m, H-3′, H-4′), 3.20 (1H, d, J = 9.50 Hz, H-5′), 3.36 (1H, dd,J = 8.75 Hz, H-6′), 3.66 (1H, dd, J = 5.50, 12.00 Hz, H-6″), 3.84 (1H, dd, J = 2.00, 14.50 Hz, H-2′), 5.50 (1H, d, $^2J_{1',2'}$ = 10.50 Hz, 1′-H), 7.28(2H, d, J = 3.00 Hz, H-2_{Ph}, H-6_{Ph}), 7.37 (1H, t, J = 7.50 Hz, H-6), 7.47 (3H, m, H-3_{Ph}, H-4_{Ph}, H-5_{Ph}), 7.57 (1H, d, J = 8.00 Hz, H-8), 7.71 (1H, d, J = 7.00 Hz, H-7), 8.06 (1H, d, J = 7.00 Hz, H-5). ^{13}C NMR (500 MHz, CD_3OD): δ = 62.64 (C-6′), 71.23 (C-4′), 72.99 (C-2′), 80.07 (C-5′), 82.57 (C-3′), 86.18 (C-1′), 121.00 (C-6), 127.37 (C-8), 127.77 (C-5), 127.83 (C-4_{ph}), 130.58 (C-2_{Ph}, C-6_{ph}), 130.61 (C-3_{Ph}, C-5_{ph}), 130.78 (C-1_{Ph}), 136.41 (C-4a), 137.21, 149.28 (C-8a), 156.86 (C-2), 163.70 (C-4).

3-(4-Methoxyphenyl)-2-(β-D-glucopyranosylsulfanyl)-2,3-dihydroquinazolin-4(*1H*)-one (9e): Yield: 0.286 g (62%), mp: 120–122 °C. MS: *m/z:* 446 (M^+, 0.5%). Calculated for $C_{21}H_{22}N_2O_7S$ (446.47): C, 57.68; H, 4.84; N, 6.73. Found: C, 57.40; H, 5.08; N, 6.72. IR (KBr): ν 3450 (OH), 1682 (C═O) cm^{-1}.^{1}H NMR (500 MHz, CD_3OD): δ = 3.32 (2H, m, H-3′, H-4′), 3.47 (1H, d, J = 9.50 Hz, H-5′), 3.66 (1H, dd, J = 5.50, 12.00 Hz, H-6′), 3.66 (1H, dd, J = 5.50, 12.00 Hz, H-6″), 3.84 (1H, dd, J = 2.00, 14.50 Hz, H-2′), 3.90 (3H, s, OCH_3), 5.60 (1H, d, $^2J_{1',2'}$ = 10.50 Hz, 1′-H), 7.13 (2H, d, J = 6.50 Hz, H-3_{Ph}, H-5_{Ph}), 7.29 (1H, d, J = 8.00 Hz, H-3_{Ph}, H-5_{Ph}), 7.48 (3H, t, J = 7.50 Hz, H-6), 7.68 (1H, d, J = 8.00 Hz, H-8), 7.82 (1H, d, J = 7.00 Hz, H-7), 8.17 (1H, d, J = 7.00 Hz, H-5). ^{13}C NMR (500 MHz, CD_3OD): δ = 56.15 (OCH_3), 62.64 (C-6′), 71.24 (C-4′), 73.00 (C-2′), 80.08 (C-5′), 82.57 (C-3′), 86.16 (C-1′), 115.89 (C-3_{Ph}, C-5_{ph}), 115.96 (C-6), 120.98 (C-8), 127.78 (C-5), 129.47(C-2_{Ph}, C-6_{ph}), 131.69 (C-1_{Ph}), 136.16 (C-4a), 149.31 (C-8a), 157.62 (C-4_{Ph}), 162.44 (C-2), 163.98 (C-4).

3-Ethyl-2-(β-D-galactopyranosylsulfanyl)-2,3-dihydroquinazolin-4(*1H*)-one (9f): Yield: 0.22 g (57%), mp: 206–208 °C. MS: *m/z*: 368 (M^+, 0.4%). Calculated for $C_{16}H_{20}N_2O_6S$ (368.41): C, 52.16; H, 5.47; N, 7.60. Found: C, 51.87; H, 5.68; N, 7.44. IR (KBr): ν 3404 (OH), 1664 (C═O) cm^{-1}.^{1}H NMR (500 MHz, CD_3OD-d_4): δ = 1.39 (3H, t, J = 7.00 Hz, $N_3CH_2CH_3$), 3.33 (2H, m, H-3′, H-4′), 3.66 (1H, m, H-5′), 3.73 (1H, t, J = 9.00 Hz, H-6′), 3.84 (1H, dd, J = 5.00, 9.00 Hz, H-6′), 4.00 (1H, dd, J = 2.50, 12.00 Hz, H-2′), 4.22 (1H, q, J = 7.00 Hz, $N_3CH_2CH_3$), 5.75 (1H, d, J = 10.50 Hz, H-1′), 7.45 (1H, t, J = 7.00 Hz, H-6), 7.60 (1H, d, J = 8.00 Hz, H-8), 7.70 (1H, t, J = 7.00 Hz, H-7), 8.15 (1H, d, J = 7.00 Hz, H-5). ^{13}C NMR (500 MHz, CD_3OD-d_4): δ = 13.59 ($N_3CH_2CH_3$), 40.99 ($N_3CH_2CH_3$)), 62.03(C-6′), 70.50(C-4′), 76.68(C-2′), 76.68(C-5′), 81.35(C-3′), 87.10(C-1′), 120.55 (C-6), 127.56 (C-5, C-8), 128.70 (C-7), 135.00 (C-4a), 148.80 (C-8a), 156.00(C-2), 163.20(C-4).

3-Allyl-2-(β-D-galactopyranosylsulfanyl)-2,3-dihydroquinazolin-4(*1H*)-one (9g): Yield: 0.23 g (57%), mp: 184–185 °C. MS: *m/z*: 380 (M^+, 0.5%). Calculated for $C_{17}H_{20}N_2O_6S$ (354.09): C, 53.67; H, 5.30; N, 7.36. Found: C, 53.52; H, 5.42; N, 7.21. IR (KBr): ν 3419 (OH), 1684 (C═O) cm^{-1}.^{1}H NMR (500 MHz, CD_3OD-d_4): δ = 3.33 (2H, m, H-3′, H-4′), 3.65 (1H, m, H-5′), 3.74 (1H, dd, J = 3.50, 9.00 Hz, H-6′), 3.80 (1H, t, J = 9.00 Hz, H-6″), 3.99 (1H, dd, J = 5.00, 12.00 Hz, H-2′), 4.83 (2H, t, J = 1.75 Hz, H-1_{allyl}),5.26 (2H, m, H-2_{allyl}), 5.74 (1H, d, J = 10.50 Hz, H-1′), 5.92 (2H, m, H-3_{allyl}),7.47 (1H, t, J = 7.00 Hz, H-6), 7.62 (1H, d, J = 8.00 Hz, H-8), 7.79 (1H, t, J = 6.50 Hz, H-7), 8.17 (1H, d, J = 7.00 Hz, H-5).^{13}C NMR (500 MHz, CD_3OD-d_4): δ = 47.49 (C-1_{allyl}), 62.34 (C-6′), 70.52 (C-4′), 71.63 (C-2′), 76.67(C-5′), 81.34(C-3′), 87.29(C-1′), 118.75 (C-3_{allyl}), 120.48 (C-6), 127.32 (C-8), 127.62 (C-5), 127.68 (C-7), 132.29 (C-2_{allyl}), 135.93 (C-4a), 148.82 (C-8a), 156.39 (C-2), 163.20 (C-4).

3-Phenyl-2-(β-D-galactopyranosylsulfanyl)-2,3-dihydroquinazolin-4(*1H*)-one (9h): Yield: 0.32 g (72%), mp: 154–156 °C. MS: *m/z:* 416 (M^+, 0.5%). Calculated for $C_{20}H_{20}N_2O_6S$ (416.45): C, 57.68; H, 4.84; N, 6.73. Found: C, 57.48; H, 5.20; N, 6.49. IR (KBr): ν 3419 (OH), 1688 (C═O) cm^{-1}.^{1}H NMR (500 MHz, CD_3OD): δ = 3.33 (2H, m, H-3′, H-4′), 3.59–3.74 (3H, m, H-5′, H-6′, H-6″), 3.96 (1H, dd, J = 2.5, 12.00 Hz, H-2′), 5.63 (1H, d, $^2J_{1',2'}$ = 10.00 Hz, 1′-H), 7.40 (2H, d, J = 3.00 Hz, H-2_{Ph}, H-6_{Ph}), 7.49 (1H, t, J = 7.50 Hz, H-6), 7.59 (3H, m, H-3_{Ph}, H-4_{Ph}, H-5_{Ph}), 7.69 (1H, d, J = 8.00 Hz, H-8), 7.75 (1H, d, J = 7.00 Hz, H-7), 8.16 (1H, d, J = 7.00 Hz, H-5). ^{13}C NMR (500 MHz, CD_3OD): δ = 62.09 (C-6′), 70.47 (C-4′), 72.49 (C-2′), 81.20 (C-5′), 82.58 (C-3′), 86.67 (C-1′), 121.02 (C-6), 127.38 (C-8), 127.79 (C-5), 127.86(C-4_{ph}), 130.60 (C-2_{Ph}, C-6_{ph}), 130.65 (C-3_{Ph}, C-5_{ph}), 130.78 (C-1_{Ph}), 136.42 (C-4a), 137.27, 149.29 (C-8a), 157.05 (C-2), 163.71 (C-4).

3.3. Molecular docking studies

All the molecular modeling studies were carried out on Intel® Core™ i3 CPU, 2.40 GHZ processor, and 3 GB memory with Windows 7 operating system using Molecular Operating Environment (MOE 2008-10 Chemical Computing Group, Canada) as the computational software. For the docking studies, the crystal structure of Epidermal Growth Factor Receptor tyrosine kinase (EGFR) with its co-crystallized ligand (4-anilinoquinazolineerlo-tinib) was obtained from the freely accessible Protein data bank (PDB code: 1M17) [48], verification process was performed by re-docking of the co-crystallized ligand into the active site using the default settings. S-glycosylated nucleosides derivatives were constructed 2D using ChemBio-office 2015, converted to 3D by builder interface of MOE program, and then were subjected to energy minimization with MMFF94X force and the partial charges were automatically calculated. Different conformers for each compound are imported by systematic conformational of the MOE and saved in an mdbdatabase file to be docked into the active site of the receptor. Each complex was analyzed for interaction, 2D images were taken by using the MOE visualizing tool.

3.4. In vitro cytotoxic activity

Cytotoxic efficacy of some derivatives against two cancer cell lines including liver cancer (HepG-2), breast Michigan cancer foundation-7 (MCF-7), and normal human cell line (GMSC) using the MTT assay [49]. Each cell line was propagated in a complete medium composed of DMEM (High Glucose w/stable Glutamine w/Sodium Pyruvate, Biowest) or RPMI-1640 (Lonza Verviers SPRL, Belgium) supplemented with 10% fetal bovine serum (Seralab, UK) and 1% Antibiotic (Antibiotic antimycotic, Biowest). The cells were incubated in 5% CO_2 humidified at 37 °C for growth according to the standard cell culture work [50]. Cells were treated for 48 h with serial concentrations of compounds (0.01, 0.1, 1, 10, 100 μM), and hence the percentages of cell survival were determined using Graph Pad Prism 7.0. Values of IC_{50} were calculated using ORIGIN® 2018.

3.5. Apoptotic assay

HepG2 cells were treated with DMSO (control) and compound **9a** (50 μM-treated) for 48 h. At the end of treatments, cells were collected, and total RNA was extracted using Rneasy® Mini Kit (Qiagen, Hilden, Germany) according to manufacturer's instructions. cDNA synthesis was performed with 500 ng of RNA using i-Script cDNA synthesis kit (BioRad, Hercules, USA) following manufacturer's instructions. Real-time RT-PCR reactions consisted of 25 μL Fluocycle®II SYBR® (Euroclone, Milan, Italy), 1.5 μL of both 10 μM forward and reverse primers, 3 μL cDNA, and 19 μL of H_2O. All reactions were performed for 35 cycles using this temperature profiles: 95 °C for 5 m (initial denaturation); 95 °C for 15 min (Denaturation), 55 °C for 30 min (Annealing), and 72 °C for 30 min (Extension) [51]. Primer used were β-Actin FOR: 5′-GCACTCTTCCAGCCTTCCTTCC-3′, REV: 5′-GAGCCGCC GATCCACACG-3′, P53 FOR: 5′-CTTTGAGGTGCGTGTTTGTG-3′, REV: 5′-GTGGTTTCTTCTTTGGCTGG-3′, MDM2 FOR: 5′-TCTAGGAGATTTG TTTGGCGT-3′, REV: 5′-TCACAGATGTACCTGAGTCC-3′, PUMA FOR:5′ GAGGAGGAACAGTGGGC-3′, REV: 5′-CTAATTGGGCTCCATCTCGG-3′, BAX FOR: 5′-TTTGCTTCAGGGTTTCATCC-3′, REV: 5′-CAGTTGAAGTT GCCGTCAGA-3′

4. Conclusions

In the present study, we have carried out the successful synthesis of hitherto unreported 3-substituted-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones **4a-e**, 3-substituded-2-alkylsulfanyl-2,3-dihydro-1*H*-benzo [g] quinazolin-4-ones **5a-o**, 3-substituted-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylsulfanyl)-2,3-dihydro-1*H*-quinazolin-4-ones **8a-j** and 3-substituted-2-(β-D-glucopyranosylsulfanyl)-2,3-dihydro-1*H*-quinazolin-4-ones **9a-h**. The conformational analyses of their most stable configurations were establishedby NMR spectroscopy. Molecular docking calculations selected some of analyzed derivatives as promising compounds (**8c, 8g, 9c** and **9a**) based on their good binding affinities towards the EGFR tyrosine kinase molecular target. The *in vitro* cytotoxic activity against MCF-7 and HepG2 cell lines showed effective antiproliferative activity of the analyzed derivatives with lower IC_{50} values especially **9a** with IC_{50} = 2.09 and 2.08 μM against MCF-7 and HepG2, respectively, and their treatments were safe against the normal cell line (GMSC). Moreover, RT-PCR reaction investigated the apoptotic pathway for the compound **9a**, which activated the P53 genes and its related genes. Finally, we recommend further *in vivo* liver cancer model, preclinical and clinical investigations for this compound so that it can be developed as a chemotherapeutic anti-cancer drug.

Declaration of competing interest

There is no conflict of interest between the Authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2019.107832.

References

[1] S. Xue, J. McKenna, W.-C. Shieh, O. Repič, A facile synthesis of C2,N3-Disubstituted-4-quinazolone, J. Org. Chem. 69 (2004) 6474–6477, https://doi.org/10.1021/jo049118e.
[2] E. Honkanen, A. Pippuri, P. Kairisalo, P. Nore, H. Karppanen, I. Paakkari, Synthesis and antihypertensive activity of some new quinazoline derivatives, J. Med. Chem. 26 (1983) 1433–1438, https://doi.org/10.1021/jm00364a014.
[3] Y. Zhou, D.E. Murphy, Z. Sun, V.E. Gregor, Novel parallel synthesis of N-(4-oxo-2-substituted-4H-quinazolin-3-yl)-substituted sulfonamides, Tetrahedron Lett. 45 (2004) 8049–8051, https://doi.org/10.1016/j.tetlet.2004.08.183.
[4] P. Panneerselvam, R.V. Pradeepch, ran, S.K. Sridhar, Synthesis, characterization and biological activities of novel 2-Methyl-Quinazolin-4(3H)-Ones, Indian J. Pharm. Sci. 65 (2003) 268–273.
[5] F.M. Refaie, A.Y. Esmat, S.M.A. Gawad, A.M. Ibrahim, M.A. Mohamed, The anti-hyperlipidemic activities of 4(3H) quinazolinone and two halogenated derivatives in rats, Lipids Health Dis. 4 (2005) 22, https://doi.org/10.1186/1476-511X-4-22.
[6] N.S. Habib, K.A. Ismail, A.A. el-Tombary, T.A. Abdel, Antilipidemic agents, Part. IV: synthesis and antilipidemic testing of some heterocyclic derivatives of hexadecyl and cyclohexyl hemisuccinate esters, Die Pharmazie 55 (2000) 495–499.
[7] E.M. Jessy, A.T. Sambanthan, J. Alex, C.H. Sridevi, K.K. Srinivasan, Synthesis and biological evaluation of some novel quinazolones, Indian J. Pharm. Sci. 69 (2007) 476, https://doi.org/10.4103/0250-474X.34571.
[8] V. Alagarsamy, V.R. Solomon, K. Dhanabal, Synthesis and pharmacological evaluation of some 3-phenyl-2-substituted-3H-quinazolin-4-one as analgesic, anti-inflammatory agents, Bioorg. Med. Chem. 15 (2007) 235–241, https://doi.org/10.1016/j.bmc.2006.09.065.
[9] H. Georgey, N. Abdel-Gawad, S. Abbas, Synthesis and anticonvulsant activity of some quinazolin-4-(3H)-one derivatives, Molecules 13 (2008) 2557–2569, https://doi.org/10.3390/molecules13102557.
[10] L.-P. Guan, Q.-H. Jin, G.-R. Tian, K.-Y. Chai, Z.-S. Quan, Synthesis of some quinoline-2(1H)-one and 1, 2, 4 - triazolo [4 , 3 -a] quinoline derivatives as potent anticonvulsants, J. Pharm. Pharm. Sci. 10 (2007) 254–262.
[11] F. Hassanzadeh, M.R. Khajouei, G.H. Hakimelahi, E. Jafari, G.A. Khodarahmi, Synthesis of some new 2,3-disubstituted-4(3H)quinazolinone derivatives, Res Pharm Sci 7 (2012) 23–30.
[12] B. Malawska, New anticonvulsant agents, Curr. Top. Med. Chem. (2005) 5, https://doi.org/10.2174/1568026053386944.
[13] Archana, V.K. Srivastava, A. Kumar, Synthesis of some newer derivatives of substituted quinazolinonyl-2-oxo/thiobarbituric acid as potent anticonvulsant agents, Bioorg. Med. Chem. 12 (2004) 1257–1264, https://doi.org/10.1016/j.bmc.2003.08.035.
[14] J. Li, Y. Meng, Y. Liu, Z.-Q. Feng, X.-G. Chen, F84, a quinazoline derivative, exhibits high potent antitumor activity against human gynecologic malignancies, Investig. New Drugs 28 (2010) 132–138, https://doi.org/10.1007/s10637-009-9225-9.
[15] P.M. Chandrika, T. Yakaiah, A.R.R. Rao, B. Narsaiah, N.C. Reddy, V. Sridhar, J.V. Rao, Synthesis of novel 4,6-disubstituted quinazoline derivatives, their anti-inflammatory and anti-cancer activity (cytotoxic) against U937 leukemia cell lines, Eur. J. Med. Chem. 43 (2008) 846–852, https://doi.org/10.1016/j.ejmech.2007.06.010.
[16] K.M. Foote, A.A. Mortlock, N.M. Heron, F.H. Jung, G.B. Hill, G. Pasquet, M.C. Brady, S. Green, S.P. Heaton, S. Kearney, N.J. Keen, R. Odedra, S.R. Wedge, R.W. Wilkinson, Synthesis and SAR of 1-acetanilide-4-aminopyrazole-substituted quinazolines: selective inhibitors of Aurora B kinase with potent anti-tumor activity, Bioorg. Med. Chem. Lett 18 (2008) 1904–1909, https://doi.org/10.1016/j.bmcl.2008.02.002.
[17] S.-L. Cao, Y.-P. Feng, Y.-Y. Jiang, S.-Y. Liu, G.-Y. Ding, R.-T. Li, Synthesis and in vitro antitumor activity of 4(3H)-quinazolinone derivatives with dithiocarbamate side chains, Bioorg. Med. Chem. Lett 15 (2005) 1915–1917, https://doi.org/10.1016/j.bmcl.2005.01.083.
[18] S.M. El-Messery, G.S. Hassan, M.N. Nagi, E.-S.E. Habib, S.T. Al-Rashood, H.I. El-Subbagh, Synthesis, biological evaluation and molecular modeling study of some new methoxylated 2-benzylthio-quinazoline-4(3H)-ones as nonclassical antifolates, Bioorg. Med. Chem. Lett 26 (2016) 4815–4823, https://doi.org/10.1016/j.bmcl.2016.08.022.
[19] S.T. Al-Rashood, I.A. Aboldahab, M.N. Nagi, L.A. Abouzeid, A.A.M. Abdel-Aziz, S.G. Abdel-hamide, K.M. Youssef, A.M. Al-Obaid, H.I. El-Subbagh, Synthesis, dihydrofolate reductase inhibition, antitumor testing, and molecular modeling study of some new 4(3H)-quinazolinone analogs, Bioorg. Med. Chem. 14 (2006) 8608–8621, https://doi.org/10.1016/j.bmc.2006.08.030.
[20] A.K. Tiwari, A.K. Mishra, A. Bajpai, P. Mishra, R.K. Sharma, V.K. Pandey,

V.K. Singh, Synthesis and pharmacological study of novel pyrido-quinazolone analogues as anti-fungal, antibacterial, and anticancer agents, Bioorg. Med. Chem. Lett 16 (2006) 4581–4585, https://doi.org/10.1016/j.bmcl.2006.06.015.
[21] E. De Clercq, Antiviral drugs in current clinical use, J. Clin. Virol. 30 (2004) 115–133, https://doi.org/10.1016/j.jcv.2004.02.009.
[22] A. Matsuda, T. Sasaki, Antitumor activity of sugar-modified cytosine nucleosides, Cancer Sci. 95 (2004) 105–111, https://doi.org/10.1111/j.1349-7006.2004.tb03189.x.
[23] D.M. Huryn, M. Okabe, AIDS-driven nucleoside chemistry, Chem. Rev. 92 (1992) 1745–1768, https://doi.org/10.1021/cr00016a004.
[24] T. Pathak, Azidonucleosides: synthesis, reactions, and biological properties, Chem. Rev. 102 (2002) 1623–1668, https://doi.org/10.1021/cr0104532.
[25] M.M. Faul, B.E. Huff, S.E. Dunlap, S.A. Frank, J.E. Fritz, S.W. Kaldor, M.E. LeTourneau, M.A. Staszak, J.A. Ward, J.A. Werner, L.L. Winneroski, Synthesis of 2′,3′-dideoxy-3′-hydroxymethylcytidine; a unique antiviral nucleoside, Tetrahedron 53 (1997) 8085–8104, https://doi.org/10.1016/S0040-4020(97)00500-0.
[26] C. Len, G. Mackenzie, Synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides having variations at either or both of the 2′- and 3′-positions, Tetrahedron 39 (2006) 9085–9107, https://doi.org/10.1016/j.tet.2006.07.050.
[27] A.A. El-Barbary, A.I. Khodair, E.B. Pedersen, C. Nielsen, S-Glucosylated, Hydantoins as new antiviral agents, J. Med. Chem. 37 (1994) 73–77, https://doi.org/10.1021/jm00027a009.
[28] A.M. al-Obaid, H.I. el-Subbagh, A.I. Khodair, M.M. Elmazar, 5-substituted-2-thiohydantoin analogs as a novel class of antitumor agents, Anti Canccer Drugs 7 (1996) 873–880.
[29] A.I. Khodair, Synthesis of 2-thiohydantoins and their S-glucosylated derivatives as potential antiviral and antitumor agents, Nucleosides Nucleotides Nucleic Acids 20 (2001) 1735–1750, https://doi.org/10.1081/NCN-100105908.
[30] A.I. Khodair, Glycosylation of 2-thiohydantoin derivatives. Synthesis of some novel S-alkylated and S-glucosylated hydantoins, Carbohydr. Res. 331 (2001) 445–453, https://doi.org/10.1016/S0008-6215(01)00040-4.
[31] F. Wang, P. Zhao, C. Xi, Copper-catalyzed one-pot synthesis of 2-thioxo-2,3-dihydroquinazolin-4(1H)-ones from ortho-bromobenzamides and isothiocyanates, Tetrahedron Lett. 52 (2011) 231–235, https://doi.org/10.1016/j.tetlet.2010.11.010.
[32] N.M. Abdel Gawad, H.H. Georgey, R.M. Youssef, N.A. El-Sayed, Synthesis and antitumor activity of some 2, 3-disubstituted quinazolin-4(3H)-ones and 4, 6- disubstituted- 1, 2, 3, 4-tetrahydroquinazolin-2H-ones, Eur. J. Med. Chem. 45 (2010) 6058–6067, https://doi.org/10.1016/j.ejmech.2010.10.008.
[33] I.R. Siddiqui, P.K. Singh, V. Srivastava, S. Yadav, J. Singh, A novel versatile strategy for synthesis of new series of 4(3H)-quinazolinone N-nucleosides, IJC-B 49B (11) (2010) 1535–1541.
[34] A.H. Shamroukh, A.E. Rashad, F.M.E. Abdelmegeid, The chemistry of pyrido[2,3-d]pyrimidines and their applications, J. Chem. Pharm. Res. 8 (2016) 734–772.
[35] A.-R.B.A. El-Gazzar, H.N. Hafez, H.-A.S. Abbas, S- and C-nucleosidoquinazoline as new nucleoside analogs with potential analgesic and anti-inflammatory activity, Eur. J. Med. Chem. 44 (2009) 4249–4258, https://doi.org/10.1016/j.ejmech.2009.05.025.
[36] J. Girniene, G. Apremont, A. Tatibouët, A. Sackus, P. Rollin, Small libraries of fused quinazolinone-sugars. Access to quinazolinedione nucleosides, Tetrahedron 60 (2004) 2609–2619, https://doi.org/10.1016/j.tet.2004.01.032.
[37] T.-C. Chien, C.-S. Chen, F.-H. Yu, J.-W. Chern, X.I. Nucleosides, Synthesis and antiviral evaluation of 5'-alkylthio-5'-deoxy quinazolinone nucleoside derivatives as S-adenosyl-L-homocysteine analogs, Chem. Pharm. Bull. 52 (2004) 1422–1426.
[38] M.F. Abdel-Megeed, M.A. Saleh, Y.L. Aly, I.M. Abdo, Synthesis, conformational and configurational studies of some new acetylated glycosides of 2-Thio-3-aryl-4(3H)-quinazolinones, Their Thiono and 3,1-Benzothiazin-2,4-dithione, Nucleosides and Nucleotides 14 (1995) 1985–1996, https://doi.org/10.1080/15257779508010718.
[39] A.A. El-Barbary, A.Z.A. El-Ezz, A.M. Sharaf, C. Nielsen, The Synthesis of Some New Quinazolone Derivatives of Potential Biological Activity, Phosphorus, Sulfur, and Silicon and the Related Elements, vol. 181, (2006), pp. 1895–1912, https://doi.org/10.1080/10426500500543834.
[40] A. Saeed, S. ul Mahmood, H. Ishida, Synthesis and crystal structure of 3-(4-Methoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one, Crystals 1 (2011) 171–177, https://doi.org/10.3390/cryst1030171.
[41] N.S. Devi, S.J. Singh, O.M. Singh, An efficient one-pot multicomponent synthesis of 2,3-Dihydro-3-alkyl/aryl-2-thioxoquinazolin-4(1H)-ones under solvent-free conditions, Synlett 23 (2012) 2111–2115, https://doi.org/10.1055/s-0032-1316698.
[42] R.V. Sheorey, A. Thangathiruppathy, V. Alagarsamy, Synthesis, analgesic and anti-inflammatory activities of 3- ethyl-2-substituted amino-3H-quinazolin-4-ones, Trop. J. Pharm. Res. 12 (2013) 583–589, https://doi.org/10.4314/tjpr.v12i4.21.
[43] V. Alagarsamy, P. Parthiban, Design and synthesis of novel 3-(Phenyl)-2-(3-substituted propylthio) quinazolin-4-(3H)-ones as a new class of H1-antihistaminic agents, J. Heterocycl. Chem. 51 (2014) 1615–1620, https://doi.org/10.1002/jhet.1720.
[44] N. Azizi, M. Edrisi, Practical approach to 2-thioxo-2,3-dihydroquinazolin-4(1H)-one via dithiocarbamate–anthranilic acid reaction, Chin. Chem. Lett. 28 (2017) 109–112, https://doi.org/10.1016/j.cclet.2016.06.012.
[45] G.A. El-Hiti, A. Hussain, A.S. Hegazy, M.H. Alotaibi, Thioxoquinazolines: synthesis, reactions and biological activities, J. Sulfur Chem. 32 (2011) 361–395, https://doi.org/10.1080/17415993.2011.601417.
[46] S.V. Pestova, E.S. Izmest'ev, S.A. Rubtsova, A.V. Polukeev, A.V. Kutchin, Synthesis of thioglycosides with nitrogen-containing heterocyclic fragments, Russ. J. Org. Chem. 54 (2018) 1041–1044, https://doi.org/10.1134/S1070428018070126.
[47] W.R. Bowman, M.R.J. Elsegood, T. Stein, G.W. Weaver, Radical reactions with 3H-quinazolin-4-ones: synthesis of deoxyvasicinone, mackinazolinone, luotonin A, rutaecarpine and tryptanthrin, Org. Biomol. Chem. 5 (2006) 103–113, https://doi.org/10.1039/B614075K.
[48] J. Stamos, M.X. Sliwkowski, C. Eigenbrot, Structure of the epidermal growth factor receptor kinase domain alone and in complex with a 4-anilinoquinazoline inhibitor, J. Biol. Chem. 277 (2002) 46265–46272, https://doi.org/10.1074/jbc.M207135200.
[49] T. Mosmann, Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays, J. Immunol. Methods 65 (1983) 55–63, https://doi.org/10.1016/0022-1759(83)90303-4.
[50] R.I. Freshney, Culture of tumor cells, Culture of Animal Cells, John Wiley & Sons, Inc., 2010, pp. 463–479, , https://doi.org/10.1002/9780470649367.ch24.
[51] E. Da Pozzo, V. La Pietra, B. Cosimelli, F. Da Settimo, C. Giacomelli, L. Marinelli, C. Martini, E. Novellino, S. Taliani, G. Greco, p53 functional inhibitors behaving like pifithrin-β counteract the alzheimer peptide non-β-amyloid component effects in human SH-SY5Y cells, ACS Chem. Neurosci. 5 (2014) 390–399, https://doi.org/10.1021/cn4002208.