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Original article

S- and *C*-nucleosidoquinazoline as new nucleoside analogs with potential analgesic and anti-inflammatory activity

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ABSTRACT

Thioglycosides and *C*-glycosides have received considerable attention, because they are widely employed as biological inhibitors, inducers and ligands for affinity chromatography of carbohydrate-processing enzymes and proteins. Moreover, they are promising candidates in synthetic carbohydrate chemistry as convenient and versatile glycosyl donors. Among these glycosyl donors are the thioglycosyl and *N*-glycosyl heterocycles that are sufficiently stable under a variety of reaction conditions and have the ability to be readily converted into a variety of other functionalities. We report here, the synthesis of 2-thioxo-quinazolines **1a–c** which were used as a base to the synthesis of *S*-nucleoside of types **10**, **11** and acyclic *C*-nucleoside analogs of type **14** and their analgesic and anti-inflammatory activities were evaluated giving good results.

1. Introduction

Nucleoside analogs constitute an important class of therapeutic agents in the treatment of cancers and viral infections [1]. The mode of action of these derivatives is based upon their intracellular conversation to their phosphorylted forms (nucleotides), which can interact with different cellubiosynthesis. During the last decades, an intensive research was dedicated to the discovery of more effective, selective, and non-toxic new nucleoside derivatives [2]. These efforts have concerned the chemical modification of the base and/or the sugar moiety of natural nucleosides. In the latter, the main modifications involved changes in the sugar moiety like, inversion of hydroxyl group configurations, their elimination leading to dideoxy- or dideoxy-didehydro nucleosides, their substitution/functionalization by various synthetic groups, or cleavage of the sugar ring leading to acyclic nucleosides. Also, modifications of the sugar moiety of nucleosides may lead to significant changes in the spectrum of their biological activity and degree of selective toxicity, as well as in their physico-chemical properties. In the course of our ongoing research on the synthesis and biological evaluation of modified heterocyclic and nucleoside analogs, we became interested in a stereo-selective strategy for the preparation of *S*-nucleosides and *C*-nucleosides.

Surprisingly, although a tremendous work has been done in the synthesis of new series of nucleoside analogs, few works have been reported regarding the synthesis of *S*- and *C*-nucleosides [3,4]. This fact prompted us to elaborate a synthetic route to reach such kind of compounds. Also, The pharmacodynamic versatility of quinazoline moiety has been documented not only in many of its synthetic derivatives but also in several naturally occurring alkaloids isolated from animals, families of plant kingdoms and from microoraganism [5–7]. These isolated quinazolines derivatives were found to have wide range of biological properties including anti-tumor, sedative, analgesic, antidiabetic, antibacterial, anti-inflammatory, antifungal and anticancer [8–14]. In addition, characterization of potential *N*-methyl-D-asparatate (NMDA) and chlolecystokinin antagonists II-lipophilicity studies on quinazoline are also documented [15].

2. Results and discussion

The key intermediates for the synthesis of thioglycosides and acyclic glycosides are shown in the Scheme 1. 4-Aryl-7-dimethyl-3,4,6,8-tetrahydro-2-thioxo-quinazolin-5-ones (**1a–c**) were prepared by a one-pot-reaction of 5,5-dimethylcyclohexane-1,3-diones (Dimadon), aldehydes and thiourea in absolute ethanol in presence of hydrochloric acid as acid catalyst. Compounds **1a–c** on reflux with hydrazine hydrate (99%) yielded the desired 4-aryl-2-hydrazino-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-ones (**2a–c**) in good yields (over 80%), Scheme 1. The IR spectra of compound **1b** show intense

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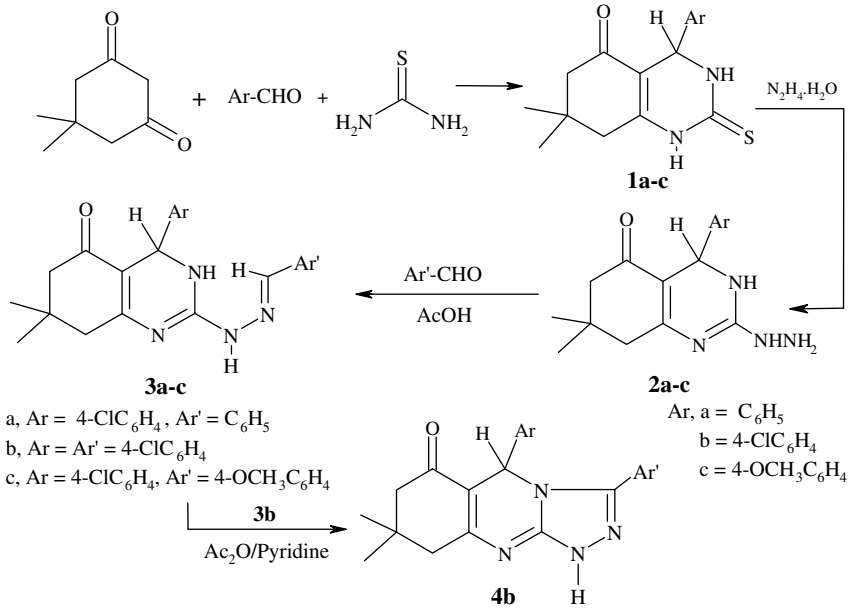


Scheme 1.

peaks at 3290 cm^{-1} for (NH), 1704 cm^{-1} for carbonyl (C═O) and 1225 cm^{-1} for thioxo (C═S) streatching. ^{1}H NMR spectrum of **1b** showed a double duplet at δ 7.23 (J = 8.1 Hz) and 7.33 (J = 8.1 Hz) for aromatic (4H) protons and a two broad signalst at δ 8.90 and 10.00 ppm indicating the presence of two NHs, in addition to the signals corresponding to methylene protons around δ 1.88–2.18 ppm and two singlet signals at δ 0.90, 1.05 due to two methyl groups. Data from the elemental analyses have been found to be in conformity with the assigned structure. Also, the molecular ion recorded in the mass spectrum is also in agreement with the molecular weight of the compound. Furthermore, the ^{13}C NMR of the compound **1b** revealed that the signal corresponding to the *C*-2 (–C═S) was around δ 174 ppm.

Compounds **1a–c** were found to be useful for the syntheses of the interesting *S*-glycosides. As a model experiment the alkylation of **1** was carried out by the reaction of one equivalent of methyl-iodide with the potassium salt **5** generated in situ by the reaction of **1** with alcoholic potassium hydroxide. The structure of the new 2-methylthio-quinazoline **6** was confirmed by all spectroscopic data. The ^{13}C NMR spectrum as an example, reveled that the corresponding signal of the *C*-2 (C–SCH_3) appeared at δ 159 ppm. The NMR spectrum of the 2-thioxo- (**1**) and 2-methylthio-quinazoline (**6**) indicated that the site of the alkylation is the sulfur atom rather than the nitrogen atom (Fig. 1).

Analogously, the reaction of potassium salt **5** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**9a**) or 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**9b**) in acetone afforded the *S*-glycosylated nucleosides **10a**,**b** in good yields (62–70%), (Scheme 2). Thin layer chromatography (chloroform: methanol, 8:2) indicated the formation of the pure compounds. The structures of the *S*-glycoside **10a**,**b** were confirmed by elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR) (see Tables 4–6). The ^{1}H NMR spectrum of compound **10a** as an example, showed the anomeric proton of the glucose moiety as a doublet at δ 5.55 ppm with a coupling constant J = 11.00 Hz indicating β-configuration of the anomeric center. The other protons of the glucopyranose ring resonated at δ 4.02-5.39 ppm, while the four acetoxy groups appeared as four singlets at δ 2.12–2.33 ppm. The ^{13}C NMR revealed the absence of the thione carbon atom at about 174 ppm and a resonance of –N═C–N– carbon atom (C-2) at δ 158 ppm was indicated to the chemical shift of the corresponding carbon atom (Fig. 1). The signals at δ 169.3, 169.5, 169.9, 170.0 ppm were due to the four acetoxy carbonyl atoms (4C═O), and the four signals at δ 35.20-38.50 ppm were assigned to the acetate methyl carbon atoms. Also, the five signals at δ 67.90, 69.37, 72.75, 75.56, 80.89 ppm were assigned to C-4′, C-2′, C-3′, C-5′ and C-1′, respectively. Moreover, the IR spectra of compounds **10** revealed the absence of the stretching signal of a thione group. Similarly, the reaction of heterocycle base **5** with 2,3,5-tri-*O*-acetyl-α-D-ribofuranosyl bromide (**9c**) furnished the *S*-glycosylated product **10c**. The assignment of structures of this product is based on their elemental analysis and the spectral data (see Tables 4–6).

Furthermore, we developed a preparative alternative for the quinazoline thioglycosides **10a**,**b**. Silylation of compound **1b** afforded the intermediate silylated product **7**, which reacted with β-D-glucose pentaacetate **8a** or β-D-galactose pentaacetate **8b** in dry acetone in the presence of stannic chloride to furnish the S-glycosyl products **10a**,**b** (Scheme 2).

Also, according to El-Gazzar et al. [16], 2-hydrazino derivative **2b** gave the 2-(aryl-methylenehydrazone)-qunazolin-5-one derivatives **3a–c** (Scheme 1) when **2b** was treated with the appropriate aldehyde in boiling acetic acid for 30 min. Compounds **3a–c** gave compatible spectral and analytical data. The arylhydrazones **3b** could be cyclized into the corresponding 3,4-di(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-*b*]quinazolin-6-one (**4**), when treated with a mixture of acetic anhydride–pyridine (2:1).

Analogously, the required hydrazones **11a–f** were prepared by condensation of 2-hydrazino-quinazoline **2b** with the appropriate aldohexoses and aldopentoses (Scheme 3). The structures of the new hydrazones **11a–f** were confirmed by their elemental analyses and spectral data (Tables 4–6). Stirring of 2-(glycosylhydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one derivatives (**11a–f**) at room temperature in a mixture of acetic anhydride–pyridine (2:1) afforded the respective 3-(penta-*O*-acetylglycosyl/or tetra-*O*-acetylglycosyl)-4-aryl-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo-[3,4-*b*]quinazolin-6-ones (**13a–f**). The structures of the acetylated derivatives were deduced from their combustion analyses, spectral (IR, ^{1}H NMR and ^{13}C NMR) data and as depicted in Scheme 3.

Surprisingly, in this case, 3-(penta-*O*-acetylglycosyl/or tetra-*O*-acetylglycosyl)-4-aryl-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo-[3,4-*b*]quinazolin-6-one derivatives **13** were obtained directly from

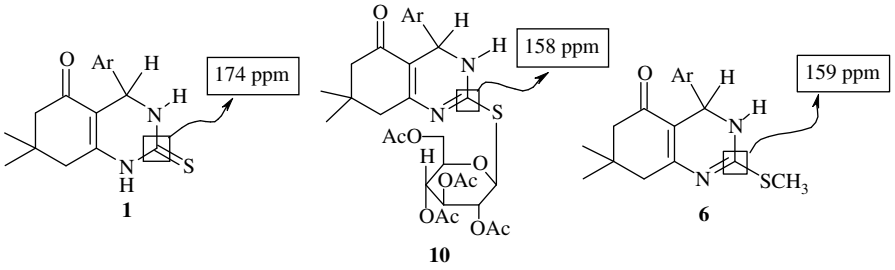
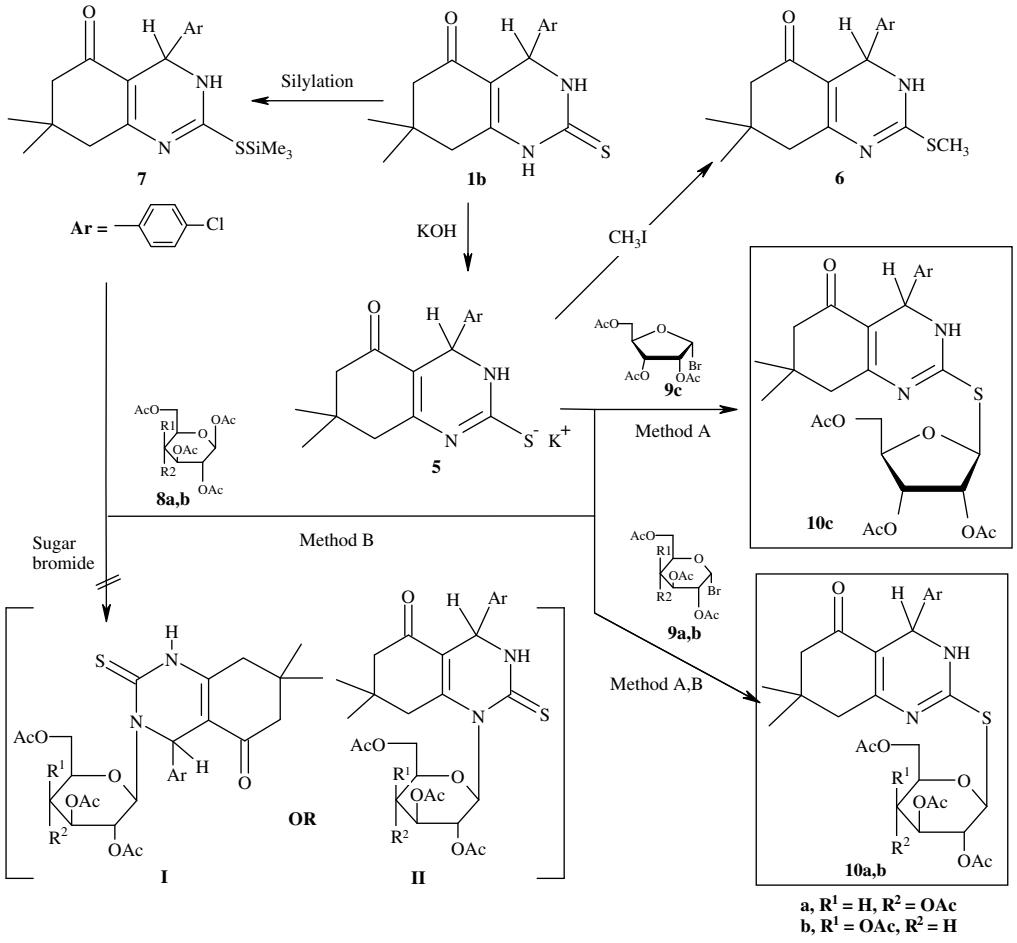


Fig. 1.

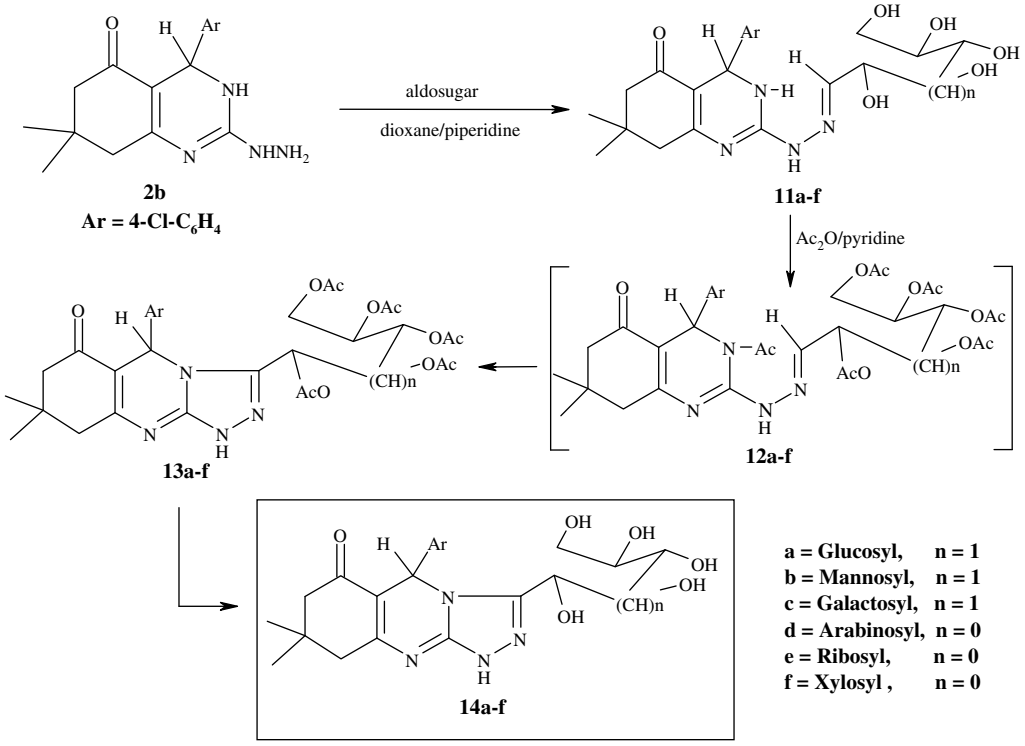
the reaction of 2-glycosylhydrazones **11** with acetic anhydride without separating the 3-*N*-acetyl derivatives **12** (Scheme 3).

De-protection of the acyclic *C*-nucleosides **13a**–**f** could be achieved when they were stirred in methanolic ammonia solution (10%) at room temperature to give in a moderate to good yields of 3-(glycosyl)-4-aryl-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-*b*]quinazolin-6-ones (**14a**–**f**). Structures **14** were confirmed by spectral and elemental analyses (see Tables 4 and 5). Their ^{1}H NMR spectra showed no absorption signals for the acetyl protons but showed the multiplet signal supported to the hydroxyl protons in the region δ 3.51-3.84 (D_2O exchangeable), the signals due to the protons of the sugar moiety at δ 3.77–5.72. In addition, the signals supported the two methylene and the two methyl protons.

The ^{1}H NMR spectrum of **14a**, as an example showed three multiplet absorption bands for three methylene groups around 1.63–2.80, and very broad absorption bands at δ 3.51 supported to the five hydroxyl groups (D_2O exchangeable) and the signals at δ 3.86 (m, 1H, H-4′), 4.19 (m, 2H, H-5′, H-5″), 4.47 (m, 1H, H-3′), 4.72 (m, 1H, H-2′), 5.65 (m, 1H, H-1′), which supported the CHs of the sugar moiety and in between the singlet signal due to the proton at C-5 at δ 5.27. Also showed the aromatic protons at δ 7.18 (d, 2H, Ar-*H*, $J = 8.4$ Hz), 7.42 (d, 2H, Ar-*H*, $J = 8.4$ Hz) and the broad signal at δ 9.15 corresponding to NH, D_2O exchangeable, respectively (Table 5). Also the ^{13}C NMR spectrum of **14b** showed two signals at δ 21.30 and 21.64 corresponding to $2CH_3$ groups, three signals at δ 28.31, 29.17 and 30.95 due to $3CH_2$ groups, the signals at δ 67.15, 67.45,



Scheme 2.



Scheme 3.

70.18 and 71.60 due to the carbon atoms of the sugar moiety (4 CH), also the signals corresponding to *C*-4 and *C*-7 at δ 90.52 and 91.31, eight lines around 126.68-158.56 supported to ten sp^2 carbon atoms and the absorption signal correspond to the carbonyl group at δ 191.41 (Table 6).

3. Pharmacological screening

Anti-inflammatory activity of the synthesized compounds **1a–c**, **2b**, **4**, **10a–c** and **14a–f** were evaluated by carrageenan-induced paw oedema method. The compounds were tested at an oral dose of 70 mg kg^{-1} body mass and were compared with the standard drug ibuprofen at the same oral dose. The tested compounds showed anti-inflammatory activity ranging from 50 to 86% (Table 1), and the standard drug ibuprofen showed 92% inhibition after 4 h. 1,2,4-Triazolo[3,4-*b*]quinazolin-6-one derivative (**14a**) having an glucosyl group showed the maximum activity (86%), whereas the 2-hydrazine quinazoline (**2b**) showed moderate activity and for the starting material 2-thiooxo-quinazoline (**1a**) the activity was found to be minimal (50%). It was observed that 1,2,4-triazolo[3,4-*b*]quinazolin-6-one derivatives **14a–f** having *C*-glycosyl (Glucosyl, mannosyl, galactosyl, arabinosyl, ribosyl and xylosyl) groups at the 3rd position showed high activity (86, 82, 85, 82, 82 and 84%) respectively. However, the activity was found to be reduced for *S*-nucleoside derivatives **10a–c**.

The compounds that showed anti-inflammatory activity higher than 80% were tested for analgesic activity (Table 2). Compounds **14a–f** showed analgesic activity ranging from 57 to 73%, whereas the standard drug ibuprofen showed 84% at a 70 mg kg^{-1} oral dose. Among all the tested compounds, the *C*-glycosyl derivative having 3-glucosyl group **14a** showed maximum activity (73%). When this group is replaced by 3-galactosyl **14c** and 3-mannosyl **14b**, there was a significant decrease in the activity. Among all the tested compounds, 3-ribosyl-triazolo[3,4-*b*]quinazolin-6-one (**14e**) showed minimum activity (56.6), whereas 3-arabinosyl-triazolo[3,4-*b*]quinazolin-6-one (**14d**) derivative showed significant analgesic activity (71%).

The compounds that were screened for analgesic activity were further screened for their ulcerogenic activity (Table 3). All the compounds were tested at an oral dose 200 mg kg^{-1} body mass. The maximum reduction in ulcerogenic activity (mean severity index ± SEM, $n = 6$ was 0.5 ± 0.2), found in triazolo[3,4-*b*]quinazolin-6-one (**14a**), having the 3-glucosyl group at position 3. In triazolo[3,4-*b*]quinazolin-6-one derivative, maximum reduction (0.5 ± 0) was found in compound (**14e**), having ribosyl group,

Table 1
Anti-inflammatory effect of compounds against carrageenan-induced hind paws oedema in rats.

Compound no.	Dose (mg kg^{-1}, 1% CMC)	Anti-inflammatory activity[a] (mean inhibition ± SEM %)
Control		–
1a	70	50 ± 3.0[b]
1b	70	69 ± 3.0[b]
1c	70	71 ± 5.0[d]
2b	70	71 ± 2.6[b]
4	70	68 ± 2.7[b]
10a	70	75 ± 2.0[b]
10b	70	76 ± 3.0[c]
10c	70	76 ± 2.1[b]
14a	70	86 ± 1.7[c]
14b	70	82 ± 1.7[c]
14c	70	85 ± 1.9[c]
14d	70	82 ± 0.9[b]
14e	70	82 ± 2.0[d]
14f	70	84 ± 2.0[d]
Ibuprofen	70	92 ± 1.0

Anti-inflammatory activity of the tested compounds were measured with respect to the control and compared with respect to the standard drug.
[a] $n = 6$.
[b] $P < 0.0001$.
[c] $P < 0.001$.
[d] $P < 0.05$.

Table 2
Effects of the compounds on acetic acid induced abdominal writhing test in mice.

Compound no.	Dose (mg kg^{-1}, 1% CMC)	Analgesic activity[a] (mean inhibition ± SEM %)
Control		–
14a	70	73 ± 0.9[b]
14b	70	57 ± 0.9[b]
14c	70	59 ± 0.5[b]
14d	70	71 ± 1.2[b]
14e	70	56.6 ± 1.1[b]
14f	70	59.5 ± 0.5[b]
Ibuprofen	70	83.5 ± 0.7[b]

Analgesic activity of the tested compounds were measured with respect to the control and compared with respect to the standard drug.
[a] $n = 6$.
[b] $P < 0.0001$.

whereas the galactosyl group present in triazolo[3,4-*b*]quinazolin-6-one derivative **14c** showed the maximum severity index (0.8 ± 0.2). The other three compounds **14b**,**d** and **14f** 3-mannosyl, 3-ribosyl and 3-xylosyl-triazolo[3,4-*b*]quinazolin-6-one derivatives, respectively, showed moderate severity indexes. The standard drug ibuprofen showed a high severity index of 1.8 ± 0.2.

4. Experimental

4.1. Chemistry

All melting points were taken on Electrothermal IA 9100 series digital melting point apparatus. Microanalytical data (in accord with the calculated values) were performed by Vario, Elementar apparatus (Shimadzu), (Table 4). The IR spectra (KBr) were recorded on a Perkin–Elmer 1650 spectrometer (USA). ^{1}H and ^{13}C NMR spectra were determined on a JEOL EX-270 and JEOL ECA-500. Chemical shifts were expressed in ppm relative to $SiMe_4$ as internal standards and DMSO-d_6 as solvent. Mass spectra were recorded on 70 eV EI Ms-QP 1000 EX (Shimadzu, Japan), (Tables 5 and 6).

4.2. 4-(Aryl)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one-2-thiones (*1a*-*c*)

General procedure. A mixture of 5,5-dimethylcyclohexan-1,3-dione (Dimadon) (0.01 mol), aldehydes (0.01 mol) and thiourea (0.01 mol) in absolute ethanol (30 ml) in presence of concentrated hydrochloric acid (37%, 3 ml) was refluxed for 10–18 h (TLC), then allowed to cool and poured into cold water (100 ml) and neutralized the solution with ammonium hydroxide. The solid product was collected and crystallized from ethanol to give (**1a**–**c**), as white crystal in good yields.

Table 3
Ulcerogenic activity.[a]

Compound no.	Dose (mg kg^{-1}, 1% CMC)	Ulcerogenic activity[a] (mean severity index ± SEM)
Control		0.0 ± 0.0[b]
14a	200	0.5 ± 0.2[b]
14b	200	0.6 ± 0.1[c]
14c	200	0.8 ± 0.2[d]
14d	200	0.6 ± 0.2[c]
14e	200	0.5 ± 0.0[b]
14f	200	0.5 ± 0.1[c]
Ibuprofen	200	1.8 ± 0.2

Ulcerogenic activities of the tested compounds were compared with respect to the standard drug.
[a] $n = 6$.
[b] $P < 0.0001$.
[c] $P < 0.001$.
[d] $P < 0.05$.

Table 4
Physical constants of newly synthesized compounds.

No.	Yield (%)	M.p. (°C)	Mol. form. (Mol. wt.)	Microanalysis		
				C	H	N
1a	83	220–222	$C_{16}H_{18}N_2OS$	67.10	6.33	9.78
			(286.4)	67.11	6.29	9.80
1b	89	245–247	$C_{16}H_{17}ClN_2OS$	59.89	5.34	8.73
			(320.8)	59.85	5.29	8.69
1c	80	237–239	$C_{17}H_{20}N_2O_2S$	64.52	6.37	8.85
			(316.4)	64.51	6.34	8.83
2a	76	263–265	$C_{16}H_{20}N_4O$	67.58	7.09	19.70
			(284.3)	67.55	7.13	19.67
2b	90	258–260	$C_{16}H_{19}ClN_4O$	60.28	6.01	17.57
			(318.79)	60.26	6.04	17.59
2c	86	226–229	$C_{17}H_{22}N_4O_2$	64.94	7.05	17.82
			(314.3)	64.89	7.02	17.79
3a	80	190–192	$C_{23}H_{23}ClN_4O$	67.89	5.69	13.77
			(406.9)	67.84	5.65	13.69
3b	81	179–181	$C_{23}H_{22}Cl_2N_4O$	62.59	5.02	12.69
			(441.3)	62.53	4.97	12.71
3c	78	228–230	$C_{24}H_{25}ClN_4O_2$	65.97	5.77	12.82
			(436.9)	65.95	5.73	12.69
4	65	307–309	$C_{23}H_{20}Cl_2N_4O$	62.87	4.59	12.75
			(439.3)	62.85	4.56	12.71
6	76	179–181	$C_{17}H_{19}ClN_2OS$	60.97	5.72	8.36
			(334.8)	61.02	5.69	8.39
10a	70	169–171	$C_{30}H_{35}ClN_2O_{10}S$	55.34	5.42	4.30
			(651.1)	55.38	5.29	4.28
10b	68	193–195	$C_{30}H_{35}ClN_2O_{10}S$	55.34	5.42	4.30
			(651.1)	55.41	5.35	4.33
10c	62	154–157	$C_{27}H_{31}ClN_2O_8S$	55.56	5.40	4.84
			(579.0)	55.49	5.39	4.79
11a	76	259–261	$C_{22}H_{29}ClN_4O_6$	54.94	6.08	11.65
			(480.9)	54.91	6.11	11.67
11b	78	267–270	$C_{22}H_{29}ClN_4O_6$	54.94	6.08	11.65
			(480.9)	54.90	6.09	11.64
11c	71	239–241	$C_{22}H_{29}N_4ClO_6$	54.94	6.08	11.65
			(480.9)	54.93	6.09	11.63
11d	67	227–230	$C_{21}H_{27}ClN_4O_5$	55.94	6.04	12.43
			(450.9)	55.92	6.08	12.38
11e	59	245–248	$C_{21}H_{27}ClN_4O_5$	55.94	6.04	12.43
			(450.9)	55.99	6.06	12.40
11f	57	219–221	$C_{21}H_{27}ClN_4O_5$	55.94	6.04	12.43
			(450.9)	55.89	6.02	12.47
13a	80	211–213	$C_{32}H_{37}ClN_4O_{11}$	55.77	5.41	8.13
			(689.1)	55.73	5.39	8.09
13b	85	224–226	$C_{32}H_{37}ClN_4O_{11}$	55.77	5.41	8.13
			(689.1)	55.75	5.40	8.10
13c	79	201–203	$C_{32}H_{37}ClN_4O_{11}$	55.77	5.41	8.13
			(689.1)	55.74	5.43	8.08
13d	72	187–190	$C_{29}H_{33}ClN_4O_9$	56.45	5.39	9.08
			(617.0)	56.39	5.41	9.11
13e	68	164–167	$C_{29}H_{33}ClN_4O_9$	56.45	5.39	9.08
			(617.0)	56.41	5.37	9.12
13f	74	172–174	$C_{29}H_{33}ClN_4O_9$	56.45	5.39	9.08
			(617.0)	56.48	5.40	9.06
14a	64	231–233	$C_{22}H_{27}ClN_4O_6$	55.17	5.68	11.70
			(478.9)	55.13	5.71	11.65
14b	61	240–243	$C_{22}H_{27}ClN_4O_6$	55.17	5.68	11.70
			(478.9)	55.1	5.65	11.67
14c	67	219–221	$C_{22}H_{27}ClN_4O_6$	55.17	5.68	11.70
			(478.9)	55.12	5.69	11.73
14d	53	213–216	$C_{21}H_{25}ClN_4O_5$	56.19	5.61	12.48
			(448.9)	56.23	5.57	12.39
14e	58	205–207	$C_{21}H_{25}ClN_4O_5$	56.19	5.61	12.48
			(448.9)	56.18	5.63	12.54
14f	60	195–197	$C_{21}H_{25}ClN_4O_5$	56.19	5.61	12.48
			(448.9)	56.18	5.58	12.37

4.2.1. 4-Phenyl-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one-2-thione (*1a*)

The compound was obtained from the reaction of benzaldehyde, as a white powder crystallized from ethanol.

Table 5
Mass, IR, ^{1}H NMR spectral data of newly synthesized compounds.

Compd. no.	Mass (*m/z*) (%)	IR (ν, cm^{-1})	^{1}H NMR (δ, ppm) (DMSO-d_6)
1a	[M$^+$], 286 (100)	3300 (br, NH's), 1700 (C=O), 2939 (CH alkyl), 1235 (C=S)	δ 0.91 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.00–2.02 (d, 2H, CH_2), 2.17–2.20 (d, 2H, CH_2), 5.32 (s, 1H, C5-*H*), 6.73–7.00 (m, 2H, Ar-*H*), 7.10–7.23 (m, 2H, Ar-*H*), 8.35, 9.80 (2br, 2H, 2NH).
1b	[M$^+$ + 1], 321 (29), [M$^+$], 320 (100)	3290 (br, NH's), 1704 (C=O), 1225 (C=S)	δ 0.90 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.88–2.18 (m, 4H, 2CH_2), 5.38 (br, 1H, C5-*H*), 7.23 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.33 (d, 2H, J = 8.1 Hz, Ar-*H*), 8.90, 10.00 (2br, 2H, 2NH).
1c	[M$^+$], 316 (100)	3310 (br, NH's), 3025 (CH aryl), 1238 (C=S), 1706 (C=O)	δ 0.90 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 2.01–2.04 (d, 2H, CH_2), 2.19-2.23 (d, 2H, CH_2), 3.47 (br, 2H, 2NH with H_2O of DMSO), 3.63 (s, 3H, OCH_3), 5.09 (s, 1H, C5-*H*), 6.73 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.02 (d, 2H, J = 8.1 Hz, Ar-*H*).
2a	[M$^+$], 284 (100)	3285 (br, NH's), 3032 (CH aryl), 2920 (CH alkyl), 1703 (C=O)	δ 0.94 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.93–2.00 (d, 2H, CH_2), 2.13–2.18 (d, 2H, CH_2), 5.17 (s, 1H, C–H), 7.09–7.16 (m, 2H, Ar-*H*), 7.20–7.26 (m, 2H, Ar-*H*), 8.25 (br, 2H, NH_2), 9.10, 10.65 (2br, 2H, 2NH).
2b	[M$^+$ + 1], 320 (31), [M$^+$], 319 (87)	3295 (br, NH's), 3038 (CH aryl), 2927 (CH alkyl), 1700 (C=O)	δ 0.85 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.86–2.14 (m, 4H, 2CH_2), 5.30 (s, 1H, C5-*H*), 5.74 (br, 1H, NH), 7.23 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.33 (d, 2H, J = 8.1 Hz, Ar-*H*), 8.15 (br, 2H, NH_2), 9.30 (br, 1H, NH).
2c	[M$^+$], 314 (100)	3340 (br, NH's), 3040 (CH aryl), 2917 (CH alkyl), 1702 (C=O)	δ 0.86 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 2.00 (d, 2H, CH_2), 2.18 (d, 2H, CH_2), 3.87 (s, 3H, OCH_3), 5.27 (s, 1H, C5-*H*), 6.89 (d, 2H, J = 8.3 Hz, Ar-*H*), 7.11 (d, 2H, J = 8.3 Hz, Ar-*H*), 8.07 (br, 2H, NH_2), 9.60, 10.40 (2br, 2H, 2NH).
3a	[M$^+$ + 1], 407 (27), [M$^+$], 406 (100)	3350 (br, NH's), 3026 (CH aryl), 2937 (CH alkyl), 1698 (C=O)	δ 0.89 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.89–2.00 (d, 2H, CH_2), 2.10–2.16 (d, 2H, CH_2), 5.28 (s, 1H, C5-*H*), 7.00 (d, 2H, Ar-*H*, J = 8.0 Hz)), 7.11–7.18 (m, 2H, Ar-*H*), 7.23–7.34 (m, 3H, Ar-*H*), 7.41 (d, 2H, Ar-*H*, J = 8.0 Hz), 8.25 (s, 1H, azomethin proton), 9.30, 10.60 (2br, 2H, 2NH).
3b	[M$^+$ + 1], 442 (25), [M$^+$], 441 (76)	3325 (br, NH's), 3051 (CH aryl), 2943 (CH alkyl), 1700 (C=O)	δ 0.92 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.95–2.30 (m, 4H, 2CH_2), 5.34 (s, 1H, C5-*H*), 7.25 (d, 2H, J = 8.2 Hz, Ar-*H*), 7.30 (d, 2H, J = 8.2 Hz, Ar-*H*), 7.56 (d, 2H, J = 8.2 Hz, Ar-*H*), 7.72 (d, 2H, J = 8.2 Hz, Ar-*H*), 8.50 (s, 1H, azomethin proton), 8.90, 10.00 (2br, 2H, 2NH).
3c	[M$^+$ + 1], 437 (30), [M$^+$], 436 (100)	3290 (br, NH's), 3034 (CH aryl), 2923 (CH alkyl), 1699 (C=O)	δ 0.90 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.93–2.31 (m, 4H, 2CH_2), 3.89 (s, 3H, OCH_3) 5.30 (s, 1H, C5-*H*), 7.11 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.22 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.54 (d, 2H, J = 8.2 Hz, Ar-*H*), 7.60 (d, 2H,J =8.2 Hz, Ar-*H*), 8.23 (s,1H, azomethin proton), 8.75, 10.20 (2br, 2H, 2NH).
4	[M$^+$ + 1], 440 (23), [M$^+$], 439 (89)	3250 (br, NH), 3024 (CH aryl), 2919 (CH alkyl), 1689 (C=O)	δ 0.94 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.90–2.25 (m, 4H, 2CH_2), 5.46 (s, 1H, C5-*H*), 7.24 (d, 2H, J = 8.2 Hz, Ar-*H*), 7.32 (d, 2H, J = 8.2 Hz, Ar-*H*), 7.58 (d, 2H, J = 8.2 Hz, Ar-*H*), 7.80 (d, 2H, J = 8.2 Hz, Ar-*H*), 10.30 (br, 1H, NH).
6	[M$^+$ + 1], 335 (20) [M$^+$], 334 (100)	3320 (br, NH), 3039 (CH aryl), 1688 (C=O)	δ 0.98 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.02 (m, 4H, 2CH_2), 3.10 (s, 3H, SCH_3), 5.35 (s, 1H, C5-*H*), 7.26 (d, 2H, J = 8.2 Hz, Ar-*H*), 7.35 (d, 2H, J =8.2 Hz, Ar-*H*), 10.15 (br,1H, NH).
10a	–	3280 (br, NH), 3037 (CH aryl), 2928 (CH alkyl), 1690–1715 (5C=O)	δ 0.89 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.82–2.04 (m, 4H, 2CH_2), 2.12–2.33 (4s, 12H, 4CH_3CO), 4.02 (m, 1H, H-5′), 4.26 (m, 2H, H-6′, H-6″), 5.10 (t, 1H, H-4′), 5.21 (m, 1H, H-2′), 5.39 (t, 1H, J = 9.34 Hz, H-3′), 5.40 (s, 1H,C5-*H*), 5.73 (d, 1H, J =11.0, H-1′), 7.29 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.43 (d, 2H, J = 8.1 Hz, Ar-*H*), 9.80 (br, 1H, NH).
10b	–	3300 (br, NH), 3029 (CH aryl), 2914 (CH alkyl), 1692–1715 (5C=O)	δ 0.87 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.89–2.04 (m, 4H, 2CH_2), 2.14–2.29 (4s, 12H, 4CH_3CO), 3.92 (m, 1H, H-5′), 4.20 (m, 2H, H-6′, H-6″), 5.07 (t, 1H, H-4′), 5.11 (m, 1H, H-2′), 5.39 (s, 1H, C5-*H*), 5.43 (t, 1H, J = 9.40 Hz, H-3′), 5.69 (d,1H, J =10.8,H-1′), 7.18 (d, 2H, J = 8.5 Hz, Ar-*H*), 7.38 (d, 2H, J = 8.5 Hz, Ar-*H*), 10.00 (br, 1H, NH).
10c	–	3320 (br, NH), 3032 (CH aryl), 2916 (CH alkyl), 1689–1710 (4C=O)	δ 0.88 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.89–2.09 (m, 4H, 2CH_2), 2.11–2.31 (3s, 9H, 3CH_3CO), 3.52 (m, 2H, H-5′, H-5″), 3.71 (m, 1H, H-4′), 3.96 (m, 1H, H-3′), 4.21 (m, 1H, H-2′), 4.58 (d, 1H, J =3.72 Hz, H-1′), 5.33 (s, 1H,C5-*H*), 7.20 (d, 2H, J = 8.3 Hz, Ar-*H*), 7.36 (d, 2H, J = 8.3 Hz, Ar-*H*), 9.80 (br,1H, NH).
11a	[M$^+$ + 1], 481 (19) [M$^+$], 480 (100)	3500–3200 (br, OH, NH), 3040 (CH aryl), 2935 (CH alkyl), 1705 (C=O)	δ 0.92 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.89–2.05 (m, 4H, 2CH_2), 3.59 (m, 5OH, D_2O exchangeable), 3.78 (m, 1H, H-5′), 4.30 (m, 2H, H-6′, H-6″), 4.41 (m, 1H, H-4′), 4.54 (m, 1H, H-3′), 5.22 (s, 1H, C5-*H*), 5.49 (m, 1H, H-2′), 7.17 (d, 2H, J = 8.3 *H*, Ar-*H*), 7.31 (d, 2H, J = 8.3 Hz, Ar-*H*), 8.01 (m, 1H, H-1′), 9.10, 10.25 (2brs, 2NH, D_2O exchangeable).
11b	[M$^+$ + 1], 481 (23) [M$^+$], 480 (100)	3500–3180 (br, OH, NH), 3039 (CH aryl), 2917 (CH alkyl), 1700 (C=O)	δ 0.90 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.86–2.06 (m, 4H, 2CH_2), 3.52 (m, 5OH), 3.79 (m, 1H, H-5′), 4.22 (m, 2H, H-6′, H-6″),4.47 (m, 1H, H-4′),4.55 (m, 1H, H-3′), 5.19 (s, 1H, C5-*H*), 5.43 (m, 1H, H-2′), 7.19 (d, 2H, Ar-*H*, J = 8.2 Hz), 7.29 (d, 2H, Ar-*H*, J = 8.2 Hz), 7.93 (m, 1H, H-1′), 9.35, 10.60 (2brs, 2NH).
11c	[M$^+$ + 1], 481 (20) [M$^+$], 480 (89)	3500–3150 (br, OH, NH), 3037 (CH aryl), 2924 (CH alkyl), 1702 (C=O)	δ 0.88 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.82–2.03 (m, 4H, 2CH_2), 3.54 (m, 5OH), 3.80 (m, 1H, H-5′), 4.17 (m, 2H, H-6′, H-6″), 4.39 (m, 1H, H-4′), 4.52 (m, 1H, H-3′), 5.19 (s, 1H, C5-*H*), 5.59 (m, 1H, H-2′), 7.23 (d, 2H, J = 8.0 Hz, Ar-*H*), 7.34 (d, 2H, J = 8.0 Hz, Ar-*H*), 8.00 (m, 1H, H-1′), 8.95, 10.00 (2brs, 2NH).

Table 5 (*continued*)

Compd. no.	Mass (*m*/*z*) (%)	IR (ν, cm^{-1})	^1H NMR (δ, ppm) (DMSO-d_6)
11d	$[M^+ + 1]$, 451 (36) $[M^+]$, 450 (76)	3460–3120 (br, OH, NH), 3028 (CH aryl), 2928 (CH alkyl), 1710 (C=O)	δ 0.87 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.80–2.00 (m, 4H, $2CH_2$), 3.68 (m, 4H, 4OH, D_2O exchangeable), 4.35 (m, 1H, H-3′), 4.49 (m, 1H, H-4′), 4.67 (m, 2H, H-5′, H-5″), 5.12 (dd, 1H, H-2′, J = 7.80 Hz), 5.23 (s, 1H, C5-*H*), 7.26 (d, 2H, J =8.4 Hz, Ar-*H*), 7.45 (d, 2H, J = 8.4 Hz, Ar-*H*), 7.67 (d, 1H, H-1′, J = 7.80 Hz), 9.20, 10.30 (2brs, 2NH, D_2O exchangeable).
11e	$[M^+ + 1]$, 451 (19) $[M^+]$, 450 (69)	3400–3100 (br, OH, NH), 3021 (CH aryl), 2929 (CH alkyl), 1708 (C=O)	δ 0.91 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.83–2.03 (m, 4H, $2CH_2$), 3.63 (m, 4H, 4OH), 4.32 (m, 1H, H-3′), 4.44 (m, 1H, H-4′), 4.69 (m, 2H, H-5′, H-5″), 5.10 (dd, 1H, H-2′, J = 7.67 Hz), 5.20 (s, 1H, C5-*H*), 7.22 (d, 2H, J = 8.5 Hz, Ar-*H*), 7.40 (d, 2H, J = 8.5 Hz, Ar-*H*), 7.78 (d, 1H, H-1′, J = 7.75 Hz), 9.80, 10.70 (2brs, 2H, 2NH).
11f	$[M^+ + 1]$, 451 (30) $[M^+]$, 450 (88)	3430–3150 (br, OH, NH), 3018 (CH aryl), 2931 (CH alkyl), 1705 (C=O)	δ 0.89 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.87–2.09 (m, 4H, $2CH_2$), 3.65 (m, 4H, 4OH), 4.29 (m, 1H, H-3′), 4.37 (m, 1H, H-4′), 4.69 (m, 2H, H-5′, H-5″), 5.13 (dd, 1H, H-2′, J = 7.72 Hz), 5.26 (s, 1H, C5-*H*), 7.18 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.31 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.67 (d, 1H, H-1′, J = 7.83 Hz), 9.15, 10.45 (2brs, 2NH).
13a	$[M^+ + 1]$, 690 (17) $[M^+]$, 689 (68)	3270 (br, NH) 3036 (CH aryl), 2919 (CH alkyl), 1687–1720 (6C=O)	δ 0.90 (s, 3H, CH_3), 1.07(s, 3H, CH_3), 1.80–2.30 (m, 19H, $2CH_2$ +$5CH_3$), 3.98–4.20 (m, 2H, H-5′, H-5″), 4.40 (m, 1H, H-4′), 5.10 (t, 1H, H-3′, J = 8.23 Hz), 5.25 (t, 1H, H-2′, J = 7.86 Hz), 5.36 (s, 1H, C5-*H*), 5.95 (d, 1H, H-1′, J = 8.27 Hz), 7.23 (d, 2H, J = 8.2 Hz, Ar-*H*), 7.38 (d, 2H, J = 8.2 Hz, Ar-*H*), 9.90 (br, NH, D_2O exchangeable)
13b	$[M^+ + 1]$, 690 (22) $[M^+]$, 689 (91)	3250 (br, NH), 3038 (CH aryl), 2923 (CH alkyl), 1688–1715 (6C=O)	δ 0.82 (s, 3H, CH_3), 0.99(s, 3H, CH_3), 1.93–2.36 (m, 19H, $2CH_2$ +$5CH_3$), 3.97–4.14 (m, 2H, H-5′, H-5″), 4.30–4.41 (m, 1H, H-4′), 4.88–4.99 (m, 2H, H-3′, H-2′), 5.74 (s, 1H, C5-*H*), 5.97 (d, 1H, H-1′, J =8.19 Hz) 7.20 (d, 2H, Ar-*H*, J = 8.2 Hz), 7.35 (d, 2H, Ar-*H*, J = 8.2 Hz), 9.79 (br, NH).
13c	$[M^+ + 1]$, 690 (19) $[M^+]$, 689 (88)	3290 (br, NH) 3029 (CH aryl), 2927 (CH alkyl), 1690–1718 (6C=O)	δ 0.83 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.90–2.34 (m, 19H, $2CH_2$ + $5CH_3$), 3.95–4.18 (m, 2H, H-5′, H-5″), 4.29–4.34 (m, 1H, H-4′), 4.83–4.95 (m, 2H, H-3′, H-2′), 5.68 (s, 1H, C5-*H*), 5.93 (d, 1H, H-1′, J = 8.21 Hz) 7.26 (d, 2H, Ar-*H*, J = 8.1 Hz), 7.38 (d, 2H, Ar-*H*, J =8.1 Hz), 9.79 (br, NH).
13d	$[M^+ + 1]$, 618 (27) $[M^+]$, 617 (100)	3300 (br, NH) 3023 (CH aryl), 2919 (CH alkyl), 1692–1719 (5C=O)	δ 0.87 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.95–2.36 (4 CH_3+ $2CH_2$), 4.23–4.34 (m, 2H, H-4′, H-4″), 5.25 (t, 1H, H-3′, J = 8.6 Hz), 5.23 (s, 1H, C-*H*), 5.40 (t, 1H, H-2″, J = 8.6 Hz), 5.60 (d, 1H, H-1′, J = 8.5 Hz), 7.20 (d, 2H, Ar-*H*, J = 8.4 Hz), 7.42 (d, 2H, Ar-*H*, J = 8.4 Hz), 10.40 (br, NH).
13e	$[M^+ + 1]$, 618 (19) $[M^+]$, 617 (87)	3320 (br, NH) 3027 (CH aryl), 2909 (CH alkyl), 1695–1715 (5C=O)	δ 0.90 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.99–2.38 (4 CH_3+ $2CH_2$), 4.19–4.30 (m, 2H, H-4′, H-4″), 5.23 (t, 1H, H-3′, J = 8.5 Hz), 5.28 (s, 1H, C5-*H*), 5.39 (t, 1H, H-2″, J = 8.7 Hz), 5.64 (d, 1H, H-1′, J = 8.5 Hz), 7.16 (d, 2H, Ar-*H*, J = 8.4 Hz), 7.38 (d, 2H, Ar-*H*, J = 8.4 Hz), 10.20 (br, NH).
13f	$[M^+ + 1]$, 618 (17) $[M^+]$, 617 (69)	3390 (br, NH), 3030 (CH aryl), 2931 (CH alkyl), 1689–1723 (5C=O)	δ 0.89 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.89–2.29 (4 CH_3+ $2CH_2$), 4.17–4.27 (m, 2H, H-4′, H-4″), 5.20 (t, 1H, H-3′, J = 8.3 Hz), 5.26 (s, 1H, C-*H*), 5.42 (t, 1H, H-2″, J = 8.6 Hz), 5.68 (d, 1H, H-1′, J = 8.4 Hz), 7.19 (d, 2H, Ar-*H*, J = 8.3 Hz), 7.35 (d, 2H, Ar-*H*, J =8.3 Hz), 11.00 (br, NH).
14a	$[M^+ + 1]$, 479 (29) $[M^+]$, 478 (73)	3500–3100 (br, OH, NH), 3039 (CH aryl), 2932 (CH alkyl), 1692 (C=O)	δ 0.90 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.89–2.06 (m, 4H, $2CH_2$), 3.51 (m, ,5H,5OH, D_2O exchangeable), 3.86 (m, 1H, H-4′), 4.19 (m, 2H, H-5′, H-5″), 4.47 (m, 1H, H-3′), 4.72 (m, 1H, H-2′), 5.27 (s, 1H, C5-*H*), 5.65 (m, 1H, H-1′), 7.18 (d, 2H, J = 8.4 Hz, Ar-*H*), 7.42 (d,2H, J = 8.4 Hz,Ar-*H*), 9.15 (br, NH).
14b	$[M^+ + 1]$, 479 (18) $[M^+]$, 478 (65)	3500–3100 (br, OH, NH), 3033 (CH aryl), 2928 (CH alkyl), 1698 (C=O)	δ 0.94 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.86–2.03 (m, 4H, 2CH2), 3.60 (m, 5OH), 3.89 (m, 1H, H-4′), 4.17 (m, 2H, H-5′, H-5″), 4.54 (m, 1H, H-3′), 4.76 (m, 1H, H-2′), 5.25 (s, 1H, C5-*H*), 5.67 (m, 1H, H-1′), 7.21 (d, 2H, J = 8.2 Hz, Ar-*H*), 7.39 (d, 2H, J =8.2 Hz, Ar-*H*), 9.70 (br, NH).
14c	$[M^+ + 1]$, 479 (22) $[M^+]$, 478 (64)	3500–3150 (br, OH, NH), 3040 (CH aryl), 2938 (CH alkyl), 1695 (C=O)	δ 0.86 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.83–2.00 (m, 4H, $2CH_2$), 3.62 (m, 5OH), 3.77 (m, 1H, H-4′), 4.16 (m, 2H, H-5′, H-5″), 4.52 (m, 1H, H-3′), 4.71 (m, 1H, H-2′), 5.30 (s, 1H, C5-*H*), 5.72 (m, 1H, H-1′), 7.18 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.33 (d, 2H, J =8.1 Hz, Ar-*H*), 10.00 (br, NH).
14d	$[M^+ + 1]$, 449 (18) $[M^+]$, 448 (68)	3430–3100 (br, OH, NH), 3023 (CH aryl), 2939 (CH alkyl), 1716 (C=O)	δ 0.89 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.88–2.03 (m, 4H, $2CH_2$), 3.84 (m, 4OH, D2O exchangeable), 4.33 (m, 1H, H-3′), 4.56 (m, 2H, H-4′, H-4″), 5.17 (t, 1H, H-2′, J = 7.6 Hz), 5.31 (s, 1H, C5-*H*), 5.61 (d, 1H, H-1′, J = 7.8 Hz), 7.16 (d, 2H, J = 8.4 Hz, Ar-*H*), 7.28 (d, 2H, J = 8.4 Hz, Ar-*H*), 10.30 (br, NH).
14e	$[M^+ + 1]$, 449 (17) $[M^+]$, 448 (73)	3500–3100 (br, OH, NH), 3021 (CH aryl), 2930 (CH alkyl), 1715 (C=O)	δ 0.92 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.89–2.06 (m, 4H, $2CH_2$), 3.78 (m, 4OH), 4.29 (m, 1H, H-3′), 4.59 (m, 2H, H-4′, H-4″), 5.21 (s, 1H, C5-H), 5.29 (t, 1H, H-2′, J = 7.4 Hz), 5.64 (d, 1H, H-1′, J = 7.9 Hz), 7.20 (d, 2H, J = 8.6 Hz, Ar-*H*), 7.36 (d, 2H, J = 8.6 Hz, Ar-*H*), 10.15 (br, NH).
14f	$[M^+ + 1]$, 449 (20) $[M^+]$, 448 (76)	3440–3100 (br, OH, NH), 3024 (CH aryl), 2929 (CH alkyl), 1710 (C=O)	δ 0.85 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.87–2.02 (m, 4H, $2CH_2$), 3.73 (m, 4OH), 4.35 (m, 1H, H-3′), 4.57 (m, 2H, H-4′, H-4″), 5.15 (t, 1H, H-2′, J = 7.7 Hz), 5.30 (s, 1H, C5-*H*), 5.69 (d, 1H, H-1′, J = 7.8 Hz), 7.19 (d, 2H, J = 8.4 Hz, Ar-*H*), 7.40 (d, 2H, J = 8.4 Hz, Ar-*H*), 10.55 (br, NH).

Table 6
^{13}C NMR spectral data of some newly synthesized compounds.

Compd. no.	^{13}C NMR (δ, ppm) (DMSO-d_6)
1b	δ 20.39, 20.49 ($2CH_3$), 27.39, 28.64 (2 CH_2), 91.20, 91.34 (2C, C-4 + C-7), 127.98, 129.21, 133.19, 140.95, 142.78, 153.74 (6 line for 8 sp^2 carbons), 174.3 (C=S), 192.20 (C=O).
2b	δ 20.36, 20.45 ($2CH_3$), 27.41, 28.63 (2 CH_2), 90.77, 91.21 (2C, C-4 + C-7), 127.85, 129.34, 133.29, 140.79, 142.95, 153.86, 158.90 (7 line for 9 sp^2 carbons), 191.15 (C=O).
6	δ 20.50, 20.64 ($2CH_3$), 27.33, 28.78 (2 CH_2), 31.42 (1C, SCH_3), 91.09, 91.75 (2C, C-4 + C-7), 128.45, 129.54, 133.89, 140.73, 142.79, 153.96, 159.00 (7 line for 9 sp^2 carbons), 192.00 (C=O).
10a	δ 20.40, 21.26 ($2CH_3$), 28.51, 29.36 (2 CH_2), 34.87 (CH_2), 35.20, 36.13, 36.78, and 38.50 (4 CH_3), 67.90 (C-4′), 69.37 (C-2′), 72.75 (C-3′), 75.56 (C-5′), 80.69 (C-1′), 89.73, 90.45 (2C, C-4 + C-7), 127.29, 128.56, 133.47, 141.85, 144.46, 153.89, 158.00 (7 line for 9 sp^2 carbons), 169.31, 169.54, 169.95, 169.98 (4C=O ester) 190.65 (C=O).
11b	δ 20.39, 21.12 ($2CH_3$), 28.40, 29.21 (2 CH_2), 32.86 (CH_2), 67.29, 67.68, 70.31 and 71.53 (4 CH), 90.23, 91.18 (2C, C-4 + C-7), 126.30, 128.16, 133.49, 140.90, 142.52, 143.78, 153.87, 158.66 (8 line for 10 sp^2 carbons), 190.65 (C=O)
13b	δ 20.41, 20.50 ($2CH_3$), 28.21, 29.13 (2 CH_2), 32.38 (CH_2), 38.15, 38.57, 38.88, 39.81, 40.71 (5 CH_3), 67.04, 67.24, 70.03 and 70.83 (4 CH), 90.77, 91.21 (2C, C-4 + C-7), 127.85, 129.34, 133.29, 140.79, 141.27, 142.95, 153.86, 158.90 (8 line for 10 sp^2 carbons), 168.90, 169.31, 169.54, 169.95, 169.98 (5C=O ester), 192.78 (C=O)
14b	δ 21.30, 21.64 ($2CH_3$), 28.31, 29.17 (2 CH_2), 30.95 (CH_2), 67.15, 67.45, 70.18 and 71.60 (4 CH), 90.52, 91.31 (2C, C-4 + C-7), 126.68, 128.56, 134.41, 141.80, 142.33, 143.86, 153.95, 158.56 (8 line for 10 sp^2 carbons), 191.41 (C=O)

*4.2.2. 4-(4-Chlorophenyl)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one-2-thione (**1b**)*

The compound was obtained from the reaction of 4-chlorobenzaldehyde, as a white powder crystallized from ethanol.

*4.2.3. 4-(4-Anisyl)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one-2-thione (**1c**)*

The compound was obtained from the reaction of 4-anisaldehyde, as a white powder crystallized from ethanol.

*4.3. 4-Aryl-2-hydrazino-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**2a–c**)*

General procedure. A suspension of compound **1a–c** (0.01 mol) in hydrazine hydrate (99%, 20 ml) was stirred under reflux for 10 h. The reaction mixture was allowed to cool to room temperature. The solid precipitated was filtered off, washed with ethanol, dried and crystallized from dimethylformamide to produce **2a–c** in high yields.

*4.3.1. 4-Phenyl-2-hydrazino-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**2a**)*

The compound was obtained from the reaction of **1a**, as a yellow powder, crystallized from DMF.

*4.3.2. 4-(4-Chlorophenyl)-2-hydrazino-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**2b**)*

The compound was obtained from the reaction of **1b**, as a yellow powder, crystallized from DMF.

*4.3.3. 4-(4-Anisyl)-2-hydrazino-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**2c**)*

The compound was obtained from the reaction of **1c**, as a yellow powder, crystallized from DMF.

*4.4. 4-(4-Chlorophenyl)-2-(arylmethylenehydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**3a–c**)*

General procedure. A mixture of **2b** (0.01 mol) and the appropriate aromatic aldehyde (0.01 mol) was stirred under reflux in glacial acetic acid (30 mL) for 30 min. The reaction mixture was allowed to cool to room temperature, whereby the solid formed was filtered off and crystallized from appropriate solvent to produce (**3a–c**) in high yield.

*4.4.1. 4-(4-Chlorophenyl)-2-(phenylmethylenehydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**3a**)*

It was obtained from compound **2b** (0.01 mol) and benzaldehyde (0.01 mol) as yellow crystals, crystallized from DMF.

*4.4.2. 4-(4-Chlorophenyl)-2-(4-chlorophenylmethylenehydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**3b**)*

It was obtained from compound **2b** (0.01 mol) and 4-chlorobenzaldehyde (0.01 mol) as yellow crystals, crystallized from DMF.

*4.4.3. 4-(4-Chlorophenyl)-2-(4-anisylmethylenehydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**3c**)*

It was obtained from compound **2b** (0.01 mol) and 4-anisaldehyde (0.01 mol) as yellow crystals, crystallized from DMF.

*4.5. 3,4-Di(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-*b*]quinazolin-6-one (**4**)*

A solution of compound **3b** (0.01 mol) in acetic anhydride–pyridine (30 ml, 2:1) was stirred at room temperature for 24 h, poured onto water (100 ml) and the solid formed was collected by filtration and crystallized from dioxane to afford **4**.

*4.6. 4-(4-Chlorophenyl)-2-methylthio-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**6**)*

To a warmed ethanolic KOH solution (prepared by dissolving 0.01 mol of KOH in 50 mL ethanol) was added each of compound **1b** (0.01 mol), the heating was continued for 30 min and the mixture was allowed to cool to room temperature, and the proper methyliodide (0.012 mol) was added. The mixture was stirred under reflux for 5 h, then cooled to room temperature, poured into cold water (100 mL). The solid product precipitated was filtered off washed with 100 mL water. The product was dried to produce (**6**), as pale yellow crystals, crystallized from ethanol.

*4.7. Preparation of the acetylated thionucleosides (**10a–c**)*

Method A. To a solution of **1b** (0.01 mol) in aqueous potassium hydroxide (0.01 mol) in distilled water (5 ml) was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco-/or galactopyranosyl bromide (**9a**,**b**) or 2,3,5-tri-*O*-acetyl-α-D-ribofuranosyl bromide (**9c**) (0.015 mol) in acetone (40 ml). The reaction mixture was stirred at room temperature for 24 h (under TLC control). The solvent was evaporated under reduced pressure at 40 °C, and the crude product was filtered off and washed with distilled water to remove KBr formed. The product was dried, and crystallized from ethanol to afford **10a–c**.

Method B. Compound **1b** (0.01 mol) was stirred under reflux, and dry conditions in 50 ml hexamethyldi-silane (HMDS) in the presence of ammonium sulfate (0.01 mol) for 50–60 h. The clear solution formed was cooled and the solvent was evaporated in vacuo to give the silylated compound **7** as yellow oil. The latter oil was dissolved in acetonitrile (10 ml) and was added to a solution of sugar acetate in acetonitrile (5 ml) followed by addition of $SnCl_4$

(1.8 ml). The reaction mixture was stirred at room temperature for 16–20 h (under TLC control). The mixture was poured into saturated sodium bicarbonate solution and extracted the thioglycosides by diethylether + ethylacetate (1:1, 100 ml). Evaporate the solvent under reduced pressure to furnish crude nucleosides which were purified by column chromatography (30% ethylacetate in ether) to afford the pure thioglycosides **10a**,**b**.

*4.7.1. 4-(4-Chlorophenyl)-7-dimethyl-3,4,6,8-tetrahydro-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl-thio)-3H-quinazolin-5-one-2-thione (**10a**)*

It was obtained from compound **1b** (0.01 mol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)bromide (**9a**) (0.01 mol) as yellow powder, crystallized from benzene.

*4.7.2. 4-(4-Chlorophenyl)-7-dimethyl-3,4,6,8-tetrahydro-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl-thio)-3H-quinazolin-5-one-2-thione (**10b**)*

It was obtained from compound **1b** (0.01 mol) and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)bromide (**9b**) (0.01 mol) as yellow powder, crystallized from n-hexane.

*4.7.3. 4-(4-Chlorophenyl)-7-dimethyl-3,4,6,8-tetrahydro-2-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl-thio)-3H-quinazolin-5-one-2-thione (**10c**)*

It was obtained from compound **1b** (0.01 mol) and 2,3,5-tri-*O*-acetyl-α-D-ribofuranosyl)bromide (**9c**) (0.01 mol) as yellow powder, crystallized from n-hexane.

*4.8. 4-(Chlorophenyl)-2-(glycosylhydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**11a**–**f**)*

General procedure. A mixture of **2b** (0.01 mol), the appropriate mono-sacchride (aldohexoses and or aldopentoses) (0.01 mol) and a catalytic amount of piperidine was heated at reflux in dioxane (50 mL) for 15–20 h, the reaction mixture was allowed to cool to room temperature, the precipitate was filtered off, washed with ethanol, dried and crystallized to afford the title compounds.

*4.8.1. 4-(Chlorophenyl)-2-(glucosylhydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**11a**)*

It was obtained from D-glucose (10 mmol), as a white powder, crystallized from dioxane.

*4.8.2. 4-(Chlorophenyl)-2-(mannosylhydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**11b**)*

It was obtained from D-mannose (10 mmol), as a white powder, crystallized from ethanol.

*4.8.3. 4-(Chlorophenyl)-2-(galactosylhydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**11c**)*

It was obtained from D-galactose (10 mmol), as a white powder crystallized from dioxane.

*4.8.4. 4-(Chlorophenyl)-2-(arabinosylhydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**11d**)*

It was obtained from D-arabinose (10 mmol), as a white powder, crystallized from ethanol.

*4.8.5. 4-(Chlorophenyl)-2-(ribosylhydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**11e**)*

It was obtained from D-ribose (10 mmol), as a white powder, crystallized from ethanol.

*4.8.6. 4-(Chlorophenyl)-2-(xylosylhydrazon)-7-dimethyl-3,4,6,8-tetrahydro-quinazolin-5-one (**11f**)*

It was obtained from D-xylose (10 mmol), as a white powder, crystallized from ethanol.

*4.9. 3-(Penta-*O*-acetyl/or tetra-*O*-acetlyglycosyl)-4-aryl-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**13a**-**f**)*

General procedure. A solution from each of **11a**–**f** (10 mmol) in a mixture of acetic anhydride-pyridine (40 mL, 2:1), was stirred at room temperature for 24 h, poured onto water (100 mL). The mixture was then extracted with chloroform several times (150 mL), after the removal of chloroform under reduced pressure; the precipitate was filtered off, dried, and crystallized from the proper solvent to obtain **13a**–**f**.

*4.9.1. 3-(1′,2′,3′,4′,5′-Penta-*O*-acetylglucosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**13a**)*

It was obtained from **11a** as white powder, crystallized from benzene.

*4.9.2. 3-(1′,2′,3′,4′,5′-Penta-*O*-acetylmannosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,-4-triazolo [3,4-b]quinazolin-6-one (**13b**)*

It was obtained from **11b** as white powder, crystallized from benzene.

*4.9.3. 3-(1′,2′,3′,4′,5′-Penta-*O*-acetylglactoosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo [3,4-b]quinazolin-6-one (**13c**)*

It was obtained from **11c** as white powder, crystallized from cyclohexane.

*4.9.4. 3-(1′,2′,3′,4′-Tetra-*O*-acetylarabinosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**13d**)*

It was obtained from **11d** as white powder, crystallized from benzene.

*4.9.5. 3-(1′,2′,3′,4′-Tetra-*O*-acetylribosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**13e**)*

It was obtained from **11e** as white powder, crystallized from cyclohexane.

*4.9.6. 3-(1′,2′,3′,4′-Tetra-*O*-acetylxylosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**13f**)*

It was obtained from **11f** as white powder, crystallized from benzene.

*4.10. 3-(Glycosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**14a**–**c**)*

General procedure. A solution from each of **13a**–**f** (0.05 mol) in methanol (10% ammonia solution, 50 mL), was stirred at room temperature for 24 h, and then neutralized with hydrochloric acid solution (pH control). The precipitate formed was filtered off, wash with cold water, dried and crystallized, to obtain **14a**–**f** respectively.

*4.10.1. 3-(Glucosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**14a**)*

It was obtained from **13a** as a white powder, crystallized from ethanol.

*4.10.2. 3-(Mannosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**14b**)*

It was obtained from **13b** as a white powder, crystallized from ethanol.

*4.10.3. 3-(Galactosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**14c**)*

It was obtained from **13c** as a white powder, crystallized from ethanol.

*4.10.4. 3-(Arabinosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**14d**)*

It was obtained from **13d** as a white powder, crystallized from ethanol.

*4.10.5. 3-(Ribosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**14e**)*

It was obtained from **13e** as a white powder, crystallized from ethanol.

*4.10.6. 3-(Xylosyl)-4-(4-chlorophenyl)-7-dimethyl-1,4,6,8-tetrahydro-1,2,4-triazolo[3,4-b]quinazolin-6-one (**14f**)*

It was obtained from **13f** as a white powder crystallized from ethanol.

4.11. Pharmacological screening

Adult male Sprague-Dawley rats, weighing 150–200 g were used for anti-inflammatory and ulcerogenic activity, whereas Swiss albino mice of both sex weighing 25–30 g were used for analgesic activity. International principles and local regulations concerning the care and used of laboratory animals were taken into account [17]. The animals had free access to standard commercial diet and water adlibitum and were kept in rooms maintained at $22 \pm 1\ ^{\circ}C$ with 12 h light dark cycle. The experimental protocol was approved by the animal ethics committee of National Research Center, Cairo, Egypt. All the compounds (70 mg kg^{-1} body mass) and the reference NSAID Ibuprofen (70 mg kg^{-1} body mass) were suspended in 1% carboxymethyl cellulose (CMC) and administered orally using animal feeding needle. The control groups received appropriate volumes of vehicle (1% CMC, oral) only.

4.11.1. Anti-inflammatory assay

This activity was performed by the following procedure of Winter et al. [18], on groups of six animals each. A freshly prepared suspension of carrageenan (1.0% m/V, 0.1 mL) was injected in the planer region of the right hind paw of each rat. One group was kept as control and the animals of other group were pretreated with the test drugs (70 mg kg^{-1} body mass) suspended in 1.0% CMC given orally 1 h before the carrageenan treatment. The volume was measured before and after 4 h of carrageenan treatment using a pleythysmometer.

4.11.2. Analgesic activity

Mice were kept individually in the test cage before acetic acid injection and habituated for 30 min. Screening of analgesic activity was performed after *p.o.* administration of test drugs at a dose of 70 mg kg^{-1} body mass. The compounds which exhibited good anti-inflammatory activity comparable to that of ibuprofen were screened for analgesic activity. All compounds were dissolved in 1.0% CMC solution. One group was kept as control and received *p.o.* 1% CMC. After 1 h of drug administration, 0.10 mL of 1% acetic acid solution was given to mice intraperitoneally. The acetic acid induced writhing test [19] showed stretching movements involving arching of the back, elongation of the body and extension of hind limbs which were counted for 5–15 min of acetic acid injection.

4.11.3. Ulcerogenicty activity

Acute ulcerogenesis test was done according to Cioli et al. [20]. Wister rats were divided into different groups consisting of six animals each. Ulcerogenic activity was evaluated after *p.o.* administration of the test compounds or ibuprofen at the dose 200 mg kg^{-1} body mass. Control rats received *p.o.* the vehicle (suspension of 1% methylcellulose). Food but not water was removed 24 h before administration of the test compounds. After the drug treatment, the rats were fed normal diet for 17 h and were then sacrificed. The stomach was removed and opened along the greater curvature, washed with distilled water and cleaned gently by dipping in saline. The mucosal damage was examined by means of a magnifying glass. For each stomach the mucosal damage was assessed according to the following scoring system: 0.5 redness; 1.0 spot ulcers; 1.5 hemorrhagic streaks; 2.0 ulcers >3 but ≤ 5; 3.0 ulcers >5. The mean score of each treated group minus the mean score of control group was regarded as severity index of gastric mucosal damage.

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