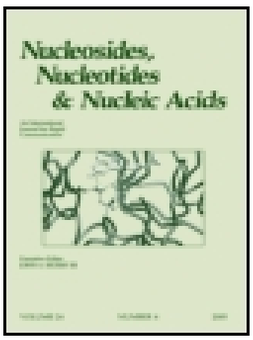

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis and Biological Evaluation of 2-Oxo/Thioxoquinoxaline and 2-Oxo/Thioxoquinoxaline-Based Nucleoside Analogues

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ABSTRACT

Several O- and S-quinoxaline glycosides have been prepared by glycosidation of 3-methyl-2-oxo(thioxo)-1,2-dihydroquinoxalines **1a,b** with α-D-glucopyranosyl, α-D-galactopyranosyl, and α-D-lactosyl bromide in the presence of K_2CO_3 followed by deacetylation with Et_3N/H_2O. Furthermore, alkylation of **1a,b** with 4-bromobutyl acetate, 2-acetoxyethoxymethyl bromide, and 3-chloropropanol afforded the corresponding O- and S-acycloquinoxaline nucleosides. Reaction of **1b** with chloroacetic acid followed by condensation with sulfacetamide and sulfadiazine in the presence of Et_3N/THF and ethyl chloroformate gave the corresponding sulfonamide derivatives **14** and **15**, respectively. The structures of new compounds were confirmed by using IR, ^1H, ^{13}C NMR spectra and microanalysis. Some of these compounds were screened in vitro for antitumor and antifungal activities.

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2-Oxo(thioxo)quinoxaline; cyclic/acyclic nucleosides; sulfonamide; biological evaluation

Introduction

Quinoxaline is an important nitrogen-containing heterocyclic compound containing a ring complex made up of benzene and pyrazine rings. For example, quinoxaline is a part of various antibiotics such as echinomycin, levomycin, and actinolutin that are known to inhibit growth of gram-positive bacteria.[1,2] Derivatives of quinoxaline have different pharmacological activities such as antibacterial,[3–9] antifungal,[10,11] antiviral,[12] antineoplastic,[13,14] antidepressant,[15,16] anticonvulsant,[17] anti-inflammatory,[18,19] and antithrombotic,[20] NMDA antagonistic,[21] antiglucoma,[22] antimalarial,[23] antituberculosis,[24,25] and anti-HIV activities.[26] In addition, quinoxaline compounds possess intrinsic diuretic, uterotonic, hypertensive, and phosphodiesterase inhibitor activity. These are also used in agricultural field as herbicides, fungicides, and insecticides. In addition, quinoxaline derivatives are also useful in the formation of dyes, efficient electron

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luminescent materials, organic semiconductor, cavitands, and dehydoannulenes.[27–29] 3-Methyl-2(1*H*)-quinoxalinones have been postulated as important intermediates for the synthesis of various useful heterocyclic compounds.[30–33] Hence, preparation of 3-methyl-2(1*H*)-quinoxalinones has attracted considerable attention in recent years. These compounds are generally prepared by the condensation of *o*-phenylenediamine with pyruvic acid, but multiple by-products are obtained when asymmetrical diamines were used as starting materials.[34] In addition, these compounds can also be obtained by some other regioselective methods.[35–37] Continuing our search for nucleosides with biological activities,[38–40] we wish to report the synthesis of 3-methyl-2(1*H*)quinoxalinone/thione (**1a,b**) and their *O- and S*-cyclic/acyclic nucleosides.

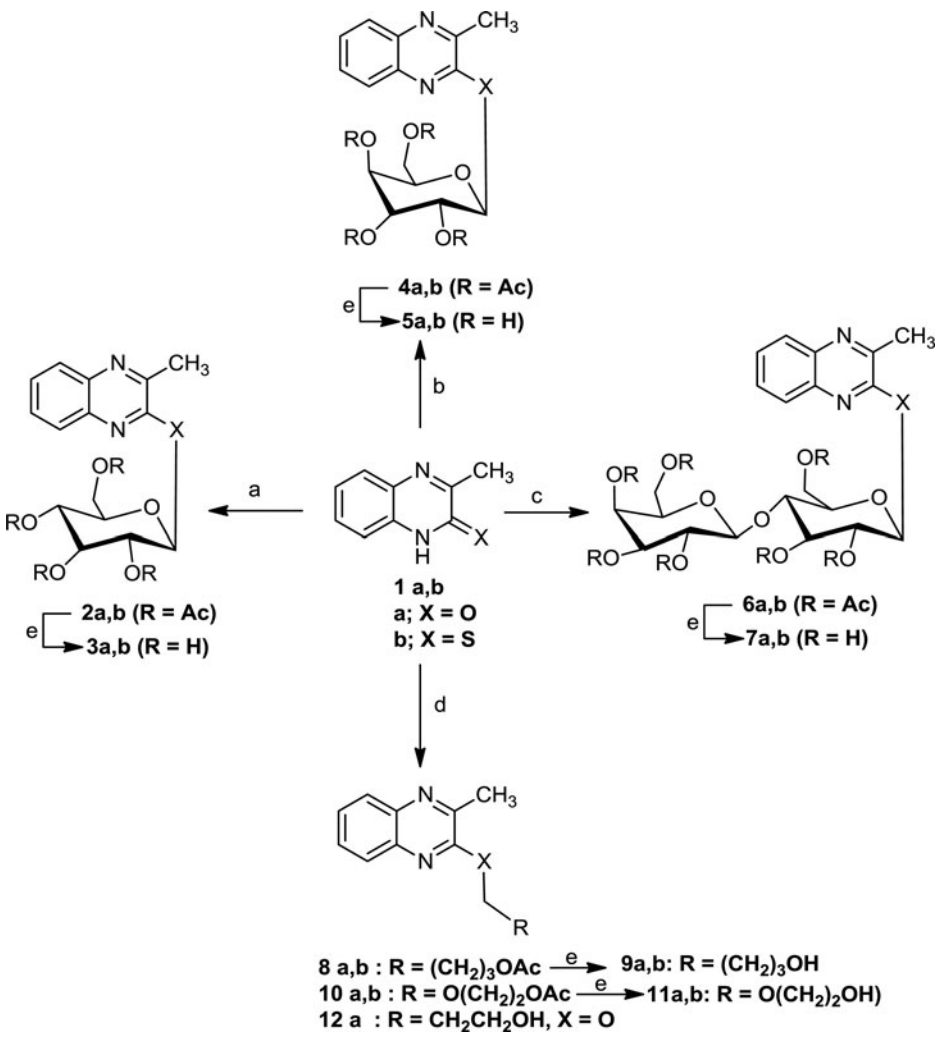
Results and discussion

Chemistry

3-Methyl-2(1*H*)quinoxalinone/thione (**1a,b**) (Scheme 1) were synthesized by the reaction of *o*-phenylenediamine with sodium pyruvate in water according to the procedure given in literature.[32,41] Analyses are reported in the experimental section due to the difference in melting points. Compounds **1a,b** were obtained as an amido tautomer as suggested by the presence of bands in IR spectra characteristic for NH and C=O/C=S of amide/thioamide functional groups. Compounds **1a,b** were coupled with different organohalide compounds in the presence of K_2CO_3 in dry *N,N*-dimethylformaide (DMF) to give amide nucleoside analogues (Scheme 1).

Deacetylation with triethylamine (TEA) in H_2O/MeOH was effective if these coupling agents gave O-acetylated products. Products before and after deacetylation were purified by recrystallization with ethanol. Structures of these separated coupling products were confirmed by IR, NMR, and elemental analysis. Compounds **1a,b** were coupled with peracetylated α-D-glucopyranosyl, α-D-galactopyranosyl, and α-D-lactosyl bromide, leading to the formation of the corresponding *O*- and *S*-glycosides **2a,b**, **4a,b**, and **6a,b**, respectively. The deacetylation of these glycosides gave the deacetylated products **3a,b**, **5a,b**, and **7a,b**, respectively. In all these compounds, the acetylated *O*-β-glycosides were obtained in yields ranging from 59–86%. Formation of the *O*- and *S*-glycosides was confirmed by IR bands, which revealed the absence of amidic C=O and C=S functional groups at 1665 and 1326 cm^{-1} for each compound. These resulting nucleosides have a β-configuration as indicated by the ^{1}H NMR coupling constant of anomeric protons ($J > 7.5$ Hz) due to diaxial coupling with H-2′.

The acyclic nucleosides analogue were synthesized by the coupling of **1a,b** with three different substituted alkyl halides (Scheme 1) (namely 4-bromobutyl acetate,[42] 2-acetoxyethoxymethyl bromide,[43] and 3-chloropropanol) to give, after deprotection, the *O*- and *S*-alkylation products **9a,b, 11a,b**, and **12a**, respectively, in



Scheme 1 The cyclic and acylic nucleosides of quinoxaline derivatives (**1a,b**). Reaction conditions and reagents: (a), (b), and (c) Glucosyl/galactosyl and lactosyl bromode, K_2CO_3, dry DMF (12 h), r.t. (d) 4-bromobutyl acetate, 2-acetoxyethoxymethyl bromide, and 3-chloropropanol, K_2CO_3, dry DMF (12 h), r.t. (e) MeOH/Et_3N and few drops of water (6 h), r.t.

good yields (Scheme 1). The products lacked the IR bands corresponding to the amide C=O and C=S functional groups in contrast to the results that we observed in our previous work.[44] Other published work showed that a 2-oxoquinoxaline structure is also glycosylated at the 2-oxo or 2-thioxo position under the same conditions.[45] Furthermore, similar 2-oxoquinoxaline compound was also reported to couple with ethyl bromoacetate at the 2-oxo position under reaction conditions similar to those used in our work.[46] Compound **13** was obtained from the alkylation of 3-methyl-2(1*H*)-quinoxalinethione (**1b**) using chloroacetic acid in refluxing ethanolic KOH[47] (Scheme 2). The chemical structure was confirmed by IR spectrum and chemical properties due to the free-COOH group making compound **13** soluble in alkaline solutions. Compound **13** was reacted with sulfacetamide

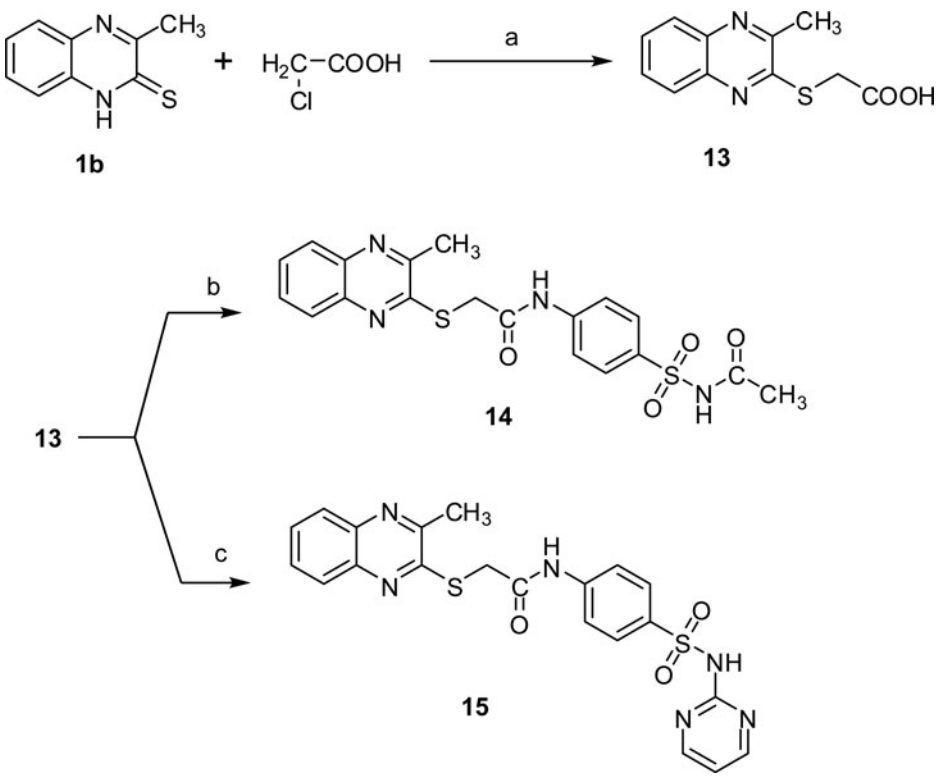
and sulfadiazine in tetrahydrofuran (THF), triethylamine (TEA), and ethyl chloroformate, leading to compounds **14** and **15** in good yields (>80%) respectively (Scheme 2).

The structures of **14** and **15** were confirmed by IR, ^{1}H NMR, mass spectroscopy, and elemental analyses. The IR spectrum of **14** displayed bands at 3423, 3356, 1729, and 1651 cm^{-1} characteristic for 2NH and 2C=O functional groups, respectively. The mass spectrum showed a parent ion peak at m/e (M^+) = 430 (3.19%). ^{1}H NMR spectrum for compound **15** showed signals at δ 2.63 and 4.14 ppm characteristic for CH_3 and SCH_2CO, respectively, in addition to signal at δ 10.24 ppm for two NH protons. The mass spectrum showed a parent ion at m/e (M^+) = 367 (2.25%). The elemental analyses of compounds **14** and **15** are in agreement with the assigned structure.

Biology

Evaluation of antitumor activities

Cytotoxic activity. The cytotoxic effects of the prepared compounds (**2b**, **5a**, **7a**, **8b**, **11a, 14**, and **15**) were assessed toward hepatocellular carcinoma (HEPG-2) and



Scheme 2 Sulfonamide derivatives of quinoxaline **1a,b**. Reaction conditions and reagents: (a) Chloroacetic acid, EtOH, KOH, reflux (6 h). (b) Sulfacetamide, THF, Et_3N, ethylchloroflormate, r.t. (2 h). (c) Sulfadiazine, THF, Et_3N, ethylchloroformate, r.t. (2 h).

Table 1. Cytotoxic activity of the prepared compounds (**1–7**) toward HEPG-2 and A549 tumor cell lines.

Sample	Compound	IC_{50} (μg/mL)	
		HEPG-2	A549
1	**2b**	121.92	162.3
2	**5a**	59.25	56.23
3	**7a**	37.78	23.3
4	**8b**	102.2	111.7
5	**11a**	66.13	61.57
6	**14**	78.13	56.81
7	**15**	128.3	182.16

(A549) cell lines, using MTT as assay.[48] After 24-h growth of cells on 96 microtiter plates, under standard growth conditions, various concentrations of each compound (10–100 μg/mL) were added to wells of monolayer cells incubated for 48 h at 37°C in a 5% CO_2 incubator. After incubation, the cells were stained with the MTT reagent, washed with 70% ethanol, and the developed color was measured by an ELISA Reader at 570 nm. The assay was based on the ability of active mitochondrial dehydrogenase of living tumor cells to cleave the tetrazolium ring of yellow MTT, forming dark blue insoluble formazan crystals. After solubilization of crystals, the number of viable cells was expressed by the development of dark blue color of soluble formazan at 570 nm. The relative cell viability was calculated by the the following equation:

$$\left([A_{570} \text{ of sample}]/[A_{570} \text{ of control}]\right) \times 100.$$

From the profile of cytotoxic activity (Table 1 and Figure 1), compounds **5a** and **7a** displayed the highest cytotoxic activity toward A549 cells (IC_{50} 56 μg/mL, IC_{50} 23 μg/mL) and HEPG-2 (IC_{50} 59 μg/mL and IC_{50} 38 μg/mL) respectively. Compounds **11a** and **14** exhibit a weak anti-proliferative activity toward A549 cells (IC_{50} 62 μg/mL and IC_{50} 57 μg/mL) and HEPG-2 cells (IC_{50} 66 μg/mL and IC_{50} 78 μg/mL), respectively. However, compounds **2b**, **8b**, and **15** have little cytotoxic activity toward A549 as revealed from the values of half-inhibitory concentrations (IC_{50}), 162, 112, and 182 μg/mL, respectively. The tumor cell line A549 was more vulnerable to all the prepared compounds, compared with the relative resistance of HEPG-2 cells.

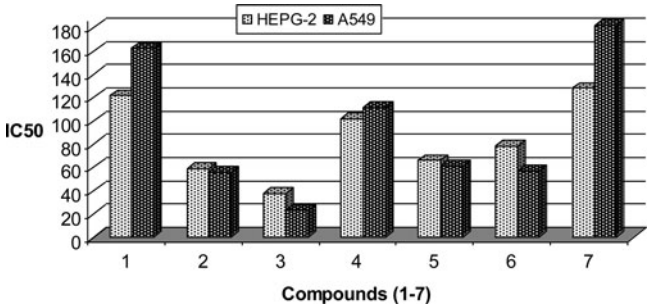


Figure 1. Cytotoxic activity of the prepared compounds (**1–7**) toward HEPG-2 and A549 tumor cell lines.

Table 2. Antimicrobial activity of prepared compounds against *Bacillus subtilis* and *Aspergillus carneus*.

	Diameter of inhibition zone (cm)	
Compound	Aspergillus carneus	Bacillus subtilis
2a	0.2	0
2b	0.1	0
3a	1.1	0
3b	1.1	0
4a	0.3	0
4b	1.2	0
5a	1.7	0.1
5b	0.2	0
7a	1.5	0.4
7b	0.4	0
12a	0.2	0
14	0.1	0
15	0.2	0

Evaluation of antimicrobial activities

The concentration of tested compounds was 0.05 g/10 mL dissolved in DMF. The DMF was used as a negative control for the tested fungal isolate. The antimicrobial activity of the prepared compounds (**2a,b**, **3a,b**, **4a,b**, **5a,b**, **7a,b**, **12a**, **14**, and **15**) was assessed by the cup diffusion method.[49] Standard Dox's agar medium was prepared, and prior to solidification, the medium was seeded with the spore suspension of *Aspergillus carneus*. After incubation of plates for 5 h, holes were made on each plate, injected under aseptic conditions with 500 μL of tested compounds, dissolved in DMSO, against negative control of DMSO solution. The plate cultures were incubated at 30°C for five days, and the development of the inhibition growth zones was observed daily.

From the growth profile of bacterial isolate, *A. carneus*, all the prepared compounds have a relative antimicrobial activity with obvious fluctuation. From the antifungal profile (Table 2), compound **5a** has the maximum antifungal activity, followed by compound **4b**, with similar activity of compounds **3a** and **3b** among the experimented compounds. However, the other synthesized compounds (**2a**, **2b**, **4a**, **5b**, **7b**, **12a**, **14**, and **15**) displayed a fairly inhibitory effect on the viability of tested fungal isolate.

Conclusions

In summary, we have described the synthesis of some *O*- and *S*-cyclic and acyclic quinoxaline nucleosides via alkylation of quinoxalines **1a,b** with glucosyl, galactosyl, and lactosyl bromide and acyclic alkylating agents; in addition, quinoxaline sulfonamide derivatives were synthesized. The in vitro growth inhibitory activities of some new synthesized nucleosides against A549 and HEPG-2 tumor cell lines revealed modest cytotoxic activity, with the most potential compounds being **5a** and **7a**. In addition, compounds **3a,b**, **4b**, **5a**, and **7a** showed moderate activity against *Aspergillus carneus*, while no activity was observed against *Bacillus subtilis*.

Experimental

All melting points were uncorrected and measured using an electro thermal IA 9100 apparatus. The IR spectra (KBr discs) were recorded on a Pye Unicam Sp-3–300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer (Cairo University, Cairo, Egypt). The operation frequency was 300 MHz for ^{1}H and 75.5 MHz for ^{13}C NMR using JOEL-JNM-LA 300-MHz spectrometer. The coupling constants (*J*) are given in hertz. The chemical shifts are expressed on δ (ppm) scale using TMS as a standard reference. Biological evaluations were carried by holding company for Biological Products and Vaccines (Vacsera), Giza, Cairo, Egypt, and the Microbiology Laboratory, Faculty of Science, Zagazig University, Zagazig, Egypt. Elemental analyses were determined on a Perkin Elmer 240 (Microanalysis Center, Cairo University, Egypt).

General procedure for synthesis of compound (1a)

o-Phenylenediamine (5.4 g, 0.5 mol) was dissolved in warm water (60 mL); then was added sodium pyruvate (5.6 g, 0.5 mol) in water (20 mL) portion-wise; after stirring for 1 h, the mixture was acidified with dilute HCl to pH 3. Crystals were separated and collected by filtration and recrystallized from hot water.

General procedure for synthesis of compound (1b)

A mixture of 3-methyl-2-(1*H*)-quinoxalinone (**1a**) (0.01 mol) and P_2S_5 (0.01 mol) was refluxed in dry pyridine (20 mL) for 5 h. The solvent was evaporated and the residue was treated with dilute acetic acid. The solid product was removed by filtration and crystallized from absolute ethanol to give (**1b**).

General procedure for alkylation

In separate experiments, a mixture of **1a** (10 mmol) and potassium carbonate (11 mmol) in dry DMF (15 mL) was stirred for 1 h, and halide (glucosyl bromide, galactosyl bromide, lactosyl bromide, 4-bromobutylacetate, 2-acetoxyethoxymethyl bromide, or 3-chloropropanol (11 mmol)) was added portion-wise to the well-stirred reaction mixture. Stirring was continued overnight at room temperature. The solvent was evaporated, and the residue was washed with water, and treated with ethanol. The obtained precipitate was collected by filtration and recrystallized from ethanol. Similar experiments were carried out with **1b**.

General procedure for deacetylation of 2a,b, 4a,b, 6a,b, 8a,b, and 9a,b

A mixture of the compound (10 mmol) in methanol (20 mL), triethylamine (1 mL), and few drops of water was stirred for 6 h at room temperature, and then the solvent was removed under reduced pressure. The residue was crystallized from ethanol.

2-((3-Methylquinoxalin-2-yl)thio)acetic acid (13)

A solution of **1b** (14.7 mmol) in ethanol (30 mL), KOH (14.7 mmol), and chloroacetic acid (14.7 mmol) was refluxed for 2 h. The hot mixture was filtered and the ethanolic solution was evaporated under reduced pressure. The residue was dissolved in distilled water and acidified with diluted HCl to pH 3. The precipitate was collected by filtration, washed with cold distilled water, and dried in an oven at 40–45°C to provide (**13**), which was recrystallized from ethanol.

General procedure for preparing 14 and 15

An anhydrous solution of **13** (11.4 mmol) and TEA (11.4 mmol) in THF (30 mL) was cooled to 0–5°C. To this solution, an aliquot of ethylchloroformate (11.4 mmol) was added drop-wise with continuous stirring. The resulting mixture was left for 30 min, with continuous stirring at 0–5°C. A cold aqueous solution (10 mL) of sulfadiazine or sulfacetamide (11.4 mmol) and TEA (11.4 mmol) was added to the above mixture. The final mixture was vigorously stirred for 2 h at room temperature, diluted with water (30 mL), and was extracted with diethyl ether (2 × 20 mL). The aqueous phase was acidified with diluted HCl to pH = 3, and extracted with ethyl acetate (3 × 20 mL). The extracts were pooled together, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was treated with petroleum ether (60/80), the precipitated product was collected, dried, and recrystallized from ethanol to give **14** and **15** in good yields.

3-Methylquinoxalin-2(1H)-one (1a)

Colorless crystals; yield 85%, m.p. 238–240°C [lit. 245°C].[32] IR (KBr): 3433 cm^{-1} (NH) and 1665 cm^{-1} (C=O, amide). ^{1}H NMR (DMSO-d_6): $\delta = 2.59$ (s, 3H, CH_3), 7.26 (m, 2H, Ar-H), 7.46 (d, 1H, $J = 7.2$ Hz, Ar-H), 7.70 (d, 1H, $J = 8.4$ Hz, Ar-H), 12.26 (s, 1H, NH). Anal. Calcd. for $C_9H_8N_2O$ (159.16): C, 67.91; H, 4.43; N, 17.60. Found: C, 67.94; H, 4.45; N, 17.56.

3-Methylquinoxaline-2(1H)-thione (1b)

Orange-brown crystals; yield 86%, m.p. 229–230°C [lit. 250–251°C].[32] IR (KBr): 3428 cm^{-1} (NH) and 1326 cm^{-1} (C=S). ^{1}H NMR (DMSO-d_6): $\delta = 2.59$ (s, 3H, CH_3), 7.26 (m, 2H, Ar-H), 7.43 (d, 1H, $J = 7.5$ Hz, Ar-H), 7.70 (d, 1H, $J = 8.45$ Hz, Ar-H), 12.26 (s, 1H, NH). Anal. Calcd. for $C_9H_8N_2S$ (176.24): C, 61.34; H, 4.58; N, 15.90. Found: C, 61.28; H, 4.62; N, 15.87.

2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosyloxy)-3-methyl- quinoxaline (2a)

Colorless crystals; yield 62%, m.p. 138–140°C. IR (KBr): 1757 and 1730 cm^{-1} (C=O, acetoxy). ^{1}H NMR (DMSO-d_6): $\delta = 1.96$, 1.98, 2.02, and 2.05 (4 s, 12H, 4C$\underline{H_3}$CO), 2.59 (s, 3H, CH_3), 4.03 (dd, 1H, $J_{5',6'} = 4.63$, $J_{6',6''} = 12.16$ Hz, H-6′), 4.10 (dd, 1H, $J_{5',6''} = 4.81$, $J_{6',6''} = 12.16$ Hz, H-6″), 4.25 (m, 1H, H-5′), 5.03 (t, 1H, $J_{3',4'} = 9.56$ Hz, H-4′), 5.22 (t, 1H, $J_{1',2'} = 9.30$ Hz, H-2′), 5.53 (t, 1H, $J_{2',3'} = 9.30$ Hz, H-3′), 6.21 (d, 1H, $J_{1',2'} = 10.5$ Hz, H-1′), 7.76–8.01 (m, 4H, Ar-H). ^{13}C NMR (DMSO-d6, δ

ppm): 19.8, 20.0, 20.1, 21.1 ($4CH_3$, CH_3CO) 33.8 (CH_3-quinoxaline), 62.20 (C-6′), 65.1 (C-4′), 66.13 (C-3′), 68.8 (C-2′), 71.23 (C-5′), 94.10 (C-1′), 126.8, 128.5, 128.9, 129.2, 134.9, 157.1, 160.1, 161.2, 169.1, 169.9, 170.2, and 171.5 (Ar-C and C=O). Anal. Calcd. for $C_{23}H_{26}N_2O_{10}$ (490.46): C, 56.32; H, 5.34; N, 5.71. Found: C, 56.29; H, 5.39; N, 5.75.

2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosylsulfanyl) -3-methyl- quinoxaline (2b)

Colorless crystals; yield 60%, m.p. 158–160°C. IR (KBr): 1753 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): $\delta = 1.78$, 1.98, 2.01, and 2.02 (4s, 12H, $4CH_3CO$), 2.59 (s, 3H, CH_3), 4.01 (dd, 1H, $J_{5',6'} = 4.65$, $J_{6',6''} = 12.15$ Hz, H-6′), 4.10 (dd, 1H, $J_{5',6''} = 4.80$, $J_{6',6''} = 12.15$ Hz, H-6″), 4.26 (m, 1H, H-5′), 5.03 (t, 1H, $J_{3',4'} = 9.58$ Hz, H-4′), 5.22 (t, 1H, $J_{1',2'} = 10.2$ Hz, H-2′), 5.54 (t, 1H, $J_{2',3'} = 9.0$ Hz, H-3′), 6.21 (d, 1H, $J_{1',2'} = 10.5$ Hz, H-1′), 7.74–8.01 (m, 4H, Ar-H). Anal. Calcd. for $C_{23}H_{26}N_2O_9S$ (506.53): C, 54.54; H, 5.17; N, 5.53. Found: C, 54.51; H, 5.20; N, 5.56.

2-(β-D-glucopyranosyloxy)-3-methylquinoxaline (3a)

Colorless crystals; yield 82%, m.p. 188–190°C. IR (KBr): 3427 cm^{-1} (broad, 4OH). ^1H NMR (DMSO-d_6): $\delta = 2.49$ (s, 3H, CH_3), 3.18 (m, 6H, H-6′, H-6″, H-5′, H-4′, H-3′ and H-2′), 3.47 (t, 1H, $J = 5.64$ Hz, OH-6′, D_2O exchangeable), 4.05 (t, 1H, $J = 6.60$ Hz, OH-4′, D_2O exchangeable), 4.39 (t, 1H, $J = 5.83$ Hz, OH-3′, D_2O exchangeable), 4.80 (t, 1H, $J = 4.96$ Hz, OH-2′, D_2O exchangeable), 5.78 (d, 1H, $J = 9.93$ Hz, H-1′), 7.28 (m, 2H, Ar-H), 7.46 (d, 1H, $J = 7.2$ Hz, Ar-H), 7.70 (d, 1H, $J = 8.4$ Hz, Ar-H). Anal. Calcd. for $C_{15}H_{18}N_2O_6$ (322.31): C, 55.90; H, 5.63; N, 8.69. Found: C, 55.94; H, 5.61; N, 8.65.

2-(β-D-glucopyranosylsulfanyl)-3-methylquinoxaline (3b)

Colorless crystals; yield 84%, m.p. 194–196°C. IR (KBr): 3364 cm^{-1} (broad, 4OH). ^1H NMR (DMSO-d_6): $\delta = 2.59$ (s, 3H, CH_3), 3.21–3.61 (m, 6H, H-6′, H-6″, H-5′, H-4′, H-3′, and H-2′), 5.65 (d, 1H, $J = 9.30$ Hz, H-1′), 7.28–7.90 (m, 4H, Ar-H). Anal. Calcd. for $C_{15}H_{18}N_2O_5S$ (338.38): C, 53.24; H, 5.36; N, 8.28. Found: C, 53.21; H, 5.38; N, 8.31.

2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-galactopyranosyloxy)-3-methyl- quinoxaline (4a)

Colorless crystals; yield 65%, m.p. 160–162°C. IR (KBr): 1747 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): $\delta = 1.94$, 1.96, 1.97, and 2.17 (4s, 12H, $4CH_3CO$), 2.59 (s, 3H, CH_3), 4.07 (dd, 1H, $J_{5',6'} = 6.21$, $J_{6',6''} = 11.96$ Hz, H-6′), 4.10 (dd, 1H, $J_{5',6''} = 6.43$, $J_{6',6''} = 11.96$ Hz, H-6″), 4.57 (m, 1H, H-5′), 5.36 (dd, 1H, $J_{3',2'} = 8.23$, $J_{3',4'} = 2.50$ Hz, H-3′), 5.39 (dd, 1H, $J_{1',2'} = 8.10$, $J_{2',3'} = 8.23$ Hz, H-2′), 5.49 (dd, 1H, $J_{3',4'} = 2.50$, $J_{4',5'} = 3.60$ Hz, H-4′), 6.43 (d, 1H, $J = 8.10$ Hz, H-1′), 7.69–7.95 (m, 4H, Ar-H). Anal. Calcd. for $C_{23}H_{26}N_2O_{10}$ (490.46): C, 56.32; H, 5.34; N, 5.71. Found: C, 56.35; H, 5.36; N, 5.68.

2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-galactopyranosylsulfanyl) -3-methyl-quinoxaline (4b)

Colorless crystals; yield 62%, m.p. 160–163°C. IR (KBr): 1751 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): $\delta = 1.75$, 1.96, 2.01, and 2.13 (4s, 12H, $4CH_3CO$), 2.59 (s, 3H, CH_3), 3.95 (dd, 1H, $J_{5',6'} = 6.25$, $J_{6',6''} = 12.10$ Hz, H-6′), 4.03 (dd, 1H, $J_{5',6''} = 5.10$, $J_{6',6''} = 12.10$ Hz, H-6″), 4.51 (m, 1H, H-5′), 5.34 (dd, 1H, $J_{2',3'} = 8.96$, $J_{3',4'} = 3.9$ Hz, H-3′), 5.41 (dd, 1H, $J_{1',2'} = 10.8$, $J_{2',3'} = 8.96$ Hz, H-2′), 5.49 (t, 1H, $J_{3',4'} = 3.9$, $J_{4',5'} = 3.6$ Hz, H-4′), 6.16 (d, 1H, $J_{1',2'} = 10.8$ Hz, H-1′), 7.73–7.99 (m, 4H, Ar-H). ^{13}C NMR (DMSO-d6, δ ppm): 20.08, 20.11, 20.23, 20.64 ($4CH_3$, CH_3CO) 33.4 (CH_3-quinoxaline), 60.6 (C-6′), 66.12 (C-4′), 68.2 (C-2′), 71.0 (C-3′), 72.2 (C-5′), 79.2 (C-1′), 126.2, 128.4, 128.8, 129.1, 135.1, 156.1, 160.1, 161.1, 168.8, 169.9, 170.0, 171.6 (Ar-C and C=O). Anal. Calcd. for $C_{23}H_{26}N_2O_9S$ (506.53): C, 54.54; H, 5.17; N, 5.53. Found: C, 54.58; H, 5.15; N, 5.51.

2-(β-D-Galactopyranosyloxy)-3-methylquinoxaline (5a)

Colorless crystals; yield 85%, m.p. 179–180°C. IR (KBr): 3410 cm^{-1} (broad, 4OH). ^1H NMR (DMSO-d_6): $\delta = 2.59$ (s, 3H, CH_3), 3.57 (m, 3H, H-3′, H-6′, and H-6∋′), 3.63 (m, 3H, H-2′, H-4′, and H-5′), 4.61 (m, 2H, OH-4′, OH-6′, D_2O exchangeable), 4.92 (d, 1H, $J = 5.13$ Hz, OH-3′), 5.21 (d, 1H, $J = 4.2$ Hz, OH-2′, D_2O exchangeable), 6.03 (d, 1H, $J = 7.8$ Hz, H-1′), 7.60–7.95 (m, 4H, Ar-H). Anal. Calcd. for $C_{15}H_{18}N_2O_6$ (322.31): C, 55.90; H, 5.63; N, 8.69. Found: C, 55.86; H, 5.60; N, 8.72.

2-(β-D-Galactopyranosylsulfanyl)-3-methylquinoxaline (5b)

Colorless crystals; yield 86%, m.p. 189–190°C. IR (KBr): 3415 cm^{-1} (broad, 4OH). ^1H NMR (DMSO-d_6/D_2O): $\delta = 2.59$ (s, 3H, CH_3), 3.38 (m, 3H, H-3′, H-6′, and H-6″), 3.59 (m, 3H, H-2′, H-4′, and H-5′), 5.63 (d, 1H, $J = 10.2$ Hz, H-1′), 7.25–7.93 (m, 4H, Ar-H). Anal. Calcd. for $C_{15}H_{18}N_2O_5S$ (338.38): C, 53.24; H, 5.36; N, 8.28. Found: C, 53.19; H, 5.33; N, 8.30.

2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-(2′,3′,5′-tri-O-acetyl-β-D-glucopyranosyloxy)-3-methylquinoxaline (6a)

Brown powder; yield 59%, m.p. 191–192°C. IR (KBr): 1749 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): $\delta = 1.89$, 1.90, 1.92, 1.94, 1.98, 2.00, and 2.10 (7s, 21H, $7CH_3CO$), 2.59 (s, 3H, CH_3), 4.00–4.02 (m, 3H, H-2′b, H-6′a and H-6′b), 4.18 (dd, 1H, $J_{6''a,6'a} = 11.49$, $J_{5'a,6''a} = 5.61$ Hz, H-6″a), 4.28 (m, 1H, H-5′b), 4.73 (dd, 1H, $J_{6''b,5'b} = 6.32$ Hz, H-6″b), 4.86 (m, 1H, H-5′a), 4.95 (dd, 1H, $J_{1'b,2'b} = 7.86$ Hz, H-1′b), 5.13 (dd, 1H, $J_{4'b,3'b} = 3.4$, $J_{4'b,5'b} = 3.8$ Hz, H-4′b), 5.21 (dd, 1H, $J_{2'a,1'a} = 8.97$, $J_{2'a,3'a} = 8.40$ Hz, H-2′a), 5.25 (dd, 1H, $J_{3'a,4'a} = 9.15$, $J_{4'a,5'a} = 9.60$ Hz, H-4′a), 5.36 (d, 1H, $J_{3'b,4'b} = 3.4$ Hz, H-3′b), 5.42 (dd, 1H, $J_{3'a,2'a} = 8.40$, $J_{3'a,4'a} = 9.15$ Hz, H-3′a), 6.46 (d, 1H, $J_{1'a,2'a} = 8.97$ Hz, H-1′a), 7.69–7.98 (m, 4H, Ar-H). Anal. Calcd. for $C_{35}H_{42}N_2O_{18}$ (778.71): C, 53.98; H, 5.44; N, 3.60. Found: C, 54.01; H, 5.42; N, 3.64.

2-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-(2′,3′,5′-tri-O-acetyl-β-D-glucopyranosylsulfanyl)-3-methylquinoxaline (6b)

Colorless powder; yield 62%, m.p 160–163°C, IR (KBr): 1755, 1724 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): δ = 1.79, 1.80, 1.97, 2.00, 2.02, 2.32, and 2.34 (7s, 21H, 7 CH_3CO), 2.59 (s, 3H, CH_3), 4.03–4.07 (m, 3H, H-2′b, H-6′a, and H-6′b), 4.2 (dd, 1 H, $J_{6''a,6'a}$ = 11.40, $J_{5'a,6''a}$ = 5.75 Hz, H-6″a), 4.24 (m, 1H, H-5′b), 5.06 (dd, 1H, $J_{6''b,5'b}$ = 6.35 Hz, H-6″b), 5.11 (m, 1H, H-5′a), 5.14 (dd, 1H, $J_{1'b,2'b}$ = 7.96 Hz, H-1′b), 5.17 (dd, 1H, $J_{4'b,3'b}$ = 3.23, $J_{4'b,5'b}$ = 3.74 Hz, H-4′b), 5.24 (dd, 1H, $J_{2'a,1'a}$ = 8.94, $J_{2'a,3'a}$ = 8.10 Hz, H-2′a), 5.50 (dd, 1H, $J_{3'a,4'a}$ = 9.15, $J_{4'a,5'a}$ = 9.60 Hz, H-4′a), 5.53 (d, 1H, $J_{3'b,4'b}$ = 3.23 Hz, H-3′b), 5.93 (dd, 1H, $J_{3'a,2'a}$ = 8.10, $J_{3'a,4'a}$ = 9.15 Hz, H-3′a), 6.23 (d, 1H, $J_{1'a,2'a}$ = 8.94 Hz, H-1′a), 7.55–7.92 (m, 4H, Ar-H). ^{13}C NMR (DMSO-d6, δ ppm): 20.9, 21.0, 21.09, 21.1, 22.3, 22.5, 26.8 (7CH_3, acetyl groups) 33.6 (CH_3-quinoxaline), 60.7 (C-6′a), 61.3 (C-6′b), 68.1 (C-3′a), 68.9 (C-2′b), 71.0 (C-2′a), 72.0 (C-3′b), 72.6 (C-4′a), 73.5 (C-4′b), 78.6 (C-5′b), 78.9 (C-5′a), 83.5 (C-1′a), 94.6 (C-1′b), 126.7, 128.6, 129.3, 129.7, 135.6, 157.0, 159.2, 160.8, 169.5, 169.9, 170.2, 170.3, 170.6, 171.2, 171.5 (Ar-C) and C=O). Anal. Calcd. for $C_{35}H_{42}N_2O_{17}S$ (794.78): C, 52.89; H, 5.33; N, 3.52. Found: C, 52.80; H, 5.32; N, 3.51.

2-(β-D-galactopyranosyl)-(1→4)-(β-D-glucopyranosyloxy)-3-methylquinoxaline (7a)

Brown crystals; yield 83%, m.p. 190–192°C, IR (KBr): 3433 cm^{-1} (broad, 7 OH). ^1H NMR (DMSO-d_6): δ = 2.59 (s, 3H, CH_3), 3.04–3.52 (4 m, 12H, H-2′b, H-3′b, H-4′b, H-5′b, H-6′b, H-6“b, H-2′a, H-3′a, H-4′a, H-5′a, H-6′a, H-6”a), 4.19 (d, 1H, OH-4′b), 4.31 (d, 1H, OH-6′b), 4.63 (d, 1H, J = 4.28 Hz, OH-3′b), 4.89 (d, 1H, OH-2′b), 4.99 (d, 1H, OH-6′a), 5.21 (d, 1H, OH-3′a), 5.73 (d, 1H, OH-2′a), 5.82 (d, 1H, $J_{1'b,2'b}$ = 7.65 Hz, H-1′b), 6.10 (d, 1H, $J_{1'a,2'a}$ = 8.84 Hz, H-1′a), 7.3–7.95 (m, 4H, Ar-H). Anal. Calcd. for $C_{21}H_{28}N_2O_{11}$ (484.45): C, 52.06; H, 5.83; N, 5.78. Found: C, 52.04; H, 5.84; N, 5.79.

2-(β-D-galactopyranosyl)-(1→4)-(β-D-glucopyranosylsulfanyl)-3-methylquinoxaline (7b)

Colorless powder; yield 82%, m.p. 189–191°C, IR (KBr): 3443 cm^{-1} (broad, 7 OH). ^1H NMR (DMSO-d_6): δ = 2.56 (s, 3H, CH_3), 3.01–3.62 (4 m, 12H, H-2′b, H-3′b, H-4′b, H-5′b, H-6′b, H-6“b, H-2′a, H-3′a, H-4′a, H-5′a, H-6′a, H-6”a), 4.18 (d, 1H, OH-4′b), 4.33 (d, 1H, OH-6′b), 4.60 (d, 1H, J = 4.28 Hz, OH-3′b), 4.87 (d, 1H, OH-2′b), 4.99 (d, 1H, OH-6′a), 5.20 (d, 1H, OH-3′a), 5.71 (d, 1H, OH-2′a), 5.84 (d, 1H, $J_{1'b,2'b}$ = 7.65 Hz, H-1′b), 6.12 (d, 1H, $J_{1'a,2'a}$ = 8.84 Hz, H-1′a), 7.32–7.95 (m, 4H, Ar-H). Anal. Calcd. for $C_{21}H_{28}N_2O_{10}S$ (500.52): C, 50.39; H, 5.64; N, 5.60. Found: C, 50.37; H, 5.66; N, 5.58.

2-(4-Acetoxybutyloxy)-3-methylquinoxaline (8a)

Yellow powder; yield 55%, m.p. 110–112°C. IR (KBr): 1732 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): δ = 1.76 (m, 2H, CH_2), 1.83 (m, 2H, CH_2), 1.99 (s, 3H, CH_3CO), 2.59 (s, 3H, CH_3), 4.09 (t, 2H, J = 6.0 Hz, OCH_2), 4.47 (t, 2H, J = 6.3

Hz, CH_2OCO), 7.55–7.92 (m, 4H, Ar-H). Anal. Calcd. for $C_{15}H_{18}N_2O_3$ (274.32): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.65; H, 6.59; N, 10.18.

2-(4-Acetoxybutylsulfanyl)-3-methylquinoxaline (8b)

Yellow powder; yield 55%, m.p. 130–133°C. IR (KBr): 1734 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): δ = 1.60 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 1.97 (s, 3H, CH_3CO), 2.59 (s, 3H, CH_3), 3.32 (t, 2H, J = 7.2 Hz, CH_2), 3.45 (t, 2H, J = 6.0 Hz, CH_2O), 7.65–7.93 (m, 4H, Ar-H). Anal. Calcd. for $C_{15}H_{18}N_2O_2S$ (290.38): C, 62.04; H, 6.25; N, 9.65. Found: C, 62.01; H, 6.27; N, 9.67.

2-(4-Hydroxybutyloxy)-3-methylquinoxaline (9a)

Colorless crystals; yield 65%, m.p. 150–152°C. IR (KBr): 3427 cm^{-1} (broad, 4OH). ^1H NMR (DMSO-d_6): δ = 1.58 (m, 2H, CH_2), 1.81 (m, 2H, CH_2), 2.59 (s, 3H, CH_3), 3.47 (q, 2H, J = 6.3 Hz, $C\underline{H}_2OH$), 4.09 (t, 2H, J = 5.12 Hz, OCH_2), 4.46 (t, 1H, J = 5.4 Hz, OH, D_2O exchangeable), 7.53–7.90 (m, 4H, Ar-H). Anal. Calcd. for $C_{13}H_{16}N_2O_2$ (232.28): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.25; H, 6.92; N, 12.03.

2-(4-Hydroxybutylsulfanyl)-3-methylquinoxaline (9b)

Colorless powder; yield 75%, m.p. 170°C, IR (KBr): 3426 cm^{-1} (broad, OH). ^1H NMR (DMSO-d_6): δ = 1.58 (m, 2H, CH_2), 1.77 (m, 2H, CH_2), 2.59 (s, 3H, CH_3), 3.31 (q, 2H, J = 6.6 Hz, SCH_2), 3.47 (q, 2H, J = 6.0 Hz, $C\underline{H}_2OH$), 4.43 (t, 1H, OH, D_2O exchangeable), 7.65–7.93 (m, 4H, Ar-H). Anal. Calcd. for $C_{13}H_{16}N_2OS$ (248.34): C, 62.87; H, 6.49; N, 11.28. Found: C, 62.85; H, 6.50; N, 11.26.

2-[(4-Acetoxyethoxy)methyoxy]-3-methylquinoxaline (10a)

Yellow powder; yield 50%, m.p. 150–152°C. IR (KBr): 17342 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): δ = 1.90 (s, 3H, CH_3CO), 2.59 (s, 3H, CH_3), 3.78 (t, 2H, J = 5.7 Hz, OCH_2), 4.23 (t, 2H, J = 5.7 Hz, CH_2OCO), 4.43 (s, 2H, J = 7.2 Hz, OCH_2O), 7.06–7.46 (m, 4H, Ar-H). Anal. Calcd. for $C_{14}H_{16}N_2O_4$ (276.29): C, 60.86; H, 5.84; N, 10.14. Found: C, 60.84; H, 5.85; N, 10.11.

2-[(4-Acetoxyethoxy)methylsulfanyl]-3-methylquinoxaline (10b)

Brown crystals; yield 60%, m.p. 160–162°C, IR (KBr): 1758 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): δ = 2.02 (s, 3H, CH_3CO), 2.59 (s, 3H, CH_3), 3.26 (s, 2H, SCH_2O), 4.45 (t, 2H, J = 5.1 Hz, CH_2), 4.71 (t, 2H, J = 5.1 Hz, CH_2), 7.22–7.79 (m, 4H, Ar-H). Anal. Calcd. for $C_{14}H_{16}N_2O_3S$ (292.35): C, 57.52; H, 5.52; N, 9.58. Found: C, 57.50; H, 5.54; N, 9.56.

2-((2-Hydroxyethoxy)methyloxy)-3-methylquinoxaline (11a)

Yellow crystals; yield 65%, m.p. 180–182°C, IR (KBr): 3443 cm^{-1} (br, OH). ^1H NMR (DMSO-d_6): δ = 2.59 (s, 3H, CH_3), 2.65 (t, 2H, J = 6.3 Hz, CH_2), 3.31 (t, 1H, OH, D_2O exchangeable) 3.79 (q, 2H, J = 7.2 Hz, $C\underline{H}_2OH$), 6.39 (s, 2H, OCH_2O), 7.23–7.70 (m, 4H, Ar-H). Anal. Calcd. for $C_{12}H_{14}N_2O_3$ (234.25): C, 61.53; H, 6.02; N, 11.96. Found: C, 61.51; H, 6.04; N, 11.94.

2-((2-Hydroxyethoxy)methylsulfanyl)-3-methylquinoxaline (11b)

Yellow crystals; yield 75%, m.p. 175–178°C, IR (KBr): 3350 cm^{-1} (OH). ^1H NMR (DMSO-d_6): $\delta = 2.59$ (s, 3H, CH_3), 3.38 (s, 2H, SCH_2O), 3.84 (t, 2H, $J = 5.4$ Hz, CH_2), 4.64 (m, 2H, CH_2), 5.82 (s, 1H, OH, D_2O exchangeable), 7.34–7.78 (m, 4H, Ar-H). Anal. Calcd. for $C_{12}H_{14}N_2O_2S$ (250.32): C, 57.58; H, 5.64; N, 11.19. Found: C, 57.56; H, 5.62; N, 11.17.

3-(3-Methylquinoxalin-2-yloxy)propan-1-ol (12a)

Yellow crystals; yield 70%, m.p. 189–191°C. IR: 3441 (OH). ^1H NMR (DMSO-d_6): $\delta = 1.71$ (m, 2H, CH_2), 2.59 (s, 3H, CH_3), 2.65 (t, 2H, $J = 6.3$ Hz, $OC\underline{H}_2$), 3.31(t, 1H, $J = 5.4$ Hz, OH, D_2O exchangeable), 3.79 (q, 2H, $J = 6.9$ Hz, $C\underline{H}_2$-OH), 7.23–7.70 (m, 4H, Ar-H). ^{13}C NMR (DMSO-d6, δ ppm): 30.1 (CH_2), 33.6 (CH_2OH), 33.7 (CH_3-quinoxaline), 68.9 (OCH_2), 126.8, 128.6, 128.5, 129.0, 135.0, 156.8, 160.1, 161.0 (Ar-C). Anal. Calcd. for $C_{12}H_{14}N_2O_2$ (218.25): C, 66.04; H, 6.47; N, 12.84. Found: C, 66.02; H, 6.49; N, 12.81.

2-(2-Methylquinoxalin-3-ythio)acetic acid (13)

Colorless crystals; yield 70%, m.p. 180–183°C. IR (KBr): 3480 cm^{-1} (OH) and 1710 cm^{-1} (C=O, acid). Anal. Calcd. for $C_{11}H_{10}N_2O_2S$ (234.27): C, 56.39; H, 4.30; N, 11.96. Found: C, 56.37; H, 4.28; N,11.98.

N-(4-(N-Acetylsulfamoyl)phenyl)-2-((3-methylquinoxalin-2-yl)thio)-acetamide (14)

Yellow crystals; yield 82%, m.p. 166°C (decomposed). IR (KBr): 3423, 3356 cm^{-1} (2NH), 1726 cm^{-1} ($CH_3\underline{CO}NHSO_2$) and 1651 cm^{-1} ($CH_2\underline{CO}NH$). Mass spectra: M^+ (m/e) = 430 (3.19%) as parent ion and $m/e = 79.90$ (100%), 63.90 (83.01%). Anal. Calcd. for $C_{19}H_{18}N_4O_4S_2$ (430.50): C, 53.01; H, 4.21; N, 13.01. Found: C, 53.00; H, 4.24; N, 13.04.

2-(((3-Methylquinoxalin-2-yl)thio)-N-(4-(pyrimidin-2-yl)sulfamoyl)phenyl) acetamide (15)

Yellow crystals; yield 85%, m.p. 176°C (decomposed). IR (KBr): 3435 br, cm^{-1} (2NH), 1667 cm^{-1} (C=O, amide). ^1H NMR (DMSO-d_6): $\delta = 2.63$ (s, 3H, CH_3), 4.14 (s, 2H, SCH_2CO), 7.21 (s, 2H, Ar-H), 7.73 (m, 5H, Ar-H), 7.86 (d, 2H, $J = 9.3$ Hz, Ar-H), 7.96 (d, 2H, $J = 9.3$ Hz, Ar-H) and 10.24 (s, 2H, 2NH). Mass spectra: M^+ (m/e) = 367 (2.25%), $m/e = 63.95$ (69.26%), 79.95 (91.37%), 102.1 (54.18%), 143.05 (58.53%), 188.05 (50.78%), 189.05 (100%). Anal. Calcd. for $C_{21}H_{18}N_6O_3S_2$ (466.45): C, 54.06; H, 3.89; N, 18.01. Found: C, 54.09; H, 3.96; N, 18.04.

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