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MAOS of Quinoxalines, Conjugated Pyrazolylquinoxalines and Fused Pyrazoloquinoxalines from L-Ascorbic and D-Isoascorbic Acid

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Microwave-assisted organic synthesis (MAOS) has been used to accelerate the conversion of L-ascorbic acid (**1**) and D-isoascorbic acid (**2**) to the title heterocycles by conversion to 3-(L-*threo*- or D-*erythro*-glycerol-1-yl)quinoxaline-2-carboxylic acid o-aminoanilides (**7** and **8**), which were transformed to lactones **9** and **10**, respectively, under acidic condition. The acetylation of compounds **9** and **10** afforded 3-(L-*threo*- or D-*erythro*-2,3-di-O-acetyl-glycerol-1-yl)quinoxaline-2-carboxylic- γ -lactones (**11** and **12**). Treatment of **10** with phenylhydrazine gave the hydrazides **13**. 3-[1-Phenylhydrazono-L-*threo*-2,3,4-trihydroxybutyl]-1H-quinoxalin-2-one (**14**) and its D-*erythro*-analog **15** were prepared from **1** and **2**. Subsequent cyclizations gave the respective pyrazolylquinoxalines **16** and **17** and pyrazolo[3,4-*b*]quinoxalines **26** and **27**. The regioselectivities of allylation and epoxypropylation of **16** and **17** were investigated and could be interpreted by the semiempirical AM1 method. Degradation of **26** or **27** gave 1-phenylpyrazolo[3,4-*b*]quinoxaline-3-carboxaldehyde (**28**). Degradation of **14** or **15** gave aldehyde **29**. The combination of using microwave (MW) and bentonite, as a support, has improved the yields in less reaction times in addition to performing the reactions under environmentally clean conditions.

Keywords Microwave, Bentonite, Quinoxalines, Quinoxalinones, Pyrazolylquinoxalines, Pyrazoloquinoxalines, AM1 method, Alkylation, Ascorbic acid

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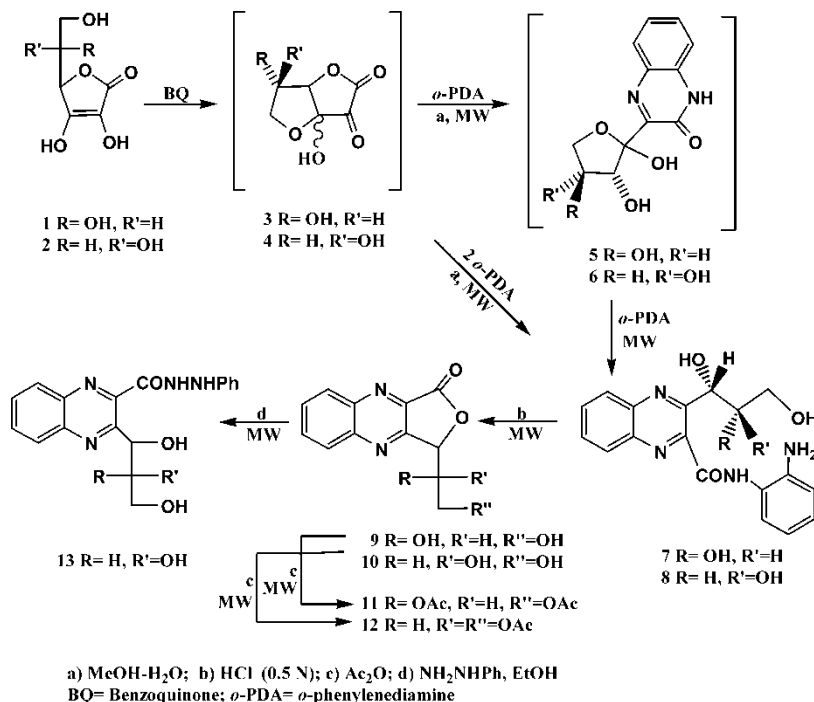
INTRODUCTION

Acceleration of organic, organometallic, and solid state reactions by microwave (MW) irradiation have paved the way for applying this technique in organic synthesis^[1–3] to enhance reaction rates and improve environmental as well as economical aspects. Moreover, MW may also play a role in the stereo- or regioselectivities of the reactions.^[4] Recently, we have successfully used MW in our laboratory for accelerating organic reactions.^[3] The availability of carbohydrates as renewable biomasses has attracted attention to make their use as precursors for materials of various applications^[5,6] based on innovative technologies and biological activities. Much work from our laboratory has utilized carbohydrates as raw materials for the synthesis of various types of heterocycles.^[6,7] L-Ascorbic acid and D-isoascorbic acid were used as precursors for variant heterocycles, such as the quinoxaline ring. The attraction toward this ring system was motivated by its incorporation in natural products and its potent biological activities.^[8] Accordingly, the microwave-assisted organic synthesis (MAOS) of quinoxalines, conjugated pyrazolylquinoxalines, and fused pyrazoloquinoxalines from L-ascorbic acid (**1**) and its D-erythro analog **2** has been investigated and compared with conventional procedures.^[9–17]

RESULTS AND DISCUSSION

3-(L-Threo-Glycerol-1-yl)quinoxaline-2-carboxylic acid o-aminoanilide (**7**) was obtained in 87% yield by MW irradiation, for 1 min, of L-ascorbic acid (**1**) with two equivalents of o-phenylenediamine in the presence of benzoquinone, while the conventional procedure^[10] required much more time to obtain a comparable yield. The reaction is assumed to proceed via the oxidation of **1** to the respective dehydroascorbic acid, which, upon reaction with two equivalents of o-phenylenediamine, gave **7** via **5**.^[18] Acid hydrolysis of **7** required 7 min of irradiation to afford 53% of 3-(L-threo-glycerol-1-yl)quinoxaline-2-carboxylic- γ -lactone (**9**). Similarly, **2** was oxidized to **4** and converted to 3-(D-erythro-glycerol-1-yl)quinoxaline-2-carboxylic acid o-aminoanilide (**8**) via **6**, which upon hydrolysis gave **10**. Acetylation of **9** and **10** was performed in the MW oven for 2 min to give 93% and 86% yields, respectively, of **11** and **12**. Hydrazinolysis of **10** gave 3-(D-erythro-glycerol-1-yl)quinoxaline-2-carboxylic acid phenylhydrazide (**13**) (Sch. 1).

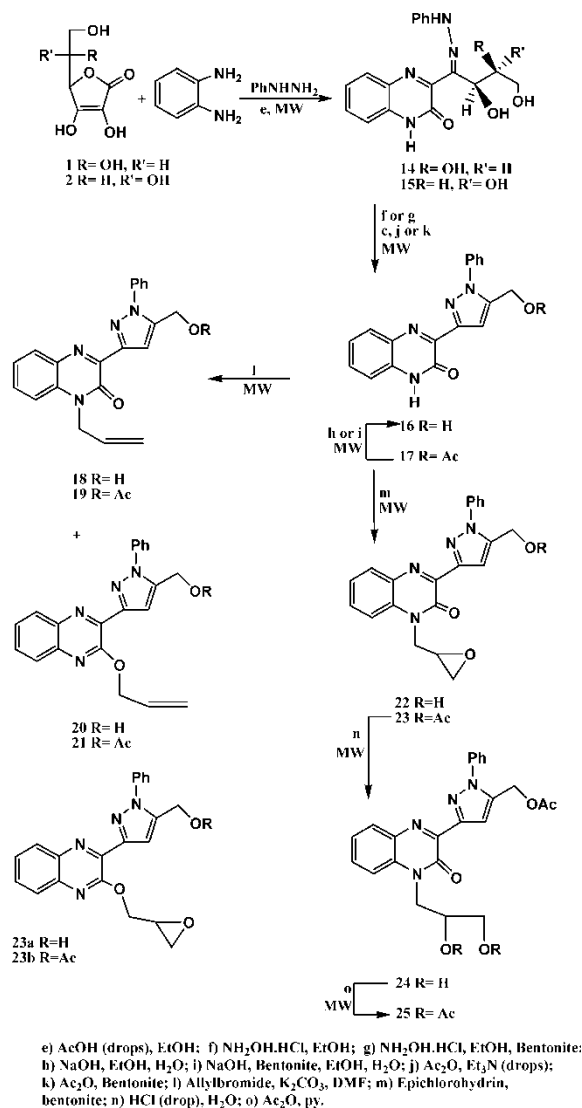
Synthesis of 3-(1-phenylhydrazono-L-threo-2,3,4-trihydroxybutyl)-1H-quinoxalin-2-one (**14**) was achieved in 86% yield by MW irradiation for 2.5 min of L-ascorbic acid (**1**) with o-phenylenediamine and phenylhydrazine in the presence of acetic acid; the conventional method^[9] required a much longer time (1 h) of heating to give 73% yield. The reaction required one equivalent only of o-phenylenediamine, which presumably proceeded via the



Scheme 1: Reaction of ascorbic acids with *o*-phenylene diamine.

formation of **5**, whose reaction with phenylhydrazine gave **14**. Similarly, D-isoascorbic acid gave **15**.

Dehydrative cyclization of **14** or **15** could take place by incorporating the hydrazone residue with either the glycerol side chain or the quinoxaline ring. When their dehydrations have been carried out by the action of hydroxylamine hydrochloride under MW irradiation for 4 min, the yield of 3-[5-(hydroxymethyl)-1-phenylpyrazol-3-yl]-1*H*-quinoxalin-2-one (**16**) was 65%, while the presence of bentonite as a support gave a comparable yield (71%). Using acetic anhydride as a dehydrating agent gave **17** in 84% yield. Addition of drops of triethylamine did not improve the yield, but a better yield (95%) was obtained upon supporting the reactants on bentonite. Getting the same product from **14** or **15** was due to the loss of their chirality as a result of dehydrative elimination. Deacetylation of **17** with aqueous sodium hydroxide under MW irradiation for 2.5 min gave low yield (40%) of **16**, but again a much better yield (92%) was obtained from the same reactants when supported on bentonite. On the other hand, the reaction did not proceed successfully when **17** was supported on bentonite without the presence of sodium hydroxide (Sch. 2).



Scheme 2: Alkylation of quinoxalinone.

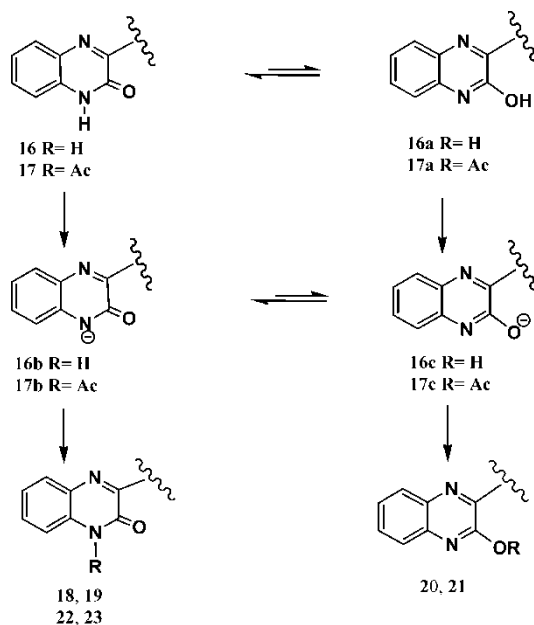
Alkylation of **16** by allyl bromide in the presence of potassium carbonate under MW irradiation gave the *N*- and *O*-allyl derivatives **18** and **20** in 57% and 30% yield, respectively. Similarly, **17** gave **19** and **21**, where the *N*-isomeric product was also the major one. On the other hand, reaction of **16** or **17** with epichlorohydrin in the presence of bentonite under MW irradiation afforded the *N*-(epoxy)-propylated derivatives **22** and **23** in 60% and 63% yields, respectively, whereas the corresponding *O*-(epoxy)-propylated derivatives **23a**

and **23b** could not be detected. Surprisingly, reaction of **17** with epichlorohydrin in the presence of potassium carbonate in DMF gave the dihydroxypropyl derivative **24** under MW conditions and the conventional method, the structure of which was confirmed by its identity with the product resulting from the ring opening of the oxirane ring in **23**, by aqueous acid, to give the respective diol in **24**. Moreover, its acetylation gave the corresponding di-*O*-acetyl derivative **25**.

The above results of alkylation of the quinoxaline ring attracted our attention to investigate the regioselectivity that has taken place via a theoretical approach by using the AM1 semiempirical method as a part of the MOPAC computational package. The AM1 semiempirical method offers more accurate parameterization than other methods.^[19]

In order to determine the factors affecting the regioselectivity of the alkylation of the quinoxalinone ring, its tautomerism was considered. There are two tautomeric forms for that ring, the lactam **16** and **17** and the lactim forms **16a** and **17a**, which upon abstraction of a proton, would form the respective intermediates **b** and **c**, presumably in an equilibrated state, whose ratio could be a determinant factor for the ratio of the obtained *N*- and *O*-alkylated products (Sch. 3). The aqueous phase semiempirical calculated heats of formation and relative stabilities (RS) of quinoxaline derivatives **16** and **17** as well as their intermediates and alkylated products are listed in Table 1. The heats of formation values suggest that the tautomeric lactam form and its deprotonated form in **b** are favored over the lactim form and its deprotonated form **c**. Thus, the relative stabilities of **16** and **16b** are higher than the respective forms of **a** and **c** by $-9.75 \text{ kcal mol}^{-1}$ and $-3.31 \text{ kcal mol}^{-1}$. The heat of formation of the lactam form of compound **17** is smaller than that of form **a** ($\text{RS} = -10.53 \text{ kcal mol}^{-1}$) and the deprotonated **b** is also smaller than **c** ($\text{RS} = -10.47 \text{ Kcal mol}^{-1}$). Such results could explain the favored attack of the alkylating agent on the *N*-position more than that on the *O*-position. Moreover, the heats of formation (ΔH) of the *N*-alkylated derivatives indicate their stability over the *O*-alkylated one. The energy occupied orbital values of the form **b** of both compounds **16** and **17** is preferred because their values of energy (HOMO) are smaller than that in the **c** form, which was required for giving the best orbital overlap between the occupied orbital of **16** or **17** and the unoccupied orbital of the alkylating reagents, where the frontier orbitals of the two reactants should be on the same energy gap or possess approximate minimal energy values.^[19]

The second type of dehydrative cyclization in **14** or **15** by elimination of one molecule of water between the hydrazone residue and the quinoxalinone ring took place to form a pyrazole fused to the quinoxaline ring; in this case no loss of chirality can take place whereby **26** and **27**, respectively, were obtained (Sch. 4). This cyclization had taken place under MW



Scheme 3: Tautomerism in quinoxalinone.

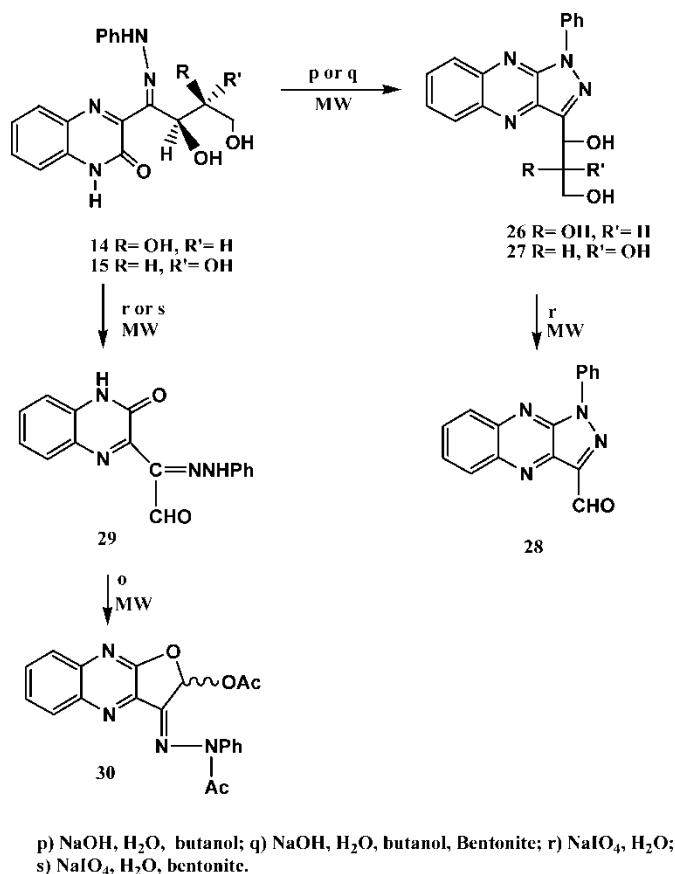
irradiation, in the presence of aqueous sodium hydroxide solution to give **26** in 60% yield and **27** in 89% yield, but when bentonite was used as support, the yield was 89% and 95%, respectively, without any experimental problems.

Table 1: AM1 calculations^a of the studied molecules.

Comp. No	ΔH kcal mol ⁻¹	RS ^b kcal mol ⁻¹	E LUMO eV	E HOMO eV
16	80.61	-9.75	-0.836	-8.690
16a	90.36		-0.718	-9.078
16b	50.83	-3.308	2.079	-3.976
16c	54.14		2.100	-3.984
17	215.98	-10.53	-0.470	-8.752
17a	226.51		-0.905	-9.014
17b	190.09	-10.47	2.382	-3.818
17c	200.56		2.539	-4.216
18	108.01	-10.34	-0.773	-8.614
20	118.34		-0.736	-8.634
23	247.07	-7.36	-0.439	-8.741
23b	254.43		-0.880	-8.615

^aCalculations in the aqueous phase.

^bRS: relative stability in kcal mol⁻¹. RS = $\Delta H_{\text{one}} - \Delta H_{\text{ol}}$, minus sign indicates the predominance of the form "one."



Scheme 4: Synthesis of fused quinoxalines.

3-Carboxaldehyde-1-phenyl-pyrazolo[3,4-*b*]quinoxaline (**28**) has been formed by irradiation of a suspension of **26** or **27** in an aqueous solution of sodium metaperiodate in MW for 6 min. The cleavage of **14** or **15** under MW irradiation for 2 min gave 3-[1-(phenylhydrazono)glyoxal-1-yl]-2-quinoxalinone (**29**), which was acetylated under MW irradiation for 1 min to obtain compound **30** (Table 2).

In conclusion, conversion of L-ascorbic and D-isoascorbic acids to quinoxalines, quinoxalinones, conjugated pyrazolylquinoxalinones, and fused pyrazoloquinoxalines was successfully carried out by applying MW irradiation. The procedures avoided the use of many amounts of solvents and were completed in much shorter times under better environmental conditions. The use of bentonite as a support has improved the yields in most cases. The mode of alkylation could be explained by the computational methods.

Table 2: Comparison of Results from microwave (MW) and conventional method (CM).

Comp. No	Reagent ^c	Time		Yield (%)		Mp (°C) Found/literature
		MW (min)	CM (h)	MW	CM	
7	a	2	2	91	87 ⁽¹⁰⁾	178/180–181 ⁽¹⁰⁾
8	a	2	2	94	67 ⁽¹¹⁾	219–220/218–219 ⁽¹¹⁾
9	b	7	24	76	60 ⁽⁹⁾	187/187 ⁽⁹⁾
10	b	7	24	69	72 ⁽¹¹⁾	183–185/184–186 ⁽¹¹⁾
11	c	2		93		94–95
12	c	2	0.5	86	77 ⁽¹¹⁾	180/178–179, ⁽¹¹⁾ 184 ⁽¹³⁾
13	d	4	2	80		163–165/165–167 ⁽¹¹⁾
14	e	2.5	1.5	86	80 ⁽⁹⁾	219/216 ⁽⁹⁾
15 ^a	e	2.5	1.5	86	93 ⁽¹²⁾	200–202/203 ⁽¹³⁾ /205 ⁽¹²⁾
	f	4	8	65	70 ⁽⁹⁾	255–257/255 ⁽⁹⁾ /250–252 ⁽¹⁴⁾
16 ^b	g	2		71		
	f	6		76		
16	g	4		95		
	h	2.5		40		
	i	2		92		
17 ^a	c	7	0.25	84	90 ⁽¹⁴⁾	250/249–250 ⁽¹⁴⁾
	j	8		75		
	k	7		95		
17 ^b	c	6		75		
	j	8		70		
	k	7		88		
18	l	7	2	57	41 ⁽¹⁵⁾	171–172/176 ⁽¹⁵⁾
19	l	5	4	53	47	182/195–196 ⁽¹⁵⁾
20	l	7	2	30	20 ⁽¹⁵⁾	104–106/105–108 ⁽¹⁵⁾
21	l	5	4	27	20	98–100
22	m	18	—	64	—	194–196
23	m	20	—	60	—	182
24	n	8	6	86	74	208
25	o	3	24	90	85	158–160
26	p	4	1	60	95 ⁽⁹⁾	196–198/194 ⁽⁹⁾
	q	2		89		
27	p	2		89	82	212–214/212–213 ⁽¹⁶⁾
	q	2		95		
28 ^a	r	6	24	67	75	
28 ^b	r	4		60		146–148/144 ⁽¹⁶⁾
29 ^a	r	2	24	84	86	250/242 ⁽¹²⁾ /244 ⁽¹⁷⁾
	s	2		92		
29 ^b	r	4		84		
	s	2		90		203–204/200–202 ^(7g)
30	o	1	2	90	90 ^(7g)	

^aFrom L-ascorbic acid.

^bFrom D-isoascorbic acid.

^cReagents shown in the schemes.

EXPERIMENTAL

General Methods

Melting points were determined on a Melt-temp apparatus and are uncorrected. TLC was performed on Baker–Flex silica gel 1B-F plates using n-hexane ethyl acetate (H/E) as developing solvents, and the spots were detected by their characteristic colors and by UV light absorption. Irradiation was done in a domestic microwave oven E.M. 230 M (800-watt output power). Table 2 shows the data of melting points and references for the compounds known in the literature. The known compounds prepared under MWI were identified mainly by melting points and IR spectra. The reactions were performed in closed Teflon vessels. ^1H NMR and ^{13}C NMR spectra were recorded on a Jeol spectrometer (500 MHz). The chemical shifts are expressed on δ -scale using Me_4Si as a standard, and coupling constant values are given in Hz. Microanalyses were performed in the Microanalysis Unit at the Faculty of Science, Cairo University. The theoretical calculations of the corresponding products were done by using AM1 semiempirical method as a part of the MOPAC 7.0 program.

3-(L-Threo- or D-erythro-glycerol-1-yl)quinoxaline-2-carboxylic Acid α -Aminoanilide (**7** or **8**)

A mixture of ascorbic acid **1** or **2** (0.2 g, 1.14 mmol) and benzoquinone (0.13 g) in methanol-water (1:1, 3 mL) was stirred for 2 h at rt, treated with a suspension of *O*-phenylenediamine (0.25 g, 2.27 mmol) in methanol (1 mL), and then irradiated for 2 min. The solid that separated out after cooling was filtered off and successively washed with water and ethanol to obtain **7** R_f 0.23 and **8** R_f 0.28 (H/E 1/2).

3-(L-Threo- or D-erythro-glycerol-1-yl)quinoxaline-2-carboxylic- γ -lactone (**9** or **10**)

A suspension of **7** or **8** (0.1 g, 0.28 mmol) in water (2 mL) was treated with HCl (0.1 mL) and subjected to MW irradiation for 7 min, then kept at 0°C overnight. The products **9** and **10** were filtered off and washed with ethanol; R_f 0.43; R_f 0.53 (H/E 1/2), respectively.

3-(L-Threo- or D-erythro-2,3-Di-O-acetyl-glycerol-1-yl)quinoxaline-2-carboxylic- γ -lactone (**11** or **12**)

A suspension of **9** or **10** (0.1 g, 0.41 mmol) in acetic anhydride (2 mL) was irradiated for 2 min. The mixture was poured onto crushed ice and the product was filtered and successively washed with water and ethanol; R_f 0.60 (H/E 2/1).

3-(*D*-Erythro-Glycerol-1-yl)quinoxaline-2-carboxylic acid phenyl hydrazides

A mixture of **10** (0.1 g, 0.41 mmol) in ethanol (2 mL) and hydrazine hydrate (0.5 mL) was irradiated for 4 min, then concentrated. The product was filtered off; R_f 0.18 (H/E 1/3).

3-(1-Phenylhydrazono-2,3,4-trihydroxybut-1-yl)quinoxalin-2-ones (14** or **15**)**

A suspension of **1** or **2** (1 mmol) in water (4 mL) and ethanol (3 mL) was treated with *O*-phenylenediamine (1 mmol), phenyl hydrazine (1 mmol), and acetic acid (0.15 mL). The reaction mixtures were irradiated for 4 min to give red crystals of **14** R_f 0.17 (H/E 1/3) or **15** R_f 0.2 (H/E 1/3).

3-(5-Hydroxymethyl-1-phenylpyrazol-3-yl)quinoxalin-2-one (17**)**

A mixture of **14** or **15** (0.56 mmol), hydroxylamine hydrochloride (0.04 g), bentonite (0.20 g), and ethanol (4 mL) was subjected to MW irradiation, and then ice water was added to give colorless crystals of **16**, R_f 0.18 (H/E 1/1). Alternatively, a mixture of **17** (0.28 mmol), bentonite (0.10 g), and sodium hydroxide (0.10 g) in ethanol-water (1:1, 6 mL) was subjected to MW irradiation for 2 min. Acetic acid was added to give **16**.

3-(5-(Acetoxymethyl)-1-phenylpyrazol-3-yl)-quinoxalin-2-one (17**)**

Bentonite (0.5 g) was added to a suspension of **14** or **15** (1.40 mmol) in acetic anhydride (4 mL). The mixture was irradiated by MW for 7 min and then cooled. Crushed ice was added and the precipitate was filtered. The product **17** was extracted with ethanol and crystallized in colorless needles, R_f 0.37 (H/E 1/1). Alternatively, a suspension of **14** or **15** (1.40 mmol) in acetic anhydride (4 mL) and drops of triethylamine was irradiated for 8 min, then processed as above to give **18**.

Allylation of 3-(5-(hydroxymethyl)- or 3-(5-(acetoxymethyl)-1-phenyl-pyrazol-3-yl)quinoxalin-2-one (16** or **17**)**

A mixture of **16** or **17** (0.47 mmol) and potassium carbonate (0.07 g) in DMF (5 mL) was treated with allyl bromide (0.04 mL), then subjected to irradiation with MW for 5–7 min. The crude product was recrystallized from ethanol to give two products from each compound: **18** and **20** from **16**, and **19** and **21** from **17**.

1-*N*-Allyl-3-(5-(hydroxymethyl)-1-phenylpyrazol-3-yl) quinoxalin-2-one (18)

R_f 0.45 (H/E 1/1)

1-*N*-Allyl-3-(5-(acetoxymethyl)-1-phenyl-pyrazol-3-yl) quinoxalin-2-one (19)

R_f 0.48 (H/E 1/1). ^1H NMR (500 MHz, CDCl_3): δ = 2.06 (s, 3H, CH_3CO), 5.01 (d, 2H, J = 4.6 Hz, H-3', H-3''), 5.13 (d, 2H, J = 6.85 Hz, $\text{CH}_2\text{-O}$), 5.20 (d, 1H, J = 16.8 Hz, H-1'), 5.30 (d, 1H, J = 10.7 Hz, H-1''), 5.95–6.03 (m, 1H, H-2'), 7.30–7.87 (10H, Ar-H). ^{13}C NMR (CDCl_3): δ_c = 20.9 (CH_3CO), 44.7 (C-2'), 56.6 (C-3'), 76.9 (C-1'), 113.0, 114.1, 118.2, 123.9, 125.7, 128.9, 129.3, 130.5, 131.2, 132.5, 133.3, 138.4, 139.1 (C-aromatic), 147.7 (CH_2O), 153.9 (C=N), 170.3 (CO). Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_3$ (400.15): C, 68.99; H, 5.03; N, 13.99. Found: C, 68.85; H, 5.28; N, 13.86.

1-*O*-Allyl-3-(5-(hydroxymethyl)-1-phenyl-pyrazol-3-yl) quinoxalin-2-one (20)

R_f 0.50 (H/E 1/1).

1-*O*-Allyl-3-(5-(acetoxymethyl)-1-phenyl-pyrazol-3-yl) quinoxalin-2-one (21)

R_f 0.56 (H/E 1/1). ^1H NMR (500 MHz, CDCl_3): δ = 2.09 (s, 3H, CH_3), 5.16 (d, 2H, J = 1.5 Hz, H-3', H-3''), 5.17 (d, 2H, J = 2.3 Hz, $\text{CH}_2\text{-OAc}$), 5.37 (dd, 1H, $J_{1',1''}$ = 10.7 Hz, $J_{1'',2'}$ = 1.5 Hz, H-1''), 5.59 (dd, 1H, Hz, $J_{1',1''}$ = 1.5 Hz, H-1'), 6.22–6.28 (m, 1H, H-2'), 7.40–8.17 (10H, Ar-H). ^{13}C NMR (CDCl_3): δ_c = 23.1 (CH_3CO), 38.9 (C-2'), 56.4 (C-3'), 67.6 (C-1'), 112.2, 118.5, 125.6, 126.7, 126.9, 128.9, 129.4, 129.6, 129.9, 130.9, 132.7, 138.4, 138.9, 139.1 (C-aromatic), 139.9 (CH_2O), 140.9 (C-N), 147.7 (C=N), 170.5 (CO).

1-(2,3-Epoxyprop-1-yl)-3-(5-(hydroxymethyl or 3-(5-(acetoxymethyl)-1-phenyl-pyrazol-3-yl)-quinoxalin-2-one (22 or 23)

A mixture of **17** or **18** (0.14 mmol), bentonite, and epichlorohydrin (0.02 mL) in DMF (4 mL) was irradiated in MW oven for 18–20 minutes. The product was extracted from ethanol to give **23** and **24**, respectively. Data of **23**: ^1H NMR (500 MHz, DMSO-d_6): δ = 3.72 (ddd, 1H, $J_{3',2}$ = 5.3 Hz, $J_{3'',3'}$ = 6.1 Hz, H-3''), 3.81 (ddd, 1H, $J_{3',2'}$ = 4.6 Hz, $J_{3',3''}$ = 6.1 Hz, H-3'), 4.13–4.19 (m, 1H, H-2'), 4.37–4.40 (m, 2H, $\text{CH}_2\text{-N}$), 4.54 (d, 2H, J = 6.1 Hz, $\text{CH}_2\text{-O}$), 5.62 (dd, 1H, J = 5.3 Hz, J = 6.1 Hz, OH, D_2O exchangeable),

7.34–7.85 (10H, Ar-H). ^{13}C NMR (CDCl_3): $\delta_{\text{c}} = 48.2$ (C-3), 54.6 (C-1), 68.2 (C-2), 111.6, 115.8, 124.2, 124.7, 128.7, 129.8, 130.2, 130.9, 132.9, 133.6, 139.6 (C-aromatic), 147.3 (CH_2O), (C-N), 154.2 (C=N). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_3$ (374.39): C, 67.37; H, 4.85; N, 14.86. Found: C, 67.05; H, 4.60; N, 14.59. Data of **24** ^1H NMR (500 MHz, $\text{DMSO}-d_6$): $\delta = 1.98$ (s, 3H, CH_3CO), 3.71 (dd, 1H, $J_{3',2} = 5.3$ Hz, $J_{3',3''} = 10.7$ Hz, H-3''), 3.81 (dd, 1H, $J_{3,2} = 4.6$ Hz, $J_{3',3''} = 10.7$ Hz, H-3'), 4.12–4.18 (m, 1H, H-2'), 4.39 (ddd, 2H, $J_{1',1''} = 9.2$ Hz, $J_{1',2'} = 4.6$ Hz, $J_{1'',2'} = 4.9$ Hz, H-1', H-1''), 5.15 (s, 2H, $\text{CH}_2\text{-O}$), 7.35–7.85 (m, d, 10H, Ar-H). ^{13}C NMR (CDCl_3): $\delta_{\text{c}} = 20.9$ (CH_3CO), 48.2 (C-3'), 54.6 (C-1'), 68.2 (C-2'), 111.9, 115.8, 124.2, 125.4, 129.4, 130.0, 130.2, 131.0, 132.9, 133.7, 138.8, 139.2 (C-aromatic), 147.4 (CH_2O), 154.2 (C=N), 170.7 (C=O). Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_4$ (416.42): C, 66.34; H, 4.84; N, 13.45. Found: C, 66.07; H, 4.65; N, 13.19.

3-(5-(Acetoxymethyl)-1-phenyl-pyrazol-3-yl)-1-(2,3-dihydroxypropyl)-quinoxalin-2-one (24)

Method A. A mixture of **17** (0.2 g, 0.6 mmol) and potassium carbonate (0.1 g, 0.7 mmol) in DMF was heated for 1 h, the epichlorohydrin (0.08 mL, 0.8 mmol) was added, and the reaction mixture was stirred at rt for 3 h, and then the mixture was poured onto ice water. After successive washing with water, the precipitate was recrystallized from ethanol to give **24** in 60% yield, which could be also given under the same conditions by using microwave irradiation for 6 min.

Method B. A suspension of **23** (0.14 mmol) in distilled water (3 mL) and a drop of HCl was refluxed for 4 h, and then the solvent was evaporated under reduced pressure. The residue was extracted with chloroform and crystallized from ethanol to give compound **24** as colorless crystals. R_f 0.27 (H/E 1/2). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): $\delta = 1.98$ (s, 3H, CH_3CO), 3.48 (q, 2H, $J_{3,2} = 5.3$ Hz, $J_{3,3'} = 10.7$ Hz, $J_{3',2'} = 5.3$ Hz, $J_{3',3''} = 10.7$ Hz, H-3', H-3''), 3.93–3.94 (m, 1H, H-2'), 4.35 (dd, 2H, $J_{\text{cis}} = 4.6$ Hz, $J_{\text{gem}} = 8.4$ Hz, H-1', H-1''), 4.81 (dd, 1H, $J = 5.3$ Hz, $J = 6.1$ Hz, OH, D_2O exchangeable), 4.96 (d, 1H, $J = 5.3$ Hz, OH, D_2O exchangeable), 5.15 (s, 2H, $\text{CH}_2\text{-O}$), 7.34–7.98 (m, d, 10H, Ar-H). ^{13}C NMR (CDCl_3): $\delta_{\text{c}} = 21.0$ (CH_3CO), 56.7 (C-1'), 64.6 (C-3'), 69.4 (C-2'), 113.0, 116.0, 124.0, 125.4, 129.3, 130.0, 130.2, 130.8, 133.0, 138.7, 139.3 (C-aromatic), 147.6 (CH_2O), 147.7 (C-N), 154.2 (C=N), 170.4 (CO). Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_5$ (434.44): C, 63.59; H, 5.10; N, 12.90. Found: C, 63.61; H, 4.82; N, 13.05.

3-(5-(Acetoxymethyl)-1-phenyl-pyrazol-3-yl)-1-(2,3-di-O-acetoxypropyl)-quinoxalin-2-one (25)

A solution of **24** (0.2 g, 0.46 mmol) in pyridine (2 mL) and acetic anhydride (2 mL) was irradiated for 3 min, then poured onto ice water. The product that

separated off was recrystallized from ethanol. R_f 0.37 (H/E 1/1). ^1H NMR (500 MHz, CDCl_3): δ = 1.93, 2.07, 2.09 (3 s, 9H, $3 \times \text{CH}_3\text{CO}$), 4.30 (dd, 1H, $J_{1',1''} = 12.2$ Hz, $J_{1',2'} = 5.3$ Hz, H-1'), 4.37–4.41 (m, 1H, H-1''), 4.45 (t, 1H, $J_{3',2'} = 6.9$ Hz, $J_{3',3''} = 13.7$ Hz, H-3'), 4.78 (dd, 1H, $J_{3'',2'} = 5.3$ Hz, $J_{3'',3'} = 14.5$ Hz, H-3''), 5.13 (s, 2H, CH_2O), 5.51–5.55 (m, 1H, H-2'), 7.35–8.07 (10H, Ar-H). ^{13}C NMR (CDCl_3): δ_c = 20.9 ($2 \times \text{CH}_3\text{CO}$), 29.8 (CH_3CO), 56.5 (C-1'), 64.6 (C-3'), 69.4 (C-2'), 112.9, 113.8, 124.2, 125.7, 129.0, 129.3, 130.6, 131.4, 132.7, 138.5, 139.0 (C-aromatic), 147.5 (CH_2O), 147.8 (C-N), 154.3 (C=N), 170.2, 170.4, 170.6 ($3 \times \text{CO}$). Anal. Calcd for $\text{C}_{27}\text{H}_{26}\text{N}_4\text{O}_7$ (518.51): C, 62.54; H, 5.05; N, 10.81. Found: C, 62.37; H, 4.98; N, 10.59.

3-(1-Threo- or D-erythro-glycerol-1-yl)-1-phenyl-pyrazolo (3,4-b)quinoxalines (26 or 27)

A suspension of **14** or **15** (1.40 mmol) in 0.01 N sodium hydroxide (25 mL), bentonite (0.50 g), and 1-butanol (1.5 mL) was irradiated in a MW oven for 2 min to give yellow crystals of **21** or **22**; R_f 0.2 (H/E 1/3).

1-Phenyl-pyrazolo(3,4-b)quinoxaline-3-carboxaldehyde (28)

A mixture of **26** or **27** (0.22 mmol) in a solution of sodium metaperiodate (0.4 mmol) in water (2 mL) was subjected to irradiation in a MW oven to give orange crystals of **24**; R_f 0.7 (H/E 2/1).

3-Cyano-1-phenyl-pyrazolo(3,4-b)quinoxaline (31) 3-(1-(Phenylhydrazono)glyoxal-1-yl)-quinoxaline-2 (29)

A mixture of **14** or **15** (0.42 mmol) and bentonite (0.15 g) in a solution of sodium metaperiodate was subjected to irradiation in MW oven for 2 min. The product was extracted with ethanol, then recrystallized from ethanol; R_f 0.48 (H/E 1/1).

2-Acetoxy-3-(2-acetyl-2-phenylhydrazono)-2,3-dihydrofuro(2,3-b)quinoxaline (30)

The compound **32** (0.05 g, 0.067 mmol) was dissolved in pyridine (1.5 mL) and acetic anhydride (3 mL), then irradiated for 1 min, allowed to cool, and left over night at rt. The reaction mixture was poured onto crushed ice, and the product that separated out was filtered off, washed repeatedly with water, and recrystallized from ethanol in pale yellow; R_f 0.67 (H/E 1/1).

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