Synthesis and novel chemical reaction for a new class of 3-(1', 2'-dihydroxyeth-1'-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline series "*C*-nucleosides" as antiviral agents

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Abstract: Numerous acyclic-*C*-nucleosides showed efficacy antiviral activities. In this work we prepared and checked the anti-hepatitis B activity of two new class of pyrazolo [3, 4-b] quinoxaline-*C*-nucleosides typically 3-(1', 2'-dihydroxyeth-1'-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline and 3-(1`, 2`, 3`-trihydroxyprop-1`-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline. The later prepared using one-pot reaction between *O*-phenylenediamine, aldo or keto hexoses or pentoses, and phenyl hydrazine hydrochloride, it prepared using two other methods to prove the mechanism of the one-pot reaction. 3-(1', 2'-dihydroxyeth-1'-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline reacted with thionyl chloride, to produce novel class of mono halogenated sulfite dimer using Y. Fakhreldin reaction. The novel reaction can conclude as follow (1`, 2` dihydroxyeth-1`-yl) -*C*-nucleosides react with thionyl chloride to produce {1' Deoxy, 2' Chloro eth-1'-yl) -*C*-nucleoside} {(1"deoxy, 2"-hydroxy eth-1"-yl) -*C*-nucleoside} 1', 1" Sulfite. Some of the *C*-nucleosides synthesized, showed promising Anti-hepatitis B activity.
[Y. Fakhreldin, S.M. El-Kousy, M.M. Abbasi, and M. El Ashry. **Synthesis and novel chemical reaction for a new class of 3-(1', 2'-dihydroxyeth-1'-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline series "*C*-nucleosides" as antiviral agents.** *Life Sci J* 2012; 9(4):5098-5103]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 760

Keywords: phenylpyrazolo [3, 4-b] quinoxaline, Fakhreldin, c-nucleosides.

1. Introduction

C-Nucleoside is a group of *C*-glycosylated hetero cycles in which the anomeric carbon attached to the hetero cycle by a carbon-carbon bond. This linkage is more durable towards hydrolytic and enzymatic reagents than the carbon-nitrogen bond of *N*-nucleosides, which makes *C*-nucleosides powerful tools for biochemical investigations and antimitotic or antiviral research[1]. Few members of this class of naturally occurring compounds such as showdomycin, formycin, and oxazinomycin possess diverse biological properties that are in several instances, of medical significance. The frequently fundamental biological properties of these substances have made them attractive targets for chemical synthesis, but as yet this has proved to be a more formidable task than the preparation of *N*-nucleosides. [2, 3]

2. Results and discussion

In this work 3(D-erythro-1`, 2`, 3`-trihydroxyprop-1`-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline **2**$_{a\ c}$ prepared using the following three methods:

- Method 1: Condensing D- Gulose, or D-mannose, or D-Glucose [4, 5], or D-altrose or D-fructose, *O*-phenylenediamine, and phenyl hydrazine hydrochloride.
- Method 2: Dehydrative cyclization of D-glucosazone with *O*-phenylenediamine.
- Method 3: Action of phenyl hydrazine hydrochloride on 2 (1`, 2`, 3`, 4` tetrahydroxybut-1`-yl) quinoxaline **1**.

Preparing **2**$_{a\ c}$ using method 1 and 2 prove that the configuration of the hydroxide group at C1'-3' of either the aldoses or ketoses does not affect the pyrazolo[3, 4-b]quinoxaline ring formation, and Osazone can be the intermediate compound in the one-pot reaction. Preparing **2**$_{a\ c}$ using method 3 proves the cyclization. The course of the reaction based on the founding from preparing **2**$_{a\ c}$ using methods 1, 2, and 3demonstrate in scheme (1). D-galactose condensed with *O*-phenylenediamine, and phenyl hydrazine hydrochloride in one-pot reaction to form 3-(D-threo 1`, 2`, 3`-trihydroxyprop-1`-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline **3**$_{a\ c}$.

One-pot reaction between D-xylose or D ribose or D-arabinose, *O*-phenylenediamine, and phenyl hydrazine hydrochloride afforded 3-(D- 1`, 2` dihydroxyeth-1`-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline **4**$_{a\ c}$. Synthesis of 3-(L-1`, 2`-dihydroxyeth-1`-yl) pyrazolo [3, 4-b]quinoxaline accomplished by the one-pot reaction between L-arabinose with *O*-phenylenediamine and phenyl hydrazine hydrochloride.

4, 5-Dimethyl-*O*-phenylenediamine reacted with sugar and phenyl hydrazine hydrochloride in one-pot reaction to produce the corresponding 6, 7-

dimethyl pyrazolo [3, 4-b] quinoxaline-*C*-nucleosides **2**$_{b\ c}$, **3**$_{b\ c}$, **4**$_{b\ c}$ and **5**$_{b\ c}$. To facilitate interpretation of the spectral data, the synthesized compounds **2**$_{b\ c}$, **3**$_{b\ c}$, **4**$_{b\ c}$ and **5**$_{b\ c}$ acetylated using acetic anhydride in pyridine to give the corresponding crystalline acetyl derivatives **2**$_{b\ d}$, **3**$_{b\ d}$, **4**$_{b\ d}$, and **5**$_{b\ d}$.

Y. Fakhreldin Reaction: Yasser Elmoghazy Fakhreldin et al. discovered that (1`, 2` dihydroxyeth-1`-yl) -*C*-nucleosides react with thionyl chloride to produce {1' Deoxy, 2' Chloro eth-1'-yl) -*C*-nucleoside} {(1"deoxy, 2"-hydroxy eth-1"-yl) -*C*-nucleoside} 1', 1" Sulfite.

Compound **4**$_{a\ c}$ treated with thionyl chloride to produce {3-(1' Deoxy, 2' Chloro eth-1'-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline} {3 (1"deoxy, 2"-hydroxy eth-1"-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline} 1', 1" Sulfite **6**. ^{1}H NMR spectrum of **6** showed duplication of the pyrazolo [3, 4-b] quinoxaline moiety. Compound **6** mass spectra showed the molecular ion peak at m/z = 676 and the elemental analysis indicated its formula C_{34} H_{25} N_8 O_4 Cl S. Compound **6** treated with morpholine as a nucleophile and resulted in the cleavage of the molecule into the compounds **4**$_{ac}$ and **7**. The ^{1}HNMR spectra of **7** showed the appearance of morpholine protons. Compound **7** mass spectra showed the molecular ion peak at m/z = 375 and the elemental analysis indicated its formula $C_{21}H_{21}N_5O_2$.

Anti-hepatitis B virus activity of the prepared compounds

The hepato plasma cell line Hep. G2-2. 2.15 were used to evaluate the antiviral effect of the tested compounds against HBV[7]. The cells were incubated in growth medium (RPMI-1640, 10% heat-inactivated fetal calf serum (FCS) and antibiotic) at 37°C, 5% CO_2 with and without tested compound. Quantitation of HBV-DNA performed using a semi-quantitative PCR followed by DIG PCR ELISA[8]. The cytotoxic effect of the compounds assessed by culturing the hep. G2-2. 2.15 cells in the presence of compounds as for the antiviral assay; the viability of the cell were analyzed using a MTT-assay. Compound **3**$_{a\ c}$ showed moderate inhibition of viral replication and slight cytotoxic effect. Compounds **2**$_{a\ c}$ and **4**$_{a\ c}$ showed almost no effect on viral replication, while compounds **5**$_{a\ c}$, **2**$_{b\ c}$, **3**$_{b\ c}$, **4**$_{b\ c}$, **2**$_{b\ d}$ and **5**$_{b\ c}$ were highly toxic. Compounds **2**$_{a\ d}$, **3**$_{a\ d}$, **4**$_{a\ d}$, **5**$_{a\ d}$, and **5**$_{b\ d}$ were moderately cytotoxic. It observed that the presence of the 6, 7-dimethyl groups in the 1-phenylpyrazolo [3, 4-b] quinoxaline moiety afforded a highly cytotoxic effect.

3. Experimental

Melting points are uncorrected and were taken on Electro thermal 9100 apparatus. IR spectra were recorded on Carl Zeise spectrophotometer model "UR 10" using KBr. ^{1}HNMR determined on Jeol 270 MHz using tetramethylsilane as an internal standard. Mass spectrum (MS) were recorded on Finigan SSQ 7000 mass spectrometer. Microanalysis performed by the Central Service Laboratory at University of Cairo.

General methods for synthesis of 1-phenylpyrazolo [3, 4-b] quinoxaline-C-nucleosides

Method 1: Add *O*-phenylenediamine (0.01 mol), phenylhydrazine hydrochloride (0.05mol), 3 ml glacial acetic acid and 0.5 g of sodium acetate to sugar solution (0.01 mol in 100 ml water). Heat the reaction mixture at 100 °C for 6-8 hours, and then cool to 20 °C. Wash the produce precipitate with water and 30% ethanol and recrystallize it from ethanol.

Method 2: Add *O*-phenylenediamine (0.01 mol), phenyl hydrazine hydrochloride (0.02 mol), 1 ml glacial acetic acid, and 0.1 g of sodium acetate to a solution of osazone (0.01mol in 60 ml water). Heat the reaction mixture at 100 °C for 4-6 hours, and then cool to 20°C. Wash the precipitate with water and 30% ethanol recrystallize it from ethanol.

Method 3: Add phenyl hydrazine hydrochloride (0.03 mol), 2 ml glacial acetic acid and 0.1 g sodium acetate to a solution of 2 (D-ribo1`,2`,3`,4` tetrahydroxytetr-1`-yl) quinoxaline (0.01mol in 60 ml water). Heat the reaction mixture at 100°C for 5 hours then cool to 20°C. Wash the produce precipitate with water and 30% ethanol recrystallize it from ethanol.

3-(D-erythro 1`, 2`, 3`trihydroxy prop-1`-yl)-1-phenyl pyrazolo [3, 4-b] quinoxaline **2**$_{a\ c}$

2$_{a\ c}$ prepared using D- Gulose, D-mannose, D-Glucose, D-altrose or D-fructose in method 1 and using glucosazone in method 2. It also prepared using and 2 (D-ribo1`, 2`, 3`, 4` tetrahydroxy tetr-1`-yl) quinoxaline[6] in method 3. Products from methods 1, 2, and 3 compared using melting point, mixed melting and IR fingerprinting at 900-1300 cm^{-1}. Method 1, 2, and 3 products showed same melting point, mixed melting and IR fingerprinting at 900-1300 cm^{-1}; yield in average was 66%. Product recrystallized from ethanol, m.p. 218-220°C. Anal. Calc. for: $C_{18}H_{16}N_4O_3$: C, 64.29; H, 4.76; N, 16.67. Found: C, 64.28; H, 4.77; N, 16.60. IR: broad band at 3460 cm^{-1} (OH), 1598 cm^{-1} (C=N). ^{1}H NMR (DMSO-d6): δ 3.57-

3.76 (m, 2H, 3'-H), 4.3-4.5 (m, 1H, 2'-H), 4.71-5.31 (m, 3H, 3 OH), 5.85 (d, 1H, *J* = 4.8 Hz, 1'-H), 7.2-8.3 (m, 9H, Ar-H). Mass: m/z (M+ 336, 4%).

3-(D-threo 1`, 2`, 3`-trihydroxyprop-1`-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline **3**$_{a\ c}$

Using D-Galactose and method 1: Product recrystallized from ethanol and yield was 64%; m.p. 198-200°C. Anal. Calc. for $C_{18}H_{16}N_4O_3$: C, 64.29; H, 4.76; N, 16.67. Found: C, 64.26; H, 4.80; N, 16.62. IR: broad band at 3340 cm^{-1} (OH), 1596 cm^{-1} (C=N). ^{1}H NMR (DMSO-d6): δ 3.55-3.74 (m, 2H, 3'-H), 4.23-4.51 (m, 1H, 2'-H), 4.71-5.3 (m, 3H, 3OH), 5.86 (d, 1H, *J*=6 Hz, 1'-H), 7.21-8.32 (m, 9H, Ar-H). Mass: m/z (M+ 336, 6%).

3-(D-1', 2'-dihydroxyeth-1'-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline **4**$_{a\ c}$

Using D-arabinose, D-xylose or D-ribose and method 1, product recrystallized from ethanol and yield was 61%; m.p 212-214°C. Anal. Calc. for $C_{17}H_{14}N_4O_2$: C, 66.67; H, 4.57; N, 18.30. Found: C, 66.61; H, 4.53; N, 18.25. IR: broad band at 3450 cm^{-1} (OH), 1596 cm^{-1} (C=N). ^{1}H NMR (DMSO-d6): δ 4.05-4.30 (m, 2H, 2'-H), 4.93 (t, 1H, *J* = 6.2 Hz, OH), 5.26 (q, 1H, *J* = 5.6 Hz, OH), 5.86 (d. 1H, *J* = 5.0 Hz, 1'-H), 7.39-8.43 (m, 9H, Ar-H). Mass: m/z (M+ 306, 7%).

3-(L-1', 2'-Dihydroxyeth-1'-yl)-1-phenylpyrazolo [3, 4-b]quinoxaline **5**$_{a\ c}$

Using L-arabinose and method 1, product recrystallize from ethanol; yield was 60%; m.p. 216-218°C. Anal. Calc. for $C_{17}H_{14}N_4O_2$: C, 66.67; H, 4.57; N, 18.30. Found: C, 66.60; H, 4.52; N, 18.23.IR: broad band at 3440 cm^{-1} (OH), 1597 cm^{-1} (C=N); ^{1}H NMR (DMSO-d6): δ 4.01-4.22 (m, 2H, 2'-H), 4.94 (t, 1H, *J* = 6 Hz. OH), 5.29 (q, 1H, *J*=5.8 Hz, OH), 5.87 (d, 1H, *J* = 4.6 Hz, 1'-H), 7.35-8.43 (m, 9H, Ar-H). Mass: m/z (M+ 306, 5%).

Synthesis of 3-(sugar)-6, 7-dimethyl-1-phenylpyrazolo [3, 4-b] quinoxaline analogues; using 4, 5-dimethyl-*O*-phenylenediamine instead of *O*-phenylenediamine with different hexoses and pentoses in method 1.

3-(D-erythro-1`, 2`, 3` trihydroxyprop-1`-yl)-6, 7-dimethyl-1-phenylpyrazolo [3, 4-b] quinoxaline **2**$_{b\ c}$

Using D-mannose and method 1; recrystallize product from ethanol; yield 72%; m.p 200-202°C. Anal. Calc. for $C_{20}H_{20}N_4O_3$: C, 65.93; H, 5.49; N, 15.38. Found: C, 65.85; H, 5.48; N, 15.32. IR: broad band at 3390 cm^{-1} (OH), 1598 cm^{-1} (C=N). ^{1}H NMR (DMSO-d6): δ 2.40 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.82-3.92 (m, 2H, 3'-H), 4.44 (q, 1H, *J* = 5.5 Hz, 2'-H), 4.56-4.75 (m, 2H, 2OH), 5.03-5.12 (m, 1H, OH), 5.84 (d, 1H, *J* = 4.8 Hz, 1'-H), 7.33-8.48 (m, 7H, Ar-H). Mass: m/z (M+ 364, 6%).

3-(D-threo-1`, 2`, 3` trihydroxyprop-1`-yl) 6, 7-Dimethyl-1-phenylpyrazolo [3, 4-b] quinoxaline **3**$_{b\ c}$

Using D- galactose and method 1; recrystallize product from ethanol; yield 73%; m.p 189-191°C. Anal. Calc. for $C_{20}H_{20}N_4O_3$: C, 65.93; H, 5.49; N, 15.38. Found: C, 65.81; H, 5.41; N, 15.29. IR: broad band at 3400 cm^{-1} (OH), 1595 cm^{-1} (C=N). ^{1}H NMR (DMSO-d6): δ 2.39 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.61-3.70 (m, 2 H, 3'-H), 4.38 (q, 1H, *J* = 5.3 Hz, 2'-H), 4.68 (t, 1H, *J* = 5.6 Hz, OH), 4.89 (d, *J* = 5.6 Hz, OH), 5.21 (t, 1H, *J*=5.6 Hz, OH), 5.48 (d, 1 H, *J*=6.2 Hz, 1'-H), 7.30-8.42 (m, 7 H, Ar-H). Mass: m/z (M+ 364, 4%).

3-(D-1, 2 dihydroxyeth-1'-yl)-6, 7-dimethyl-1-phenylpyrazolo [3, 4-b] quinoxaline **4**$_{b\ c}$

Using D-Arabinose, recrystallize from ethanol, yellow needles; yield 69%; m.p. 184-186°C. Anal. Calc. for $C_{19}H_{18}N_4O_2$: C, 68.26; H, 5.39; N, 16.77. Found: C, 68.15; H, 5.33; N. 16.72. IR: broad band at 3390 cm^{-1} (OH), 1593 cm^{-1} (C=N). ^{1}H NMR (DMSO-d6): δ 2.28 (s, 6H, 2CH_3), 4.09-4.20 (dd, 2 H, 2'-H), 5.01(t, 1H, *J*= 5.8 Hz, OH), 5.26 (q, 1H, *J* = 5.9 Hz, OH), 5.81 (d, 1 H, *J* = 5.2 Hz, 1'-H), 7.27-8.35 (m, 7H, Ar-H). Mass: m/z (M+ 334, 3%).

3-(L-1, 2 dihydroxyeth-1'-yl)-6, 7-dimethyl-1-phenylpyrazolo [3, 4-b] quinoxaline **5**$_{b\ c}$

Using L-arabinose and method 1; recrystallize Product from ethanol; yield 68%; m.p. 216-218°C. Anal. Calc. for $C_{19}H_{18}N_4O_2$: C, 68.26; H, 5.39; N, 16.77. Found: C, 68.12; H, 5.28; N, 16.71. IR: broad band at 3402 (OH), 1597 cm^{-1} (C=N); ^{1}H NMR (DMSO-d6): δ 2.49 (s, 6 H, 2CH_3), 4.03-4.18 (m, 2H, 2'-H), 4.93 (t, 1H, *J* = 6 Hz, OH), 5.24 (q, 1H, *J* = 5.2 Hz, OH), 5.80 (d, 1H, *J* = 4.6 Hz, 1'-H), 7.23-8.41 (m, 7 H, Ar-H). Mass: m/z (M+ 334, 4%).

Acetylation of 1-pheny pyrazolo [3, 4-b] quinoxaline-C-nucleosides

General method

Add acetic anhydride (3 ml) to a solution of 1-phenyl pyrazolo [3, 4-b] quinoxaline-*C*-nucleoside (0.3 m mol) in 3 ml of pyridine. The reaction mixture stirred for 30 hrs at room temperature, and then poured onto crushed ice. The precipitate so formed filtered off and washed successfully with water, then recrystallized from the proper solvent.

3-(D-erythro 1`, 2`, 3` tri O acetyl prop-1`-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline **2**$_{a\ d}$

Compound **2**$_{a\ c}$ acetylated; recrystallized from 50% ethanol; yield 80%; m.p. 116-118°C.

Anal. Calc. for $C_{24}H_{22}N_4O_6$: C, 62.34; H, 4.76; N, 12.12. Found C, 62.31; H, 4.71; N, 12.07. IR: 1743 (C=O), 1597 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 2.05 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.77 (s, 3H, $COCH_3$), 4.6 (m, 2H, 3'-H), 6.12 (q, 1H, *J* = 3.24 Hz, 2'-H), 6.82 (d, 1H, *J* = 5.7 Hz, 1'-H), 7.30-8.51 (m, 9H, Ar-H). Mass: m/z (M+ 462, 7%).

3-(D-threo 1`, 2`, 3` tri O acetyl prop-1`-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline **$3_{a\ d}$**

Compound $3_{a\ c}$ acetylated; recrystallized from 50% ethanol, yield 81%; m.p. 100-102°C. Anal. Calc. for $C_{24}H_{22}N_4O_6$: C, 62.34; H, 4.76; N, 12.12. Found: C, 62.32: H, 4.73; N, 12.07. IR: 1748 cm^{-1} (C=O), 1597cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 2.08 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.26 (s. 3H, $COCH_3$), 4.39- 4.51 (m, 2H, 3'-H), 6.14 (q, 1H, *J* = 4.26 Hz, 2'-H), 6.9 (d. 1 H, *J* = 6.1 Hz, 1'-H), 7.30-8.51 (m, 9H, Ar-H). Mass: m/z (M+ 462, 4%).

3-(D- 1`, 2` di O acetyl eth-1`-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline **$4_{a\ d}$**

Compound **$4_{a\ c}$** acetylated; recrystallized from 50% ethanol; yield 84%; m.p 118-120°C. Anal. Calc. for $C_{21}H_{18}N_4O_4$: C, 64.61; H, 4.62; N. 14.36. Found: C, 64.54; H, 4.54; N, 14.24. IR: 1738 cm^{-1} (C=O), 1598 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 2.09 (s, 3H, $COCH_3$), 2.26 (s, 3H, $COCH_3$), 4.95 (d, 2H, *J* = 5.8 Hz, 2'-H), 6.83 (t, 1H, *J* = 5.8 Hz, 1'-H), 7.26-8.46 (m, 9H, Ar-H). Mass: m/z (M+ 390, 3%).

3-(L-1`, 2` Di O acetyl eth-1`-yl) -1-phenylpyrazolo-[3, 4-b]quinoxaline **$5_{a\ d}$**

Compound **$5_{a\ c}$** acetylated, recrystallized from 50% ethanol; yield 83%; m.p. 128-130°C. Anal. Calc. for $C_{21}H_{18}N_4O_4$: C, 64.61; H, 4.62; N, 14.36. Found: C, 64.52; H, 4.56; N, 14.22. IR: 1743 cm^{-1} (C=O), 1569 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 2.08 (s, 3H, $COCH_3$). 2.25 (s, 3H, $COCH_3$), 4.95 (d, 2H, *J* = 5.8 Hz, 2'-H), 6.83 (t-1H, *J* = 5.7 Hz, 1'-H), 7.26-8.46 (m, 9H. Ar-H). Mass: m/z (M+ 390, 4%).

3-(D-erythro 1`, 2`, 3` tri O acetyl prop-1`-yl) 6, 7-dimethyl-1-phenylpyrazolo [3, 4-b] quinoxaline **$2_{b\ d}$.** Compound **$2_{b\ c}$** acetylated, recrystallized from isopropyl alcohol; yield 85%; m.p. 140-142 °C. Anal. Calc. for $C_{26}H_{26}N_4O_6$: C, 63.67; H, 5.31; N, 11.43. Found: C, 63.48; H. 5.21; N, 11.22. IR: 1731 cm^{-1} (C=O), 1597 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 2.01 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.23 (s, 3H, $COCH_3$), 2.54 (s, 6H, $2CH_3$), 4.49-4.66 (2dd, 2H, 3'-H), 6.10 (q, 1H, *J* = 3.1 Hz, 2'-H), 6.77 (d, 1H, *J* = 5.4 Hz, 1'-H), 7.26-8.46 (m, 7H, Ar-H). Mass: m/z (M+ 490, 4%).

3-(D-threo 1`, 2`, 3` tri O acetyl prop-1`-yl) 6, 7-dimethyl-1-phenylpyrazolo [3, 4 b] quinoxaline **$3_{b\ d}$**

Compound **$3_{b\ c}$** acetylated, recrystallized from isopropyl alcohol; yield 84%; m.p. 138-140 °C. Anal. Calc. for $C_{26}H_{26}N_4O_6$: C, 63.67; H, 5.31; N, 11.43. Found: C, 63.65; H, 5.28; N, 11.31. IR: cm^{-1} 1748 (C=O), 1601 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.04 (s, 6H, 2 $COCH_3$), 2.06 (s, 3H, $COCH_3$). 2.55 (s, 6H, $2CH_3$); 4.22-4.52 (2dd, 2H, 3'-H), 6.11 (q, 1H, *J* = 4.2 Hz, 2'-H), 6.85 (d, 1H, J = 6.4 Hz, 1'-H), 7.26-8.45(m, 7H, Ar-H). Mass: m/z (M+ 490, 7%).

3-(D-1`, 2` di O acetyl eth-1`-yl) 6, 7-dimethyl-1-phenylpyrazolo [3, 4-b] quinoxaline **$4_{b\ d}$**

Compound **$4_{b\ c}$** acetylated, recrystallized from isopropyl alcohol; yield 80%; m.p. 93-95°C. Anal. Calc. for $C_{23}H_{22}N_4O_4$: C, 66.03; H, 5.26; N, 13.40. Found: C, 65.91; H, 5.17; N, 13.25. IR: 17.47 cm^{-1} (C=O), 1597 cm^{-1} (C=N): ^1H NMR ($CDCl_3$): δ 2.08 (s, 3H, $COCH_3$), 2.24 (s, 3H, $COCH_3$), 2.53 (s, 6H, $2CH_3$), 4.93(d, 2H, *J* = 6 Hz. 2'-H), 6.81 (t, 1H, *J* = 5.7 Hz, 1'-H), 7.26-8.45(m,7H, Ar-H). Mass: m/z (M+ 418, 5%).

3-(L-1`, 2` di O acetyl eth-1`-yl) 6, 7-dimethyl-1-phenylpyrazolo [3, 4-b] quinoxaline **$5_{b\ d}$**

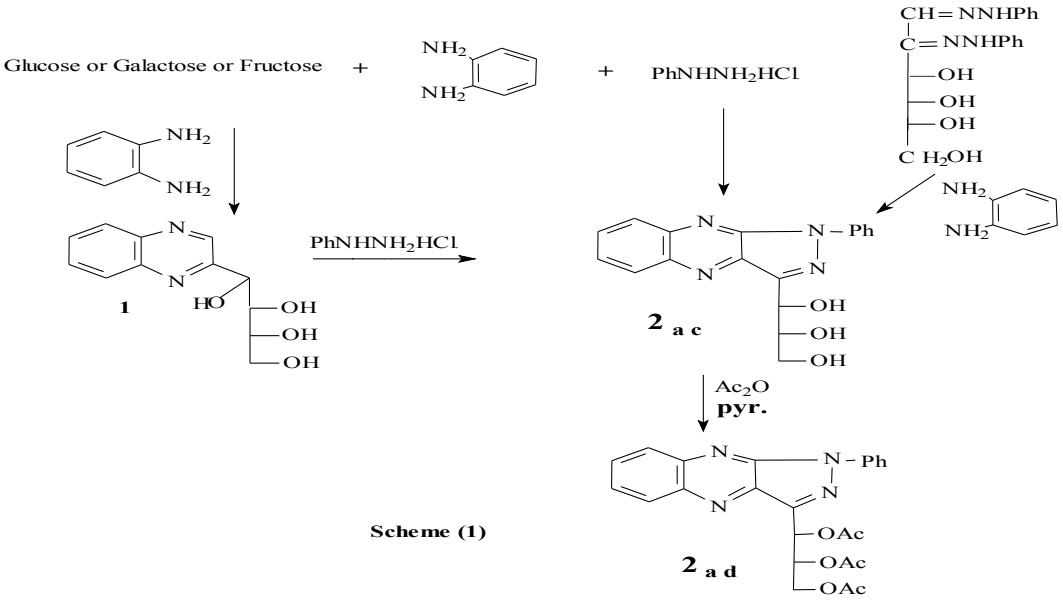
Compound $5_{b\ c}$ acetylated, recrystallized from isopropyl alcohol; yield 80%; m.p. 93-95 °C. Anal. Calc. for $C_{23}H_{22}N_4O_4$: C, 66.03; H, 5.26; N, 13.40. Found: C, 65.90; H, 5.15; N, 13.31. IR: cm^{-1} 1747 (C=O), 1599 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 2.08 (s, 3H, $COCH_3$); 2.44 (s, 3H, $COCH_3$), 2.50 (s, 6H, $2CH_3$), 4.94(d, 2H, *J* = 5.8H, 2'-H), 6.81(t, 1H, *J* = 5.9 Hz, 1'-H), 7.26-8.44(m, 7H, Ar-H). Mass: m/z (M+ 418, 6%).

{3-(1' Deoxy, 2' Chloro eth-1'-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline} {3 (1''deoxy, 2''-hydroxy eth-1''-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline} 1', 1'' Sulfite **6.**

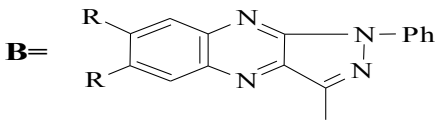
Compound **$4_{a\ c}$** (1 m mol) in 3 ml of acetonitrile and 0.1 ml of thionyl chloride cooled to 0°C and stirred for ½ hour. The produced material washed several times with diethyl ether, then dried to give **6** in 70% yield; m.p. 148-150 °C. Anal. Calc. for $C_{34}H_{25}N_8Cl\ S\ O_4$: C, 60.36; H, 3.70; N, 16.57; CI, 5.18; S, 4.73. Found: C, 60.28; H, 3.64; N, 16.43; Cl, 5.12; S, 4.70. IR: broad band at 3422 cm^{-1} (OH), 1599 cm^{-1} (C=N), 1207 cm^{-1} (S=O); ^1H NMR ($CDCl_3$): δ 5.00-5.03 (m, 4H, 2'-H, 2''-H), 5.85(t, 1H, *J* = 9.4 Hz. OH), 6.22 (t, 1H, *J*= 8.1 Hz, 1'-H), 6. 67 (t, 1H, *J* = 5.9 Hz, 1''-H), 7.26-8.46(m. 18H, Ar-H). Mass: m/z (M+ 676, 8%).

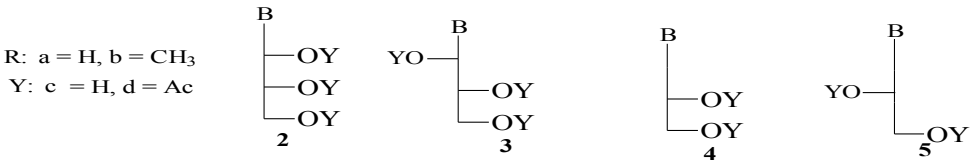
3-(D-1'-hydroxy-2'- N-morpholino eth-1'-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline **7**

Compound **6** (1 m mol) treated with excess morpholine and left overnight at room temperature under stirring. The product separated on column (4 x 60 cm) of silica gel with1:2 ether: pet. ether as an eluent, to give compounds $\mathbf{4}_{a\,c}$ and **7.** Compound **7** isolated in 31% yield; m.p. 90-92 °C. Anal. Calc. for $C_{21}H_{21}N_5O_2$: C, 67.20; H, 5.60: N, 18.67. Found: C, 67.12; H, 5.54; N, 18.54. IR: broad band at 3320 cm^{-1} (OH), 1585 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 2.59-2.72 (m, 4H, morpholino-H), 2.86-2.95 (m, 4H, morpholino-H), 3.73-3.83(m, 2H, 2'-H), 4.06- 4.10(m, 1H, OH), 4.55(t, 1H, *J* = 8.3 Hz, 1'-H), 7.26-8.48(m, 9H, Ar-H). Mass: m/z (M+ 375, 5%).

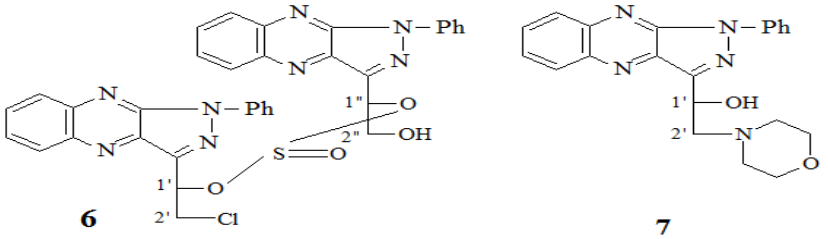


Scheme (1)





Scheme(2)



Scheme (3)

Compound #	% cytotoxicity	% Inhibition
$2_{a\,c}$	12.0	0.0
$2_{b\,c}$	52.0	37.0
$3_{a\,c}$	5.1	35.0
$3_{b\,c}$	89.4	24.0
$4_{a\,c}$	23.8	0.0
$4_{b\,c}$	94.0	**11.0**
$5_{a\,c}$	52.0	3.0
$5_{b\,c}$	94.0	**54.0**
$2_{a\,d}$	30.9	44.0
$2_{b\,d}$	97.2	0.0
$3_{a\,d}$	26.6	22.0
$3_{b\,d}$	93.0	40.0
$4_{a\,d}$	34.7	44
$4_{b\,d}$	66.5	25.0
$5_{a\,d}$	29.0	18.0
$5_{b\,d}$	24.0	33.0
7	7.5	10.0

Concentration =100 μ *M*.

4. Conclusion

New class of 3-(1', 2'-dihydroxyeth-1'-yl)-1-phenylpyrazolo [3, 4-b] quinoxaline and 3-(1`, 2`, 3`trihydroxy prop-1`-yl)-1-phenyl pyrazolo [3, 4-b] quinoxaline series "C-nucleosides" prepared and checked for antiviral activity. Presented a new chemical reaction called "Y. Fakhreldin reaction": (1`, 2` dihydroxyeth-1`-yl) compounds, react with thionyl chloride, to produce {1' Deoxy, 2' Chloro eth-1'-yl) compound} {(1"deoxy, 2"-hydroxy eth-1"-yl) compound} 1', 1" Sulfite.

Acknowledgments

I would like to express my gratitude towards my parents, wife and children & members of Tanta and Minufiya Universities for their kind co-operation and encouragement which help me in completion of this paper.

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10/4/2012

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