SYNTHESIS OF ORGANOFLUORINE COMPOUNDS UTILIZING 3-[1-(3-FLUOROPHENYLHYDRAZONO)-D-*ERYTHRO*-2,3,4-TRIHYDROXYBUTYL]-QUINOXALIN-2*(1H)*-ONE AS A PRECURSOR

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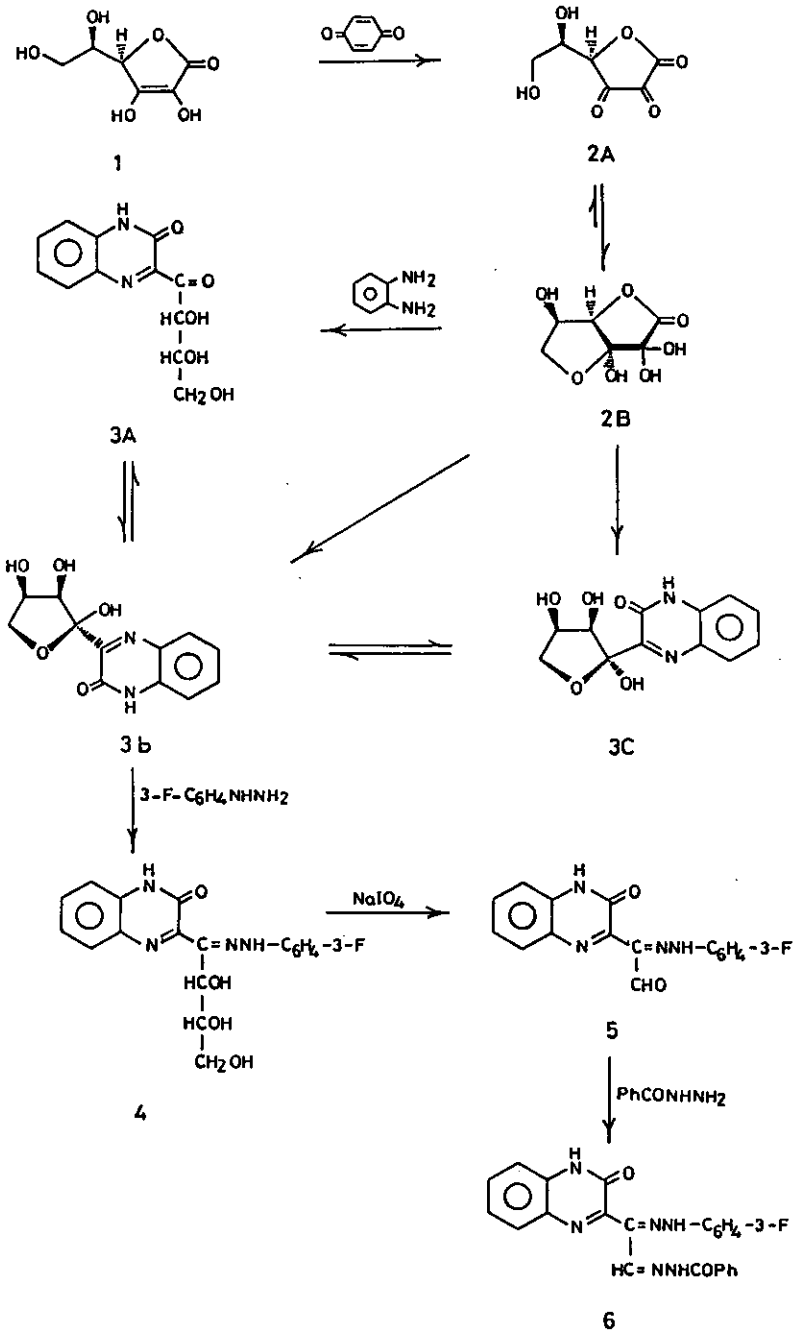
Abstract - The reaction of D-*erythro*-2,3-hexodiulosono-1,4-lactone with 1,2-diaminobenzene followed by 3-fluorophenylhydrazine and the reaction of the product with dimethyl sulfate, sodium metaperiodate and acetic anhydride in pyridine have been investigated. The isopropylidenation of 3-[1-(3-fluorophenylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]quinoxalin-2*(1H)*-one under thermodynamic controlled conditions has been studied. Compounds 3-[1-(3-fluorophenylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]quinoxalin- 2*(1H)*-one and its *N*-methyl derivative undergo dehydrative cyclisation in boiling acetic anhydride to the corresponding pyrazolylquinoxalinones.

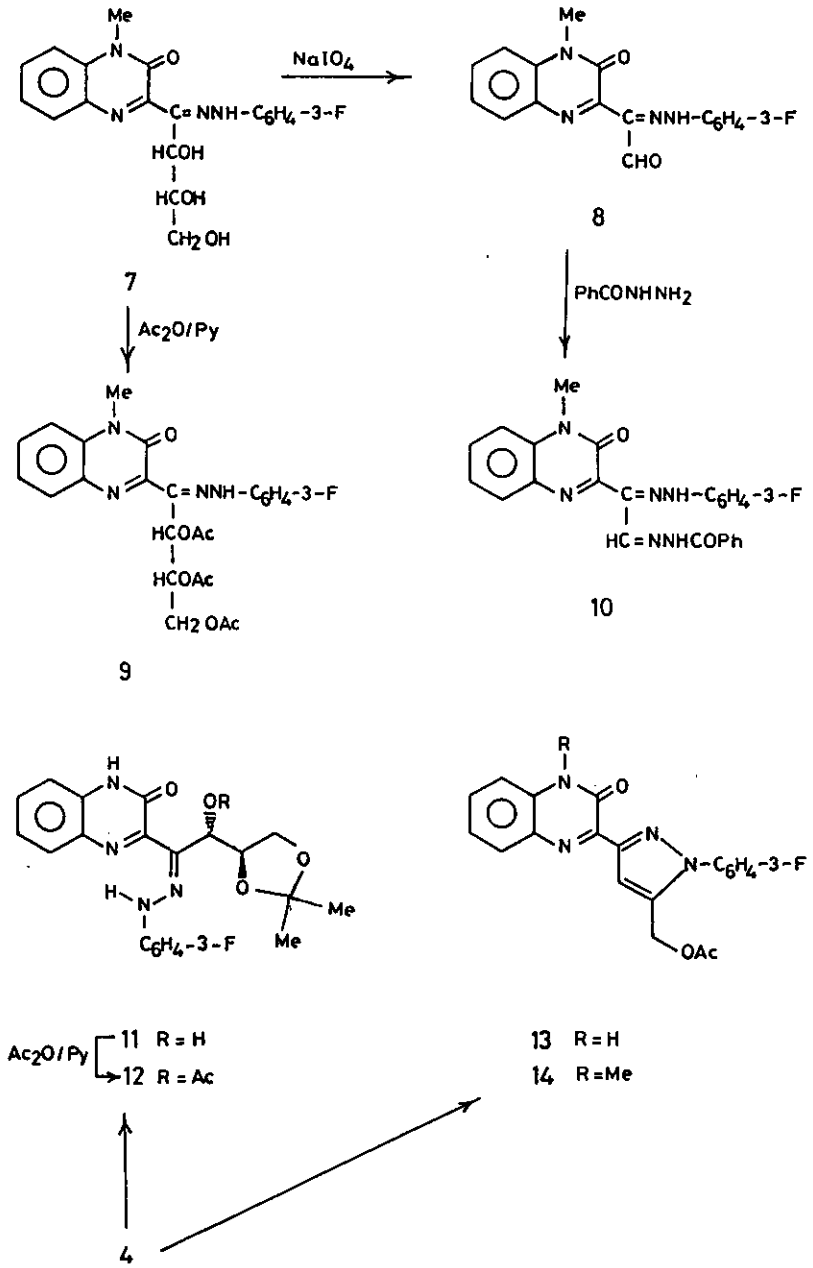
Organic compounds containing fluorine atoms are attractive compounds from the biological point of view.[1] The hypnotic activity of a number of 6-fluoroalkylquinoxaline-2,3-diones has been patented,[2] and the quinoxalinedione was reported to have hypotensive activity in dogs.[3] The insecticidal properties of compounds containing fluorine[4] as well as 6-nitroquinoxaline-2,3-dione[5] have been reported. The carbon frame for constructing the quinoxalin-2-one ring could be dehydro-D-erythorbic acid (D-*erythro*-2,3-hexodiulosono-1,4-lactone (2). The reaction of 2 with 1,2-diaminobenzene was first studied by Erlbach and Ohle,[6] who isolated 3-(D-*erythro*-2,3,4-trihydroxy-1-oxobutyl)quinoxalin-2*(1H)*-one (3). The structure (3) was recently reinvesti-



Scheme 1

gated.[7-9] This compound is an excellent precursor for constructing heterocycles containing the quinoxaline ring. Having the above aspects in mind, we have investigated the synthesis of the quinoxaline and pyrazole containing fluorine atoms. The starting material 3-[1-(3-fluorophenylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]quinoxalin-2*(1H)*-one (**4**) was prepared from dehydro-D-isoascorbic acid (**2**) by its sequential reactions with a molar equivalent of 1,2-diaminobenzene followed by 3-fluorophenylhydrazine. Both C-1 and C-2 of **2** were utilized in constructing the quinoxalinone ring.[10] The C-3 carbonyl in **3A** participates in the formation of the cyclic hemiacetals (**3b**) and (**3C**) as a consequence of its interaction with the terminal hydroxy group. Although, the solution of **3** contains **3A** as a minor species, it readily reacted with 3-fluorophenylhydrazine to give the hydrazone (**4**). Its ir spectrum showed the presence of band at 1665 cm^{-1} due to the amide group.

When hydrazone (**4**) was subjected to the action of sodium periodate, it gave 3-[1-(3-fluorophenylhydrazono)glyoxal-1-yl]quinoxalin-2*(1H)*-one (**5**). Such reaction provides a simple route to glyoxalylquinoxalin-2*(1H)*-one; a potential precursor to other heterocyclic compounds.[9] Reaction of the aldehyde (**5**) with benzoylhydrazine gave the corresponding mixed bishydrazone,3-[2-(benzoylhydrazono)-1-(3-fluorophenylhydrazono)glyoxal-1-yl]quinoxalin-2*(1H)*-one(**6**), which lacked the aldehydic band (1715 cm^{-1}) in its ir spectrum that present in its precursor (**5**). The reaction of 3-[1-arylhydrazono-D-*erythro*-2,3,4-trihydroxybutyl]quinoxalin-2*(1H)*-one with a boiling sodium hydroxide solution was reported to give 1-aryl-3-(D-*erythro*-glycerol-1-yl]pyrazolo[3,4-*b*]quinoxaline.[11] The reaction presumably proceeds *via* the formation of the sodium salt. On the other hand, when the sodium salt was treated at room temperature with dimethyl sulfate the isolated product was assigned the respective *N*-methyl derivative. Thus, 3-[1-(3-fluorophenylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]-1-methylquinoxalin-2-one (**7**) was prepared. Its elemental analysis agreed with the molecular formula $C_{19}H_{19}N_4O_4F$, indicating that monomethylation had taken place. The ir spectrum of **7** showed two bands at 1640 (OCN) and 3470 cm^{-1} (OH). Acetylation of **7** with acetic anhydride and pyridine afforded 3-[1-(3-fluorophenylhydrazono)-D-*erythro*-2,3,4-triacetoxybutyl]-1-methylquinoxalin-2-one (**9**), whose structure was deduced from ir and ^{1}H-nmr spectra. The ir spectrum showed bands at 1665 (OCN), 1750 cm^{-1} (OAc group). Its ^{1}H-nmr spectrum showed three singlets at δ 1.90, 1.93 and 1.97 due to three acetyl groups, in addition to a singlet at δ 3.6 (due to *N*-Me). Although,


Me
N
O
C= NNH-C6H4-3-F
HCOH
HCOH
CH2 OH
7
NaIO4
CHO
8
Ac2O/Py
HCOAc
HCOAc
CH2 OAc
9
PhCONHNH2
HC = NNHCOPh
10
H
OR
Me
Me
C6H4-3-F
R
OAc
Ac2O/Py
11 R = H
12 R = Ac
13 R = H
14 R = Me
4

Scheme 2

that signals confirmed the presence of the substituents, it did not confirm their assigned positions. However, the downfield location of the protons of the butyl side chain upon acetylation did confirm that the acetyl groups were introduced on the hydroxyl groups and consequently, the methyl group was introduced on the nitrogen of the heterocyclic ring. Thus, the doublet of H-2 appeared at δ 6.1, the multiplet of H-3 at δ 5.6 and the multiplet of H-4, 4′ at δ 4.3. Periodate oxidation of **7** afforded 3- [1-(3-fluorophenylhydrazono)glyoxal-1-yl]-1-methylquinoxalin-2-one (**8**). The ir spectrum of the aldehyde (**8**) showed a band at 1680 cm^{-1} (due to the CHO group) in addition to another band at 1655 cm^{-1} (due to OCN group). Its ^{1}H-nmr spectrum showed a singlet at δ 3.6 (due to *N*-Me), a multiplet at δ 6.7-7.9 (due to aromatic protons), a singlet at δ 9.5 (due to formyl proton) and singlet at δ 11.1 (due to NH proton). The presence of the formyl group was also confirmed by its reaction with benzoylhydrazine to give 3-[2-(benzoylhydrazono)-1-(3-fluorophenylhydrazono)glyoxal-1-yl]-1-methylquinoxalin-2-one (**10**). The ir spectrum of **10** showed the absence of an formyl band. This sequence of reactions further confirmed the location of the methyl group in **7**. Isopropylidenation of 3-[1-(3-fluorophenylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]quinoxalin-2*(1H)*-one (**4**) with acetone and a catalytic amount of sulfuric acid gave a product (**11**) possessing α terminal 1,3-dioxolane ring. Acetylation of **11** afforded the corresponding mono-*O*-acetyl derivative (**12**). The ^{1}H-nmr spectrum of **12** showed a downfield shift of the doublet of the glycerolyl H-2 upon acetylation of **11** [from δ 5.1 to 6.6], whereas the locations of H-4, 4′ (δ 4.2) and H-3 (δ 4.5) were not affected by acetylation. This indicated that the acetylation occurred on position-2 and the isopropylidene ring occupied positions 3 and 4. When **4** and **7** were boiled with acetic anhydride they afforded 3-[5-(acetoxymethyl)-1-(3-fluorophenyl)pyrazol-3-yl]quinoxalin-2*(1H)*-one (**13**) and 3-[5-(acetoxymethyl)-1-(3-fluorophenyl)pyrazol-3-yl]-1-methylquinoxalin-2-one (**14**), respectively. Their structures were confirmed by ir and ^{1}H-nmr spectra. The ir showed two bands at 1660 (OCN) and 1735 cm^{-1} (OAc group). Their ^{1}H-nmr spectra showed a singlet at δ 2.0-2.1 (due to one OAc), a singlet at δ 5.2 due to a methylene protons whose downfield location indicated its attachment to an acetoxy group. The aromatic protons appeared at δ 7.4-8.0, and the amide proton at δ 12.0 in case of **13**, whereas **14** did not show such a singlet but showed a singlet at δ 3.7 (due to *N*-methyl group).

EXPERIMENTAL

General methods: Melting points were determined with a Meltemp apparatus with a 76 mm immersion thermometer, and are uncorrected. Ir spectra were recorded with a Unicam SP 1025

spectrophotometer. ^{1}H-Nmr spectra were measured with an EM-390 spectrometer using tetramethylsilane (Me_4Si) as a reference. The spectra are reported with chemical shits (δ) downfield from Me_4Si. Microanalyses were performed in the Unit of Microanalysis, Cairo University, Cairo, Egypt.

3-[1-(3-Fluorophenylhydrazono)-D-*erythro* -2,3,4-trihydroxybutyl]quinoxalin-2*(1H)*-one (4). A suspension of D-isoascorbic acid (1) (17.6 g; 0.1 mol) and *p*-benzoquinone (10.8 g; 0.1 mol) in ethanol (150 ml) was stirred for 90 min at room temperature. The resulting homogeneous dark yellow solution was treated with a solution of 1,2-diaminobenzene (10.8 g; 0.1 mol) in ethanol (100 ml) and water (500 ml) and then heated until boiling for 5 min. The reaction mixture was then treated with a solution of 3-fluorophenylhydrazine hydrochloride (16.3 g; 0.1 mol) in ethanol (150 ml) and sodium acetate (8.2; 0.1 mol) in water (100 ml), and the mixture was boiled for 5-10 min, whereby red crystalline product separated out. It was recrystallized from ethanol to give red crystals (24.3 g, 65%); mp 220° C; ν_{max} (KBr): 1610 (C=N), 1665 (OCN), 3450 cm^{-1} (OH); ^{1}H-nmr (DMSO-d_6): δ 3.8-4.0, 4.1-4.7, 4.9-5.3, 5.8-6.1 (4m, 7 H, glycerolyl protons), 6.4-7.9 (m, 8H, aromatic protons), 10.3, 10.5 (2s, 1 H, 3:1, NH), 12.5 (brs, 1 H, NH). Anal. Calcd for $C_{18}H_{17}N_4O_4F$: C, 58.2; H, 4.6; N, 15.0. Found: C, 58.4; H, 4.4; N, 14.7.

3-[1-(3-Fluorophenylhydrazono)glyoxal-1-yl]quinoxalin-2*(1H)*-one (5). A suspension of 4 (0.3 g; 0.8 mmol) in distilled water (20 ml) was treated with a solution of sodium metaperiodate (0.43 g; 1.6 mmol) in distilled water (20 ml). The mixture was stirred for 1 h and then left overnight in the dark at room temperature. The product was filtered off and recrystallized from ethanol in orange crystals (0.2 g, 80%); mp 260°C; ν_{max}(KBr): 1615 (C=N), 1665 (OCN), 1715 (CHO), 3130 cm^{-1} (NH); ^{1}H-nmr (DMSO-d_6): δ 6.7-7.9 (m, 8 H, aromatic protons), 9.6 (s, 1 H, formyl proton), 11.3 (s, 1 H, NH) and 12.7 (s, 1 H, NH). Anal. Calcd for $C_{16}H_{11}N_4O_2F$: C, 62.1; H, 3.6; N, 18.0. Found: C, 62.0; H, 3.6; N, 17.8.

3-[2-(Benzoylhydrazono)-1-(3-fluorophenylhydrazono)glyoxal-1-yl]quinoxalin-2*(1H)*-one (6). A solution of 5 (1.6 g; 5.1 mmol) in *N,N*-dimethylformamide (10 ml) and ethanol (10 ml) was treated with benzoylhydrazine (0.7 g; 5.1 mmol) and then heated for 5 min. The product that separated out was filtered off, washed with ethanol. The product was recrystallized from ethanol and *N,N*-dimethylformamide in yellow crystals (1.5 g, 68%); mp 240°C; ν_{max}(KBr): 1610 (C=N), 1670 (OCN), 3140, 3260 cm^{-1} (NH); ^{1}H-nmr (DMSO)-d_6): δ 6.6-8.1 (m, 14H, aromatic and methine protons), 8.2, 8.8 (2s, 2H, 2NH) and 10.4 (brs, 1H, NH). Anal. Calcd for $C_{23}H_{17}N_6O_2F$: C, 64.6; H, 4.0; N, 19.6. Found: C, 64.5; H, 4.1; N, 19.4.

3-[1-(3-Fluorophenylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]-1-methylquinoxalin-2-one (7). A suspension of **4** (5.0 g; 13.4 mmol) in a solution of sodium hydroxide (3.0 g; 75.0 mmol) in 40% aqueous ethanol (375 ml) was heated on a water-bath till dissolution. Dimethyl sulfate (5 ml; 52.7 mmol) was then added and the mixture was left at room temperature for 10 h with occasional shaking. The product that separated out was filtered off, washed with water and then recrystallized from ethanol in orange crystals (3.0 g, 59%); mp 178°C; ν_{max}(KBr): 1615 (C=N), 1640 (OCN), 3470 cm^{-1} (OH); ^{1}H-nmr (DMSO-d_6): δ 3.4 (s, 3 H, *N*-Me), 3.9-4.1, 4.3-4.7, 5.1-5.4, 6.0-6.2 (4m, 7 H, glycerolyl protons), 6.5-8.0 (m, 8 H, aromatic protons), 10.0 (s, 1 H, NH). Anal. Calcd for $C_{19}H_{19}N_4O_4F$: C, 59.2; H, 4.9; N, 14.5. Found: C, 58.8; H, 5.0; N, 14.7.

3-[1-(3-Fluorophenylhydrazono)-D-*erythro*-2,3,4-triacetoxybutyl]-1-methylquinoxalin-2-one (9). A cold solution of **7** (0.3 g; 0.8 mmol) in dry pyridine (5 ml; 16.8 mmol) was treated with acetic anhydride (5 ml; 53.0 mmol). The reaction mixture was kept overnight at room temperature and then poured onto crushed ice and the product that separated out was filtered off, washed with a dilute solution of 10% sodium bicarbonate, water and ethanol. The product was crystallized from ethanol in orange crystasls (3.0 g, 77%); mp 143°C; ν_{max} (KBr): 1615 (C=N), 1665 (OCN), 1750 (OAc); ^{1}H-nmr (DMSO-d_6): δ 1.90, 1.93, 1.97 (3s, 9 H, 3 OAc), 3.6 (s, 3 H, *N*-Me), 4.3 (m, 2 H, H-4, 4′), 5.6 (m, 1 H, H-3), 6.1 (d, $J_{1,2}$ 6 Hz, 1 H, H-2), 6.6-7.9 (m, 8 H, aromatic protons) and 10.4 (s, 1 H, NH). Anal. Calcd for $C_{25}H_{25}N_4O_7F$: C, 58.7; H, 4.9; N, 10.9. Found: C, 58.8; H, 4.7; N, 10.7.

3-[1-(3-Fluorophenylhydrazono)glyoxal-1-yl]-1-methylquinoxalin-2-one (8). A suspension of **7** (0.6 g; 1.5 mmol) in distilled water (40 ml) was treated with a solution of sodium metaperiodate (0.6 g; 3.0 mmol) in distilled water (40 ml). The mixture was stirred for 1 h and then left overnight in the dark at room temperature. The product was filtered off, and recrystallized from ethanol in orange crystals (0.4 g, 80%); mp 165°C; ν_{max}(KBr): 1615 (C=N), 1655 (OCN), 1680 (CHO), 3320 cm^{-1} (NH); ^{1}H-nmr (DMSO-d_6): δ 3.6 (s, 3 H, *N*-Me), 6.7-7.9 (m, 8 H, aromatic protons), 9.5 (s, 1 H, formyl proton) and 11.1 (s, 1 H, NH). Anal. Calcd for $C_{17}H_{13}N_4O_2F$: C, 63.1; H, 4.0; N, 17.2. Found: C, 63.0; H, 3.7; N, 17.1.

3-[2-(Benzoylhydrazono)-1-(3-fluorophenylhydrazono)glyoxal-1-yl]-1-methylquinoxalin-2-one (10). A solution of **8** (0.3 g; 0.9 mmol) in ethanol (30 ml) was treated with a solution of benzoylhydrazine (0.1 g; 0.9 mmol) in ethanol (20 ml) and then heated for 15 min. The product that separated out was filtered off, washed with ethanol. The product was recrystallized from ethanol in yellow crystals (0.3 g, 73%); mp 265°C; ν_{max}(KBr): 1595 (C=N), 1670 (OCN), 3280 cm^{-1}

(NH); ^{1}H-nmr (DMSO-d_6): δ 3.8 (s, 3 H, *N*-Me), 6.6-8.8 (m, 14 H, aromatic and methine protons), 10.5 (s, 1 H, NH) and 11.8 (s, 1 H, NH). Anal. Calcd for $C_{24}H_{19}N_6O_2F$: C, 65.3; H, 4.3; N, 18.9. Found: C, 65.3; H, 4.1; N, 17.2.

3-[3,4-*O*-Isopropylidene-1-(3-fluorophenylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]quinoxalin-2(*1H*)-one (11). A suspension of **4** (1.0 g; 2.7 mmol) in dry acetone (40 ml) was stirred vigorously for 1 h and few drops of sulfuric acid were added till dissolution. The reaction mixture was neutrallized with solid anhydrous sodium carbonate and filtered. The inorganic salt was washed with acetone. The combined washing and filtrate were evaporated. The product was recrystallized from ethanol in orange crystals (0.8 g, 73%); mp 190-192°C; ν_{max}(KBr): 1660 (OCN) and 3500 cm^{-1} (OH); ^{1}H-nmr ($CDCl_3$): δ 1.3, 1.4 (2s, 6 H, 2 Me), 3.6 (t, J 7.5 Hz, 1 H, OH), 4.2 (m, 2 H, H-4, 4′), 4.5 (m, 1 H, H-3), 5.1 (d, $J_{2,3}$ 6 Hz, 1 H, H-2), 6.5-7.9 (m, 8 H, aromatic protons). Anal. Calcd for $C_{21}H_{21}N_4O_4F$: C, 61.3; H, 5.1; N, 13.5. Found: C, 61.4; H, 5.4; N, 13.8.

3-[2-*O*-Acetyl-3,4-*O*-isopropylidene-1-(3-fluorophenylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]quinoxalin-2(*1H*)-one (12). A cold solution of **11** (0.1 g; 0.24 mmol) in pyridine (5 ml; 61.8 mmol) was treated with acetic anhydride (2 ml; 21.2 mmol). The reaction mixture was left overnight at room temperature. The reaction mixture was poured onto crushed ice. The product that separated was filtered off, washed repeatedly with water and dried. The product was recrystallized from ethanol in orange crystals (0.08 g; 73%); mp 140°C; ν_{max}(KBr): 1660 (OCN) and 1730 cm^{-1} (OAc); ^{1}H-nmr ($CDCl_3$): δ 1.3, 1.4 (2s, 6 H, 2 Me), 2.1 (s, 3 H, OAc), 4.2 (m, 2 H, H-4, 4′), 4.8 (m, 1 H, H-3), 6.6 (d, $J_{2,3}$ 9 Hz, 1 H, H-2), 6.6-7.8 (m, 8 H, aromatic protons). Anal. Calcd for $C_{23}H_{23}N_4O_5F$: C, 60.9; H, 5.1; N, 12.3. Found: C, 61.1; H, 4.8; N, 12.5.

3-[5-(Acetoxymethyl)-1-(3-fluorophenyl)pyrazol-3-yl]quinoxalin-2(*1H*)-one (13). A solution of **4** (0.9 g; 2.4 mmol) in acetic anhydride (12 ml; 127.2 mmol) was heated under reflux for 15 min. The mixture was cooled, diluted with ice cold water and the product that separated out was filtered off, washed with water, and dried. It was crystallized from ethanol in colorless needles (0.6 g; 66%); mp 226°C; ν_{max}(KBr): 1615 (C=N), 1660 (OCN), 1735 (OAc), 3430 cm^{-1} (NH); ^{1}H-nmr ($CDCl_3$): δ 2.1 (s, 3 H, OAc), 5.2 (s, 2 H, CH_2), 7.4-8.0 (2m, 9 H, aromatic and pyrazolyl protons) and 12.0 (brs, 1 H, NH). Anal. Calcd for $C_{20}H_{15}N_4O_3F$: C, 63.6; H, 4.0; N, 14.8. Found: C, 63.6; H, 4.1; N, 15.0.

3-[5-(Acetoxymethyl)-1-(3-fluorophenyl)pyrazol-3-yl]-1-methylquinoxalin-2-one (14). A solution of **7** (0.5 g; 1.3 mmol) in acetic anhydride (6 ml; 63.6 mmol) was heated under reflux for 15 min. The mixture was cooled and poured onto crushed ice. The product that separated out

was filtered off, washed with water, and dried. It was crystallized from ethanol in colorless needles (0.4 g, 79%); mp 183°C; ν_{max}(KBr): 1600 (C=N), 1645 (OCN), 1735 cm^{-1} (OAc); ^{1}H-nmr ($CDCl_3$): δ 2.2 (s, 3 H, OAc), 3.7 (s, 3 H, *N*-Me), 5.2 (s, 2 H, CH_2), 7.2-7.8 (m, 9 H, aromatic and pyrazolyl protons). Anal. Calcd for $C_{21}H_{17}N_4O_3F$: C, 64.4; H, 4.4; N, 14.2. Found: C, 64.2; H, 4.2; N, 14.0.

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