Antioxidant and Antitumor Activities of New Synthesized Aromatic C-Nucleoside Derivatives

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Abstract: The carbohydrazide 1 was used as the precursor for the synthesis of a number of new aromatic C-nucleosides containing 1,3,4-oxadiazole 7, [1,3,4]oxadiazolo[2,3-a]isoindole 10b and pyrazole units 18. On the other hand, the thiosemicarbazone 20 was used as the key intermediate for synthesis of 1,3,4-oxadiazole and 1,2,4-triazole-3-thione derivatives 21 and 23. The antioxidant activities of the prepared compounds were evaluated. The carbohydrazide 1 in particular was found to have potent antioxidant and antitumor activity.

Keywords: oxoindoline; isopropylidene; pyrrole; indole; isoindole; oxadiazole; pyrazole; antioxidant

1. Introduction

A number of nucleoside analogues have been found to show a broad spectrum of biological effects such as antifungal [1,2], antibacterial [1–3], antitumor [3–5], antiviral [3,4,6–14] anti-inflammatory [15] and analgesic [15] activities. Moreover, 2'-deoxy-2'-fluoro-2'-C-methyl nucleoside analogues have showed promising activity against HCV replication [16]. In addition, nucleoside derivatives display inhibition of
glucose-6-phosphatase and showed antihyperglycemic effects [17], as well as inhibition of SAH hydrolase [18]. C-Nucleosides are a subtype of these compounds that are of great interest owing to their potential biological activity together with their higher stabilities than that of the corresponding N-nucleosides. In light of these interesting biological activities and continuation of our research work to explore potent bioactive nitrogen containing molecules [1,2], some aromatic C-nucleoside derivatives were prepared and characterized by analytical and spectral methods.

2. Results and Discussion

2.1. Chemistry

Condensation of the carbohydrazide derivative 1B [19] with carbonyl compounds 2a–e, afforded the corresponding carbohydrazone derivatives 3a–e in 88%–100% yields. Their structures were confirmed by IR, 1H-NMR, two dimensionnal 1H-NMR (COSY), 13C-NMR and mass spectral data. The 1H-NMR spectrum (DMSO-d6) of compound 3c, for example, showed five singlets around δ 11.94, 11.14, 8.13, 6.83 and 6.74, supporting the presence of NH(1), NH(2) (D2O exchangeable), azomethine (CH=N), CH(pyrole) and CH(furan) protons, respectively. Signals of the sugar protons of these derivatives 3a–e were assigned from the 2D 1H-NMR spectrum of compound 3c, and the characteristic chemical shifts as compared with those reported for carbohydrazones [1], whereby, four doublets appearing at δ 5.14, 4.75, 4.60, 4.46 ppm were assigned to 1'-OH, H-1', 2'-OH and 3'-OH, respectively, and a triplet at δ (4.35) ppm for 4'-OH. Two multiplets at δ 3.56–3.50 and 3.42–3.40 ppm were assigned for H-2' overlapped with H-3' and H-4'a, and the other multiplet for H-4'b. A broad singlet at δ 2.47 ppm corresponded to the acetyl protons (COCH3), followed by two singlets at δ 2.43 and 2.28 ppm due to methyl protons at the position-2 of the furan ring and CH3(pyrole), respectively (see Experimental Section and Scheme 1).

Periodate oxidation of 3e afforded the corresponding 5-formyl derivative 4, whose infrared spectrum showed the aldehyde carbonyl functional group at γ 1,689 cm−1. In addition the 1H-NMR spectrum (DMSO-d6) of this product, showed a high field singlet at δ 9.60 ppm for the aldehyde proton (CHO). The mass spectrum showed the molecular ion peak at m/z 297 (M+, 22.54%).

Acetylation of compounds 3b and 3e, afforded the corresponding acetyl derivatives 5 and 6, in 95% and 100% yield, respectively, as indicated by their spectral data. Oxidative cyclization [1,2,20] of the carbohydrazone 5, gave the 1,3,4-oxadiazole derivative 7 which lacked the carbonyl and NH bands in its infrared spectrum. The mass spectrum gave the parent ion peak at m/z 559 (M+, 18.83%). (see Experimental Section and Scheme 2).

On the other hand, boiling of the tetrayltetraacetate 7 with hydrazine hydrate resulted in the corresponding tetrahydroxybutyl derivative 8 in 97% yield. Its IR spectrum showed the hydroxyl groups (OH) at γ 3387–3200 cm−1, while the corresponding 1H-NMR spectrum revealed the four hydroxyl protons at δ 5.23–4.37 ppm, and the mass spectrum showed the molecular ion peak in agreement with expected molecular weight of compound 8. Moreover, dehydrative cyclization of the tetraol derivative 8 with aqueous acetic acid (10%) afforded the aromatic C-nucleoside 9 in 63% yield, as detected from its spectral data. Its 1H-NMR spectrum (DMSO-d6) showed only two D2O-exchangeable hydroxyl protons for 2'-OH and 3'-OH, as two doublets at δ 5.16 and 5.03 ppm,
respectively. The mass spectrum showed the expected molecular ion peak in agreement with its structure.

Scheme 1. Synthesis of carbohydrazones 3a–e and 4.

Scheme 2. Synthesis of aromatic C-nucleosides 5–9.
Condensative cyclization of carbohydrazone 3a with acetic anhydride in the presence of anhydrous sodium acetate gave a cyclized product that according to physical and chemical studies, could not be reconciled with the structure of 10a, that but rather was compatible with that of [1,3,4]oxadiazolo[2,3-a]isoindole 10b. The infrared spectrum of this compound showed the disappearance of the carboxylic acid hydroxyl group, sugar hydroxyl groups, and CONH absorption bands. It showed instead an acetoxyl (OAc) group at $\gamma 1,744$ cm$^{-1}$ and carbonyl groups at $\gamma 1,725$ and 1,712 cm$^{-1}$. Its $^1$H-NMR spectrum (CDCl$_3$) showed the disappearance of signals corresponding to the sugar protons at the $\delta 3.00$–5.00 ppm region, and only displayed the aromatic protons as a doublet at $\delta 7.84$ ($J = 7.65$ Hz) for Ar-H$_{(a)}$, a triplet at $\delta 7.65$ ($J = 7.65$ Hz) for Ar-H$_{(b)}$, a triplet at $\delta 7.56$ ($J = 7.65$ Hz) for Ar-H$_{(c)}$, and a doublet at $\delta 7.53$ ($J = 7.65$ Hz) for Ar-H$_{(d)}$, followed by a singlet attributed to CH$_{(\text{furan})}$ at $\delta 7.00$ ppm. Three singlet signals that appeared in the upper field region at $\delta 2.56$, 2.27 and 2.14 ppm were attributed to the CH$_3$ (furan), COCH$_3$ and O-acetyl protons, respectively. It is noteworthy that the integration of the OAc protons ($\delta 2.14$ ppm), indicated only one O-acetyl group, in accord with structure 10b. Moreover, the proposed mechanism for formation of 10b may proceed as illustrated in Schemes 3 and 4.

In addition, condensation of anhydro derivative 11 [2] with $p$-nitrobenzaldehyde, indoline-2,3-dione (isatin) and D-galactose in acidic medium afforded the corresponding aromatic C-nucleosides 12–14, respectively. Compounds 12 and 13 were also obtained by acid-catalyzed dehydrative cyclization of 3b and 3e, respectively. Their structures were deduced from the respective spectral data. The signals of the sugar protons of anhydro structures 12 and 13 were assigned from the characteristic chemical shifts as compared with those reported for diol derivatives [2]. Although the coupling constant value ($J_{1',2'} = 6.85$ Hz) of 12 cannot define the anomic configuration [21], however, it could be $\beta$- in accordance with the configuration its precursor [2]. On the other hand, the anomic configuration of 13 can be ascertained from the large observed coupling constant value ($J_{1',2'} = 9.00$ Hz) which indicates a trans arrangement of the base moiety and the 2'-hydroxyl group, i.e., $\beta$-D-configuration.

Furthermore, acetylation of 12 and 13, afforded the acetylated structures 15 and 16, in 79% and 67% yields, respectively. The infrared spectra showed OAc absorption bands at $\gamma 1,753$, 1,745 cm$^{-1}$, respectively. The $^1$H-NMR spectra (CDCl$_3$) of these products revealed two singlet signals at $\delta 2.00$–2.11 ppm attributed to two O-acetyl groups. Their mass spectra showed the expected molecular ion peaks in agreement with their proposed structures.

**Scheme 3.** Synthesis of [1,3,4]oxadiazolo[2,3-a]-isoindole 10b.
Scheme 4. Proposed mechanism for formation of [1,3,4]oxadiazolo[2,3-a]isoindole 10b.

The isopropylidene derivative 17 has been prepared from 13 in yield 88%. Its anomeric configuration was confirmed from the zero coupling constant value ($J_{1'2'} = 0.00$ Hz), as a β-D-configuration [2,21,22]. The mass spectrum showed the expected molecular ion peak in agreement with its structure (Scheme 5).

The pyrazole derivative 18 was obtained in 100% yield from the reaction of carbohydrazide 1 with pentane-2,4-dione as previously reported on other systems [23]. The infrared spectrum showed the disappearance of absorption bands corresponding to NH and NH$_2$. Its $^1$H-NMR spectrum (DMSO-$d_6$), revealed three singlets at δ 6.18, 2.48 and 2.16 ppm for CH$_2$(pyrazole), CH$_3$(pyrazole-a) and CH$_3$(pyrazole-b) protons, respectively. The molecular ion peak recorded in the mass spectrum was in accordance with its molecular weight. Furthermore, the O-acetyl derivative 19 was prepared, in which the signals of the sugar protons of this product were assigned from its 2D $^1$H-NMR spectrum (Scheme 6).

Moreover, condensation of 1 with phenyl isothiocyanate gave the corresponding thiosemicarbazide derivative 20 [24]. Intramolecular cyclization of this thiosemicarbazide using an improved procedure involving treatment with potassium iodide and iodine in the presence of sodium hydroxide [25] resulted in 1,3,4-oxadiazole product 21 [24] in 95% yield. The tetra-O-acetyl derivative 22 was obtained in 85% yield, the signals of the sugar protons of this product were assigned from its 2D $^1$H-NMR spectrum.
spectrum, the mass spectrum showed the molecular ion peak at \( m/z \) 529 (M\(^+\), 19.12\%), and \(^{13}\)C-NMR (CDCl\(_3\)) spectrum confirmed the structure (Scheme 7).

**Scheme 5.** Synthesis of aromatic C-nucleosides 12–17.

**Scheme 6.** Synthesis of pyrazole derivatives 18 and 19.
Scheme 7. Synthesis of 1,3,4-oxadiazoles 21 and 22.

Alternatively, heating the thiosemicarbazide 20 with aqueous sodium hydroxide (10%) [25] gave a product 23, whose infrared spectrum showed a C=\text{N} absorption at \( \gamma 1,624 \text{ cm}^{-1} \) with the disappearance of the CONH absorption. Moreover, acetylation of 23, gave 5-(5-(1',2',3',4'-tetraacetoxybutyl)-2-methylfuran-3-yl)-4-phenyl-2-N-acetyl-1,2,4-triazole-3(4H)-thione (24) in 97% yield. The \(^1\text{H-NMR} \) spectrum (CDCl\(_3\)) revealed the disappearance of the NH proton and showed a singlet due to \( N \)-acetyl protons at \( \delta 2.77 \text{ ppm} \), followed by three singlets at \( \delta 2.01, 1.99, \) and 1.97 ppm for four O-acetyl groups. The mass spectrum showed a molecular ion peak in accordance with its molecular formula (Scheme 8).

Scheme 8. Synthesis of 4-phenyl-2\( H \)-1,2,4-triazole-3(4\( H \))-thiones 23–26.
Dehydration of 23, afforded 2',3'-diol 25 in yield of 80% (Scheme 8). The anomeric configuration of 25 can be confirmed as β-D-configuration ($J_{1',2'} = 9.00$ Hz). The mass spectrum showed the expected molecular ion peak at $m/z$ 359 (M+, 20.21%). The characteristic alcohol M-H2O peak appeared at $m/z$ 341 (20.21), while the M-SH peak was seen at $m/z$ 326 (20.21). The loss of a furanose moiety (C$_4$H$_8$O$_3$) from the molecular ion appeared at $m/z$ 255 (20.91). Furthermore, periodate oxidation of 23, afforded the corresponding 2-carbaldehyde derivative 26.

2.2. Bioactivity Screening of New Synthesized Aromatic C-Nucleosides

2.2.1. Antioxidant Activity Screening (Using the DPPH Assay)

The diphenylpicrylhydrazyl (DPPH) assay method is based on the reduction of the free radical DPPH with an odd electron which gives a maximum absorption at 517 nm. When antioxidants react with DPPH, giving DPPD-H the absorbance decreases due to decolorization with respect to the number of electrons captured. EC$_{50}$ values for each examined compound as well as standard preparations were calculated according to the method Shahwar et al. [26]. A lower EC$_{50}$ value is associated with a higher radical scavenging activity. As shown in Tables 1 and 2 and Figures 1–6 the DPPH radical scavenging activities of the prepared compounds 1, 3c–e, 4–6, 13, and 16–26 in terms of EC$_{50}$ values were the highest in the case of compounds 20, 3c, 3d, 1 and 22 (0.380, 0.418, 0.448, 0.590 and 0.590 mg, respectively) compared to the EC$_{50}$ of vitamin E used as standard (0.705). Meanwhile nearly the same activities were revealed in case of compounds 23 and 26 (0.720 and 0.725 mg), respectively. In addition, moderate activities were shown for compounds 3e, 4, 17 and 25 (0.800, 0.800, 0.825 and 0.815 mg), respectively. Lower activities were observed in case of compounds 5, 6, 13, 16, 18, 19, 21 and 24 with EC$_{50}$ values equal to 0.960, > 1.000, 0.900, 0.980, > 1.000, 0.930, > 1.000, > 1.000 mg, respectively, compared to the standard, see Table 2.

**Table 1.** Absorbance and free radical scavenging activities of tested compounds.

| Conc. (mg/ mL) | Compound 1 | Compound 3c | Compound 3d | Compound 3e |
|----------------|------------|-------------|-------------|-------------|
| 0.150          | 0.00       | 0.00        | 0.00        | 0.00        |
| 0.300          | 0.369      | 42.61       | 0.420       | 47.58       |
| 0.450          | 0.330      | 48.67       | 0.399       | 50.69       |
| 0.600          | 0.312      | 51.47       | 0.380       | 55.98       |
| 0.750          | 0.297      | 53.81       | 0.369       | 57.54       |
| 0.900          | 0.273      | 57.54       | 0.330       | 59.40       |
| 1.000          | 0.232      | 63.91       | 0.297       | 60.03       |

| Conc. (mg/ mL) | Compound 4 | Compound 5 | Compound 6 | Compound 13 |
|----------------|------------|------------|------------|-------------|
| 0.150          | 0.00       | 0.00       | 0.00       | 0.00        |
| 0.300          | 0.420      | 34.68      | 0.451      | 29.86       |
| 0.450          | 0.389      | 39.50      | 0.411      | 36.08       |
| 0.600          | 0.369      | 42.61      | 0.389      | 39.50       |
| 0.750          | 0.337      | 47.58      | 0.360      | 44.01       |
| 0.900          | 0.305      | 52.56      | 0.337      | 47.58       |
| 1.000          | 0.273      | 57.54      | 0.317      | 50.69       |
Table 1. Cont.

| Conc. (mg/mL) | Compound 16 |  | Compound 17 |  | Compound 18 |  | Compound 19 |  |
|---------------|-------------|---|-------------|---|-------------|---|-------------|---|
|               | Absorbance  | % Scavenging | Absorbance  | % Scavenging | Absorbance  | % Scavenging | Absorbance  | % Scavenging |
| 0.150         | 0.000       | 0.00          | 0.000       | 0.00          | 0.000       | 0.00          | 0.000       | 0.00          |
| 0.300         | 0.440       | 31.57         | 0.433       | 32.65         | 0.451       | 29.86         | 0.469       | 27.06         |
| 0.450         | 0.413       | 35.76         | 0.391       | 39.19         | 0.440       | 31.57         | 0.420       | 34.68         |
| 0.600         | 0.387       | 39.81         | 0.370       | 42.45         | 0.433       | 32.65         | 0.391       | 39.19         |
| 0.750         | 0.369       | 42.61         | 0.330       | 48.67         | 0.420       | 34.68         | 0.369       | 42.61         |
| 0.900         | 0.341       | 46.96         | 0.317       | 50.69         | 0.403       | 37.32         | 0.337       | 47.58         |
| 1.000         | 0.312       | 51.47         | 0.303       | 52.87         | 0.370       | 42.45         | 0.312       | 51.47         |

| Conc. (mg/mL) | Vitamin E | Compound 20 |  | Compound 21 |  | Compound 22 |  |
|---------------|-----------|-------------|---|-------------|---|-------------|---|
|               | Absorbance  | % Scavenging | Absorbance  | % Scavenging | Absorbance  | % Scavenging | Absorbance  | % Scavenging |
| 0.150         | 0.756      | 21.25       | 0.000       | 0.00          | 0.000       | 0.00          | 0.000       | 0.00          |
| 0.300         | 0.712      | 25.83       | 0.335       | 47.90         | 0.540       | 16.01         | 0.391       | 39.19         |
| 0.450         | 0.684      | 28.75       | 0.305       | 52.56         | 0.511       | 20.52         | 0.337       | 47.58         |
| 0.600         | 0.615      | 35.93       | 0.285       | 55.67         | 0.483       | 24.88         | 0.297       | 53.81         |
| 0.750         | 0.420      | 56.25       | 0.276       | 57.07         | 0.450       | 30.01         | 0.283       | 55.98         |
| 0.900         | 0.202      | 78.95       | 0.252       | 60.80         | 0.420       | 34.68         | 0.273       | 57.54         |
| 1.000         | 0.037      | 96.14       | 0.240       | 62.67         | 0.391       | 39.19         | 0.257       | 60.03         |

| Conc. (mg/mL) | Compound 23 |  | Compound 24 |  | Compound 25 |  | Compound 26 |  |
|---------------|-------------|---|-------------|---|-------------|---|-------------|---|
|               | absorbance  | % Scavenging | absorbance  | % Scavenging | absorbance  | % Scavenging | absorbance  | % Scavenging |
| 0.150         | 0.000       | 0.00          | 0.000       | 0.00          | 0.000       | 0.00          | 0.000       | 0.00          |
| 0.300         | 0.463       | 27.99         | 0.511       | 20.52         | 0.378       | 41.21         | 0.369       | 42.61         |
| 0.450         | 0.387       | 39.81         | 0.467       | 27.37         | 0.346       | 46.18         | 0.341       | 46.96         |
| 0.600         | 0.322       | 49.92         | 0.438       | 31.88         | 0.340       | 47.12         | 0.326       | 49.30         |
| 0.750         | 0.310       | 51.78         | 0.418       | 34.99         | 0.325       | 49.45         | 0.314       | 51.16         |
| 0.900         | 0.302       | 53.03         | 0.376       | 41.52         | 0.316       | 50.85         | 0.305       | 52.56         |
| 1.000         | 0.292       | 54.58         | 0.356       | 44.63         | 0.306       | 52.41         | 0.299       | 53.49         |

Table 2. EC_{50} values of the prepared compounds 1, 3c–3e, 4–6, 13, 16–26.

| Cpd no. | EC_{50} (mg) | Cpd no. | EC_{50} (mg) |
|---------|-------------|---------|-------------|
| Vitamin E | 0.705 | 17 | 0.825 |
| 1 [1] | 0.590 | 18 | >1.000 |
| 3c | 0.418 | 19 | 0.930 |
| 3d | 0.448 | 20 | 0.580 |
| 3e | 0.800 | 21 | >1.000 |
| 4 | 0.800 | 22 | 0.590 |
| 5 | 0.960 | 23 | 0.720 |
| 6 | >1.000 | 24 | >1.000 |
| 13 | 0.900 | 25 | 0.815 |
| 16 | 0.980 | 26 | 0.725 |
**Figure 1.** Free radical scavenging activity of vitamin E.

**Figure 2.** Free radical scavenging activity of compounds 1, 3c–e.

**Figure 3.** Free radical scavenging activity of compounds 4–6, 13.
**Figure 4.** Free radical scavenging activity of compounds 16–19.

**Figure 5.** Free radical scavenging activity of compounds 20–22.

**Figure 6.** Free radical scavenging activity of compounds 23–26.
The obtained data revealed a potential antioxidant activity of all examined compounds but with different EC$_{50}$ values compared to the standard, especially compound 20 which has a distinct thiourea group. In addition, compounds 3c and 3d revealed higher antioxidant activities as compared to the standard due to the acidic protons in the pyrrole and indole, respectively, that can be easily oxidized.

2.2.2. Anticancer Activity Screening (Cytotoxicity Against Three Cancer Cell Lines)

Different concentrations (50–1.56 µg/mL) of the examined compound 1 were used to screen their cytotoxicity against Human Breast Adrenocarcinoma Cells (MCF-7), Human Colon Carcinoma Cells (HCT) and Human Hepatocellular Liver Carcinoma Cells (HepG-2). Cytotoxic effects of these compounds on the cell viability of the cancer cell lines were observed, as shown in Tables 3 and 4 and Figures 7–9. The obtained data revealed that the carbohydrazide 1 has excellent cell growth inhibitory effects on HepG-2, HCT and MCF-7 with IC$_{50}$s equal to 10.200, 8.400 and 11.700 µg, respectively compared to the IC$_{50}$ of the doxorubicin (1.200, 0.469) and vinblastine (6.100) standards used, see Table 5.

Table 3. Effect of standard compounds on cell viability using cytotoxic assay.

| Conc. (µg/mL) | Doxorubicin for HCT Viability % | Doxorubicin for HepG-2 Viability % | Vinblastine for MCF-7 Viability % |
|---------------|---------------------------------|-----------------------------------|---------------------------------|
| 50.000        | 6.82                            | 10.95                             | 7.82                             |
| 25.000        | 8.89                            | 14.29                             | 15.18                            |
| 12.500        | 14.83                           | 16.90                             | 29.6                             |
| 6.250         | 16.16                           | 21.03                             | 48.75                            |
| 3.125         | 22.28                           | 30.32                             | 60.35                            |
| 1.560         | 34.64                           | 48.25                             | 76.24                            |
| 0.780         | 45.78                           | 57.44                             | ….                               |
| 0.390         | 51.08                           | ….                               | ….                               |
| 0.000         | 100.00                          | 100.00                            | 100.00                           |

Table 4. Effect of different concentrations of compound 1 on cell viability using cytotoxic assay.

| Conc. (µg/mL) | Viability % for HCT | Viability % for HepG-2 | Viability % for MCF-7 |
|---------------|---------------------|------------------------|-----------------------|
| 50.000        | 10.68               | 11.56                  | 14.68                 |
| 25.000        | 19.09               | 26.34                  | 30.49                 |
| 12.500        | 27.25               | 39.18                  | 47.84                 |
| 6.250         | 61.87               | 68.47                  | 64.98                 |
| 3.125         | 83.08               | 89.05                  | 79.82                 |
| 1.560         | 94.62               | 93.78                  | 90.18                 |
| 0.000         | 100.00              | 100.00                 | 100.00                |
**Figure 7.** Viability activity against HepG-2 of compound 1.

![Graph of cell viability against concentration for HepG-2](image)

**Figure 8.** Viability activity against HCT-116 of compound 1.

![Graph of cell viability against concentration for HCT-116](image)

**Figure 9.** Viability activity against MCF-7 of compound 1.

![Graph of cell viability against concentration for MCF-7](image)

**Table 5.** IC\(_{50}\) of compound 1 on cell viability using cytotoxic assay compared to standards.

| Standard | HCT | HepG-2 | MCF-7 |
|----------|-----|--------|-------|
| IC\(_{50}\) (µg/mL) | 0.469 | 1.20   | 6.10   |
| Cpd. 1   | 8.400 | 10.20  | 11.70  |
3. Experimental

3.1. General Procedures

Melting points were determined with a Melt-temperature apparatus and are uncorrected. TLC was performed on Baker-Flex silica gel 1B-F plates and the spots were detected by UV light absorption. IR spectra were recorded on a Perkin Elmer spectrometer. \(^{1}\)H-NMR and \(^{13}\)C-NMR were recorded on JEOL JNM ECA 500 MHz and 300 MHz instruments using tetramethylsilane as an internal standard. Mass spectra were recorded on a GCMS DI Analysis Shimadzu Qp-2010 Plus. Solutions were evaporated under diminished pressure unless otherwise stated. ChemDraw-Ultra-8.0 has been used in generating the names of the prepared compounds.

3.2. Chemistry

3.2.1. 5-(1',2',3',4'-Tetrahydroxybutyl)-2-methylfuran-3-carbohydrazide (1)

Mp 200–201 °C (Lit. [1], 198 °C); IR(KBr) cm\(^{-1}\): 3400–3137 (OH, NH), 1674 (C=O); \(^{1}\)H-NMR (DMSO-\(d_6\)); \(\delta\): 2.46 (s, 3H, CH\(_3\)(furan)), 3.34–3.40 (m, 3H, H-4'b, NH\(_2\) with H\(_2\)O of DMSO), 3.44–3.58 (m, 3H, H-3', H-2', H-4'a), 4.36 (t, 1H, 4'-OH, \(J_{3',4'}\) = 5.35 Hz, D\(_2\)O-exchangeable), 4.48 (d, 1H, 3'-OH, \(J_{3',2'}\) = 6.85 Hz, D\(_2\)O-exchangeable), 4.61 (d, 1H, 2'-OH, \(J_{2',2'}\) = 5.35 Hz, D\(_2\)O-exchangeable), 4.73 (d, 1H, H-1', \(J_{1',2'}\) = 5.35 Hz), 5.14 (d, 1H, 1'-OH, \(J_{1',2'}\) = 6.10 Hz, D\(_2\)O-exchangeable), 6.70 (s, 1H, CH(furan)), 9.79 (s, 1H, NH, D\(_2\)O-exchangeable).

3.2.2. General Method for the Synthesis of Carbohydrazones 3a–e

A mixture of 3-carbohydrazide 1 (1.923 mmol) and carbonyl compound (1.923 mmol) was heated under reflux in ethanol (10 mL) containing a few drops of acetic acid for 1 h. The products 3a–e that separated were filtered off and dried.

2-((5-(1',2',3',4'-Tetrahydroxybutyl)-2-methylfuran-3-carboylimino)methyl)benzoic acid (3a). Obtained in 91% yield from carbohydrazide 1 (1.923 mmol) and 2-formylbenzoic acid (1.923 mmol); recrystallized from ethanol as white crystals; mp 209–210 °C; Rf: 0.85 (chloroform–methanol; 5:1; v/v); IR (KBr) cm\(^{-1}\): 3429–3305 (OH), 3187 (NH), 1703 (CO-acid), 1653 (CO-amide), 1593 (C=N); \(^{1}\)H-NMR (DMSO-\(d_6\)); \(\delta\): 2.50 (s, 3H, CH\(_3\)(furan)), 3.46–3.49 (m, 1H, H-4'b), 3.53–3.59 (m, 3H, H-3', H-2', H-4'a), 4.36 (bs, 1H, 4'-OH, D\(_2\)O-exchangeable), 4.49 (bs, 1H, 3'-OH, D\(_2\)O-exchangeable), 4.62 (bs, 1H, 2'-OH, D\(_2\)O-exchangeable), 4.76 (s, 1H, H-1'), 5.16 (bs, 1H, 1'-OH, \(J_{1',2'}\) = 6.00 Hz, D\(_2\)O-exchangeable), 6.83 (s, 1H, CH(furan)), 7.47 (t, 1H, Ar-H(d), \(J = 7.65 \text{ Hz}\)), 7.60 (t, 1H, Ar-H(c), \(J = 7.65 \text{ Hz}\)), 7.85 (d, 1H, Ar-H(b), \(J = 7.65 \text{ Hz}\)), 8.01 (d, 1H, Ar-H(a), \(J = 7.65 \text{ Hz}\)), 9.08 (s, 1H, CH=N), 11.60 (s, 1H, NH, D\(_2\)O-exchangeable), 12.58 (bs, 1H, COOH, D\(_2\)O-exchangeable); MS: \(m/z\) (%), 393 (25.33, M\(^+\)+1), 392 (28.00, M\(^+\)), 357 (25.78), 347 (23.11), 343 (40.00), 330 (32.89), 300 (40.89), 262 (46.67), 251 (52.44), 220 (36.44), 208 (37.33), 183 (46.67), 177 (25.33), 154 (32.44), 151 (32.44), 146 (38.67), 137 (32.89), 102 (33.78), 91 (38.22), 89 (100.00), 77 (43.11), 65 (38.22), 50 (28.00); Anal. Calcd for C\(_{18}\)H\(_{20}\)N\(_2\)O\(_8\): C, 55.10; H, 5.14; N, 7.14%; found: C, 55.20; H, 5.00; N, 7.23%.
N-(4-Nitrobenzylidene)-5-(1',2',3',4'-tetrahydroxybutyl)-2-methylfuran-3-carbohydrazide (3b). Obtained in 98% yield from carbohydrazide 1 (1.923 mmol) and p-nitrobenzaldehyde (1.923 mmol); recrystallized from ethanol as yellow crystals. Rf: 0.38 (chloroform–methanol, 5:1, v/v); mp 163–164 °C; IR (KBr): 3447–3202 (OH, NH), 1664 (C=O), 1585 (C=N); 1H-NMR (DMSO-d6): δ: 2.51 (s, 3H, CH₃(furan)), 3.38–3.42 (m, 1H, H-4'b), 3.46–3.51 (m, 1H, H-4'a), 3.52–3.54 (m, 1H, H-3'), 3.55–3.60 (m, 1H, H-2'), 4.36 (t, 1H, 4'-OH, J₄'-OH = 5.35 Hz, D₂O exchangeable), 4.49 (d, 1H, 3'-OH, J₃',OH = 6.90 Hz, D₂O exchangeable), 4.61 (d, 1H, 2'-OH, J₂',OH = 5.35 Hz, D₂O exchangeable), 4.77 (d, 1H, H-1', J₁',₂' = 6.10 Hz), 5.18 (d, 1H, 1'-OH, J₁',OH = 6.90 Hz, D₂O exchangeable), 6.80 (s, 1H, CH(furan)), 7.92 (d, 2H, Ar-H(b), J = 7.65 Hz), 8.26 (d, 2H, Ar-H(a), J = 8.45 Hz), 8.46 (s, 1H, CH=N), 11.67 (s, 1H, NH, D₂O exchangeable); MS: m/z (%), 394 (20.12, M++1), 393 (26.33, M+), 375 (16.86), 355 (28.11), 347 (24.85), 307 (28.99), 306 (25.44), 287 (25.74), 271 (16.27), 245 (15.98), 227 (23.08), 221 (28.99), 211 (47.04), 151 (100.00), 143 (20.71), 138 (21.60), 123 (52.66), 113 (24.26), 95 (42.31), 94 (42.31), 81 (26.33), 77 (24.26), 76 (19.53), 65 (22.49), 58 (23.99), 53 (37.28); Anal. Calcd for C₁₇H₁₉N₃O₈: C, 51.91; H, 4.87; N, 10.68%; found: C, 51.95; H, 4.81; N, 10.55%.

N-((4-Acetyl-5-methyl-1H-pyrrol-2-yl)methylene)-5-(1',2',3',4'-tetrahydroxybutyl)-2-methylfuran-3-carbohydrazide (3c). Obtained in 88% yield from carbohydrazide 1 (1.923 mmoL) and 4-acetyl-5-methyl-1H-pyrrole-2-carbaldehyde (1.923 mmoL); recrystallized from ethanol as white crystals; Rf: 0.52 (chloroform–methanol, 5:1, v/v); mp 160–161 °C; IR (KBr): 3409 (OH), 3262 (NH-pyrrole), 3222 (NH-amide), 1642 (2C=O), 1619 (C=N); 1H-NMR (DMSO-d6): δ: 2.28 (s, 3H, CH₃(pyrrole)), 2.43 (s, 3H, CH₃(furan)), 2.47 (bs, 3H, COCH₃ with DMSO), 3.42–3.40 (m, 1H, H-4'b), 3.56–3.50 (m, 3H, H-3', H-2', H-4'a), 4.35 (t, 1H, 4'-OH, J₄'-OH = 6.00 Hz, D₂O-exchangeable), 4.46 (d, 1H, H-1', J₁',₂' = 6.00 Hz), 5.14 (d, 1H, H-1', J₁',OH = 6.00 Hz, D₂O-exchangeable), 6.80 (s, 1H, CH(furan)), 6.83 (s, 1H, CH(pyrrole)), 8.13 (s, 1H, CH=N), 11.14 (s, 1H, NH(2), D₂O exchangeable), 11.94 (s, 1H, NH(1), D₂O exchangeable); 13C-NMR (DMSO-d6): δ: 13.88 (CH₃-pyrrole and CH₃-furan), 28.80 (COCH₃), 63.84, 66.56, 71.54 and 73.25 for (C-4', C-3', C-2' and C-1'), 105.90, 115.35, 115.80, 122.17, 125.93, 139, 139.5, 155.10 and 155.89 for (pyrrole and furan carbons and CH=N), 159.86 (CO-NH), 193.86 (COCH₃); MS: m/z (%), 394 (53.39, M+1), 393 (69.49, M'), 392 (44.07, M'), 361 (57.63), 359 (71.19), 358 (55.93), 357 (59.32), 344 (62.71), 340 (55.93), 323 (64.41), 311 (60.17), 259 (59.32), 254 (57.63), 242 (79.66), 233 (53.39), 228 (72.88), 223 (66.95), 206 (55.08), 195 (71.19), 191 (64.41), 185 (60.17), 180 (64.41), 158 (59.32), 148 (66.10), 123 (66.95), 116 (64.41), 108 (55.93), 106 (68.64), 91 (100.00), 75 (55.93), 63 (60.17); Anal. Calcd for C₁₈H₂₃N₃O₇: C, 54.96; H, 5.89; N, 10.68%; found: C, 54.91; H, 5.77; N, 10.56%.

N-((4,5,6,7-Tetrahydro-6,6-dimethyl-4-oxo-1H-indol-2-yl)methylene)-5-(1',2',3',4'-tetrahydroxybutyl)-2-methylfuran-3-carbohydrazide (3d). Obtained in 90% yield from carbohydrazide 1 (1.923 mmol) and 4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1H-indole-2-carbaldehyde (1.923 mmol); recrystallized from ethanol as white crystals; Rf: 0.7 (chloroform–methanol, 4:1, v/v); mp 194–195 °C; IR (KBr): 3345 (OH), 3257 (NH-indole), 3158 (NH-amide), 1656 (2C=O), 1618 (C=N); 1H-NMR (DMSO-d6): δ: 0.99 (s, 6H, 2CH₃(indole)), 2.20 (s, 2H, CH₂(indole)), 2.47 (s, 3H, CH₃(furan) with DMSO), 2.67 (s, 2H, CH₂(indole)), 3.38–3.43 (m, 1H, H-4'b), 3.49–3.56 (m, 3H, H-3', H-2', H-4'a), 4.31 (t, 1H, 4'-OH,
$J_{3',OH} = 6.00 \text{ Hz, D}_2\text{O-exchangeable}$), 4.43 (d, 1H, 3'-OH, $J_{3',OH} = 6.00 \text{ Hz, D}_2\text{O-exchangeable}$), 4.75 (d, 1H, H-1', $J_{1',2'} = 6.00 \text{ Hz}$), 5.10 (d, 1H, 1'-OH, $J_{1',OH} = 9.00 \text{ Hz, D}_2\text{O-exchangeable}$), 6.60 (s, 1H, CH$_\text{furan}$), 6.74 (s, 1H, CH$_\text{indole}$), 8.17 (s, 1H, CH=N), 11.15 (s, 1H, NH$_\text{2}$, D$_2$O exchangeable), 11.90 (s, 1H, NH$_\text{1}$, D$_2$O exchangeable); MS: m/z (%), 434 (19.10, M ++1), 433 (73.03, M +), 432 (73.03), 378 (69.76), 348 (76.40), 343 (83.15), 329 (70.79), 301 (70.79), 296 (73.03), 278 (70.79), 276 (70.79), 275 (79.78), 274 (73.03), 255 (94.38), 250 (69.66), 244 (91.01), 215 (70.79), 214 (76.40), 205 (69.66), 199 (74.16), 195 (79.78), 191 (83.15), 189 (69.66), 185 (73.03), 180 (70.79), 175 (83.15), 174 (70.79), 165 (79.78), 152 (67.42), 144 (78.65), 122 (70.79), 116 (70.79), 112 (70.79), 89 (76.65), 75 (61.80), 65 (80.90), 52 (100.00); Anal. Calcd for C$_{21}$H$_{27}$N$_3$O$_7$: C, 58.19; H, 6.28; N, 9.69%; found: C, 58.14; H, 6.10; N, 9.70%.

5-[(1',2',3',4'-Tetrahydroxybutyl)-2-methyl-N-(2-oxoindolin-3-ylidene)furan-3-carbohydrazide (3e)]. Obtained in 100% yield from carbohydrazide 1 (1.923 mmol) and isatin (1.923 mmol); recrystallized from ethanol as yellow needles; mp 206–207 °C; Rf: 0.61 (chloroform–methanol; 5:1; v/v); IR (KBr) cm$^{-1}$: 3402 (OH), 3250 (2NH), 1675 (2CO), 1620 (C=N); $^1$H-NMR (DMSO-d$_6$); $\delta$: 2.55 (s, 3H, CH$_3$(furan)), 3.39–3.42 (m, 1H, H-4'b), 3.51–3.56 (m, 3H, H-3', H-2', H-4'a), 4.32 (t, 1H, 4'-OH, $J_{4',OH} = 3.00 \text{ Hz, D}_2$O-exchangeable), 4.53 (d, 1H, 3'-OH, $J_{3',OH} = 6.00 \text{ Hz, D}_2$O-exchangeable), 4.58 (d, 1H, 2'-OH, $J_{2',OH} = 3.00 \text{ Hz, D}_2$O-exchangeable), 4.79 (d, 1H, H-1', $J_{1',2'} = 6.00 \text{ Hz}$), 5.20 (d, 1H, 1'-OH, $J_{1',OH} = 6.00 \text{ Hz, D}_2$O-exchangeable), 6.52 (s, 1H, CH(furan)), 6.93 (d, 1H, Ar-H(d), $J = 9.00 \text{ Hz}$), 7.35 (t, 1H, Ar-H(b), $J = 9.00 \text{ Hz}$), 7.55 (d, 1H, Ar-H(a), $J = 9.00 \text{ Hz}$), 11.25 (bs, 1H, NH$_\text{2}$, D$_2$O-exchangeable), 13.40 (bs, 1H, NH$_\text{1}$, D$_2$O-exchangeable); MS: m/z (%), 391 (11.64, M ++2), 390 (13.87, M++1), 389 (11.13, M +), 379 (11.99), 374 (12.16), 333 (11.13), 314 (12.55), 302 (12.50), 283 (12.16), 269 (12.67), 268 (12.50), 263 (15.24), 252 (13.53), 236 (13.87), 229 (12.16), 221 (13.53), 196 (13.36), 194 (13.53), 154 (13.36), 149 (16.27), 137 (17.64), 125 (14.73), 123 (13.63), 119 (13.87), 115 (14.73), 113 (13.01), 112 (17.12), 111 (23.46), 110 (12.16), 109 (21.58), 107 (13.01), 103 (11.99), 101 (15.75), 100 (12.67), 99 (12.16), 98 (12.67), 97 (38.01), 96 (29.79), 95 (32.19), 94 (15.75), 85 (29.79), 84 (35.79), 83 (44.86), 82 (22.60), 81 (36.64), 79 (20.89), 73 (20.89), 71 (45.03), 70 (32.53), 69 (82.53), 68 (23.97), 67 (38.70), 66 (13.87), 60 (19.52), 57 (100.00), 56 (37.67), 55 (88.01), 54 (24.32); Anal. Calcd for C$_{21}$H$_{27}$N$_3$O$_7$: C, 58.19; H, 6.28; N, 9.69%; found: C, 58.14; H, 6.10; N, 9.70%.

3.2.3. 5-Formyl-2-methyl-N-(2-oxoindolin-3-ylidene)furan3-carbohydrazide (4).

A solution of compound 3e (3.856 mmol) in distilled water (20 mL) was treated dropwise with a solution of sodium metaperiodate (11.568 mmol) in distilled water (20 mL) under continuous stirring for 3 h, and the formyl derivative that separated out was filtered off, washed with water, and dried. Yield 92%; recrystallized from ethanol as yellow crystals; mp 280 °C; RF: 0.44 (chloroform–methanol; 30:1; v/v); IR (KBr) cm$^{-1}$: 3158 (2NH), 1689 (CHO), 1665 (2CO), 1623 (C=N); $^1$H-NMR (DMSO-d$_6$); $\delta$: 2.67 (s, 3H, CH$_3$(furan)), 6.93 (d, 1H, Ar-H(d), $J = 9.00 \text{ Hz}$), 7.07 (t, 1H, Ar-H(c), $J = 9.00 \text{ Hz}$), 7.36 (t, 1H, Ar-H(c), $J = 9.00 \text{ Hz}$), 7.58 (d, 1H, Ar-H(a), $J = 9.00 \text{ Hz}$), 7.84 (bs, 1H, CH(furan)), 9.60 (s, 1H, CHO), 11.34 (bs, 1H, NH$_\text{2}$, D$_2$O exchangeable), 13.48 (bs, 1H, NH$_\text{1}$, D$_2$O exchangeable); MS: m/z (%), 299 (0.83, M$^+$+2), 298 (4.73, M$^+$+1), 297 (22.54, M$^+$), 269 (7.98), 161 (6.47), 160 (56.39), 159 (11.55), 138 (9.53), 137 (100.00), 136 (6.51), 133 (5.46), 132 (34.79), 104 (19.95), 103 (7.02), 95 (27.88), 90 (5.27), 80 (25.66), 79 (5.02), 78 (6.35), 77 (26.54), 76 (12.05), 64 (26.21), 52 (17.43), 51
A solution of 1',2',3',4'-tetrahydroxybutyl derivatives 3b and 3e (2.544 mmol) in dry pyridine (10 mL) was treated with acetic anhydride (10 mL), and the mixture was kept at room temperature for 5–12 h with occasional shaking. Then it was poured onto crushed ice, the acetyl derivative that separated out, was filtered off, washed with water and dried.

N-(4-Nitrobenzylidene)-5-(1',2',3',4'-tetraacetoxybutyl)-2-methylfuran-3-carbohydrazide (5). Obtained in 95% yield from compound 3b (2.544 mmol); recrystallized from methanol as yellow crystals; Rf: 0.67 (n-hexane–ethyl acetate, 1:1, v/v); mp 158–159 °C; IR (KBr): 3286 (NH), 1741 (OAc), 1648 (CO-amide), 1580 (C=N); 1H-NMR (CDCl3); δ: 1.95, 2.03 and 2.04 (3s, 12H, 4OAc), 2.51 (s, 3H, CH3(furan)), 4.08–4.12 (dd, 1H, H-4'b, J3',4'b = 5.35 Hz, J4'b,4'a = 12.20 Hz), 4.18 (d, 1H, H-4'a, J4'b,4'a = 11.50 Hz), 5.05–5.06 (m, 1H, H-3'), 5.44 (bs, 1H, H-2'), 5.99 (d, 1H, H-1', J1',2' = 4.6 Hz), 6.98 (s, 1H, CH(furan)), 7.93 (d, 2H, Ar-H(b), J = 7.65 Hz), 8.26 (d, 2H, Ar-H(a), J = 7.65 Hz), 8.43 (s, 1H, CH=N), 11.69 (s, 1H, NH, D2O exchangeable); MS: m/z (%), 562 (10.89, M++1), 561 (15.45, M+), 546 (16.04), 520 (20.79), 515 (14.46), 489 (10.30), 439 (11.88), 397 (11.88), 385 (18.61), 345 (10.89), 324 (11.88), 273 (10.30), 265 (20.99), 252 (10.89), 227 (10.69), 180 (10.69), 109 (17.62), 108 (15.45), 94 (15.64), 81 (46.73), 80 (18.22), 72 (17.62), 69 (100.00), 66 (10.69), 65 (11.49), 57 (54.65), 55 (49.50). Anal. Calcd for C25H27N3O12: C, 53.48; H, 4.85; N, 7.48%; found: C, 53.40; H, 4.71; N, 7.50%.

5-(1',2',3',4'-Tetraacetoxybutyl)-2-methyl-N-(N'-acetyl-2-oxoindolin-3-ylidene)furan-3-carbohydrazide (6). Obtained in 100% yield from compound 3e; recrystallized from ethanol as yellow needles; mp 154–155 °C; Rf: 0.54 (n-hexane–ethyl acetate; 5:1, v/v); IR (KBr) cm−1: 3283 (NH), 1748 (OAc), 1712 (2CO & NAc), 1608 (C=N); 1H-NMR (CDCl3); δ: 2.03, 2.05, 2.10 (3s, 12H, 4OAc), 2.65 (s, 3H, CH3(furan)), 2.73 (s, 3H, N-Ac), 4.10–4.16 (dd, 1H, H-4'b, J4'a,4'b = 12.00 Hz, J4'b,3' = 3.00 Hz), 4.23–4.28 (dd, 1H, H-4'a, J4'a,4'b = 12.00 Hz, J4'a,3' = 3.00 Hz), 5.16–5.21 (m, 1H, H-3'), 5.60–5.64 (dd, 1H, H-2', J1',2' = 3.00 Hz, J2',3' = 6.00 Hz), 6.08 (d, 1H, H-1', J1',2' = 3.00 Hz), 6.70 (s, 1H, CH(furan)), 7.27 (t, 1H, Ar-H(d), J = 9.00 Hz), 7.42 (t, 1H, Ar-H(c), J = 9.00 Hz), 7.82 (d, 1H, Ar-H(b), J = 9.00 Hz), 8.23 (d, 1H, Ar-H(a), J = 9.00 Hz), 13.01 (bs, 1H, NH, D2O exchangeable); MS: m/z (%), 601 (16.75, M++2), 600 (14.35, M++1), 599 (18.90, M'), 567 (22.73), 562 (22.49), 556 (14.35), 540 (17.70), 525 (22.49), 518 (21.53), 513 (13.88), 511 (21.29), 490 (18.66), 469 (18.66), 454 (17.70), 452 (23.92), 439 (23.21), 403 (20.10), 397 (52.63), 381 (14.83), 353 (26.56), 340 (26.56), 335 (19.38), 302 (27.27), 272 (21.29), 234 (25.84), 202 (30.14), 193 (92.82), 175 (38.52), 166 (21.53), 151 (32.30), 137 (100.00), 124 (26.56), 115 (28.23), 110 (39.23), 95 (33.97), 77 (42.34), 55 (28.47), 53 (15.55). Anal. Calcd for C28H29N3O12: C, 53.48; H, 4.85; N, 7.48%; found: C, 53.40; H, 4.71; N, 7.50%.

1'-[(5-Methyl-4-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)furan-2-yl]butane-1',2',3',4'-tetracyl tetraacetate (7). A solution of compound 5 (5.523 mmol) in dry ether (75 mL) was stirred with yellow mercuric oxide (4.80 g), magnesium oxide (0.48 g), and iodine (4.00 g) at room temperature for 48 h under...
anhydrous conditions. The reaction mixture was filtered off, and the filtrate washed with potassium iodide solution, sodium thiosulphate, and water respectively, and dried over anhydrous sodium sulphate. On evaporation of the dried filtrate, a yellow crystalline mass was obtained. An additional crop was obtained by extracting the inorganic residue with chloroform which upon concentration yielded the same product. Yield (50%); recrystallized from methanol as yellow crystals; RF: 0.74 (n-hexane–ethyl acetate; 2:1; v/v); mp 147–148 °C; IR (KBr) cm⁻¹: 1750 (OAc), 1635 (C=N); ¹H-NMR (CDCl₃); δ: 1.96, 1.97, 2.05, 2.06 (4s, 12H, 4OAc), 2.65 (s, 3H, CH₃(furan)), 4.11–4.14 (dd, 1H, H-4'b, Jᵣ₄ₐ,₄₄ = 12.20 Hz, Jᵣ₄ₖₐ,₃ = 5.35 Hz), 4.20–4.23 (dd, 1H, H-4'a, Jᵣ₄ₐ,₄₄ = 12.20 Hz, Jᵣ₄ₐ₄,₃ = 3.05 Hz), 5.08–5.11 (m, 1H, H-3'), 5.46–5.49 (dd, 1H, H-2', Jᵣ₁,₂' = 5.35 Hz, Jᵣ₂,₃' = 6.90 Hz), 6.05 (d, 1H, H-1', Jᵣ₁₂' = 4.60 Hz), 7.03 (s, 1H, CH(furan)), 8.29 (d, 2H, Ar-H(b), J = 8.40 Hz), 8.40 (d, 2H, Ar-H(a), J = 9.15 Hz); MS: m/z (%), 561 (13.74, M++2), 560 (23.92, M++1), 559 (18.83), 549 (19.34), 528 (21.88), 471 (20.10), 462 (20.61), 457 (29.52), 378 (19.34), 301 (25.45), 289 (20.10), 270 (24.68), 250 (24.94), 209 (21.88), 185 (21.37), 183 (21.88), 138 (21.37), 119 (21.37), 82 (23.41), 75 (19.85), 64 (23.41), 63 (19.34), 301 (25.45), 289 (20.10), 270 (24.68), 250 (24.94), 209 (21.88), 185 (21.37), 183 (21.88), 138 (21.37), 119 (21.37), 82 (23.41), 75 (19.85), 64 (23.41), 63 (17.81), 60 (100.00), 55 (23.92), 57 (22.14); Anal. Calcd for C₂₅H₂₅N₃O₁₂: C, 53.67; H, 4.50; N, 7.51%; found: C, 53.71; H, 4.44; N, 7.44%.

1'-(5-Methyl-4-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)furan-2-yl)buxane-1',2',3',4'-tetraol (8). A solution of compound 7 (0.894 mmol) was heated with hydrazine hydrate (10 mL) in methanol (10 mL) under reflux for 1 h. The 1',2',3',4'-tetraol 8 that separated out was filtered off, washed with methanol and dried. Yield 97%; recrystallized from ethanol as pale yellow crystals; mp 147 °C; RF: 0.62 (chloroform–methanol; 5:1; v/v); IR (KBr) cm⁻¹: 3307 (OH), 1646 (C=N); ¹H-NMR (DMSO-d₆); δ: 2.64 (s, 3H, CH₃(furan)), 3.39–3.43 (m, 1H, H-4'b), 3.47–3.52 (m, 1H, H-3'), 3.54–3.56 (m, 1H, H-2'), 3.57–3.61 (m, 1H, H-4'a), 4.37 (t, 1H, 4'-OH, J₄'OH = 6.10 Hz, D₂O-exchangeable), 4.62 (d, 1H, 3'-OH, J₃'OHOH = 6.10 Hz, D₂O-exchangeable), 4.66 (d, 1H, 2'-OH, J₂'OHOH = 5.35 Hz, D₂O-exchangeable), 4.81 (d, 1H, H-1', J₁'OHOH = 7.65 Hz, D₂O-exchangeable), 6.73 (s, 1H, CH(furan)), 8.27 (d, 2H, Ar-H(b), J = 8.40 Hz), 8.39 (d, 2H, Ar-H(a), J = 8.40 Hz); MS: m/z (%), 393 (28.16, M++2), 392 (30.58, M++1), 391 (37.86, M+), 356 (43.20), 307 (48.54), 300 (100.00), 295 (39.81), 284 (49.51), 279 (44.66), 237 (40.78), 236 (41.75), 228 (40.78), 222 (42.23), 154 (57.77), 147 (43.69), 144 (45.63), 139 (30.58), 137 (75.73), 127 (38.35), 120 (39.32), 104 (67.96), 95 (46.12), 90 (49.51), 79 (43.69), 76 (94.17), 75 (61.65), 57 (48.54), 56 (93.69), 50 (60.19); Anal. Calcd for C₁₇H₁₇N₃O₈: C, 52.18; H, 4.38; N, 10.74%; found: C, 52.24; H, 4.17; N, 10.76%.

Tetrahydro-1'-(5-methyl-4-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)furan-2-yl)-furan-2',3'-diol (9). A solution of compound 8 (0.767 mmol) was heated with aqueous acetic acid (150 mL, 10%) under reflux for 8 h. After cooling the 2',3'-diol 9 that separated out was filtered off, washed with water and dried. Yield 63%; recrystallized from ethanol as a yellow powder; mp 199–200 °C; RF: 0.88 (chloroform–methanol; 5:1; v/v); IR (KBr) cm⁻¹: 3372 (OH), 1637 (C=N); ¹H-NMR (DMSO-d₆); δ: 2.66 (s, 3H, CH₃(furan)), 3.62–3.64 (dd, 1H, H-4'b, Jᵣ₄ₐ,₃ = 2.30 Hz, Jᵣ₄ₐ₄,₃ = 9.15 Hz), 4.02–4.05 (dd, 1H, H-4'a, Jᵣ₄ₐ₄,₃ = 4.55 Hz, Jᵣ₄ₐ₃,₄₄ = 9.20 Hz), 4.10–4.17 (m, 2H, H-3', H-2'), 4.54 (d, 1H, H-1', Jᵣ₁₂' = 7.60 Hz), 5.03 (d, 1H, 3'-OH, Jᵣ₃,OHOH = 3.85 Hz, D₂O-exchangeable), 5.16 (d, 1H, 2'-OH, Jᵣ₂,OHOH = 6.1 Hz, D₂O-exchangeable), 6.93 (s, 1H, CH(furan)), 8.28 (d, 2H, Ar-H(b), J = 8.40 Hz), 8.39 (d, 2H, Ar-H(a), J = 9.20 Hz); MS: m/z (%), 374 (41.04, M⁺+1), 373 (42.54, M⁺), 328 (48.51), 327 (52.99), 284 (64.93),
A solution of compound 3a (0.765 mmol) was boiled with acetic anhydride (4 mL) in the presence of anhydrous sodium acetate (0.25 g) for 7 h. The acetyl derivative that separated was filtered off and dried. Yield 59%; recrystallized from methanol as colourless crystals; Ref: 0.47 (n-hexane-ethyl acetate, 4:1, v/v); mp 168–169 °C; IR (KBr) cm⁻¹: 1744 (OAc), 1725 (COCH₃), 1712 (CO-isoindolone), 1618 (C=N); ¹H-NMR (CDCl₃); δ: 2.14 (s, 3H, OAc), 2.27 (s, 3H, COCH₃), 2.56 (s, 3H, CH₃(furan)), 7.00 (s, 1H, CH(furan)), 7.53 (d, 1H, Ar-H(d), J = 7.65 Hz), 7.56 (t, 1H, Ar-H(c), J = 7.65 Hz), 7.65 (t, 1H, Ar-H(b), J = 7.65 Hz), 7.84 (d, 1H, Ar-H(a), J = 7.65 Hz); MS: m/z (%), 356 (2.50, M++2), 355 (2.33, M++1), 354 (3.54, M+), 248 (9.62), 189 (15.92), 188 (31.58), 148 (10.09), 147 (23.86), 146 (100.00), 133 (29.25), 118 (10.27), 105 (24.07), 104 (10.66), 89 (33.82), 77 (24.16), 76 (16.31), 63 (12.12), 60 (9.15), 51 (13.03); Anal. Calcd for C₁₈H₁₄N₂O₆: C, 61.02; H, 3.98; N, 7.91%; found: C, 61.00; H, 4.00; N, 7.99%.

3.2.5. General Procedures for the Preparation of the Aromatic C-Nucleosides 12–14

**Method A.** A solution of compounds 3b and 3e (2.544 mmol) was heated with aqueous acetic acid (150 mL, 10%) under reflux for 5 h. After cooling the 3-carbohydrazones 12, 13 that separated out were filtered off, washed with water and dried.

**Method B.** A solution of 5-(2',3'-dihydroxytetrahydrofuran-1'-yl)-2-methylfuran-3-carbohydrazide (11) [4] in ethanol containing a few drops of acetic acid was treated with carbonyl compound, and the reaction mixture was refluxed on water bath for 30 min. After cooling the 3-carbohydrazones 12–14 that separated out were filtered off, washed with a little ethanol, and dried.

**N-(4-Nitrobenzylidene)-5-(tetrahydro-2',3'-dihydroxyfuran-1'-yl)-2-methylfuran-3-carbohydrazide (12).** Obtained in 90% yield from 11 (0.413 mmol) and 4-nitrobenzaldehyde (0.413 mmol); recrystallized from ethanol as yellow needles; mp 239–240 °C; Ref: 0.69 (chloroform–methanol; 5:1; v/v); IR(KBr) cm⁻¹: 3292–3245 (OH, NH), 1660 (CO-amide), 1614 (C=N); ¹H-NMR (DMSO-d₆); δ: 2.52 (s, 3H, CH₃(furan)), 3.61–3.63 (dd, 1H, H-4'b, J₃',4'b = 2.30 Hz, J₄'b,₄'a = 9.20 Hz), 4.01–4.04 (dd, 1H, H-4'a, J₃',₄'a = 4.60 Hz, J₄'b,₂' = 6.85 Hz), 4.06–4.11 (m, 2H, H-3', H-2'), 4.49 (d, 1H, H-1', J₁',₂' = 6.85 Hz), 5.02 (d, 1H, 3'-OH, J₂',OH = 3.80 Hz, D₂O-exchangeable), 5.12 (d, 1H, 2'-OH, J₁',OH = 6.10 Hz, D₂O-exchangeable), 6.88 (s, 1H, CH₃(furan)), 7.93 (d, 2H, Ar-H(b), J = 8.45 Hz), 8.26 (d, 2H, Ar-H(b), J = 8.45 Hz Hz), 8.44 (s, 1H, CH=N), 11.67 (s, 1H, NH, D₂O-exchangeable); MS: m/z (%), 376 (4.69, M⁺+1), 375 (11.01, M⁺), 317 (7.58), 212 (12.18), 211 (100.00), 153 (7.94), 151 (51.35), 137 (12.55), 123 (16.52), 115 (9.03), 105 (8.30), 95 (11.10), 81 (13.63), 79 (14.53), 77 (4.15), 70 (9.75), 63 (8.03), 61 (12.36), 55 (12.82), 53 (10.29), 52 (11.82); Anal. Calcd for C₁₉H₁₄N₂O₇: C, 54.40; H, 4.57; N, 11.20%; found: C, 54.50; H, 4.60; N, 11.11%.

5-(Tetrahydro-2',3'-dihydroxyfuran-1'-yl)-2-methyl-N-(2-oxoindolin-3-ylidene)furan-3-carbohydrazide (13). Obtained in 91% yield from 11 (0.413 mmol) and isatin (0.413 mmol); recrystallized from...
ethanol as yellow needles; mp 263–264 °C; Rf: 0.69 (chloroform–methanol; 5:1; v/v); IR (KBr) cm⁻¹: 3420 (OH), 3166 (2NH), 1763 (CO-oxindoline), 1673 (CO-amide), 1619 (C=N); ¹H-NMR (DMSO-d₆); δ: 2.57 (s, 3H, CH₃(furan)), 3.62 (2H, H-4'b, J₃'b,₄'a = 9.00 Hz), 4.01–4.06 (dd, 1H, H-4'a, J₃',₄'a = 6.00 Hz, J₄'b,₄'a = 9.00 Hz), 4.10 (bs, 2H, H-3', H-2'), 4.53 (d, 1H, H-1', J₁',₂' = 9.00 Hz), 4.94 (bs, 1H, 3'-OH, D₂O-exchangeable), 5.09 (bs, 1H, 2'-OH, D₂O-exchangeable), 6.64 (s, 1H, CH(furan)), 6.93 (d, 1H, Ar-H(d), J = 9.00 Hz), 7.07 (t, 1H, Ar-H(c), J = 9.00 Hz), 7.35 (t, 1H, Ar-H(b), J = 9.00 Hz), 7.55 (d, 1H, Ar-H(a), J = 9.00 Hz), 11.25 (bs, 1H, NH (2), D₂O-exchangeable), 13.35 (bs, 1H, NH (1), D₂O-exchangeable); MS: m/z (%), 372 (33.14, M++1), 371 (44.57, M+), 340 (37.14), 335 (37.14), 294 (40.00), 286 (49.14), 276 (40.00), 268 (37.14), 187 (40.57), 167 (44.57), 141 (40.57), 138 (40.00), 135 (49.71), 126 (43.43), 125 (44.57), 94 (100.00), 88 (46.86), 87 (49.71), 85 (55.43), 83 (62.86), 82 (77.14), 79 (48.00), 77 (45.14), 73 (66.29), 72 (42.29), 71 (60.00), 69 (85.71), 64 (69.14), 61 (43.43), 60 (65.14), 57 (82.66), 55 (72.57); Anal. Calcd for C₁₈H₁₇N₃O₆: C, 58.22; H, 4.61; N, 11.32%; found: C, 58.15; H, 4.65; N, 11.44%.

5-(Tetrahydro-2',3'-dihydroxyfuran-1'-yl)-N-2,3,4,5,6-pentahydroxyhexylidene)-2-methylfuran-3-carbohydrazide (14). Obtained in 93% yield from 11 (0.413 mmol) and D-galactose (0.826 mmol); recrystallized from ethanol as pale yellow syrup; Rf: 0.44 (chloroform–methanol, 1:1, v/v); IR (KBr) cm⁻¹: 3380–3150 (OH, NH), 1648 (CO), 1612 (C=N); MS: m/z (%), 406 (18.88, M++2), 405 (23.08, M++1), 404 (19.93, M+), 395 (24.83), 363 (26.57), 362 (25.87), 354 (23.78), 313 (25.52), 305 (24.48), 294 (23.78), 282 (24.48), 262 (28.67), 250 (26.57), 236 (24.48), 235 (28.67), 228 (28.67), 225 (23.78), 219 (28.67), 209 (24.83), 208 (30.07), 205 (25.87), 175 (25.52), 173 (25.52), 158 (24.83), 157 (26.57), 122 (27.62), 107 (28.67), 73 (100.00), 71 (39.16), 61 (40.91), 60 (81.82), 56 (26.57), 52 (26.57).

3.2.6. General Procedure for the Acetylation of the Aromatic C-Nucleosides 12 and 13

A solution of 2',3'-dihydroxyfurans 12 and 13 (0.809 mmol) in dry pyridine (15 mL) was treated with acetic anhydride (15 mL) and the mixture was kept overnight with occasional shaking at room temperature. Then it was poured onto crushed ice, the acetyl derivatives 15 and 16 that separated out were filtered off, washed with water and dried.

N-(4-Nitrobenzylidene)-5-(tetrahydro-2',3'-diacetoxyfuran-1'-yl)-2-methylfuran-3-carbohydrazide (15). Obtained in 79% yield from 12 (0.809 mmol); recrystallized from ethanol as yellow crystals; mp 173–174 °C; Rf: 0.61 (n-hexane–ethyl acetate; 1:1; v/v); IR (KBr) cm⁻¹: 3235 (NH), 1753 (OAc), 1654 (CO), 1600 (C=N); ¹H-NMR (CDCl₃); δ: 2.00, 2.06 (2s, 6H, OAc), 2.52 (s, 3H, CH₃(furan)), 3.81–3.84 (dd, 1H, H-4'b, J₃'b,₄'a = 10.70 Hz, J₄'b,₄'a = 2.30 Hz), 4.25–4.29 (dd, 1H, H-4'a, J₃'a,₄'a = 10.70 Hz, J₄'a,₂' = 6.10 Hz), 5.34–5.37 (m, 1H, H-2'), 5.40–5.42 (m, 1H, H-1'), 6.98 (s, 1H, CH(furan)), 7.93 (d, 2H, Ar-H(b), J = 8.65 Hz), 8.26 (d, 2H, Ar-H(a), J = 7.65 Hz), 8.43 (s, 1H, CH=O), 11.72 (s, 1H, NH, D₂O exchangeable); MS: m/z (%), 460 (12.29, M⁺+1), 459 (16.74, M⁺), 400 (28.39), 380 (24.15), 340 (74.79), 323 (19.49), 296 (25.21), 295 (100.00), 265 (19.92), 260 (15.47), 258 (17.16), 235 (19.92), 193 (26.91), 192 (25.21), 175 (35.17), 151 (44.28), 150 (26.69), 147 (24.58), 138 (25.00), 137 (54.03), 123 (28.39), 115 (79.87), 105 (27.54), 95 (40.89), 91 (26.27), 85 (25.64), 27 (23.31), 76 (23.52), 63 (25.64), 55 (27.54), 52 (28.39); Anal. Calcd for C₂₁H₂₁N₃O₉: C, 54.90; H, 4.61; N, 9.15%; found: C, 54.79; H, 4.69; N, 9.24%.
5-(Tetrahydro-2',3'-diacetoxyfuran-1'-yl)-2-methyl-N-(N'-acetyl-2-oxoindolin-3-ylidene)furan-3-carbohydrazide (16). Obtained in 67% yield from 13 (0.809 mmol); recrystallized from ethanol as yellow crystals; mp 162–163 °C; Rf: 0.51 (n-hexane–ethyl acetate; 5:1; v/v); IR (KBr) cm⁻¹: 3273 (NH), 1745 (OAc), 1708 (3CO), 1603 (C=N); 1H-NMR (CDCl₃); δ: 2.06, 2.11 (2s, 6H, 2OAc), 2.67 (s, 3H, CH₃(furan)), 2.73 (s, 3H, N-Ac), 3.93–3.98 (dd, 1H, H-4'b, J₄'a,₄'b = 12.00 Hz, J₄'b,₃' = 3.00 Hz), 4.36–4.41 (dd, 1H, H-4'a, J₄'a,₄'b = 12.00 Hz, J₄'a,₃' = 3.00 Hz), 4.93 (d, 1H, H-3', J₂',₃' = 6.00 Hz), 5.48–5.55 (m, 2H, H-2', H-1'), 6.74 (bs, 1H, CH(furan)), 7.27 (t, 1H, Ar-H (d), J = 9.00 Hz), 7.42 (t, 1H, Ar-H(c), J = 9.00 Hz), 7.82 (d, 1H, Ar-H (b), J = 6.00 Hz), 8.23 (d, 1H, Ar-H (a), J = 9.00 Hz), 13.03 (bs, 1H, NH, D₂O exchangeable); MS: m/z (%), 499 (5.52, M⁺+2), 498 (7.88, M⁺+1), 496 (4.73, M⁺-1), 434 (8.23), 379 (11.03), 378 (31.35), 296 (21.54), 295 (100.00), 235 (10.16), 193 (13.66), 192 (10.42), 175 (18.83), 151 (13.84), 149 (13.40), 148 (11.30), 147 (14.19), 137 (34.68), 121 (16.20), 115 (40.72), 109 (13.84), 105 (17.86), 104 (17.43), 95 (34.85), 80 (14.89), 79 (15.06), 77 (11.56), 55 (13.22), 52 (12.00), 51 (14.36); Anal. Calcd for C₂₄H₂₃N₃O₉: C, 57.95; H, 4.66; N, 8.45%; found: C, 57.88; H, 4.52; N, 8.50%.

5-(Tetrahydroj-2,2-dimethylfuro[2',3'-d][1,3]dioxol-1'-yl)-2-methyl-N-(2-oxoindolin-3-ylidene)furan-3-carbohydrazide (17). Compound 13 (0.485 mmol) was treated with FeCl₃ (0.035 g) in dry acetone (30 mL). The reaction mixture was heated under reflux for 30 min. After cooling it was poured onto cold water, the separated yellow crystals 17 was filtered off and dried. Yield 88%; recrystallized from ethanol as yellow needles; mp 220 °C; Rf: 0.75 (chloroform–methanol; 20:1; v/v); IR (KBr) cm⁻¹: 3178 (2NH), 1684 (2CO), 1615 (C=N); 1H-NMR (DMSO-d₆); δ: 1.26, 1.39 (2s, 6H, CMe₂, Δδ = 0.13), 2.54 (s, 3H, CH₃(furan)), 3.74–3.69 (dd, 1H, H-4'b, J₄'a,₄'b = 12.00 Hz, J₄'b,₃' = 3.00 Hz), 3.87 (d, 1H, H-4'a, J₄'a,₄'b = 12.00 Hz), 4.88–4.95 (m, 2H, H-3', H-2'), 4.98 (s, 1H, H-1', J₁',₂' = 0 Hz), 6.63 (bs, 1H, CH(furan)), 6.92 (d, 1H, Ar-H(d), J = 9.00 Hz), 7.06 (t, 1H, Ar-H(c), J = 9.00 Hz), 7.36 (t, 1H, Ar-H(b), J = 6.00 Hz), 7.53 (d, 1H, Ar-H(a), J = 9.00 Hz), 11.28 (s, 1H, NH(2), D₂O exchangeable), 13.35 (bs, 1H, NH(1), D₂O exchangeable); MS: m/z (%), 413 (0.88, M⁺+2), 412 (5.26, M⁺+1), 411 (20.24, M⁺), 383 (9.26), 252 (16.46), 251 (100.00), 160 (24.84), 159 (10.29), 151 (8.40), 137 (23.63), 136 (16.47), 123 (6.97), 121 (12.88), 110 (8.02), 109 (6.21), 105 (6.89), 104 (15.66), 95 (14.58), 80 (10.20), 79 (18.26), 78 (6.11), 77 (22.12), 76 (6.12), 69 (7.01), 65 (6.34), 59 (14.57), 57 (6.78), 55 (12.70), 53 (8.67), 52 (10.78), 51 (11.09); Anal. Calcd for C₂₄H₂₃N₃O₁₀: C, 57.95; H, 4.66; N, 8.45%; found: C, 57.88; H, 4.52; N, 8.50%.

(5-(1',2',3',4'-Tetrahydroxybutyl)-2-methylfuran-3-yl)(3,5-dimethyl-1H-pyrazol-1-yl)-methanone (18). A mixture of 3-carbohydrazide 1 (5 mmoL) and acetylacetone (5 mmoL) was heated under reflux in ethanol (10 mL) containing a few drops of acetic acid for 5 h. After cooling the solid 18 that separated was filtered off and dried. Yield 100%; recrystallized from ethanol as colorless needles; mp 142–143 °C; Rf: 0.55 (chloroform–methanol; 5:1; v/v); IR (KBr) cm⁻¹: 3314 (OH), 1689 (CO), 1560 (C=N); 1H-NMR (DMSO-d₆); δ: 2.16 (s, 3H, CH₃(b-pyrazole)), 2.48 (s, 6H, CH₃(furan) and CH₃(a-pyrazole)), 3.39–3.43 (m, 1H, H-4'b), 3.47–3.58 (m, 3H, H-3', H-2', H-4'a), 4.30 (bs, 1H, 4'-OH, D₂O-exchangeable), 4.48 (d, 1H, 3'-OH, J₂',OH = 6.00 Hz, D₂O-exchangeable), 4.56 (bs, 1H, 2'-OH, D₂O-exchangeable), 4.76 (d, 1H, H-1', J₁',₂' = 6.00 Hz), 5.11 (d, 1H, 1'-OH, J₁',OH = 6.00 Hz, D₂O-exchangeable), 6.18 (s, 1H, CH(pyrazole)), 6.90 (s, 1H, CH(furan)); MS: m/z (%), 325 (0.17, M⁺+1), 324 (0.30, M⁺), 306 (17.49), 234
Molecules 2014, 19

(9.75), 233 (32.42), 211 (26.86), 210 (75.30), 203 (23.37), 182 (23.85), 151 (6.04), 138 (6.24), 137
(41.72), 123 (6.09), 122 (7.28), 121 (12.20), 110 (13.35), 109 (12.02), 103 (8.55), 97 (100.00), 96
(10.91), 95 (18.16) 81 (11.08), 79 (11.69), 56 (6.59), 55 (9.48), 53 (11.53), 51 (7.48); Anal. Calcd for
C15H20N2O6: C, 55.55; H, 6.22; N, 8.64%; found: C, 55.56; H, 6.20; N, 8.59%.

(5-(1',2',3',4'-Tetraacetoxybutyl)-2-methylfuran-3-yl)(3,5-dimethyl-1H-pyrazol-1-yl)methanone (19). A
solution of compound 18 (1.543 mmoL) in dry pyridine (15 mL) was treated with acetic anhydride (15 mL)
and the mixture was kept overnight with occasional shaking at room temperature. Then it was poured
onto crushed ice and the acetyl derivative 19 that separated out was filtered off, washed with water and
dried. Yield 68%; recrystallized from ethanol as colorless needles; mp 101–102 °C; Rf: 0.74 (n-hexane–ethyl
acetate; 2:1; v/v); IR (KBr) cm⁻¹: 1751 (OAc), 1683 (CO), 1591 (C=N); ¹H-NMR (CDCl₃); δ: 2.03, 2.04, 2.06, 2.12 (4s, 12H, 4OAc), 2.23 (s, 3H, CH₃(pyrazole-b)), 2.54 (s, 3H, CH₃(furan)), 2.57 (s, 3H, CH₃(pyrazole-a)), 4.09–4.14 (dd, 1H, H-4'b, J₄'a,₄'b = 12.00 Hz, J₄'b,₃' = 3.00 Hz), 4.19–4.24
(dd, 1H, H-4'a, J₄'a,₄'b = 12.00 Hz, J₄'a,₃' = 3.00 Hz), 5.14–5.19 (m, 1H, H-3'), 5.60–5.64 (dd, 1H, H-2',
J₁',₂' = 3.00 Hz, J₂',₃' = 6.00 Hz), 5.97 (s, 1H, CH(pyrazole)), 6.08 (d, 1H, H-1', J₁',₂' = 3.00 Hz), 7.15 (s, 1H,
CH(furan)); ¹³C-NMR (CDCl₃); δ: 13.86, 14.47 and 14.58 for (2CH₃(pyrazole), CH₃(furan)), 20.74, 20.80
(2 lines for 4 OCOCH₃), 61.65, 65.70, 68.66 and 69.86 for (C-4', C-3', C-2' and C-1'), 110.97, 113.77,
116.00, 144.72, 145.84, 151.87, 162.89 for (pyrazole and furan carbons), 169.50 (CO-N), 169.70, 169.80, 169.95, 170.60 (4 OCOCH₃); MS: m/z (%), 494 (4.19, M ++2), 493 (7.52, M ++1), 492 (19.79), 192 (30.83), 180
(90.90), 179 (10.11), 175 (12.08), 151 (10.97), 150 (09.25), 138 (19.79), 137 (75.71), 136 (09.49), 123
(09.12), 122 (10.42), 121 (13.69), 115 (23.06), 110 (19.30), 109 (17.02), 103 (09.99), 98 (10.60), 97
(100.00), 96 (17.32), 95 (25.77), 83 (10.42), 81 (16.83), 80 (10.79), 79 (15.84), 73 (11.59), 71 (11.41),
69 (16.71), 67 (10.23), 61 (10.48), 57 (19.17), 55 (22.32), 54 (09.80), 53 (11.47), 51 (10.30); Anal.
Calcd for C₂₃H₂₈N₂O₁₀: C, 56.09; H, 5.73; N, 5.69%; found: C, 56.00; H, 5.62; N, 5.77%.

1-(5-(1',2',3',4'-Tetrahydroxybutyl)-2-methylfuran-3-carbo-3-yl)-4-phenyl thiosemicarbazide (20) [24].
A mixture of 5-(1',2',3',4'-tetrahydroxybutyl)-2-methylfuran-3-carbohydrazide 1 (3.846 mmol) and
phenyl isothiocyanate (3.846 mmol) are heated under reflux in ethanol (10 mL) for 2 h. After cooling
the thiosemicarbazide that separated was filtered off, washed with little ethanol, and dried. Yield (100%);
recrystallized from ethanol as white crystals; mp 133–134 °C; Rf: 0.35 (chloroform–methanol; 5:1; v/v);
IR(KBr) cm⁻¹: 3415–3264 (OH, 3NH), 1659 (CO); ¹H-NMR (DMSO-d₆); δ: 2.47 (s, 1H, CH₂-furan with DMSO), 3.34–3.41 (m, 1H, H-4'b), 3.45–3.48 (m, 1H, H-4'a), 3.50–3.57 (m, 2H, H-3',
H-2'), 4.34 (t, 1H, 4'-OH, J₄',₄'-OH = 6.15 Hz, D₂O-exchangeable), 4.42 (d, 1H, 3'-OH, J₃',₃'-OH = 6.85 Hz,
D₂O-exchangeable), 4.59 (d, 1H, 2'-OH, J₂',₂'-OH = 6.15 Hz, D₂O-exchangeable), 4.73 (d, 1H, H-1',
J₁',₂' = 7.65 Hz), 5.12 (d, 1H, 1'-OH, J₁',₁'-OH = 8.40 Hz, D₂O-exchangeable), 6.72 (s, 1H, CH (furan), 7.11
(t, 1H, Ar-H(t), J = 8.40 Hz), 7.28 (t, 2H, Ar-H(e), J = 9.15 Hz), 7.42 (bs, 2H, Ar-H(d)), 9.54 (s, 1H,
NH(c), D₂O exchangeable), 9.72 (s, 1H, NH(b), D₂O exchangeable), 9.97 (s, 1H, NH(a), D₂O
exchangeable); Anal. Calcd for C₁₇H₂₁N₃O₆S: C, 51.64; H, 5.35; N, 10.63%; found: C, 51.70; H,
5.20; N, 10.60%;
1'-(5-Methyl-4-(5-(phenylamino)-1,3,4-oxadiazol-2-yl)furan-2-yl)butane-1',2',3',4'-tetraol (21). To a suspension of thiosemicarbazide 20 (5.063 mmol) in ethanol (50 mL), sodium hydroxide solution (4 N, 5 mL) was added with shaking. A solution of iodine and potassium iodide was added dropwise with stirring till the color of iodine persisted. The precipitate 21 was filtered off, washed with sodium thiosulphate solution, then with water, and dried. Yield (95%); recrystallized from ethanol as white crystals; mp 223–224 °C; Rf: 0.71 (chloroform–methanol; 4:1; v/v); IR(KBr) cm⁻¹: 3421–3318 (OH), 3242 (NH), 1673 (C=N); 1H-NMR (DMSO-d₆); δ: 2.54 (s, 3H, CH₃(furan)), 3.41–3.55 (m, 4H, H-4'b, H-3', H-2', H-4'a,), 4.37 (t, 1H, 4'-OH, J₄',OH = 6.00 Hz, D₂O-exchangeable), 4.62 (d, 1H, 3'-OH, J₃',OH = 9.00 Hz, D₂O-exchangeable), 4.65 (d, 1H, 2'-OH, J₂',OH = 9.00 Hz, D₂O-exchangeable), 4.77 (d, 1H, 1'-OH, J₁',OH = 9.00 Hz, D₂O-exchangeable), 6.53 (s, 1H, CH(furan)), 6.96 (t, 1H, Ar-H(c), J = 9.00 Hz), 7.32 (t, 2H, Ar-H(b), J = 9.00 Hz), 7.55 (d, 2H, Ar-H(a), J = 9.00 Hz), 10.50 (s, 1H, NH, D₂O-exchangeable); MS: m/z (%), 361 (14.29, M +), 360 (27.07), 359 (18.30), 312 (19.05), 287 (17.04), 283 (26.32), 247 (19.80), 241 (17.04), 229 (177.79), 221 (23.06), 204 (18.55), 181 (17.04), 173 (20.30), 172 (15.74), 167 (17.54), 152 (20.55), 148 (16.54), 141 (21.05), 137 (15.54), 135 (24.56), 120 (21.80), 117 (18.30), 111 (27.57), 110 (9.05), 109 (20.30), 103 (19.80), 99 (21.55), 98 (26.57), 97 (31.08), 95 (30.58), 93 (25.56), 85 (34.59), 84 (29.07), 83 (51.13), 82 (24.31), 81 (37.59), 80 (39.60), 77 (26.32), 76 (18.55), 75 (17.79), 73 (29.82), 71 (49.62), 70 (32.58), 69 (67.67), 68 (29.57), 67 (38.60), 64 (28.57), 61 (19.05), 59 (30.07), 58 (100.00), 56 (27.57), 55 (93.98), 54 (30.58), 53 (26.32), 52 (19.80), 51 (23.06); Anal. Calcd for C₁₇H₁₉N₃O₆: C, 56.51; H, 5.30; N, 11.63%; found: C, 56.47; H, 5.41; N, 11.70%.

1'-(5-Methyl-4-(5-(phenylamino)-1,3,4-oxadiazol-2-yl)furan-2-yl)butane-1',2',3',4'-tetraacetate (22). A solution of compound 21 (1.108 mmol) in dry pyridine (10 mL) was treated with acetic anhydride (10 mL) and the mixture was kept overnight with occasional shaking at room temperature. Then it was poured onto crushed ice, and the acetyl derivative 22 that separated out was filtered off, washed with water and dried. Yield (85%); recrystallized from ethanol as white crystals; mp 180–181 °C; Rf: 0.5 (n-hexane–ethyl acetate; 2:1; v/v); IR(KBr) cm⁻¹: 3136 (NH), 1747 (OAc), 1622 (C=N); 1H-NMR (CDCl₃); δ: 2.04, 2.06, 2.08, 2.09 (4s, 12H, 4OAc), 2.60 (s, 3H, CH₃(furan)), 4.09–4.15 (dd, 1H, H-4'b, J₄'a,4'b = 12.00 Hz, J₄'b,3' = 6.00 Hz), 4.22–4.27 (dd, 1H, H-4'a, J₄'a,4'b = 12.00 Hz, J₄'a,3' = 3.00 Hz), 5.16–5.21 (m, 1H, H-3'), 5.59–5.63 (dd, 1H, H-2', J₁',2' = 3.00 Hz, J₂',3' = 6.00 Hz), 6.06 (d, 1H, H-1', J₁',2' = 3.00 Hz), 6.69 (s, 1H, CH(furan)), 7.07 (t, 1H, Ar-H(g), J = 9.00 Hz), 7.35 (t, 2H, Ar-H(b), J = 9.00 Hz), 7.48 (d, 2H, Ar-H(g), J = 9.00 Hz), 8.01 (bs, 1H, NH, D₂O-exchangeable); 13C-NMR (CDCl₃); δ: 13.72 (CH₃(furan)), 20.72, 20.78, 20.84 (3 lines for 4 COCH₃), 61.65 (C-4'), 65.86 (C-3'), 68.61 (C-2'), 69.79 (C-1'), 107.45 (j), 108.99 (i), 117.66 (h), 123.17 (g), 129.48 (f), 137.77 (e), 147.91 (d), 154.14 (c), 154.41 (b), 159.51 (a), 169.43, 169.74, 169.84, 170.62 (4 COCH₃); MS: m/z (%), 531 (11.12, M⁺+2), 530 (6.24, M⁺+1), 529 (19.12, M⁺), 496 (10.05), 476 (8.68), 452 (9.46), 428 (11.12), 388 (8.39), 374 (8.98), 368 (21.56), 367 (34.93), 329 (10.34), 325 (28.88), 312 (11.41), 308 (16.29), 307 (10.73), 297 (8.68), 285 (8.98), 274 (9.17), 271 (17.07), 270 (100.00), 249 (8.68), 232 (8.98), 193 (9.46), 185 (8.98), 181 (8.68), 178 (10.34), 167 (13.37), 129 (8.49), 127 (10.73), 122 (11.90), 120 (12.00), 115 (18.83), 93 (9.46), 92 (18.93), 78 (12.59), 77 (12.49), 66 (9.85), 52 (12.68); Anal. Calcd for C₂₅H₂₇N₃O₁₀: C, 56.71; H, 5.14; N, 7.94%; found: C, 56.66; H, 5.14; N, 8.01%.
5-(5-(1',2',3',4'-Tetrahydroxybutyl)-2-methylfuran-3-yl)-4-phenyl-2H-1,2,4-triazole-3(4H)-thione (23). In a round bottom flask thiosemicarbazide 20 (1.823 mmol) was refluxed with 10% aqueous sodium hydroxide solution (20 mL) for 5 h. The reaction mixture was filtered, cooled, and neutralized by gradual addition of dilute hydrochloric acid; the white precipitate of 23 was filtered off and dried. It was recrystallized from ethanol as white crystals. Yield 83%; mp 217–218 °C; Rf: 0.4 (chloroform–methanol; 5:1; v/v); IR (KBr) cm⁻¹: 3369 (OH, NH), 1624 (C=N); 1H-NMR (DMSO-d₆); δ: 2.30 (s, 3H, CH₃(furan)), 3.29–3.33 (m, 1H, H-4'b), 3.45–3.47 (m, 3H, H-3', H-2', H-4'a), 4.24–4.29 (m, 2H, 4'-OH, 3'-OH, D₂O-exchangeable), 4.45 (bs, 1H, 2'-OH, D₂O-exchangeable), 4.55 (d, 1H, H-1', J₁',₂' = 6.00 Hz), 4.91 (d, 1H, 1'-OH, J₁',OH = 6.00 Hz, D₂O-exchangeable), 5.48 (s, 1H, CH(furan)), 7.32 (m, 2H, Ar-H (c)), 7.49 (t, 3H, Ar-H(b,a), J = 3.00 Hz), 13.92 (s, 1H, NH, D₂O-exchangeable); MS: m/z (%), 379 (5.85, M +2), 378 (10.53, M+1), 377 (22.81, M⁺), 360 (12.38), 298 (8.77), 287 (26.80), 286 (100.00), 285 (30.60), 284 (10.14), 237 (7.60), 211 (9.75), 199 (9.75), 183 (7.70), 170 (7.60), 162 (7.12), 155 (8.19), 144 (8.67), 138 (8.48), 128 (8.48), 127 (8.97), 124 (8.67), 118 (9.45), 116 (7.41), 104 (9.26), 95 (9.65), 92 (7.02), 91 (8.87), 77 (31.38), 66 (8.19), 61 (14.52), 60 (7.50); Anal. Calcd for C₁₇H₁₉N₃O₅S: C, 54.10; H, 5.07; N, 11.13%; found: C, 54.22; H, 5.22; N, 11.00%.

5-(5-(1',2',3',4'-Tetraacetoxybutyl)-2-methylfuran-3-yl)-4-phenyl-2-N-acetyl-1,2,4-triazole-3(4H)-thione (24). A solution of compound 23 (1.061 mmol) in dry pyridine (15 mL) was treated with acetic anhydride (15 mL) and the mixture was kept overnight with occasional shaking at room temperature. Then it was poured onto crushed ice, and the acetyl derivative 24 that separated out was filtered off, washed with water and dried. Yield 97%; recrystallized from ethanol as pale yellow needles; mp 168–169 °C; Rf: 0.49 (n-hexane–ethyl acetate; 2:1; v/v); IR (KBr) cm⁻¹: 1747 (OAc, N-Ac), 1622 (C=N); 1H-NMR (CDCl₃); δ: 1.97, 1.99, 2.01 (3s, 12H, 4OAc), 2.50 (s, 3H, CH₃(furan)), 2.77 (s, 3H, N-Ac), 3.98-4.04 (dd, 1H, H-4'b, J₃',₄'b = 12.00 Hz, J₄'b,₃' = 6.00 Hz), 4.10–4.16 (dd, 1H, H-4'a, J₄'a,₄'b = 15.00 Hz, J₄'a,₃' = 3.00 Hz), 5.03–5.07 (m, 1H, H-3'), 5.39–5.46 (m, 1H, H-2'), 5.48 (s, 1H, CH(furan)), 5.79 (d, 1H, H-1', J₁',₂' = 3.00 Hz), 7.20–7.30 (m, 2H, Ar-H (c)), 7.53 (t, 3H, Ar-H(b,a), J = 3.00 Hz); MS: m/z (%), 589 (1.52 , M +2), 588 (3.93 , M +1), 587 (10.34, M⁺), 547 (9.46), 546 (26.15), 545 (79.56), 485 (6.60), 384 (20.24), 383 (57.91), 382 (5.92), 370 (4.92), 342 (12.32), 341 (28.54), 329 (4.49), 328 (15.48), 324 (11.95), 323 (13.76), 299 (8.53), 298 (6.72), 288 (7.01), 287 (21.33), 286 (100.00), 285 (9.11), 284 (5.98), 270 (4.66), 256 (6.60), 115 (10.38), 77 (8.82), 60 (4.34), 51 (2.25); Anal. Calcd for C₂₇H₂₉N₃O₁₀S: C, 55.10; H, 4.97; N, 7.15%; found: C, 55.11; H, 4.99; N, 7.00%.

5-(5-(1',2',3',4'-Tetrahydroxyfuran-1'-yl)-2-methylfuran-3-yl)-4-phenyl-2H-1,2,4-triazole-3(4H)-thione (25). A solution of compound 23 (1.823 mmol) in dry pyridine (15 mL) was treated with acetic anhydride (15 mL) and the mixture was kept overnight with occasional shaking at room temperature. Then it was poured onto crushed ice, and the acetyl derivative 24 that separated out was filtered off, washed with water and dried. Yield 97%; recrystallized from ethanol as pale yellow needles; mp 168–169 °C; Rf: 0.4 (n-hexane–ethyl acetate; 2:1; v/v); IR (KBr) cm⁻¹: 3407–3184 (OH, NH), 1625 (C=N); 1H-NMR (CDCl₃); δ: 1.97, 1.99, 2.01 (3s, 12H, 4OAc), 2.50 (s, 3H, CH₃(furan)), 2.77 (s, 3H, N-Ac), 3.98-4.04 (dd, 1H, H-4'b, J₄ₐ,₄ₐ = 12.00 Hz, J₄ₐ,₃ₐ = 6.00 Hz), 4.10–4.16 (dd, 1H, H-4'a, J₄ₐ,₄ₐ = 15.00 Hz, J₄ₐ,₃ₐ = 9.00 Hz), 5.03–5.07 (m, 1H, H-3'), 5.39–5.46 (m, 1H, H-2'), 5.48 (s, 1H, CH(furan)), 5.79 (d, 1H, H-1', J₁',₂' = 3.00 Hz), 7.20–7.30 (m, 2H, Ar-H(c)), 7.53 (t, 3H, Ar-H(b,a), J = 3.00 Hz); MS: m/z (%), 589 (1.52 , M +2), 588 (3.93 , M +1), 587 (10.34, M⁺), 547 (9.46), 546 (26.15), 545 (79.56), 485 (6.60), 384 (20.24), 383 (57.91), 382 (5.92), 370 (4.92), 342 (12.32), 341 (28.54), 329 (4.49), 328 (15.48), 324 (11.95), 323 (13.76), 299 (8.53), 298 (6.72), 288 (7.01), 287 (21.33), 286 (100.00), 285 (9.11), 284 (5.98), 270 (4.66), 256 (6.60), 115 (10.38), 77 (8.82), 60 (4.34), 51 (2.25); Anal. Calcd for C₂₇H₂₉N₃O₁₀S: C, 55.19; H, 4.97; N, 7.15%; found: C, 55.11; H, 4.99; N, 7.00%.
Ar-H(b,a), \( J = 3.00 \) Hz), 13.96 (bs, 1H, NH, D\textsubscript{2}O-exchangeable); MS: \( m/z (\%) \), 360 (23.69, M\textsuperscript{+1}), 359 (20.21, M\textsuperscript{+}), 357 (20.21), 341 (20.21, M\textsuperscript{+}-H\textsubscript{2}O), 326 (20.21, M\textsuperscript{+-SH}), 321 (26.48), 316 (24.74), 314 (24.74), 305 (24.39), 289 (29.97), 255 (20.91, M\textsuperscript{+-C\textsubscript{4}H\textsubscript{8}O\textsubscript{3}}), 225 (26.48), 212 (25.44), 203 (25.78), 167 (25.78), 153 (27.53), 149 (32.06), 141 (27.53), 139 (24.74), 129 (25.78), 118 (24.74), 112 (25.44), 111 (25.44), 97 (30.31), 95 (29.27), 94 (50.52), 93 (27.53), 90 (25.78), 83 (43.21), 81 (33.80), 74 (29.97), 73 (30.31), 71 (56.10), 70 (33.80), 69 (49.48), 67 (24.74), 61 (24.74), 60 (45.99), 57 (100.00), 56 (42.16), 55 (76.66), 54 (24.39), 52 (25.78); Anal. Calcd for C\textsubscript{17}H\textsubscript{17}N\textsubscript{3}O\textsubscript{4}S: C, 56.81; H, 4.77; N, 11.69%; found: C, 56.77; H, 4.77; N, 11.74%.

4-(4,5-Dihydro-4-phenyl-5-thioxo-1H-1,2,4-triazol-3-yl)-5-methylfuran-2-carbaldehyde (26). A solution of compound 23 (2.122 mmol) in distilled water (20 mL) was treated dropwise with a solution of sodium metaperiodate (6.366 mmol) in distilled water (20 mL) with continuous stirring for 5 h, the formyldervative 26 that separated out was filtered off, washed with water, and dried. Yield 48%; recrystallized from ethanol as pale yellow needles; mp 237–238 °C; RF: 0.77 (chloroform–methanol; 20:1; v/v); IR (KBr) cm\textsuperscript{−1}: 3354 (NH), 1681 (CHO), 1600 (C=N); \( \delta \) (s, 3H, CH\textsubscript{3}(furan) with DMSO), 6.65 (d, 1H, CH (furan)), 7.39 (t, 2H, Ar-H (c), \( J = 3.00 \) Hz), 7.50–7.57 (m, 3H, Ar-H(b,a)), 9.32 (s, 1H, CHO), 14.17 (s, 1H, NH, D\textsubscript{2}O exchangeable); MS: \( m/z (\%) \), 287 (6.12, M\textsuperscript{+2}), 286 (19.64, M\textsuperscript{+1}), 285 (100.00, M\textsuperscript{+}), 284 (33.49), 256 (19.21), 228 (17.85), 212 (6.13), 169 (9.29), 150 (7.92), 149 (16.37), 135 (6.34), 134 (13.27), 118 (6.39), 109 (7.29), 106 (6.53), 93 (6.00), 91 (11.22), 80 (68.01), 79 (9.20), 78 (13.83), 77 (61.00), 76 (7.14), 69 (6.12), 66 (7.25), 65 (13.54), 64 (43.58), 63 (10.89), 55 (5.63), 53 (6.78), 52 (14.86), 51 (47.93), 50 (13.88); Anal. Calcd for C\textsubscript{14}H\textsubscript{11}N\textsubscript{3}O\textsubscript{2}S: C, 58.93; H, 3.89; N, 14.73%; found: C, 58.90; H, 4.00; N, 14.88%.

3.3. Antioxidant and Anticancer Screening

3.3.1. Materials

Mammalian cell lines: MCF-7 cells (human breast cancer cell line were obtained from VACSERA Tissue Culture Unit (Cairo, Egypt). Chemicals used: Dimethyl sulfoxide (DMSO), crystal violet and trypan blue dye were purchased from Sigma (St. Louis, MO, USA). Fetal bovine serum, Dulbecco’s Modified Eagle’s Medium (DMEM), RPMI-1640, HEPES buffer solution, L-glutamine, gentamycin and 0.25% trypsin-EDAT were purchased from Lonza (St. Louis, MO, USA). Crystal violet (1%) was made from 0.5% (w/v) crystal violet and 50% methanol, then made up to volume with dd H\textsubscript{2}O and filtered through a Whatman No. 1 filter paper.

3.3.2. Cell Line Propagation

The cells were propagated in (DMEM) supplemented with 10% heat-inactivated fetal bovine serum, 1% L-glutamine, HEPES buffer and 50 \( \mu \)g/mL gentamycin. All cells were maintained at 37 °C in humidified atmosphere with 5% CO\textsubscript{2} and were subcultured two times a week. Cell toxicity was monitored by determining the effect of the examined compound on cell morphology and cell viability.
3.3.3. Cytotoxicity Evaluation Using Viability Assay

For the cytotoxicity assays, cells were seeded in 96-well plate at a cell concentration of $1 \times 10^4$ cell per well in 100 $\mu$L of growth medium. Fresh medium containing different concentrations of the test sample was added after 24 h of seeding. The microtiter plates were incubated at 37 °C in a humidified incubator with 5% CO$_2$ for a period of 48 h. Three wells were used for each concentration of the tested sample. Control cells were incubated without test sample and with or without DMSO. After incubation of the cells for 24 h at 37 °C, various concentrations of the sample (50.000, 25.000, 12.500, 6.250, 3.125 and 1.560 $\mu$g) were added each separately. The incubation was continued for 48 h and viable cells yield was determined colorimetrically using 3,4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide (MTTB). The water insoluble tetrazolium salt is converted to purple formazan by the mitochondrial dehydrogenase of viable cells. After the end of incubation period, media were aspirated and crystal violet solution (1%) was added to each well for at least 30 min. The stain was removed and plates were rinsed using tap water until all excess stain is removed. Glacial acetic acid (30%) was then added to all wells and mixed thoroughly, then the absorbance of the plates were measured after gently shaken on Microplate Reader (Tecan, Inc., city, country), at 490 nm. All results were corrected for background absorbance detected in wells without added stain. Treated sample was compared with the cell control in the absence of the tested compound. All experiments were carried out in the triplicate. The cell cytotoxic effect of the tested compound was calculated [27,28].

4. Conclusions

Some new aromatic C-nucleosides have been prepared from carbohydrate precursors. Their physical and chemical properties were studied, and some of the compounds showed potential antioxidant activities. One of these compounds has been screened for its antitumor activity.

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Author Contributions

Author contributions are equally in this work.

Conflicts of Interest

The authors declare no conflict of interest.

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**Sample Availability:** Samples of the compounds are available from the authors.

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