Research article

Synthesis of a series of new 6-nitrobenzofuran-2-carbohydrazide derivatives with cytotoxic and antioxidant activity

Muhammad Taha[a,*], Sadia Sultan[b,c,**], Mohamad Azlan[b,c], Syed Adnan Ali Shah[b,c], Waqas Jamil[d], Swee Keong Yeap[e], Syahrul Imran[b,g], Muhammad Nadeem Akhtar[f], Seema Zareen[f], Nor Hadiani Ismail[b,g], Muhammad Ali[h]

[a] Department of Clinical Pharmacy, Institute for Research and Medical Consultations (IRMC), University of Dammam, Dammam 31441, Saudi Arabia
[b] Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor D. E., Malaysia
[c] Faculty of Pharmacy, Universiti Tecknologi MARA, Puncak Alam 42300 Selangor, Malaysia
[d] Institute of Advance Research Studies in Chemical Sciences, University of Sindh Jamshoro, Hyderabad 76080, Pakistan
[e] Institute of Bioscience, Universiti Putra Malaysia, UPM Serdang, 43400 Selangor Darul Ehsan, Malaysia
[f] Faculty of Industrial Sciences & Technology, Universiti Malaysia Pahang, Lebuhraya Tun Razak 26300 Kuantan, Pahang, Malaysia
[g] Faculty of Applied Science Universiti Teknologi MARA, 40450 Shah Alam, Malaysia
[h] Department of Chemistry, COMSATS Institute of Information Technology, University Road, Abbottbad 22060, KPK, Pakistan

ARTICLE INFO

ABSTRACT

6-nitrobenzofuran-2-carbohydrazide Schiff base derivatives have been synthesized and their structure has been confirmed via H^1NMR, Mass spectrometry and elemental (CHN/S) analysis. These synthesized analogs showed significant cytotoxic and antioxidant activity. Doxorubicin (IC_{50} = 0.94 ± 0.20 μM) and n-propyl gallate (IC_{50} = 30.30 ± 0.40 μM) were used as standard in cytotoxic and antioxidant activities, respectively. Compound **1** (IC_{50} = 3.30 ± 0.90 μM), **2** (IC_{50} = 2.70 ± 0.25 μM), **3** (IC_{50} = 2.70 ± 0.25 μM), **10** (IC_{50} = 2.70 ± 1.10 μM), **11** (IC_{50} = 1.00 ± 1.20 μM), and **17** (IC_{50} = 3.75 ± 0.90 μM) showed excellent while **21** (IC_{50} = 7.50 ± 0.60 μM) and **28** (IC_{50} = 7.50 ± 0.66 μM) showed moderate anti cancer activity. Furthermore, compound **10** (IC_{50} = 17.50 ± 0.85 μM), **11** (IC_{50} = 24.20 ± 0.55 μM), **12** (IC_{50} = 21.10 ± 1.58 μM), **13** (IC_{50} = 14.60 ± 0.32 μM), **14** (IC_{50} = 29.20 ± 0.75 μM) and **15** (IC_{50} = 9.26 ± 0.15 μM) showed better antioxidant activity than the standard n-propyl gallate. This study will be useful to develop potential lead molecules with cytotoxic and antioxidant potential.

1. Introduction

Benzofuran containing heterocyclic constitutes one of the major classes of organic compounds. Its presence is evidenced in several bioactive natural products as well as pharmaceuticals and polymers [19]. Numerous derivatives of benzofuran are known for their biological and pharmacological relevancy [2,18,6]. This heterocyclic class of compounds has attracted the tremendous attention of medicinal chemists who are actively involved in the synthesis of benzofuran ring containing molecules and derivatives [7]. Several clinically approved drugs based on benzofuran moiety which are either synthetic or naturally found. There are many other substituted benzofuran derivatives containing mono and fused benzofuran ring in conjunction with other heterocyclic. Fig. 1 shows some of the drugs with their significant pharmacological activity.

Pyridylbenzofuran is known as antifungal, methoxsalen known for treating eczema and psoriasis, and fluorescein for its potential in diagnostics [8]. Further to this, pharmaceutically acceptable salts of benzofuran class of compounds are inhibitors of leukotriene biosynthesis. These compounds inhibit the mammalian 5-lipoxygenase enzyme, thus preventing the metabolism of arachidonic acid to the leukotrienes. These compounds are thus useful in the treatment of asthma, allergic disorders, inflammation, skin diseases and certain cardiovascular disorders [1].

Many biological activities are associated with these classes of compounds that include:

* Corresponding author at: Department of Clinical Pharmacy, Institute for Research and Medical Consultations (IRMC), University of Dammam, Dammam 31441, Saudi Arabia.
** Corresponding author at: Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor D. E., Malaysia.
E-mail addresses: taha_hej@yahoo.com, mtaha@uod.edu.sa (M. Taha), drsadia@puncakalam.uitm.edu.my, sadiasultan301@yahoo.com (S. Sultan).

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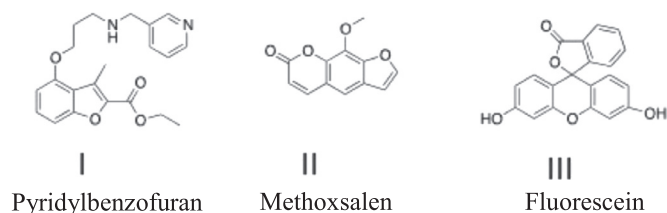Pyridylbenzofuran

II
Methoxsalen

III
Fluorescein

Fig. 1. Some important drugs having benzofuran moiety.

We have being working on various hydrazones and found them potentially active antiglycation agents ([13,9]; Khalid et al., 2013), antioxidants ([14,10]; Khalid et al., 2011), α-glucosidase inhibitors [15], β-Glucuronidase inhibitors [5,16], urease inhibitors [17] and α-amylase inhibitors [3,12]. Benzofuran hydrazones are the molecules of interest due to various pharmacological and physiological Potential. Our group already reported various bioactivities of this class of compounds such as β-Glucuronidase and anti-glycation [4,5]. The present work relates to the synthesis of a nitro substituted benzofuran hydrazone **1–30** based cytotoxic compounds with antioxidant potentials.

2. Results and discussion

2.1. Chemistry

6-nitrobenzofuran-2-carbohydrazide Schiff bases (**1–30**) were synthesized from 6-nitrobenzofuran-2-carbohydrazide which was obtained from methyl 6-nitrobenzofuran-2-carbonate by refluxing with hydrazine hydrate for 2 h. The 6-nitrobenzofuran-2-carbohydrazide was recrystallized from methanol and treated with different aldehydes in methanol for 3–4 h, in order to synthesize Schiff bases **1–30** (Scheme 1). Recrystalization of crude products by methanol produced mostly needle like crystals in 78–92% yield. The structures of 6-nitrobenzofuran-2-carbohydrazide Schiff bases were deduced by using various spectroscopic techniques and CHN analysis.

2.2. Cytotoxic activity

A series of 6-Nitrobenzofuran-2-carbohydrazide Schiff base analogs **1–30** were synthesized and evaluated their *in-vitro* cytotoxic activity as well as antioxidant potential. The cytotoxicity of compounds **1–30** was evaluated against human breast adenocarcinoma (MCF-7), cell lines. Doxorubicin ($IC_{50} = 0.94 \pm 0.20\,\mu M$) was taken as a standard reference. We also tested our starting material 6-Nitrobenzofuran-2-carbohydrazide but it showed very weak cytotoxic and antioxidant activity. The IC_{50} values revealed that various compounds possess significant cytotoxicity against MCF-7 cancer cell lines (Table 1). Compound **11** ($IC_{50} = 1.00 \pm 1.20\,\mu M$) having 2,4-di-OH substitution, was found to be the most significant compound of this series and it showed a cytotoxic activity similar to doxorubicin. Compound **10** ($IC_{50} = 2.75 \pm 1.10\,\mu M$) also showed excellent activity, but in a lesser extent than compound **11** Fig. 2.

Cytotoxic activity was dramatically lower in compound 12 that showed a 2,5-di-OH instead of a 2,3-di-OH structure *i.e.* compound **12** ($IC_{50} = 23.50 \pm 1.50\,\mu M$). This decline in activity might be due to change in position of –OH group from 2,4 to 2,3 or 2,5-di-OH. Compound **17** ($IC_{50} = 3.75 \pm 0.90\,\mu M$) also showed good activity, while all other –OH group containing analogs were found to be inactive in MCF-7 cells. The chloro substituted compounds **1** ($IC_{50} = 3.30 \pm 0.90\,\mu M$), **2** ($IC_{50} = 2.70 \pm 0.25\,\mu M$), and **3** ($IC_{50} = 2.70 \pm 0.25\,\mu M$) also showed considerable cytotoxicity for MCF-7, but comparatively Floro substituted analogs were not found to be as active as chloro substituted compounds. Compound **21** ($IC_{50} = 7.50 \pm 0.60\,\mu M$) and **28** ($IC_{50} = 7.50 \pm 1.66\,\mu M$) showed moderate activity. Compounds **22–25**, containing heterocyclic ring showed no activity against cancer cell lines. So, it is concluded that

these derivatives with slight modification may result as future cytotoxic agents.

2.3. Antioxidant activity

All the synthesized compounds **1–30** were also evaluated for DPPH radical scavenging activity. They showed varying degree of activity, ranging 9.26–94.15 μM. Compounds **10** ($IC_{50} = 17.50 \pm 0.85\,\mu M$), **11** ($IC_{50} = 24.20 \pm 0.55\,\mu M$), **12** ($IC_{50} = 21.10 \pm 1.58\,\mu M$), **13** ($IC_{50} = 14.60 \pm 0.32\,\mu M$), **14** ($IC_{50} = 29.20 \pm 0.75\,\mu M$) and **15** ($IC_{50} = 9.26 \pm 0.15\,\mu M$) showed remarkable activity and found to be far better active than the standard *n*-propyl gallate ($IC_{50} = 30.30 \pm 0.40\,\mu M$). It was observed that all compounds with 2 or more –OH are active in the DPPH radical scavenging activity. The *tri* –OH compound **15** was found to be the most active in this series. The *di* –OH compounds **10**, **11**, **12**, **13**, and **14** also showed better activity than the standard. The *mono* –OH substituted compounds **8** ($IC_{50} = 55.20 \pm 2.94\,\mu M$) and **9** ($IC_{50} = 34.11 \pm 1.32\,\mu M$) showed moderate activity. Suppression of activity was seen after replacing one of the –OH group with –OMe group in *di* –OH compounds, such as compound **16** ($IC_{50} = 70.20 \pm 3.12\,\mu M$), **17** ($IC_{50} = 84.30 \pm 3.20\,\mu M$), and **18** ($IC_{50} = 94.15 \pm 3.25\,\mu M$) weak DPPH radical scavenging activity. So this activity depends on the number of –OH groups present there, more will be the activity. All other derivatives were found to be inactive.

Antioxidant and cytotoxic potential of this compound is good for drug development as we know that the beginning of cancer is due to an imbalance in the oxidant stress in the body and if the compounds have the ability to fight with both will be very useful.

3. Experimental

3.1. General experimental

NMR Experiments were performed on Ultra Sheild Bruker FT NMR 500 MHz; CHN analyses were performed on a Carlo Erba Strumentazion-Mod-1106, Italy. Electron impact mass spectra (EI MS) were recorded on a Finnigan MAT-311A, Germany. Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by UV at 254 and 365 nm.

3.2. Experimental protocol

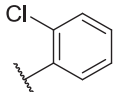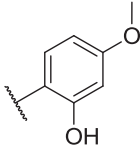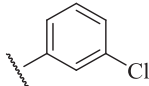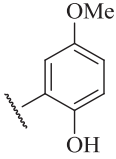#### 3.2.1. General procedure for the synthesis of 6-nitrobenzofuran-2-carbohydrazide
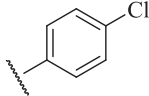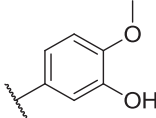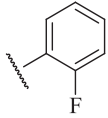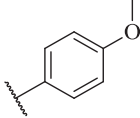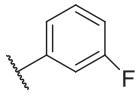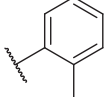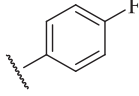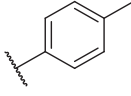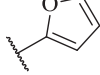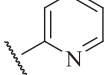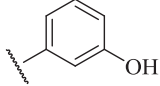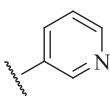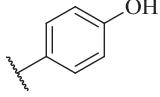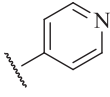
The 6-nitrobenzofuran-2-carbonate was refluxed with the mixture of hydrazine hydrated (5 mL) and methanol (15 mL) for 6 h. The excess hydrazine and methanol were evaporated to obtain the crude product which was recrystalized from methanol and yielded 90% pure 2-methoxybenzohydrazide.

3.2.2. General procedure for the synthesis 6-nitrobenzofuran-2-carbohydrazide Schiff bases 1–30

2 mmol each of 6-nitrobenzofuran-2-carbohydrazide and variously substituted aldehydes and a catalytic amount of acetic acid was refluxed for 3 h. The solvent was evaporated under vacuum, after completion of reaction (TLC) to afford crude products, after recrystallization in methanol, mostly needle like crystals of pure product was obtained in good to excellent yields.

3.3. Bioassay protocol

Human breast cancer cell line MCF-7 was purchased from American Type Culture Collection (ATCC). The cell was thawed and maintained in RPMI-1640 (Sigma, USA) supplemented with 10% Fetal Bovine Serum (FBS) (PAA, Austria) at 37 °C, 5% CO_2. Trypan blue cell

Comp.	R	IC$_{50}$ ± SEM[a] [μM]	Comp.	R	IC$_{50}$ ± SEM[a] [μM]
1		3.30 ± 0.90	16		>30
2		2.70 ± 0.25	17		3.75 ± 0.90
3		2.70 ± 0.25	18		>30
4		>30	19		>30
5		>30	20		>30
6		>30	21		7.50 ± 0.60
7		>30	22		>30
8		>30	23		>30
9		>30	24		>30

counting was used to determine the viability and cell number before the cell was subjected to colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) cell viability assay [11]. Briefly, MCF-7 cell (5 × 10^4 cell/mL) was trypsinized using TrypLE (Gibco, USA), washed, counted and seed overnight in 96 well plates (BD, USA) overnight. After that, media was removed and 200 μL of tested compounds were two fold serial diluted from row A until G with concentration ranging between 30.00 and 0.47 μg/mL in triplicates. Well H was left untouched and served as untreated control. After 72 h

of incubation time, 20 μL of MTT (5 mg/mL) was added to all well and incubated for three hours. Then, 170 μL of supernatant was discarded and the tetrazolium salt was solubilized using DMSO (Fisher, USA). The absorbance was read at 570 nm wavelength using ELISA Reader (Bio-tek Instrument, USA). The IC$_{50}$ values indicating the concentration of the tested compound that inhibited 50% of cell viability after 72 h of incubation were obtained from the dose-response curve. All the compounds were assayed for three independent biological replicates.
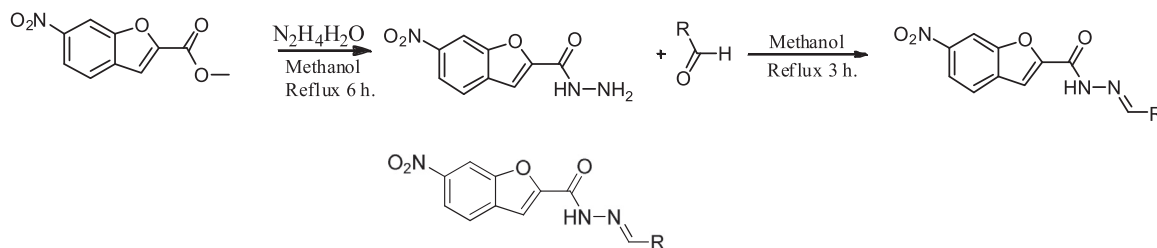
Scheme 1. 6-nitrobenzofuran-2-carbohydrazide Schiff bases.

Table 1
In vitro DPPH radical scavenging activity of 6-nitrobenzofuran-2-carbohydrazide derivatives **1–30**.

| Comp. no.	IC_{50} ($\mu M \pm SEM^a$)	Comp. no.	IC_{50} ($\mu M \pm SEM^a$)
1	N.A.	16	70.20 ± 3.12
2	N.A.	17	84.30 ± 3.20
3	N.A.	18	94.15 ± 3.25
4	37.30 ± 1.62	19	N.A.
5	90.46 ± 3.30	20	N.A.
6	88.41 ± 3.10	21	N.A.
7	N.A.	22	N.A.
8	55.20 ± 2.94	23	N.A.
9	34.11 ± 1.32	24	N.A.
10	17.50 ± 0.85	25	N.A.
11	24.20 ± 0.55	26	N.A.
12	21.10 ± 1.58	27	N.A.
13	14.60 ± 0.32	28	N.A.
14	29.20 ± 0.75	29	N.A.
15	9.26 ± 0.15	30	N.A.
n-propyl gallate[c]			30.30 ± 0.40 μM

SEM[a] is the standard error of the mean, NA[b] Not active, *n*-propyl gallate[c] standard for DDPH radical scavenging activity.
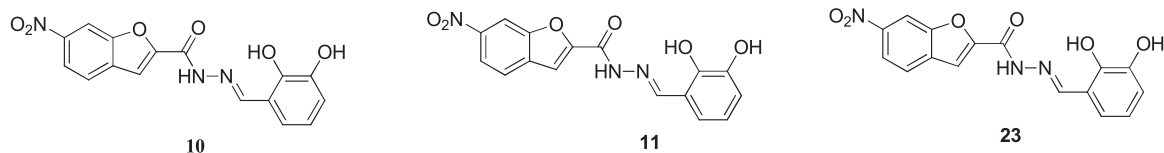
Fig. 2. Structures of compound **10**, **11** and **23**.

3.4. DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical scavenging activity

The free radical scavenging activity was measured by 1,1-diphenyl-2-picrylhydrazil (DPPH) using literature protocols. Reaction mixture contains 5 μL of test sample (1 mM in DMSO) and 95 μL of DPPH (Sigma, 300 μM) in ethanol. The reaction mixture was taken into a 96-well microtiter plate and incubated at 37 °C for 30 min. The absorbance was measured at 515 nm on microtiter plate reader (Molecular Devices, CA, USA). Percent radical scavenging activity was determined in comparison with a DMSO containing control. IC_{50} values represent the concentration of compounds to scavenge 50% of DPPH radicals. Propyl gallate was used as a positive control. Allthe chemicals used were of analytical grade (Sigma, USA)

3.5. N′-(2-chlorobenzylidene)-6-nitrobenzofuran-2-carbohydrazide (1)

Yield: 78%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 10.12 (*s*, 1H, NH), 8.94 (*s*, 1H, ArCH = NR), 8.86 (*d*, 2H, *J* = 2 Hz), 8.39 (*dd*, 1H, *J* = 2.5, 9 Hz), 8.06 (*d*, 1H, *J* = 7 Hz), 7.98 (*d*, 1H, *J* = 9 Hz), 7.95 (*s*, 1H), 7.57 (*d*, 1H, *J* = 7 Hz), 7.50–7.44 (*m*, 1H); ^{13}C NMR (75 MHz, DMSO-d6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 131.5 (C, C-1`), 134.2 (C, C-2`), 129.2(C, C-3`), 132.3 (C, C-4`), 126.8 (C, C-5`), 130.5 (C, C-6`), 154.7 (C, C-7`); Anal. Calcd for $C_{16}H_{10}ClN_3O_4$, C = 55.91, H = 2.93, Cl = 10.31, N = 12.23, O = 18.62, Found C =

55.92, H = 2.94, Cl = 10.30, N = 12.24, O = 18.61; EI MS *m/z* (% rel. abund.): 343.

3.6. N′-(3-chlorobenzylidene)-6-nitrobenzofuran-2-carbohydrazide (2)

Yield: 69%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 11.02 (*s*, 1H, NH), 8.85 (*s*, 1H), 8.50 (*s*, 1H, ArCH = NR), 8.38 (*dd*, 1H, *J* = 2.5, 10.5 Hz), 7.98 (*d*, 1H, *J* = 9.0 Hz), 7.94 (*s*, 1H), 7.81 (*s*, 1H), 7.73 (*d*, 1H, *J* = 5.0 Hz), 7.52 (*m*, 2H); ^{13}C NMR (75 MHz, DMSO-d6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 132.5 (C, C-1`), 129.3 (C, C-2`), 133.8 (C, C-3`), 131.3 (C, C-4`), 130.2 (C, C-5`), 127.0 (C, C-6`), 154.7 (C, C-7`) Anal. Calcd for $C_{16}H_{10}ClN_3O_4$, C = 55.91, H = 2.93, Cl = 10.31, N = 12.23, O = 18.62; Found C = 55.90, H = 2.94, Cl = 10.32, N = 12.24, O = 18.63; EI MS *m/z* (% rel. abund.): 343.

3.7. N′-(4-chlorobenzylidene)-6-nitrobenzofuran-2-carbohydrazide (3)

Yield: 80%; ^{1}HNMR (600 MHz, DMSO-d_6): δ 12.40 (*s*, 1H, NH), 8.85 (*d*, 1H, *J* = 2.0 Hz), 8.52 (*s*, 1H, ArCH = NR), 8.38 (*dd*, 1H, *J* = 2.0, 9.0), 7.98 (*d*, 1H, *J* = 9 Hz), 7.94 (*s*, 1H), 7.80 (*d*, 2H, *J* = 8.4 Hz), 7.56 (*d*, 2H, *J* = 8.4 Hz).); ^{13}C NMR (75 MHz, DMSO-d6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 129.2 (C, C-1`), 130.3 (C, C-2`), 129.1 (C, C-3`), 136.1 (C, C-4`), 129.0 (C, C-5`), 130.1

(C, C-6`), 154.5 (C, C-7`); Anal. Calcd for $C_{16}H_{10}ClN_3O_4$, C = 55.91, H = 2.93, Cl = 10.31, N = 12.23, O = 18.62; Found C = 55.92, H = 2.94, Cl = 10.32, N = 12.24, O = 18.61; EI MS *m/z* (% rel. abund.): 343.

3.8. N′-(2-fluorobenzylidene)-6-nitrobenzofuran-2-carbohydrazide (4)

Yield: 83%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.44 (*s*, 1H, NH), 8.86 (*d*, 1H, *J* = 1.5), 8.77 (*s*, 1H, ArCH = NR), 8.38 (*dd*, 1H, *J* = 2.5, 9.0), 7.80–7.96 (*m*, 2H), 7.94 (*s*, 1H), 7.54 (*d*, 1H, *J* = 7 Hz), 7.35-7.31 (*m*, 2H); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 118.3 (C, C-1`), 130.5 (C, C-2`), 124.1 (C, C-3`), 132.3 (C, C-4`), 115.4 (C, C-5`), 162.7 (C, C-6`), 154.5 (C, C-7`); Anal. Calcd for $C_{16}H_{10}FN_3O_4$, C = 58.72, H = 3.08, F = 5.81, N = 12.84, O = 19.56; Found C = 58.73, H = 3.07, F = 5.80, N = 12.85, O = 19.57; EI MS *m/z* (% rel. abund.): 327.

3.9. N′-(3-fluorobenzylidene)-6-nitrobenzofuran-2-carbohydrazide (5)

Yield: 79%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.44 (*s*, 1H, NH), 8.85 (*d*, 1H, *J* = 1.5 Hz), 8.53 (*s*, 1H, ArCH = NR), 8.38 (*dd*, 1H, *J* = 2.5, 9.0), 7.98 (*d*, 1H, *J* = 9 Hz), 7.94 (*s*, 1H), 7.61-7.53 (*m*, 3H), 7.33-7.30 (*t*, 1H, 8H); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 132.6 (C, C-1`), 116.3 (C, C-2`), 162.3 (C, C-3`), 117.7 (C, C-4`), 130.1 (C, C-5`), 124.5 (C, C-6`), 154.6 (C, C-7`); Anal. Calcd for $C_{16}H_{10}FN_3O_4$, C = 58.72, H = 3.08, F = 5.81, N = 12.84, O = 19.56; Found C = 58.71, H = 3.09, F = 5.80, N = 12.83, O = 19.57; EI MS *m/z* (% rel. abund.): 327.

3.10. N′-(4-fluorobenzylidene)-6-nitrobenzofuran-2-carbohydrazide (6)

Yield: 77%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.34 9 (*s*, 1H, NH), 8.86 (*d*, 1H, *J* = 1.5 Hz), 8.54 (*s*, 1H, ArCH = NR), 8.39 (*dd*, 1H, *J* = 2.0, 9.0), 7.98 (*d*, 1H, *J* = 9.0 Hz), 7.95 (*s*, 1H), 7.84-7.82 (*m*, 2H), 7.35-7.31 (*m*, 2H); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 126.7 (C, C-1`), 130.5 (C, C-2`), 115.5 (C, C-3`), 164.4 (C, C-4`), 115.5 (C, C-5`), 130.5 (C, C-6`), 154.5 (C, C-7`); Anal. Calcd for $C_{16}H_{10}FN_3O_4$, C = 58.72, H = 3.08, F = 5.81, N = 12.84, O = 19.56; Found C = 58.73, H = 3.09, F = 5.82, N = 12.83, O = 19.55; EI MS *m/z* (% rel. abund.): 327.

3.11. N′-(furan-2-ylmethylene)-6-nitrobenzofuran-2-carbohydrazide (7)

Yield: 82%; ^{1}HNMR (600 MHz, DMSO-d_6): δ 12.28 (*s*, 1H, NH), 8.85 (*d*, 1H, *J* = 1.8 Hz), 8.42 (*s*, 1H, ArCH = NR), 8.38 (*dd*, 1H, *J* = 2.0, 8.5 Hz), 7.98 (*d*, 1H, *J* = 9.0 Hz), 7.91 (*d*, 2H, *J* = 9.0 Hz), 7.01 (*d*, 1H, *J* = 3.0 Hz), 6.68-6.67 (*t*, 1H, *J* = 3.0 Hz); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167 (-C=O), 158.5 (C, C-8), 150.1(C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 143.1 (C, C-2`), 110.2 (C, C-3`), 110.4 (C, C-4`), 143.2 (C, C-5`), 154.5 (C, C-6`); Anal. Calcd for $C_{14}H_9N_3O_5$, C = 56.19, H = 3.03, N = 14.04, O = 26.73; Found C = 56.20, H = 3.02, N = 14.03, O = 26.72; EI MS *m/z* (% rel. abund.): 299.

3.12. N′-(3-hydroxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (8)

Yield: 74%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.29 (*s*, 1H, NH), 9.67 (*s*, 1H, OH), 8.85 (*d*, 1H, *J* = 2.0 Hz), 8.44 (*s*, 1H, ArCH = NR), 8.38 (*dd*, 1H, *J* = 2.0, 9.0 Hz), 7.98 (*d*, 1H, *J* = 9.0 Hz), 7.93 (*s*, 1H), 7.30 (*t*, 1H, *J* = 8.0 Hz), 7.23 (*s*, 1H), 7.14 (*d*, 1H, *J* = 7.5), 6.87 (*d*, 1H, *J* = 8 Hz); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 132.7 (C, C-1`), 121.3 (C, C-2`), 130.2 (C, C-3`), 118.2 (C, C-4`), 157.4 (C, C-5`), 116.1 (C, C-6`), 154.6 (C, C-7`); Anal. Calcd for $C_{16}H_{11}N_3O_5$, C = 59.08, H = 3.41, N = 12.92, O = 24.59; Found C = 59.09, H = 3.40, N = 12.93, O = 24.60; EI MS *m/z* (% rel. abund.): 325.

3.13. N′-(4-hydroxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (9)

Yield: 76%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 11.60 (*s*, 1H, NH), 9.90 (*s*, 1H, OH), 8.84 (*d*, 1H, *J* = 2.0 Hz), 8.42 (*s*, 1H, ArCH = NR), 8.37 (*dd*, 1H, *J* = 2.0, 9.0 Hz), 7.97 (*d*, 1H, *J* = 9.0 Hz), 7.90 (*s*, 1H), 7.60 (*d*, 2H, *J* = 8.5 Hz), 6.87 (*d*, 2H, *J* = 8.5 Hz); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167 (-C=O), 158.5 (C, C-8), 150.1(C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 123.7 (C, C-1`), 130.5 (C, C-2`), 115.7 (C, C-3`), 159.6 (C, C-4`), 115.7 (C, C-5`), 130.6 (C, C-6`), 154.5 (C, C-7`); Anal. Calcd for $C_{16}H_{11}N_3O_5$, C = 59.08, H = 3.41, N = 12.92, O = 24.59; Found C = 59.07, H = 3.42, N = 12.93, O = 24.59; EI MS *m/z* (% rel. abund.): 325.

3.14. N′-(2,3-dihydroxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (10)

Yield: 78%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 11.59 (*s*, 1H, NH), 10.23 (*s*, 1H, OH), 9.67 (*s*, 1H, OH), 8.86 (*d*, 1H, *J* = 2.0 Hz), 8.70 (*s*, 1H, ArCH = NR), 8.36 (*dd*, 1H, *J* = 2.0, 9.0 Hz), 7.99 (*d*, 1H, *J* = 9.5 Hz), 7.94 (*s*, 1H), 7.03 (*d*, 1H, *J* = 7.5 Hz), 6.88 (*dd*, 1H, *J* = 1.5, 9 Hz), 6.76 (*t*, 1H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 119.7 (C, C-1`), 123.1 (C, C-2`), 122.5 (C, C-3`), 119.3 (C, C-4`), 145.1 (C, C-5`), 144.5 (C, C-6`), 154.5 (C, C-7`); Anal. Calcd for $C_{16}H_{11}N_3O_6$, C = 56.31, H = 3.25, N = 12.31, O = 28.13; Found C = 56.32, H = 3.24, N = 12.32, O = 28.14; EI MS *m/z* (% rel. abund.): 341.

3.15. N′-(2,4-dihydroxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (11)

Yield: 79%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 11.20 (*s*, 1H, NH), 10.60 (*s*, 1H, OH), 9.92 (*s*, 1H, OH), 8.99 (*s*, 1H), 8.85 (*d*, 1H, *J* = 2.0), 8.67 (*s*, 1H, ArCH = NR), 8.38 (*dd*, 1H, *J* = 2.0, 9.0 Hz), 7.98 (*d*, 1H, *J* = 9.0 Hz), 7.92 (*s*, 1H), 7.04 (*d*, 1H, *J* = 2.0 Hz), 6.76 (*m*, 2H); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 111.1 (C, C-1`), 131.7 (C, C-2`), 108.3 (C, C-3`), 161.1 (C, C-4`), 103.1 (C, C-5`), 159.2 (C, C-6`), 154.6 (C, C-7`); Anal. Calcd for $C_{16}H_{11}N_3O_6$, C = 56.31, H = 3.25, N = 12.31, O = 28.13; Found C = 56.30, H = 3.26, N = 12.32, O = 28.12; EI MS *m/z* (% rel. abund.): 341.

3.16. N′-(2,5-dihydroxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (12)

Yield: 82%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.38 (*s*, 1H, NH), 11.27 (*s*, 1H, OH), 9.99 (*s*, 1H, OH), 8.85 (*d*, 1H, *J* = 2.0 Hz), 8.6 (*s*, 1H, ArCH = NR), 8.35 (*dd*, 1H, *J* = 2.0, 9.0 Hz), 7.97 (*d*, 1H, *J* = 9.0 Hz), 7.90 (*s*, 1H), 7.38 (*d*, 1H, *J* = 8.5 Hz), 6.36 (*dd*, 1H, *J* = 2.0, 9.0 Hz), 6.34 (*d*, 1H, *J* = 2.0); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 119.7 (C, C-1`), 117.5 (C, C-2`), 150.1 (C, C-3`), 119.5 (C, C-4`), 117.2 (C, C-5`), 150.4 (C, C-6`), 154.7 (C, C-7`); Anal. Calcd for $C_{16}H_{11}N_3O_6$, C = 56.31, H = 3.25, N = 12.31, O = 28.13; Found C = 56.32, H = 3.26, N = 12.30, O = 28.12; EI MS *m/z* (% rel. abund.): 341.

3.17. N′-(3,4-dihydroxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (13)

Yield: 81%; ^{1}HNMR (600 MHz, DMSO-d_6): δ 12.11 (s, 1H, NH), 11.02 (s, 1H, OH), 9.74 (s, 1H, OH), 8.84 (d, 1H, J = 2.4 Hz), 8.36 (dd, 1H, J = 2.0, 9.0 Hz), 8.35 (s, 1H), 7.97 (d, 1H, J = 9.0 Hz), 7.90 (s, 1H), 7.27 (d, 1H, J = 1.8 Hz), 6.97 (dd, 1H, J = 1.8, 9.0 Hz), 6.82 (d, 1H, J = 8.4); ^{13}C NMR (75 MHz, DMSO-$d6$): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 125.2 (C, C-1`), 123.1 (C, C-2`), 117.1 (C, C-3`), 146.6 (C, C-4`), 144.5 (C, C-5`), 117.3 (C, C-6`), 154.6 (C, C-7`); Anal. Calcd for $C_{16}H_{11}N_3O_6$, C = 56.31, H = 3.25, N = 12.31, O = 28.13; Found C = 56.30, H = 3.26, N = 12.30, O = 28.14; EI MS *m/z* (% rel. abund.): 341.

3.18. N′-(3,5-dihydroxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (14)

Yield: 84%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.44 (s, 1H, NH), 10.27 (s, 2H, OH), 8.99 (s, 1H), 8.85 (d, 1H, J = 2.0 Hz), 8.67 (s, 1H, ArCH = NR), 8.37 (dd, 1H, J = 2.0, 9.0 Hz), 7.98 (d, 1H, J = 9.0 Hz), 7.92 (s, 1H), 7.04 (d, 1H, J = 2.0 Hz); 6.89 (m, 1H); ^{13}C NMR (75 MHz, DMSO-$d6$): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 134.1 (C, C-1`), 108.7 (C, C-2`), 158.7 (C, C-3`), 105.1 (C, C-4`), 158.7 (C, C-5`), 108.6 (C, C-6`), 154.5 (C, C-7`); Anal. Calcd for $C_{16}H_{11}N_3O_6$, C = 56.31, H = 3.25, N = 12.31, O = 28.13; Found C = 56.32, H = 3.26, N = 12.32, O = 28.14; EI MS *m/z* (% rel. abund.): 341.

3.19. 6-nitro-N′-(2,4,6-trihydroxybenzylidene)benzofuran-2-carbohydrazide (15)

Yield: 85%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.18 (s, 1H, NH), 10.20 (s, 2H, OH), 9.60 (s, 1H, OH), 8.85 (d, 1H, J = 2.0 Hz), 8.35 (dd, 1H, J = 2.0, 9.0 Hz), 8.32 (s, 1H), 7.97 (d, 1H, J = 9.0 Hz), 7.91 (s, 1H), 6.63 (d, 2H, J = 2.0 Hz); ^{13}C NMR (75 MHz, DMSO-$d6$): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 98.1 (C, C-1`), 160.5 (C, C-2`), 95.4 (C, C-3`), 162.3 (C, C-4`), 95.5 (C, C-5`), 160.6 (C, C-6`), 154.6 (C, C-7`); Anal. Calcd for $C_{16}H_{11}N_3O_7$, C = 56.79, H = 3.10, N = 11.76, O = 31.35; Found C = 56.80, H = 3.11, N = 11.75, O = 31.34; EI MS *m/z* (% rel. abund.): 357.

3.20. N′-(2-hydroxy-4-methoxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (16)

Yield: 81%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.46 (s, 1H, NH), 11.50 (s, 1H, OH), 8.85 (d, 1H, J = 2.0 Hz), 8.64 (s, 1H, ArCH = NR), 8.36 (dd, 1H, J = 2.0, 9.0 Hz), 7.97 (d, 1H, J = 9.0 Hz), 7.91 (s, 1H), 7.49 (d, 1H, J = 8.5 Hz), 6.52 (dd, 1H, J = 2.5, 9.0 Hz), 6.50 (d, 1H, J = 2.0 Hz), 3.79 (s, 3H, OCH$_3$); ^{13}C NMR (75 MHz, DMSO-$d6$): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 110.6 (C, C-1`), 131.3 (C, C-2`), 106.7 (C, C-3`), 165.6 (C, C-4`), 101.3 (C, C-5`), 158.7 (C, C-6`), 154.6 (C, C-7`) 56.1 (C, OCH$_3$); Anal. Calcd for $C_{17}H_{13}N_3O_6$, C = 57.47, H = 3.69, N = 11.83, O = 27.02; Found C = 57.48, H = 3.70, N = 11.82, O = 27.01; EI MS *m/z* (% rel. abund.): 355.

3.21. N′-(2-hydroxy-5-methoxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (17)

Yield: 76%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.52 (s, 1H, NH), 10.56 (s, 1H, OH), 8.86 (d, 1H, J = 2.0 Hz), 8.72 (s, 1H, ArCH = NR), 8.36 (dd, 1H, J = 2.0, 8.5 Hz), 7.98 (d, 1H, J = 9.0 Hz), 7.94 (s, 1H), 7.17 (d, 1H, J = 3.0 Hz), 6.93 (dd, 1H, J = 3.0, 9.0 Hz), 6.89 (d, 1H, J = 9.0 Hz), 3.75 (s, 3H, OCH$_3$); ^{13}C NMR (75 MHz, DMSO-$d6$): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 119.3 (C, C-1`), 116.1 (C, C-2`), 154.6 (C, C-3`), 117.6 (C, C-4`), 116.7 (C, C-5`), 150.2 (C, C-6`), 154.5 (C, C-7`) 56.2 (C, OCH$_3$); Anal. Calcd for $C_{17}H_{13}N_3O_6$, C = 57.47, H = 3.69, N = 11.83, O = 27.02; Found C = 57.46, H = 3.70, N = 11.84, O = 27.03; EI MS *m/z* (% rel. abund.): 355.

3.22. N′-(3-hydroxy-4-methoxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (18)

Yield: 81%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.15 (s, 1H, NH), 9.40 (s, 1H, OH), 8.84 (d, 1H, J = 2.0 Hz), 8.70 (s, 1H, ArCH = NR), 8.36 (dd, 2H, J = 2.0, 9.0), 7.97 (d, 1H, J = 9.0 Hz), 7.90 (s, 1H), 7.30 (d, 1H, J = 2.0 Hz), 7.09 (d, 1H, J = 2.0 Hz), 7.01 (d, 1H, J = 8.5 Hz), 3.83 (s, 3H, OCH$_3$); ^{13}C NMR (75 MHz, DMSO-$d6$): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 124.8 (C, C-1`), 122.5 (C, C-2`), 115.5 (C, C-3`), 143.1 (C, C-4`), 151.4 (C, C-5`), 117.1 (C, C-6`), 154.5 (C, C-7`) 56.4 (C, OCH$_3$); Anal. Calcd for $C_{17}H_{13}N_3O_6$, C = 57.47, H = 3.69, N = 11.83, O = 27.02; Found C = 57.46, H = 3.68, N = 11.84, O = 27.01; EI MS *m/z* (% rel. abund.): 355.

3.23. N′-(4-methoxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (19)

Yield: 77%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.19 (s, 1H, NH), 8.84 (d, 1H, J = 2.0 Hz), 8.47 (s, 1H, ArCH = NR), 8.35 (dd, 1H, J = 2.0, 8.5), 7.98 (d, 1H, J = 9.0 Hz), 7.91 (s, 1H), 7.72 (d, 2H, J = 9.0 Hz), 7.06 (d, 2H, J = 8.5 Hz), 3.83 (s, 3H, OCH$_3$); ^{13}C NMR (75 MHz, DMSO-$d6$): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 123.5 (C, C-1`), 130.1 (C, C-2`), 114.2 (C, C-3`), 164.2 (C, C-4`), 114.3 (C, C-5`), 130.1 (C, C-6`), 154.6 (C, C-7`) 56.1 (C, OCH$_3$); Anal. Calcd for $C_{17}H_{13}N_3O_5$, C = 60.18, H = 3.86, N = 12.38, O = 23.58; Found C = 60.19, H = 3.87, N = 12.37, O = 23.59; EI MS *m/z* (% rel. abund.): 339.

3.24. N′-(2-methylbenzylidene)-6-nitrobenzofuran-2-carbohydrazide (20)

Yield: 84%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.29 (s, 1H, NH), 8.85 (d, 1H, J = 2.0 Hz), 8.84 (s, 1H, ArCH = NR), 8.36 (dd, 1H, J = 2.0, 8.5), 7.98 (d, 1H, J = 9.5 Hz), 7.93 (s, 1H), 7.88 (d, 1H, J = 7.5 Hz), 7.93 (t, 1H, J = 6.5 Hz), 7.28 (t, 2H, J = 9.0 Hz), 2.48 (s, 3H, CH$_3$); ^{13}C NMR (75 MHz, DMSO-$d6$): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 131.8 (C, C-1`), 128.8 (C, C-2`), 125.6 (C, C-3`), 130.6 (C, C-4`), 129.3 (C, C-5`), 138.3 (C, C-6`), 154.5 (C, C-7`) 14.4 (C, CH$_3$); Anal. Calcd for $C_{17}H_{13}N_3O_4$, C = 63.16, H = 4.05, N = 13.00, O = 19.79; Found C = 63.17, H = 4.04, N = 13.01, O = 19.80; EI MS *m/z* (% rel. abund.): 323.

3.25. N′-(4-methylbenzylidene)-6-nitrobenzofuran-2-carbohydrazide (21)

Yield: 83%; ^{1}HNMR (600 MHz, DMSO-d_6): δ 12.27 (s, 1H, NH), 8.85 (d, 1H, J = 1.8 Hz), 8.50 (s, 1H, ArCH = NR), 8.36 (dd, 1H, J = 2.0, 8.4 Hz), 7.98 (d, 1H, J = 9.0 Hz), 7.92 (s, 1H), 7.67 (d, 2H, J = 7.8 Hz), 7.31 (d, 2H, J = 7.8 Hz), 2.37 (s, 3H, CH$_3$); ^{13}C NMR (75 MHz, DMSO-$d6$): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 128.1 (C, C-1`), 128.8 (C, C-2`), 129.2 (C, C-3`), 140.2 (C, C-4`), 129.3 (C, C-5`), 128.8 (C, C-6`), 154.6 (C, C-7`) 21.0 (C, CH$_3$); Anal. Calcd for $C_{17}H_{13}N_3O_4$, C = 63.16, H = 4.05, N = 13.00, O = 19.79; Found C = 63.17, H = 4.06, N = 12.99, O = 19.78; EI MS *m/z* (% rel. abund.): 323.

3.26. 6-nitro-N′-(pyridin-2-ylmethylene)benzofuran-2-carbohydrazide (22)

Yield: 74%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.10 (s, 1H, NH), 8.84 (s, 1H), 8.65 (d, 1H, J = 4.0 Hz), 8.54 (s, 1H), 8.38 (d, 1H, J = 9.0 Hz), 8.02-7.90 (m, 4H), 7.43 (t, 1H, J = 6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 152.5 (C, C-1`), 124.1 (C, C-2`), 135.7 (C, C-3`), 125.8 (C, C-4`), 149.8 (C, C-5`), 154.5 (C, C-6`); Anal. Calcd for $C_{15}H_{10}N_4O_4$, C = 58.07, H = 3.25, N = 18.06, O = 20.63; Found C = 58.08, H = 3.24, N = 18.07, O = 20.62; EI MS m/z (% rel. abund.): 310.

3.27. 6-nitro-N′-(pyridin-3-ylmethylene)benzofuran-2-carbohydrazide (23)

Yield: 76%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.50 (s, 1H, NH), 8.89-8.86 (m, 2H), 8.65 (d, 1H, J = 4.5 Hz), 8.58 (s, 1H, ArCH = NR), 8.36 (dd, 1H, J = 2.0, 8.5), 8.19 (d, 1H, J = 7.5 Hz), 7.99 (d, 1H, J = 9.0 Hz), 7.95 (s, 1 H), 7.53 (t, 1H, J = 6.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 126.2 (C, C-1`), 136.1 (C, C-2`), 123.6 (C, C-3`), 152.1 (C, C-4`), 150.5 (C, C-6`), 154.6 (C, C-7`); Anal. Calcd for $C_{15}H_{10}N_4O_4$, C = 58.07, H = 3.25, N = 18.06, O = 20.63; Found C = 58.06, H = 3.26, N = 18.07, O = 20.64; EI MS m/z (% rel. abund.): 310.

3.28. 6-nitro-N′-(pyridin-4-ylmethylene)benzofuran-2-carbohydrazide (24)

Yield: 82%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.58 (s, 1H, NH), 8.87 (s, 1H), 8.70 (d, 2H, J = 8.0 Hz), 8.52 (s, 1H, ArCH = NR), 8.37 (dd, 1H, J = 2.0, 8.5 Hz), 7.99 (d, 2 H, J = 8.0 Hz), 7.71 (d, 2H, J = 4.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 138.2 (C, C-1`), 124.1 (C, C-2`), 149.8 (C, C-3`), 149.8 (C, C-5`), 124.1 (C, C-6`), 154.6 (C, C-7`); Anal. Calcd for $C_{15}H_{10}N_4O_4$, C = 58.07, H = 3.25, N = 18.06, O = 20.63; Found C = 58.06, H = 3.24, N = 18.07, O = 20.62; EI MS m/z (% rel. abund.): 310.

3.29. 6-nitro-N′-(thiophen-2-ylmethylene)benzofuran-2-carbohydrazide (25)

Yield: 85%; ^{1}HNMR (600 MHz, DMSO-d_6): δ 12.30 (s, 1H, NH), 8.85 (d, 1H, J = 1.8 Hz), 8.72 (s, 1H, ArCH = NR), 8.36 (d, 1H, J = 2.0 Hz), 7.98 (d, 1H, J = 9.0 Hz), 7.91 (s, 1H), 7.73 (d, 1H, J = 4.8 Hz), 7.53 (d, 1H, J = 3.0 Hz), 7.17 (t, 1H, J = 4.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 126.1 (C, C-1`), 127.2 (C, C-2`), 127.3 (C, C-3`), 126.0 (C, C-4`), 154.6 (C, C-6`); Anal. Calcd for $C_{14}H_9N_3O_4S$, C = 53.33, H = 2.88, N = 13.33, O = 20.30, S = 10.17; Found C = 53.32, H = 2.89, N = 13.34, O = 20.31, S = 10.18; EI MS m/z (% rel. abund.): 315.

3.30. N′-(3-methylbenzylidene)-6-nitrobenzofuran-2-carbohydrazide (26)

Yield: 83%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.29 (s, 1H, NH), 8.85 (d, 1H, J = 2.0 Hz), 8.83 (s, 1H, ArCH = NR), 8.36 (dd, 1H, J = 2.0, 8.5 Hz), 7.98 (d, 1H, J = 9.0 Hz), 7.92 (s, 1H), 7.88 (d, 1H, J = 7.5 Hz), 7.34 (t, 1H, J = 6.5 Hz), 7.28 (t, 2H, J = 7.5 Hz), 2.48 (s, 3H, CH$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 131.2 (C, C-1`), 126.1 (C, C-2`), 128.4 (C, C-3`), 131.6 (C, C-4`), 137.7 (C, C-5`), 129.8 (C, C-6`), 154.6 (C, C-7`) 20.9 (C, CH$_3$);Anal. Calcd for $C_{17}H_{13}N_3O_4$, C = 63.16, H = 4.05, N = 13.00, O = 19.79; Found C = 63.17, H = 4.04, N = 12.99, O = 19.80; EI MS m/z (% rel. abund.): 323.

3.31. N′-(2-hydroxybenzylidene)-6-nitrobenzofuran-2-carbohydrazide (27)

Yield: 86%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.10 (s, 1H, NH), 11.09 (s, 1H, OH), 8.85 (d, 1H, J = 2.0 Hz), 8.83 (s, 1H, ArCH = NR), 8.33 (dd, 1H, J = 2.0, 8.5 Hz), 7.96 (d, 1H, J = 9.0 Hz), 7.84 (s, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.27 (t, 1H, J = 7.5 Hz), 6.93 (d, 1H, J = 8.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 118.2 (C, C-1`), 130.5 (C, C-2`), 121.2 (C, C-3`), 132.2 (C, C-4`), 115.7 (C, C-5`), 157.7 (C, C-6`), 154.5 (C, C-7`); Anal. Calcd for $C_{16}H_{11}N_3O_5$, C = 59.08, H = 3.41, N = 12.92, O = 24.59; Found C = 59.09, H = 3.40, N = 12.93, O = 24.60; EI MS m/z (% rel. abund.): 325.

3.32. 6-nitro-N′-(2-nitrobenzylidene)benzofuran-2-carbohydrazide (28)

Yield: 79%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.64 (s, 1H, NH), 8.93 (s, 1H), 8.86 (s, 1H, ArCH = NR), 8.37 (d, 1H, J = 2.0 Hz), 8.17 (d, 1H, J = 8.0 Hz), 8.12 (d, 1H, J = 8.0 Hz), 7.98 (s, 1H), 7.97 (d, 1H, J = 5.0 Hz), 7.83 (t, 1H, J = 7.5 Hz), 7.70 (t, 1H, J = 7.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 126.2 (C, C-1`), 129.8 (C, C-2`), 134.6 (C, C-3`), 131.6 (C, C-4`), 123.7 (C, C-5`), 148.7 (C, C-6`), 154.6 (C, C-7`); Anal. Calcd for $C_{16}H_{10}N_4O_6$, C = 54.24, H = 2.85, N = 15.81, O = 27.10; Found C = 54.25, H = 2.86, N = 15.80, O = 27.11; EI MS m/z (% rel. abund.): 354.

3.33. 6-nitro-N′-(3-nitrobenzylidene)benzofuran-2-carbohydrazide (29)

Yield: 80%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.14 (s, 1H, NH), 8.82 (s, 1H), 8.60 (s, 1H, ArCH = NR), 8.60 (s, 1H), 8.57 (s, 1H), 8.37 (d, 1H, J = 9.0 Hz), 8.28 (d, 1H, J = 8.0 Hz), 8.19 (d, 1H, J = 7.5 Hz), 7.97 (d, 1H, J = 9.0 Hz), 7.75 (t, 1H, J = 8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 132.2 (C, C-1`), 135.2 (C, C-2`), 129.2 (C, C-3`), 125.9 (C, C-4`), 148.7 (C, C-5`), 124.6 (C, C-6`), 154.5 (C, C-7`); Anal. Calcd for $C_{16}H_{10}N_4O_6$, C = 54.24, H = 2.85, N = 15.81, O = 27.10; Found C = 54.25, H = 2.84, N = 15.82, O = 27.09; EI MS m/z (% rel. abund.): 354.

3.34. 6-nitro-N′-(4-nitrobenzylidene)benzofuran-2-carbohydrazide (30)

Yield: 79%; ^{1}HNMR (500 MHz, DMSO-d_6): δ 12.20 (s, 1H, NH), 8.85 (s, 1H), 8.60 (s, 1H, ArCH = NR), 8.36 (d, 1H, J = 2.0, 8.5 Hz), 8.33 (d, 2H, J = 8.5 Hz), 8.03 (d, 2H, J = 8.5 Hz), 7.98 (d, 1H, J = 9 Hz), 7.94 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167 (-C=O), 158.5 (C, C-8), 150.1 (C, C-2), 144.4 (C, C-6), 135.6 (C, C-9), 122.7 (C, C-4), 118.5 (C, C-5), 110.5 (C, C-3), 106.8 (C, C-7), 138.1 (C, C-1`), 129.5 (C, C-2`), 120.8 (C, C-3`), 168.8 (C, C-4`), 120.8 (C, C-5`), 129.6 (C, C-6`), 154.6 (C, C-7`); Anal. Calcd for $C_{16}H_{10}N_4O_6$, C = 54.24, H = 2.85, N = 15.81, O = 27.10; Found C = 54.25, H = 2.84, N = 15.80, O = 27.11; EI MS m/z (% rel. abund.): 354.

Acknowledgments

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