Synthesis, Reactions and Antioxidant Activity of 5-(3', 4'-dihydroxy-tetrahydrofuran-2'-yl)-2-methyl-3-carbohydrazide

El Sadek, Mohamed Mohamed*+•; Magd, Samir Ahmed; Hassan, Seham Yassen; Mostafa, Mohamed A.

Chemistry Department, Faculty of Science, Alexandria University, Alexandria 21231, EGYPT

Yacouf, Galila A.

Biochemistry Department, Faculty of Science, Alexandria University, Alexandria 21231, EGYPT

ABSTRACT: *In this manuscript, we describe the synthesis of the carbohydrazide 2. Acid-catalyzed condensation with several carbonyl compounds to afford the corresponding carbohydrazide derivatives 3-12. Their acetylation afforded the corresponding acetyl derivatives 13-22. Oxidative cyclization of O-acetyl derivatives 19-22 afforded the corresponding 1,3,4-oxadiazole derivatives 23-26. On the other hand, condensation of the dicarbonyl compound 27 with several aroylhydrazines to give the corresponding bisaroylhydrazones 28-32 cyclization of 28-31 afforded 1,3,4-oxadiazoles 33-36. The structures of the prepared compounds were confirmed by ^{1}HNMR and Mass Spectra. The mechanism of the formation of the products was discussed. Furthermore, the antioxidant activities of some of the prepared compounds were examined.*

KEYWORDS: *Carbohydrazides; Bisaroylhydrazones; 1, 3, 4-oxadiazoles.*

INTRODUCTION

1,3,4-Oxadiazoles are important pharmacophore[1] which plays a major role in the pharmaceutical chemistry and broad range of important biological activities such as antioxidants[2,3-5], anti-bacterial[6], anti-viral[7], anti-fungal[8], anti-cancer[9], anti-tumor[10], anti-inflammatory[11] and anti-diabetic properties[12].

RESULTS AND DISCUSSION

Chemistry

Treatment of compound **1** with hydrazine hydrate [13], afforded the hydrazide **2.** This latter was subjected to a condensation reaction with a series of various substituted R-CO-R' alkyl, aryl-carbonyl compounds to give the corresponding carbohydrazides derivatives **3-12**. ^{1}H-NMR spectra of compounds **3-8 (**DMSO-d_6**),** showed (NH) resonance as the most downfield proton signal at rang δ (11.26-9.06) ppm as a singlet, followed by the aromatic protons as a multiple at δ (7.80-6.49), for (CH=N) proton displayed at δ (8.52-8.12) ppm as multiplet for compounds **9-12**. Acetylation of **3-12** yielded the corresponding acetyl compounds **13-22**.

Their infrared spectra showed the OAc group at γ (1754-1733) instead of sugar hydroxyl groups. Also, ^{1}H-NMR spectra showed the disappearance

** To whom correspondence should be addressed.*
+ E-mail: samirahmed10387@yahoo.com
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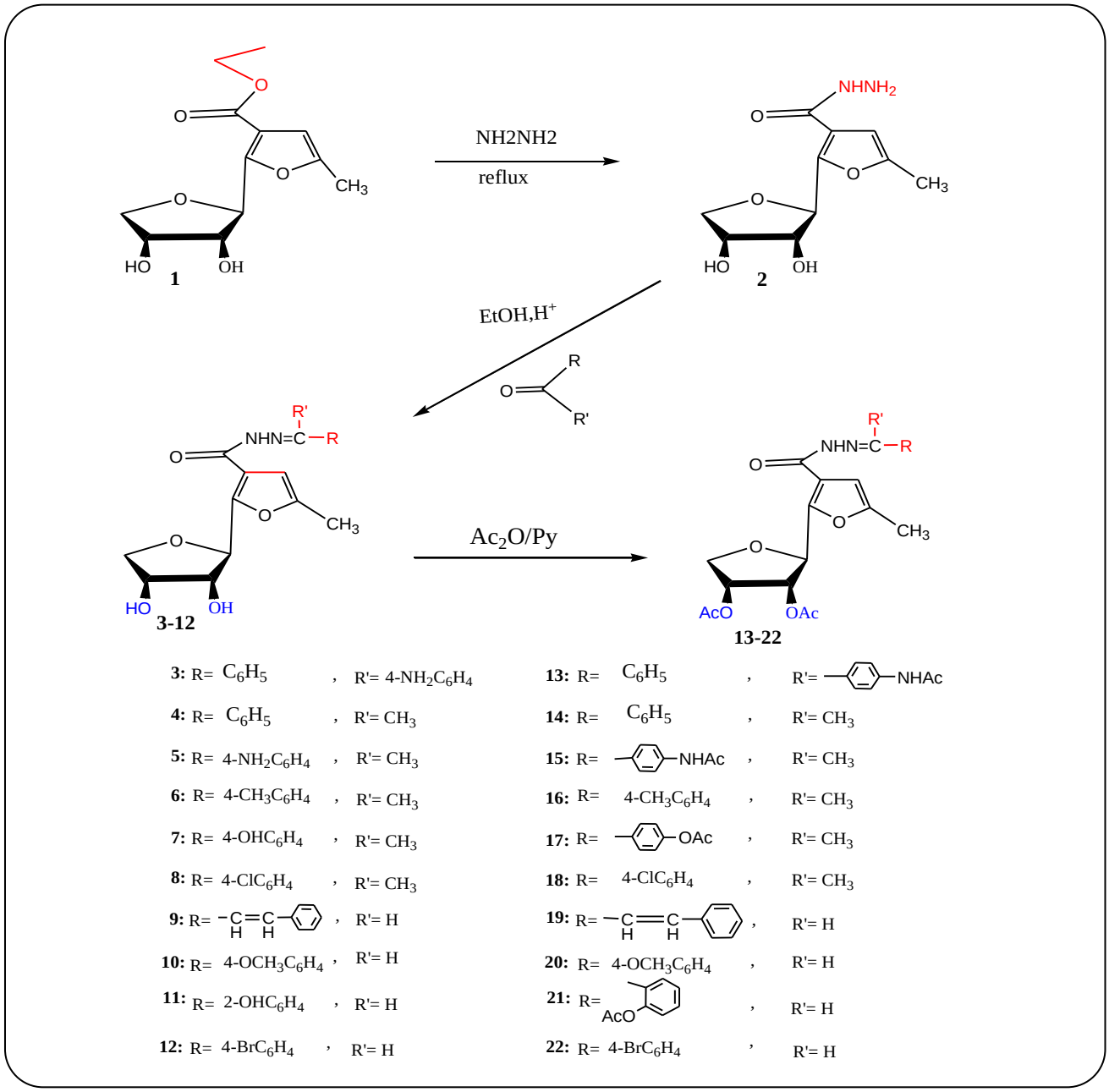
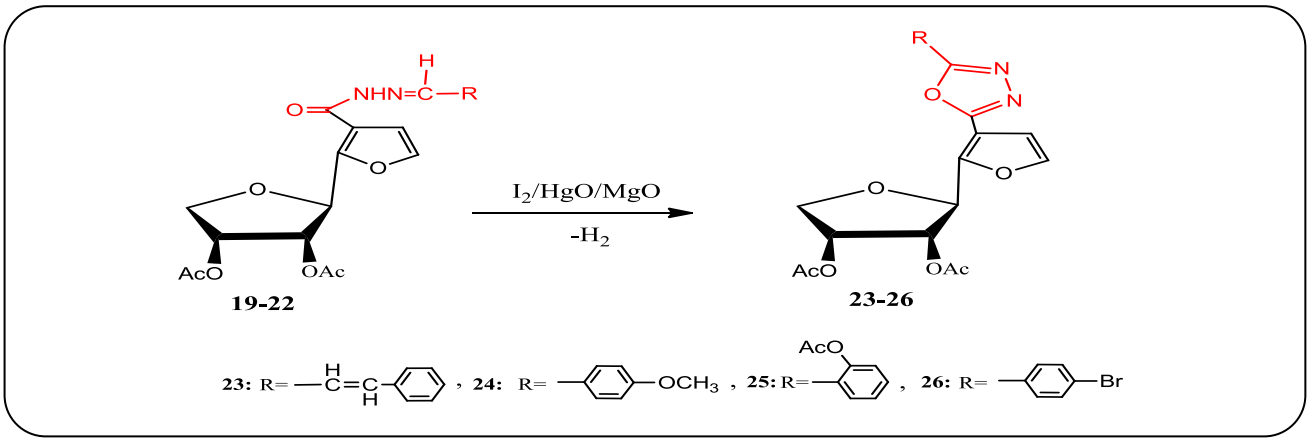


Scheme 1: Synthesis and acetylation of carbohydrazides.

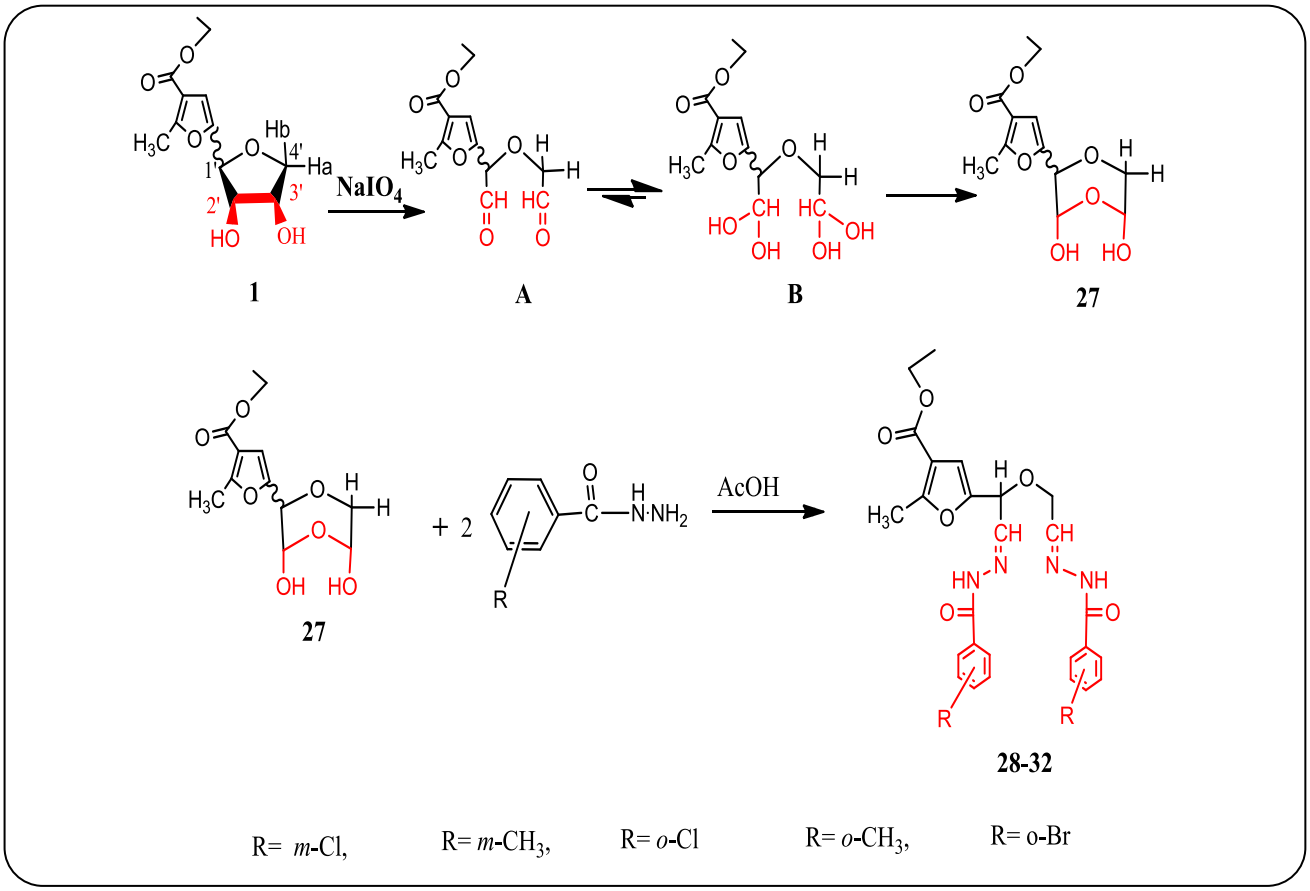
of the OH protons in the sugar region and the appearance of, the *O*-acetyl protons at (2.12-2.02). The mass spectra of compounds **13** and **14** showed the base peaks at *m/z* 29 and 318 respectively (see Experimental and Scheme 1).

Oxidative cyclization of **19-22** with iodine, yellow mercuric oxide, magnesium oxide in dry ether afforded the corresponding 1,3,4-oxadiazole derivatives **23-26** (yields 20% –30%).^{1}H-NMR spectra showed the disappearance of both (NH) and (CH=N) protons signals. The EI-MS of compounds 20 and 22 gave the base peaks at *m/z* 122 and 91/93 respectively, (see Experimental and Scheme 2).

Periodate oxidation [14] of the prepared anhydro-derivative **1** gave corresponding dialdehyde **A** as monohydrate form **B**, to which is assigned the hemialdal structure [14-16] **27**, which on condensation with a number of aroylhydrazines afforded the corresponding bisaroylhydrazones **28-32.** ^{1}H-NMR spectra of

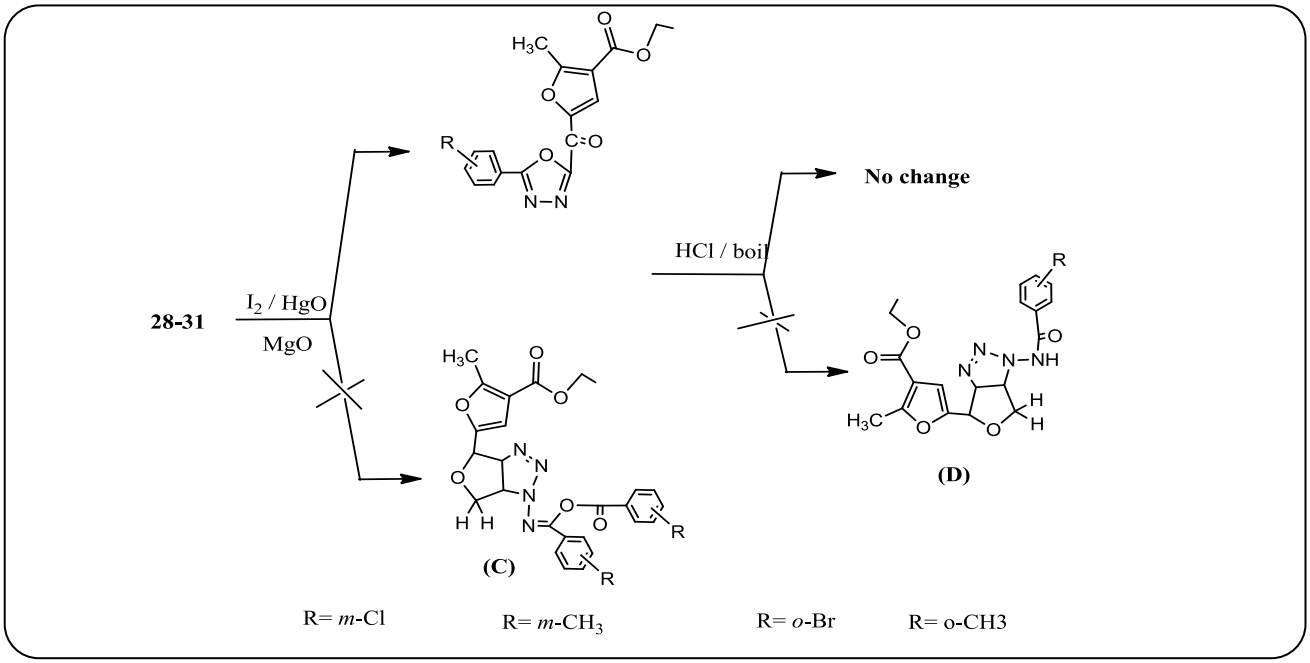


Scheme 2: Synthesis of 1,3,4-oxadiazole derivatives.



Scheme 3: Synthesis of bisaroylhydrazone derivatives 29-33.

compounds **28-32** (DMSO-d_6) showed the two (NH) protons at δ (11.55-11.82) ppm, due to the difference in the neighboring groups as two singlets, followed by the aromatic protons as multiplets at δ (7.17-7.87) ppm, two (CH=N) at δ (7.47-7.97) , and the proton at position-4 in the furan ring as singlet at δ (6.73-6.79) ppm, the methine proton was shown as doublet at δ (4.89-5.17) ppm, followed by multiple at δ (4.12-4.19) ppm for the protons of the two methylene groups (see Experimental and Scheme 3). Oxidative cyclization of bisaroylhydrazones **28-31** afforded the corresponding 1, 3, 4-oxadiazoles, instead of 1,2,3-triazoles. Vibrational spectroscopy of 1,3,4-oxadiazole derivatives (**33-36**), showed the disappearance of both(NH) and (CO-amide) groups.



Scheme 4: Synthesis of 1,3,4-oxadiazole derivatives 33-36.

These compounds (**33-36**) showed absorption bands at (1708-1715), (1592-1660) and (1467-1540) cm^{-1} corresponding to (CO-ester), (C=O) and (C=N) groups respectively. ^{1}H-NMR spectra of compounds **33-36 (**DMSO-d_6), showed the disappearance of signals corresponding to two (NH) and two (CH=N), methine and methylene protons, these oxidative cyclization products displayed the proton at postion-4 in the furan ring signal δ (7.69-8.17) ppm.

In addition, the structure of the oxidation products **33-36** was further supported through their boiling with hydrochloric acid, which didn't afford the corresponding amine derivatives D as expected from 1,2,3-triazole derivatives[17-20], (see Experimental part and Scheme 3 and 4). Moreover, the proposed mechanism[13] for formation of **33-36** may proceed via elimination of one aroylhydrazone part, (see Experimental and Scheme 5).

BIOLOGICLA ACTIVITY

Antioxdant Activity Screening (Using the DPPH Assay)

The DPPH (diphenyl picryl hydrazyl) assay method was based on the reduction of DPPH. The free radical DPPH with an odd electron gives a maximum absorption at 517 nm. When antioxidants are react with DPPH, giving DPPD-H and as consequence the absorbance decreased due to decolorization with respect to the number of electrons captured. More the decolorization more is the reducing ability. The results expressed in terms of EC_{50} (mg/mL). EC_{50} values for each examined compound as well as standard preparations calculated according to the Shahwar et al's method[89]. As showed in (Tables) and (Fig. 48-52). A lower EC_{50} value is associated with a higher radical scavenging activity [21]. DPPH radical scavenging activities of the prepared compounds **9**, **8**, **6** and **31** in terms of EC_{50} were shown to be highest as (0.57, 0.58, 0.67 and 0.67 mg), respectively compared to EC_{50} of vitamin E (0.705) as standard. Meanwhile nearly the same activities were revealed in case of compounds **16**, **29** and **12** (0.73, 0.76, 0.78 mg), respectively as compared with EC_{50} of vitamin E (0.705). Moderate activities were shown for compounds **19** and **33** (0.81 and 0.81 mg), respectively as compared to EC_{50} of vitamin E (0.705). Meanwhile lower activities were observed in case of compounds **22**, **18** and **28** with EC_{50} as (0.84, 0.88, 0.95 mg) compared to standard, (Table 32).

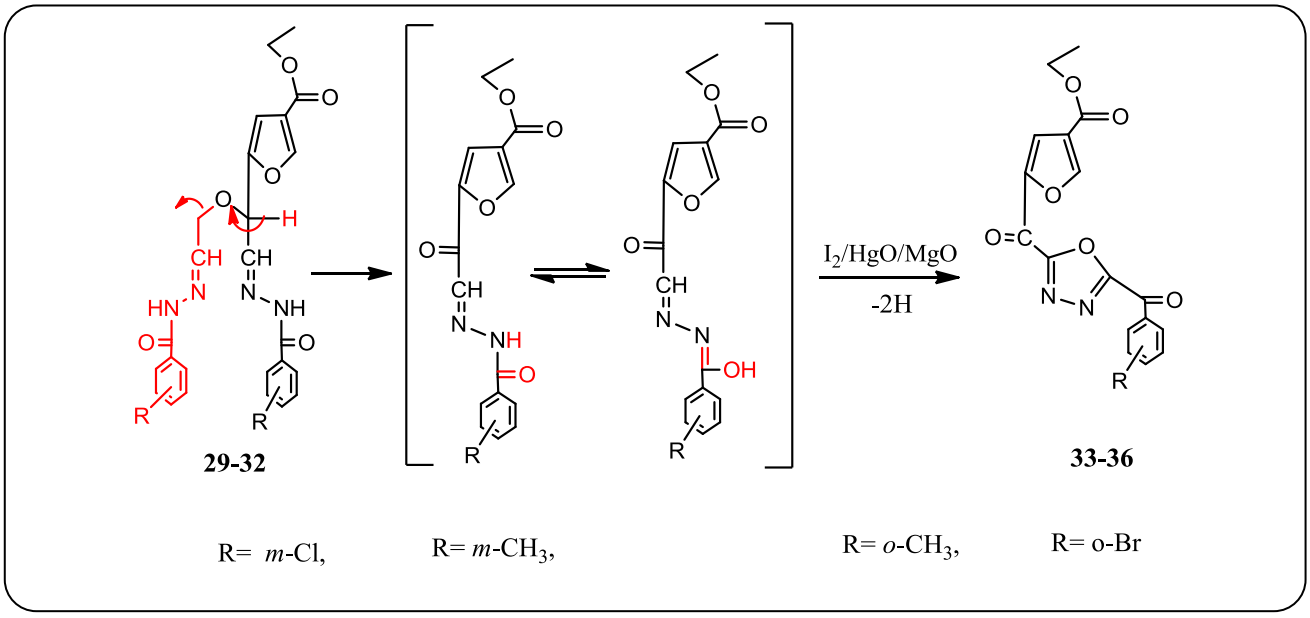
EXPERIMENTAL SECTION

General Procedures.

Melting points were determined on kofler block and are uncorrected. IR spectra were recorded on Perkin Elemer. USA Spectrometer.^{1}HNMR was recorded on JEOL JNM ECA 500 MHZ using tetramethylsilane as an internal standard. GC-EI-MS were recorded with direct

Table 1: Absorbance and free radical scavenging activities of compounds (6,16,8).

Conc. (mg/ml)	Compound no.6		Compound no.16		Compound no.8	
	Absorbance	% inhibition	Absorbance	% inhibition	Absorbance	% inhibition
0.150	1.265	8.26	1.275	7.54	1.132	17.91
0.300	1.138	18.08	1.190	13.70	1.012	26.61
0.450	0.966	20.14	0.996	27.77	0.784	43.14
0.600	0.716	48.07	0.826	40.99	0.653	52.64
0.750	0.573	58.44	0.713	48.29	0.524	62.00
0.900	0.416	69.83	0.502	63.59	0.398	71.13
1	0.252	81.72	0.360	73.89	0.205	85.13



Scheme 5: Proposed mechanism for formation of ethyl 2-methyl-5-(5-aryl-1,3,4-oxadiazole-2-carbonyl)furan-3-carboxylate.

introduction into a Shimadzu Qp-2010 instrument. Thin layer chromatography (TLC) was carried out on silica gel plates.

The ChemDraw-Ultra-12 has been used in the nomenclature of the prepared compounds.

Chemistry

5-(3', 4'-Dihydroxytetrahydrofuran-2'-yl)-2-methylfuran-3-carbohyrazide ***(2).***

M.p 168-170°C, (lit.[75]mp:185-187°C). IR(KBr) cm^{-1}; 3316, 3387(2NH), 1638(CO- amide); ^{1}H-NMR (DMSO); δ: 2.46 (s, 3H, CH_3 furan), 3.56-3.58 (d, 1H, H-4'a), 3.98-4.07 (m, 3H, H-4'b, H-3', H-2'), 4.33 (m, 2H, H-1', OH-2' exchangeable with D_2O), 4.39-4.41 (m, 1H, OH-3' exchangeable with D_2O), 4.98-5.08 (m, 2H, NH_2), 6.71 (s, 1H, CH furan), 9.24 (s, 1H, NH).

General Method for the Synthesis of Carbohydrazides ***3-12***

A mixture of 3-carbohydrazide **2** (2.37 mmol) and carbonyl compound (2.37 mmol) was heated under reflux in ethanol (10 mL) containing a few drops of acetic acid for 1 h. The products **3-12** that separated were filtered off and dried.

N'- ((4-aminophenyl) (phenyl)methylene) -5-(3,4-dihydroxytetrahydrofuran-2-yl)-2-methylfuran-3-carbohydrazide **(3).**

Yield (65%). It was recrystallized from ethanol. Rf:0.70 (chloroform–methanol, 5:1, *v/v*); mp: 206-208°C; IR (KBr) cm^{-1}; 3352(OH anhydro), 3109(NH_2 aniline), 2934(NH), 1661(CO amide), 1627(C=N); ^{1}H-NMR (DMSO); δ: 2.27-2.46 (m, 3H, CH_3 furan), 3.57-3.59 (d,

Table 2: Absorbance and free radical scavenging activities of compounds (18,9,19).

Conc. (mg/mL)	Compound no.18		Compound no.9		Compound no.19	
	Absorbance	% inhibition	Absorbance	% inhibition	Absorbance	% inhibition
0.150	1.245	9.71	1.269	7.97	1.217	11.74
0.300	1.122	16.46	0.942	31.68	1.188	13.85
0.450	1.013	26.54	0.816	40.82	0.986	28.49
0.600	0.948	31.94	0.645	53.22	0.898	34.88
0.750	0.864	37.34	0.463	66.42	0.718	47.93
0.900	0.704	48.94	0.317	74.83	0.624	54.74
1	0.518	62.43	0.141	89.77	0.495	64.10

Table 3: Absorbance and free radical scavenging activities of compounds (12,22,28).

Conc. (mg/ml)	Compound no.12		Compound no.22		Compound no.28	
	Absorbance	% inhibition	Absorbance	% inhibition	Absorbance	% inhibition
0.150	1.257	8.84	1.185	14.06	1.318	4.42
0.300	1.107	19.72	1.064	22.84	1.236	10.36
0.450	1.063	22.91	0.936	32.12	1.108	19.65
0.600	0.845	38.72	0.875	36.54	0.967	29.87
0.750	0.752	45.46	0.779	43.50	0.858	37.78
0.900	0.555	59.75	0.645	53.22	0.754	45.32
1	0.485	64.82	0.562	59.54	0.625	54.67

Table 4: Absorbance and free radical scavenging activities of compounds (29,31,33).

Conc. (mg/ml)	Compound no.29		Compound no.31		Compound no.33	
	Absorbance	% inhibition	Absorbance	% inhibition	Absorbance	% inhibition
0.150	1.289	6.52	1.255	11.16	1.308	5.14
0.300	1.141	17.25	1.142	17.18	1.186	13.99
0.450	0.992	28.06	1.016	26.18	1.008	26.90
0.600	0.793	42.49	0.845	38.72	0.917	33.50
0.750	0.665	51.77	0.563	59.17	0.758	45.03
0.900	0.583	57.72	0.417	69.76	0.614	55.47
1	0.490	64.46	0.241	82.52	0.485	64.82

1H, H-4'a), 3.97-4.06 (m, 3H, H-4'b, H-3', H-2'), 4.36-4.52 (d, 1H, H-1'), 4.95-4.97 (d, 1H, OH-2' exchangeable with D_2O), 5.07-5.08 (d, OH-3' exchangeable with D_2O), 5.57-5.59 (s, 2H, NH2 exchangeable with D_2O), 6.23 (m,1H, CH furan). Aromatic protons : 6.49-6.70 (m, 2H, *m*-H aniline), 6.98-7.16 (m, 2H, *o*-H aniline),7.26-7.37 (m, 2H, *m*-H phenyl), 7.47-7.49 (m, 1H , *p*-H phenyl), 7.51-7.55 (m, 2H, *o*-H phenyl), 9.06 (s, 1H, NH) ;Anal.calcd for $C_{23}H_{23}N_3O_5$: C,65.55;H,5.50;N,9.97; O,18.98.

5-(3,4-Dihydroxytetrahydrofuran-2-yl) -2- methyl-N'- (1-phenylethylidene)furan-3-carbohydrazide **(4)**

Yield (48%). It was recrystallized from ethanol as colourless needles; R_f: 0.72 (benzene: methanol,10:5, v/v); mp: 80-82 °C; IR (KBr) cm^{-1}; 3355 (OH anhydro),

Table 5: EC_{50} of compounds 6, 16, 8, 18, 9, 19, 12, 22, 28, 29, 31 and 33.

Cpd. no.	EC_{50} (mg)	Cpd. no.	EC_{50} (mg)
6	0.67	12	0.78
16	0.73	22	0.84
8	0.58	28	0.95
18	0.88	29	0.76
9	0.57	31	0.67
19	0.81	33	0.81

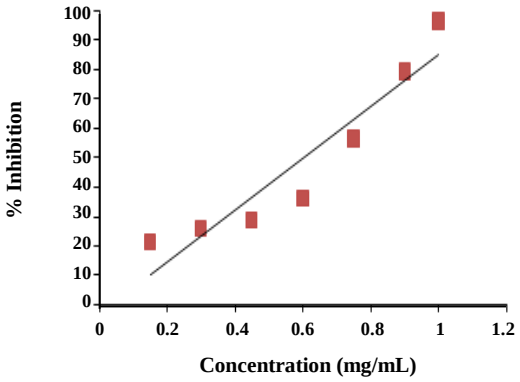


Fig. 1: % Inhibition activity of Vitamin E.

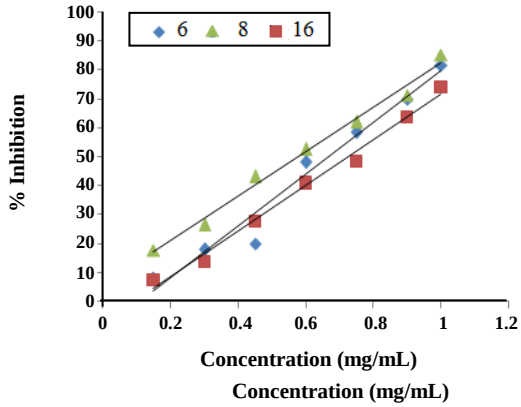


Fig. 1: % Inhibition activity of Vitamin E.

2956 (NH), 1673 (CO amide), 1624 (C=N); ^{1}H-NMR(DMSO); δ: 2.29 (s, 3H, CH_3 aceto), 2.47-2.49 (m, 3H, CH_3 furan), 3.60-3.62 (d, 1H, H-4'a), 4.00-4.02 (m, 1H, H-4'b), 4.10 (m, 2H, H-3', H-2'), 4.48-4.49 (d, 1H, H-1'), 5.00-5.01 (m, 1H, OH-3' exchangeable with D_2O), 5.09-5.11 (m, 1H, OH-2' exchange-able with D_2O), 6.89 (s, 1H, CH furan). Aromatic protons: 7.38-7.39 (d, 3H, *m*-H, 1H, *p*-H), 7.79 (d, 2H, *o*-H), 10.24 (s, 1H, NH); Anal.calcd for $C_{18}H_{20}N_2O_5$: C,62.78; H,5.85; N, 8.13 ; O,23.23.

N'- (1-(4-Aminophenyl)ethylidene) -5- (3,4-dihydroxytetrahydrofuran-2-yl)-2-methyl-furan-3-carbohydrazide **(5)**

Yield (55%). It was recrystallized from ethanol as colourless needles; R_f: 0.70 (benzene: methanol, 10:3, v/v); mp: 110-112 °C; IR (KBr) cm^{-1}: 3593 (OH anhydro), 3424(NH_2 aniline), 3343(NH), 1633(CO amide), 1590(C=N); ^{1}H-NMR (DMSO); δ: 2.17 (s, 3H, CH_3 aceto), 2.47-2.49 (m, 3H, CH_3 furan), 3.13-3.14 (d, 1H, H-4'a), 3.59-3.61 (d, 1H, H-4'b), 3.99-4.02 (m, 1H, H-3'), 4.09-4.10 (d, 1H, H-2'), 4.46-4.47 (d, 1H, H-1'), 4.99 (m, 2H, OH-3' exchangeable with D_2O), 5.09-5.10(d, 1H, OH-2' exchangeable with D_2O), 5.46 (m, 2H, NH_2), 6.52(s, 1H, CH furan). Aromatic protons: 6.53-6.86 (m, 2H, *m*-H), 7.45-7.52 (m, 2H, *o*-H), 10.03 (m, 1H, NH); Anal.calcd for $C_{18}H_{21}N_3O_5$: C,60.16; H,5.89; N,11.69; O,22.26.

5- (3,4-Dihydroxytetrahydrofuran-2-yl) -2- methyl-N'- (1-(p-tolyl)ethylidene)furan-3-carbohydrazide **(6)**

Yield (70%). It was recrystallized from ethanol as colourless needles; R_f : 0.72 (benzene: methanol, 10:3, v/v) mp: 172-174 °C; IR (KBr) cm^{-1}: 3367 (OH anhydro), 3186 (NH), 1635 (CO amide), 1556 (C=N);^{1}H-NMR(DMSO); δ: 2.21-2.25 (m, 3H, CH_3 aceto), 2.29-2.31(m, 3H, CH_3 tolyl), 2.46 (s, 3H, CH_3 furan), 3.60-3.61(d, 1H, H-4'a), 3.99-4.02 (m, 1H, H-4'b), 4.09 (m, 2H, H-3' ,H-2'), 4.47-4.48 (d, 1H, H-1'), 4.97-5.01(m, 1H, OH-3' exchangeable with D_2O), 5.06-5.10 (m, 1H, OH-2' exchangeable with D_2O), 6.87(s, 1H, CH furan). Aromatic protons: 7.19-7.20 (m, 2H, *m*-H), 7.68-7.77 (m, 2H, *o*-H), 10.19 (s, 1H, NH) ;Anal.calcd for $C_{19}H_{22}N_2O_5$: C,63.67; H ,6.19; N,7.82; O,22.32.

5- (3,4-Dihydroxytetrahydrofuran-2-yl) -N'- (1-(4-hydroxyphenyl)ethylidene)-2-methylfuran-3-carbohydrazide **(7)**

Yield (50%). It was recrystallized from ethanol as colourless needles; R_f : 0.71 (benzene: methanol,10:5,v/v) mp: 88-90 °C; IR (KBr) cm^{-1}:3424 (OH phenol), 3334 (OH anhydro), 3023 (NH), 1657 (CO- amide), 1587 (C=N); ^{1}H-NMR (DMSO); δ: 2.21 (s, 3H, CH_3 aceto), 2.43-2.51 (m, 3H, CH_3 furan), 3.59 (d, 1H, H-4'a), 3.61(m, 1H, H-4'b), 3.99-4.02 (m, 1H, H-3'), 4.09 (m, 1H, H-2', H-1'), 4.45-4.48 (m, 1H, OH-3' exchangeable with D_2O), 5.03 (m, 2H, OH-2', OH phenol exchangeable with D_2O), 6.75 (m, 1H, CH furan). Aromatic protons: 6.77-6.87 (m, 2H, *m*-H), 7.65-7.80 (m, 2H, *o*-H), 9.79 (s, 1H, NH); Anal.calcd for $C_{18}H_{20}N_2O_6$: C,59.99; H,5.59; N,7.77; O,26.64**.**

N'-(1-(4-Chlorophenyl)ethylidene)-5-(3, 4-di hydroxytetrahydro furan-2-yl)-2-methyl furan-3-carbohydrazide **(8)**

Yield (50%). It was recrystallized from ethanol as colourless needles; R_f : 0.72 (benzene: methanol,10: 5,v/v); mp: 176-178 °C;

IR (KBr) cm^{-1}: 3432 (OH anhydro), 3180 (NH), 1638 (CO amide), 1606 (C=N); ^{1}H-NMR(DMSO); δ: 2.28 (m, 3H, CH_3 aceto), 2.47-2.49 (s, 3H, CH_3 furan), 3.62 (d, IH, H-4'a), 4.09-4.10 (m, 3H, H-4'b, H-3', H-2'), 4.48-4.49 (d, 1H, H-1'), 5.00-5.10 (d, 2H, OH-3', OH-2' exchangeable with D_2O), 6.89 (s, 1H, CH furan). Aromatic protons: 7.44-7.46 (m, 2H, *m*-H), 7.80 (m, 2H, *o*-H), 10.27-10.60 (m, 1H, NH) ;Anal.calcd for $C_{18}H_{19}N_2O_5$: C,57.07; H,5.06 ; N,7.40; O,21.12.

5- (3,4-Dihydroxytetrahydrofuran-2-yl) -2- methyl -N'-phenylally-lidene)furan-3-cabohydrazide **(9)**

Yield (77%). It was recrystallized from ethanol as colourless needles; R_f : 0.72 (benzene: methanol, 10:5,v/v); mp: 150-152 °C, (lit.[75] mp:162-163°C); IR (KBr) cm^{-1}: 3409 (OH anhydro), 3241 (NH), 1656 (CO amide), 1627 (C=N),1584 (C=C); ^{1}H-NMR (DMSO); δ: 2.47-2.50 (s, 3H, CH_3 furan), 3.62 (d, 1H, H-4'a), 4.01-4.10 (m, 3H, H-4'b, H-3', H-2'), 4.47-4.48 (d, 1H, H-1'), 5.02-5.12 (d, 2H, OH-3', OH-2' exchangeable with D_2O), 6.85(s, 1H, CH furan), 7.00 (m, 2H, CH_2 alkene), Aromatic protons: 7.34-7.36 (m, 1H, *p*-H , 2H, *m*-H), 7.58-7.59 (m, 2H, *o*-H), 8.12-8.13 (d, 1H ,CH=N), 11.26 (s, 1H, NH); Anal.calcd for $C_{19}H_{20}N_2O_5$:C,64.04; H,5.66; N,7.86;

4-Dihydroxytetrahydrofuran-2-yl -N-(4-methoxybenzylidene)-2-methylfuran-3-carbohydrazide **(10)**

Yield (73%). It was recrystallized from ethanol as colourless needles; R_f : 0.74 (benzene: methanol,10:5, v/v); mp:216-218 °C; IR (KBr) cm^{-1}: 3464 (OH anhydro), 3303 (NH), 1654 (CO amide), 1605 (C=N);^{1}H-NMR (DMSO); δ: 2.45-2.51 (m, 3H, CH_3 furan), 3.60-3.62 (d, 1H, H-4'a), 3.77-3.79 (m, 3H, O-CH_3), 4.09-4.10 (m, 3H, H-4'b, H-3', H-2'), 4.48(d, 1H, H-1'), 5.02-5.12 (d, 2H, OH-3', OH-2' exchangeable with D_2O), 6.86 (s, 1H, CH furan). Aromatic protons: 6.97-6.99 (m, 2H, *m*-H), 7.61-7.62 (m, 2H, *o*-H), 8.28 (m, 1H, CH=N), 11.24 (s, 1H, NH); Anal.calcd for $C_{18}H_{20}N_2O_6$: C,59.99; H,5.59; N,7.77; O,26.64.

5-(3, 4-Di hydroxytetrahydrofuran-2-yl)-N-(2-hydroxyphenylidene)-2-methylfuran-3-carbohydrazide **(11).** Yield (70%)

It was recrystallized from ethanol as colourless needles; R_f :0.75 (benzene: methanol,10:5,v/v); mp:160-162°C; IR (KBr) cm^{-1}: 3501 (OH phenol), 3222 (OH anhydro), 3060 (NH), 1664 (CO- amide), 1616 (C=N); ^{1}H-NMR (DMSO); δ: 2.47-2.53 (m, 3H, CH_3 furan), 3.61-3.63 (d, 1H, H-4'a), 4.01-4.11 (m, 3H, H-4'b, H-3', H-2'), 4.48-4.49 (d, 1H, H-1'), 5.03-5.13 (d, 2H, OH-3', OH-2' exchangeable with D_2O), 6.87 (s, 1H, CH furan). Aromatic protons:6.88-6.90 (m, 2H, *m*-H), 7.26-7.48 (m, 1H, *o*-H, 1H, *p*-H), 8.52(m, 1H, CH=N), 11.25(s, 1H, OH-phenyl), 11.68 (s, 1H, NH); Anal.calcd for $C_{17}H_{18}N_2O_6$: C,58.96; H,5.24; N,8.09; O,27.72.

N'-(4-bromobenzylidene)-5-(3, 4-di hydroxytetrahydrofuran-2-yl)-2-methyl furan-3-carbohydrazide **(12)**

Yield (80%). It was recrystallized from ethanol as colourless needles; R_f : 0.74 (benzene: methanol,10:5,v/v) mp: 222-224 °C; IR (KBr) cm^{-1}: 3499 (OH anhydro), 3323 (NH), 1660 (CO amide), 1621 (C=N); ^{1}H-NMR (DMSO); δ: 2.47-2.51 (s, 3H, CH_3 furan), 3.60-3.62 (d, 1H, H-4'a), 4.09-4.10 (m, 3H, H-4'b, H-3', H-2'), 4.47-4.49 (d, 1H, H-1'), 5.02-5.12 (d, 2H, OH-3', OH-2' exchangeable with D_2O), 6.86 (s, 1H, CH furan). Aromatic protons : 7.62 (m, 2H , *m*-H, 2H, *o*-H), 8.31 (s, 1H, CH=N) ,11.44 (s, 1H, NH); Anal.calcd for $C_{17}H_{17}BrN_2O_5$: C,49.89; H,4.19; Br,19.53 ; N,6.85 ; O,19.55.

Reaction of Compounds **3-12** *with Acetic Anhydride*

A solution of compounds **3-12** (1gm, 2.26 mmol) in mixture of pyridine (5 ml) and acetic anhydride (5 ml) was kept overnight at room temperature with occasional shaking. Then poured mixture onto crushed ice filtered off, washed with water and dried yield.

Dimethyl(2-(4(2-(4-aminophenyl)phenyl)methylene) hydrazinecarbonyl)-5-(methyl-furan-2-yl)tetrahydrofuran-3, 4-diyl diacetate **(13).**

Yield: 45%. It was recrystallized from ethanol as needles; R_f: 0.67, (benzene: methanol, 10:5, v/v), m.p:88-90 °C; IR (KBr) cm^{-1}: 3313 (NH), 1749 (OAc), 1666 (CO amide), 1599 (C=N); ^{1}H-NMR(DMSO); δ: 1.97-2.06 (m, 9H, 1*N*-Ac , 2*O*-Ac), 2.47 (m, 3H, CH_3 furan), 3.78-3.79 (m, 1H, H-4'a), 4.23(m, 1H, H-4'b), 4.80 (m, 1H, H-3'), 5.31-5.38 (m, 2H, H-2', H-1'), 6.46-6.54 (m, 1H, CH furan), Aromatic protons: 7.25-7.44 (m, 4H aniline), 7.51-7.59 (m, 2H, *m*-H phenyl, 1H, *p*-H phenyl), 7.75-7.76 (m, 2H, *o*-H phenyl), 9.40-9.56 (m, NH amide), 10.10-10.18 (m, 1H, NH acetate); Anal.calcd for $C_{27}H_{27}N_3O_7$: C,64.15; H,5.38; N,8.31 ; O,22.15.

2-(5-Methyl-4-(2-(1-phenylethylidene)hydrazinecarbonyl) tetrahydrofuran-3,4-diyl acetate **(14)**

yield: 50%. It was recrystallized from ethanol as needles; R_f: 0.64 (benzene: methanol, 10:5, v/v); m.p:106-108°C; IR (KBr) cm^{-1}: 3178 (NH), 1751 (OAc), 1651 (CO amide), 1609 (C=N); ^{1}H-NMR($CDCl_3$); δ: 2.06-2.12 (m, 6H, 2OAc), 2.43 (m, 3H, CH_3 aceto), 2.61 (s, 3H, CH_3 furan), 3.89-3.97 (m, 1H, H-4'a), 4.36 (m, 1H, H-4'b), 4.87-4.89 (m, 1H, H-3'), 5.46-5.50 (m, 2H, H-2', H-1'), 6.93(s, 1H, CH furan). Aromatic protons: 7.45-7.48 (2H, *m*-H), 7.55-7.58 (m, 1H, *p*-H), 7.95-7.96 (m, 2H, *o*-H), 10.63 (s, 1H, NH);Anal.calcd for $C_{22}H_{24}N_2O_7$: C,61.67; H,5.65; N,6.54; O,26.14.

2-(4-(2-(1-(4-Aminophenyl)ethylidene)hydrazinecarbonyl) -5-methyl furan-2-yl)tetra-hydrofuran-3, 4 diyl acetate **(15)**

Yield: 50%. It was recrystallized from ethanol as needles R_f: 0.62, (benzene: methanol, 10:5, v/ v); m.p:88-90°C; IR (KBr) cm^{-1}: 3115 (NH), 1733 (OAc), 1660 (CO amide), 1598(C=N);^{1}H-NMR (DMSO); δ: 2.03-2.06 (m, 9H, 1*N*-AC, 2*O*-Ac), 2.25(m, 3H, CH_3 aceto), 2.47-2.49 (m, 3H, CH_3 furan), 3.60-3.61(d, 1H, H-4'a), 4.09 (d, 1H, H-4'b), 4.35 (d, 1H, H-3'), 4.47-4.51 (m, 1H, H-2'), 5.22 (m,1H,H-1'), 6.88-6.92 (m, 1H, CH furan) .Aromatic protons: 7.60 (m, 2H, *m*-H), 7.74 (m, 2H, *o*-H), 10.08(s, 1H, NH amide), 10.19-10.22 (m, 1H, NH acetate); Anal.calcd for $C_{24}H_{27}N_3O_8$: C,59.38; H,5.56; N,8.65; O,26.39.

2-(5-Methyl-4-(2-(1-(p-tolyl)ethylidene)hydrazinecarbonyl) furan-2-yl)tetrahydro-furan-3, 4-diyl diacetate **(16)**

Yield: 40%. It was recrystallized from ethanol as needles, R_f: 0.63, (benzene: methanol, 10:5, v/v); m.p:84-86 °C; IR (KBr) cm^{-1}: 3169(NH), 1754(OAc), 1650(CO amide), 1619(C=N); ^{1}H-NMR ($CDCl_3$); δ: 2.05-2.11 (s, 6H, 2OAc), 2.26 (s, 3H, CH_3 aceto), 2.37 (s, 3H, CH_3 tolyl), 2.60 (s, 3H, CH_3 furan), 3.94-3.96 (d, 1H, H-4'a), 4.36 (d, 1H, H-4'b), 4.90-4.91 (d, 1H, H-3'), 5.48-5.49 (m, 2H, H-2', H-1'), 7.08 (s, 1H, CH furan). Aromatic protons: 7.19-7.21 (m, 2H, *m*-H),7.61-7.73 (m, 2H, *o*-H), 8.91 (s, 1H, NH) Anal.calcd for $C_{23}H_{26}N_2O_7$: C,62.43; H,5.95; N,6.33; O,25.31.

2-(4-(2-(1-(4-Acetoxy phenyl) ethylidene) hydrazine carbonyl)-5-methyl furan-2-yl) tetrahydrofuran-3, 4-diyl diacetate **(17)**

yield: 60%. It was recrystallized from ethanol as needles, R_f: 0.64, (benzene: methanol, 10:5, v/v); m.p:118-120°C;IR (KBr) cm^{-1}: 3178 (NH), 1751 (OAc), 1651 (CO amide), 1609 (C=N); ^{1}H-NMR ($CDCl_3$); δ: 2.02-2.12 (m, 6H, 2*O*-Ac), 2.32 (m, 3H, *O*-Ac phenyl, 3H, CH_3 aceto), 2.59 (s, 3H, CH_3 furan), 3.95-3.97 (d, 1H, H-4'a), 4.36-4.37 (m, 1H, H-4'b), 4.87-4.88 (m, 1H, H-3'), 5.46-5.47 (m, 2H, H-2', H-1'b), 6.91 (s, 1H, CH furan), Aromatic protons: 7.17-7.25 (m, 2H, *m*-H), 7.98-8.00 (m, 2H, *o*-H), 10.64(s, 1H, NH); Anal.calcd for $C_{24}H_{26}N_2O_9$: C,59.25; H,5.39; N,5.76; O,29.60.

2-(4-(2-(1-(4-Chlorophenyl)ethylidene)hydrazinecarbonyl) -5-methylfuran-2-yl)tetra-hydrofuran-3, 4-diyl diacetate **(18)**

Yield: 50%. It was recrystallized from ethanol as needles R_f: 0.67, (benzene: methanol, 10:5, v/v), m.p: 80-81 °C; IR (KBr) cm^{-1}: 3185 (NH), 1754 (OAc), 1646 (CO amide), 1606 (C=N); ^{1}H-NMR ($CDCl_3$); δ: 2.06-2.12 (m, 6H, 2OAc), 2.27-2.58 (m, 6H, CH_3 aceto, CH_3 furan), 3.95-3.96 (m,1H, H-4'a), 4.35-5.36 (m, 1H, H-4'b), 4.85-4.91 (m, 1H, H-3'), 5.48-5.51 (m, 2H, H-2', H-1'), 6.53-6.61 (m, 1H, CH furan), Aromatic protons: 7.35-7.43 (m, 2H, *m*-H), 7.65-7.89 (m, 2H, *o*-H), 10.60 (s, 1H, NH);

Anal.calcd for $C_{22}H_{23}ClN_2O_7$: C,57.09; H,5.01; Cl,7.66; N,6.05; O,24.20.

2-(5-Methyl-4-(2-(3-phenylallaylidene)hydrazinecarbonyl) furan-2-yl)tetrahydro-furan-3, 4-diyl diacetate **(19)**

Yield: 50%. It was recrystallized from ethanol as needles R_f: 0.67, (benzene: methanol, 10:5, v/v), m.p: 80-81 °C; IR (KBr) cm^{-1}: 3185 (NH), 1754 (OAc), 1646 (CO amide), 1606 (C=N); ^{1}H-NMR ($CDCl_3$); δ: 2.06-2.12 (m, 6H, 2OAc), 2.27-2.58 (m, 6H, CH_3 aceto, CH_3 furan), 3.95-3.96 (m,1H, H-4'a), 4.35-5.36 (m, 1H, H-4'b), 4.85-4.91 (m, 1H, H-3'), 5.48-5.51 (m, 2H, H-2', H-1'), 6.53-6.61 (m, 1H, CH furan), Aromatic protons: 7.35-7.43 (m, 2H, *m*-H), 7.65-7.89 (m, 2H, *o*-H), 10.60 (s, 1H, NH); Anal.calcd for $C_{22}H_{23}ClN_2O_7$: C,57.09; H,5.01; Cl,7.66; N,6.05; O,24.20.

2- (4-(2-(4-methoxybenzylidene)hydrazinecarbonyl)-5-methylfuran-2-yl)tetrahydro-furan-3, 4-diyl diacetate **(20)**

Yield: 45%. It was recrystallized from ethanol as needles, R_f: 0.69, (benzene: methanol, 10:6, v/v), m.p:154-156 °C; IR (KBr) cm^{-1}: 3243(NH), 1749(OAc), 1646(CO amide), 1607(C=N); ^{1}H-NMR (DMSO); δ: 2.05-2.11(m,6H,2*O*-Ac), 2.58(m,3H, CH_3 furan), 3.81-3.88(m,3H, O-CH_3),3.95(m,1H,H-4'a),4.36(m,1H,H-4'b),4.83-4.88(m,1H,H-3'), 5.40-5.53 (m,2H,H-2',H-1'), 6.67 (m,1H,CH furan). Aromatic protons: 6.87-7.00(m,2H,*m*-H),7.56-7.84(m,2H,*o*-H), 8.21 (s,1H,CH=N), 9.50 (s,1H,NH); Anal.calcd for $C_{22}H_{24}N_2O_8$: C,59.45;H,5.44;N,6.30; O,28.80.

2-(4-(2-(2-acetoxybenzylidene) hydrazine carbonyl) -5-methylfuran-2-yl) tetrahydro-furan-3, 4-diyl diacetate **(21)**

Yield: 58%. It was recrystallized from ethanol as needles, R_f: 0.69, (benzene: methanol, 10: 5, v/v), m.p:70-72 °C; IR (KBr) cm^{-1}: 3244(NH), 1748(OAc), 1653(CO amide), 1613(C=N); ^{1}H-NMR (DMSO); δ: 2.07-2.12 (m, 6H, 2*O*-Ac), 2.29-2.42 (m, 3H, *O*-Ac phenyl), 2.53-2.58 (m, 3H, CH_3 furan), 3.87-3.94 (m, 1H, H-4'a), 4.34 (m,1H, H-4'b), 4.88 (m, 1H, H-3'), 5.46-5.49 (m, 2H, H-2', H-1'), 6.86 (m, 1H, CH furan). Aromatic protons: 7.08-7.21 (m, 2H, *m*-H), 7.25-7.29 (m, 1H, *p*-H), 7.38-7.41 (m, 1H, *o*-H), 7.83-7.88 (m, 1H, CH=N), 9.69-10.10 (m, 1H, NH); Anal.calcd for $C_{23}H_{24}N_2O_9$: C, 58.47; H,5.12 ; N,5.93; O,30.48.

*2- (4-(2-(4-Bromobenzylidene)hydrazinecarbonyl) -5-methylfuran-2-yl)tetrahydro-furan-3, 4-diyl diacetate **(22)***

Yield: 50%. It was recrystallized from ethanol as needles R_f: 0.65, (benzene: methanol, 10:5, v/v), m.p:110°C; IR (KBr) cm^{-1}: 3209 (NH), 1748 (OAc), 1651 (CO amide), 1586 (C=N); ^{1}H-NMR (DMSO); δ: 2.07-2.11(m, 6H, 2*O*-Ac), 2.41-2.53 (m, 3H, CH_3 furan), 3.86-3.96 (m, 1H, H-4'a), 4.28-4.38 (m, 1H, H-4'b), 4.87-4.88 (m, 1H, H-3'), 5.50-5.51 (m, 2H, H-2', H-1'), 6.61(s,1H, CH furan). Aromatic protons: 7.49-7.53 (m, 2H, *m*-H), 6.67-7.75 (m, 2H, *o*-H), 7.80(s, 1H, CH=N), 9.96 (s, 1H, NH); Anal.calcd for $C_{21}H_{21}BrN_2O_7$: C,51.13 ; H,4.29; Br,16.20; N,5.68; O,22.70.

*Reactions of Compounds **19-22** with Yellow Mercuric Oxide*

General Method: A solution of **10a–d** (4.5 mmol) in dry ether (50 mL) was stirred with yellow mercuric oxide (3.0 g), magnesium oxide (0.3 g), and iodine (2.5 g) at room temperature for 48 h under anhydrous condition. The reaction mixture was filtered off, and the filtrate washed with potassium iodide solution, sodium thiosulphate, and water, respectively, then dried over anhydrous sodium sulphate. On evaporation of the dried filtrate yellow syrup was obtained, which was crystallized from ethanol. An additional crop was obtained by extracting the inorganic residue withchloroform which upon concentration and dilution with ethanol yielded the same product.

2-(5-Methyl-4-(5-styryl-1,3,4-oxadiazol-2-yl)furan-2-yl)tetrahydrofuran-3,4-diyl diacetate **(23)**

Over yield: 25%. It was recrystallized from ethanol as needles; R_f: 0.66 (benzene: methanol, 10:5, v/v); m.p: 166-168°C; IR (KBr) cm^{-1}: 1747 (OAc), 1640 (C=N); ^{1}H-NMR (DMSO); δ: 2.02 (s, 3H, *O*-Ac), 2.08 (s, 3H, *O*-Ac), 2.63 (s, 3H, CH_3 furan), 3.86-3.88 (m, 1H, H-4'a), 4.31-4.46 (m, 1H, H-4'b), 4.93 (m, 1H, H-3'), 5.29-5.47 (m, 2H, H-2', H-1'), 6.70-6.99 (m, 1H, CH_2 alkene), 7.14 (s, 1H, CH furan). Aromatic protons: 7.27-7.39 (m, 2H, *m*-H, 1H, *p*-H), 7.56-7.85 (m, 2H, *o*-H); Anal.calcd for $C_{23}H_{22}N_2O_7$: C,63.01 ; H,5.02; N,6.39; O,25.57.

2-(4-(5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)-5-methylfuran-2-yl)tetrahydro-furan-3,4-diyldiacetate **(24)**

Over yield: 28%. It was recrystallized from ethanol as needles; R_f: 0.64 (benzene: methanol, 10:5, v/v); m.p:

160-162°C; IR (KBr) cm^{-1}: 1746 (OAc), 1652 (C=N); ^{1}H-NMR (DMSO); δ: 2.00 (s, 3H, *O*-Ac), 2.07(s, 3H, *O*-Ac), 2.64 (s, 3H, CH_3 furan), 3.82 (s, 3H, O-CH_3), 3.85 (m, 1H, H-4'a), 4.28-4.30 (dd, 1H, H-4'b), 4.90-4.91(d, 1H, H-3'), 5.440-5.447 (m, 2H, H-2', H-1'), 7.04 (s, 1H, CH furan). Aromatic protons: 7.11-7.13 (m, 2H, *m*-H), 7.95-7.97 (m, 2H, *o*-H); Anal.calcd for $C_{22}H_{22}N_2O_8$: C,59.73;H,5.01; N,6.33; O,28.93.

2-(4-(5-(2-Acetoxyphenyl)-1,3,4-oxadiazol-2-yl)-5-methylfuran-2-yl)tetrahydrofuran-3,4-diyldiacetate **(25)**

Over yield: 20%. It was recrystallized from ethanol as needles; R_f: 0.69 (benzene: methanol, 10:5, v/v); m.p: 156-158°C; IR (KBr) cm^{-1}: 1744 (OAc), 1640 (C=N); ^{1}H-NMR (DMSO); δ: 2.01 (s,3H,*O*-Ac), 2.08 (s, 3H, *O*-Ac), 2.48-2.52 (m, 3H, O-Ac phenyl), 2.65 (s, 3H, CH_3 furan), 3.85-3.87 (m, 1H, H-4'a), 4.30 (m, 1H, H-4'b), 4.84-4.93 (m, 1H, H-3'), 5.41-5.46 (m, 2H, H-2', H-1'), 7.03 (m, 1H, CH furan). Aromatic protons: 7.36 -7.37 (m, 2H, *m*-H), 7.50-7.67 (m, 1H, *p*-H), 8.07(m, 1H, *o*-H); Anal.calcd for $C_{23}H_{22}N_2O_9$: C,51.13 ; H,4.29; Br,16.20; N,5.68; O,22.70.

2-(4-(5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)-5-methylfuran-2-yl)tetrahydrofuran-3, 4-diyldiacetate **(26)**

Over yield: 30%. It was recrystallized from ethanol as needles; R_f: 0.64 (benzene: methanol, 10:5, v/v); m.p: 146-148°C; IR (KBr) cm^{-1}: 1748 (OAc), 1649 (C=N); ^{1}H-NMR (DMSO); δ: 1.99(s, 3H, OAc), 2.07(s, 3H, *O*-Ac), 2.65(s, 3H, CH_3 furan), 3.83-3.85 (dd, 1H, H-4'a), 4.27-4.30 (dd, 1H, H-4'b), 4.90-4.92 (d, 1H, H-3'), 5.43-5.44 (m, 2H, H-2', H-1'), 7.05 (s, 1H, CH furan), Aromatic protons: 7.78-7.80 (m, 2H, *m*-H), 7.95-7.96 (m, 2H, *o*-H) ; Anal.calcd for $C_{21}H_{19}BrN_2O_7$: C,51.34; H,3.90; Br,16.26; N,5.70; O,22.80.

*Synthesis of dialdehyde **27***

A solution of compound **1** (5 gm , 19 mmol) in distilled water (30 ml) was treated with a solution of sodium metaperiodate (0.23 mol) in distilled water (20 ml) dropwise with continous stirring for 3 hours. The dialdehyde that separated out was filtered off, washed with little water, and dried, yield: 50%, R_f: 0.40 (chloroform: methanol, 10:6, v/v). It was recrystallized from ethanol as colourless needles; m.p:142-144°C, (lit.[75]mp:111-113°C); IR(KBr) cm^{-1}; 1712(CO ester), 3429(OH); ^{1}H-NMR (DMSO); δ: 1.20-1.2 3(t, 3H, CH_3 ester), 3.26-3.28 (m, CH_3 furan), 4.14-4.17 (q, 2H, CH_2 ester), 4.47(s, 1H, H-3), 5.11-5.12 (d, 1H, H-2a), 5.13(d, 1H, H-2b), 6.53-6.55 (s, 1H, CH furan), 6.61(1H, H-1), 6.62(1H, H-4); Anal.calcd for $C_{12}H_{12}O_4$: C,57.14; H,4.80; O,38.06.

*Reactions of **27** with a Number of Aroylhydrazines.*

A solution of compound **27** (2.0g, 7.3 mmol) in ethanol (15 ml) containing (0.1 ml) acetic acid was treated with aroylhydrazine (2.50 g, 10.37 mmol) in ethanol (10 ml). The reaction mixture was refluxed on water bath for 15 minutes, the bisaroyl hydrazine derivative that separated out was filtered off, wash little ethanol, and dried.

Ethyl5-[2-(2-(m-chlorobenzoyl)hydrazono)-1-(2-(2-(m-chlorobenzoyl)hydrazono) ethoxy)ethyl]-2-methyl furan-3-carboxylate **(28)**

Yield: 65%. It was recrystallized from ethanol-chloroform as colourless needles; R_f : 0.54 (chloroform: methanol, 10:5, v/v); m.p: 202-204°C; IR (KBr) cm^{-1}; 3275, 3211 (2NH), 1713 (CO ester), 1661 (CO amide), 1598(C=N); ^{1}H-NMR(DMSO); δ: 1.21-1.24 (t, 3H, CH_3 ester), 2.47- 2.53 (s, 3H, CH_3 furan), 4.16-4.17 (m, 2H, H_{1a}, H_{2b}), 4.18-4.20 (q, 2H, CH_2 ester), 5.16-5.17 (d, 1H, $CH_{1'}$), 6.74 (s, 1H, CH furan), Aromatic protons: 7.50-7.53 (m, 2H, *m*-H), 7.62(m ,2H, *p*-H), 7.71-7.84 (m, 4H, *o*-H), 7.88-7.91 (m, CH=N_2, CH=$N_{2'}$), 11.74(s,1H,H_3), 11.82 (s, 1H, $H_{3'}$); Anal.calcd for $C_{26}H_{22}Cl_2N_4O_6$: C,56.03; H,3.98; Cl,12.72; N,10.05; O,17.22.

Ethyl5-[2(2-(m-methylbenzoyl)hydrazono)-1(2-(2-(m-methylbenzoyl)hydrazono) ethoxy)ethyl]-2-methyl furan-3-carboxylate **(29)**

Yield: 66%. It was recrystallized from ethanol-chloroform as colourless needles; R_f : 0.56 (chloroform: methanol, 10:5, v/v); m.p: 186-188°C; IR (KBr) cm^{-1}; 3181, 3051 (2NH), 1717 (CO ester), 1659 (CO amide), 1606(C=N); ^{1}H-NMR(DMSO); δ: 1.21-1.24(t, 3H, CH_3 ester), 2.33 (s, 6H, 2CH_3 tolyl), 2.47-2.53 (s, 3H, CH_3 furan), 4.16-4.18 (m, 2H, H_{1a}, H_{1b}), 4.19 (m, 2H, CH_2 ester), 5.14 (d, 1H, $CH_{1'}$), 6.73 (1H, CH furan), Aromatic protons: 7.36 (m, 2H, *m*-H, 2H, *p*-H), 7.60-7.65 (m, 4H, *o*-H), 7.72 (m, 1H, CH=N_2), 7.91-7.92 (m, 1H, CH=$N_{2'}$), 11.62(s, 1H, H_3), 11.72(s, 1H, $H_{3'}$); Anal.calcd for $C_{28}H_{28}N_4O_6$: C,65.11; H,4.46; N,10.85; O,18.58.

Ethyl5-[2-(2-(o-bromobenzoyl)hydrazono)-1-(2-(2-(o-bromobenzoyl)hydrazono) ethoxy)ethyl]-2-methyl furan-3-carboxlate **(30)**

Yield: 63%. It was recrystallized from ethanol-chloroform as colourless needles; R_f: 0.50 (chloroform: methanol, 10:5, v/v); m.p: 190-192°C; IR (KBr) cm^{-1}; 3179, 3049 (2NH), 1714 (CO ester), 1669 (CO amide), 1590 (C=N); ^{1}H-NMR(DMSO);δ: 1.23-1.26 (t, 3H, CH_3 ester), 2.53 (m, 3H, CH_3 furan), 4.12-4.19 (m, 2H, H_{1a}, H_{1b}), 4.20 (m, 2H, CH_2 ester), 4.89-5.16 (m, 1H, $CH_{1'}$), 6.75 (m, 1H, CH furan), Aromatic protons: 7.23-7.47 (m, 4H, *m*-H, 2H, *p*-H), 7.50-7.61 (m, 2H, *o*-H), 7.63-7.73 (m, 2H, CH=N_2, CH=$N_{2'}$), 11.70 (m, 1H, H_3), 11.81 (m, 1H, $H_{3'}$) ;Anal. calcd for $C_{26}H_{22}Br_2N_4O_6$: C,48.32; H,4.95; Br,24.73; N,8.67; O,14.85.

Ethyl5-[2(2-(o-methylbenzoyl)hydrazono)-1(2-(2-(o-methylbenzoyl)hydrazono)ethoxy)ethyl]-2-methyl furan-3-carboxylate **(31)**

Yield: 60%. It was recrystallized from ethanol-chloroform as colourless needles; R_f: 0.57 (chloroform: methanol, 10:5, v/v); m.p: 180-182°C; IR (KBr) cm^{-1}; 3197, 3052 (2NH), 1717 (CO ester), 1657 (CO- amide), 1576 (C=N.); ^{1}H-NMR(DMSO);δ: 1.23-1.26 (t, 3H, CH_3 ester), 2.32-2.47 (m, 6H, CH_3 tolyl), 2.54 (m, 3H, CH_3 furan), 4.14-4.19 (m, 2H, H_{1a}, H_{1b}), 4.20-4.22 (q, 2H, CH_2 ester), 5.13 (d, 1H, $CH_{1'}$), 6.74 (s, 1H, CH furan), Aromatic protons: 7.17-7.27 (m, 4H, *m*-H, 2H, *p*-H), 7.34-7.41 (m, 4H, *o*-H), 7.47-7.57 (m, 1H, CH=N_2), 7.75-7.77(m, 1H, CH=$N_{2'}$), 11.55 (m, 1H, H_3), 11.66 (m,1H, H_3);Anal.calcd for $C_{28}H_{28}N_4O_6$; C,65.11; H,4.46 ; N,10.85 ; O,18.58.

Ethyl5-(2-(2-(o-chlorobenzoyl)hydrazono)-1-(2-(2-(o-chlorobenzoyl)hydrazono) ethoxy)ethyl)-2-methylfuran-3-carboxylate **(32)**

Yield: 70%. It was recrystallized from ethanol-chloroform as colourless needles; R_f: 0.55 (chloroform: methanol, 10:5, v/v); m.p: 184-186°C; IR (KBr) cm^{-1}; 3065, 3199 (2NH), 1710 (CO ester), 1657 (CO amide), 1593(C=N); ^{1}H-NMR (DMSO); δ:1.22-1.24 (t, 3H, CH_3 ester), 2.47-2.53(s, 3H, CH_3 furan), 4.16-4.17 (m, 2H, H_{1a}, H_{1b}), 4.19 (q, 2H, CH_2 ester), 5.15-5.16 (d, 1H, $CH_{1'}$), 6.74(s, 1H, CH furan), Aromatic protons: 7.56-7.57 (m, 4H, *m*-H), 7.72-7.87 (m, 2H, *p*-H, m, 2H, *o*-H), 7.91 (m, 1H, CH=N_2), 7.92 (m, 1H, CH=$N_{2'}$), 11.73 (s, 1H, H_3), 11.82 (s, 1H, $H_{3'}$); Anal.calcd for $C_{26}H_{22}Cl_2N_4O_6$: C,56.03; H,3.98 ; Cl,12.72; N,10.05; O,17.72.

Oxidative cyclization of the bisaroylhydrazones ***28-31*** *(see the method number 3.2.4)*

Ethyl-2-methyl-5-(5-(m-chlorophenyl)-1,3,4-oxadiazole-2-carbonyl)furan-3-carboxylate **(33)**

Over yield: 11%. It was recrystallized from ethanol as needles; R_f: 0.67 (benzene: methanol, 10:5, v/v); m.p: 76-78°C; IR (KBr) cm^{-1}; 1708 (CO ester), 1660 (C=O), 1592 (C=N); ^{1}H-NMR (DMSO); δ: 1.28-1.31 (t, 3H, CH_3 ester), 2.47-2.69(s, 3H, CH_3 furan), 4.26 (q, 2H, CH_2 ester), Aromatic protons: 7.66-7.76 (m, 1H, *m*-H, 1H, *p*-H), 8.03 (m, 2H ,*o*-H), 8.17 (s, 1H, CH furan); Anal.calcd for $C_{17}H_{13}ClN_2O_5$: C,56.60; H,3.63; Cl,9.83 ; N,7.77; O,22.18.

Ethyl 2-methyl -5- (5-(m-tolyl) -1,3,4- oxadiazole-2-carbonyl)furan-3-carboxylate **(34)**

Over yield: 12%. It was recrystallized from ethanol as needles; R_f: 0.66 (benzene: methanol, 10:5, v/v); m.p: 73-75°C; IR (KBr) cm^{-1}; 1715(CO ester), 1654(C=O), 1589(C=N); ^{1}H-NMR (DMSO); δ: 1.20-1.30 (m, 3H, CH_3 ester), 2.35-2.49 (m, 6H, CH_3tolyl, CH_3 furan), 3.46-4.26 (m, 2H, CH_2 ester), Aromatic protons: 7.39-7.72 (5H, 1H, *m*-H, 1H, *p*-H , 2H, *o*-H , 1H, CH furan); Anal.calcd for $C_{18}H_{16}N_2O_5$: C,63.52; H,4.74; N,8.23; O,23.51.

Ethyl-2-methyl-5-(5-(o-bromophenyl)-1,3,4-oxadiazole-2-carbonyl)furan-3-carboxylate **(35)**

Over yield: 18%. It was recrystallized from ethanol as needles; R_f: 0.66 (benzene: methanol, 10:5, v/v); m.p: 73-75°C; IR (KBr) cm^{-1}; 1720 (CO ester), 1592 (C=O), 1467 (C=N); ^{1}H-NMR (DMSO); δ: 1.07-1.24 (m, 3H, CH_3 ester), 2.47- 2.61 (m,3H, CH_3 furan), 4.10-4.22 (m, 2H, CH_2 ester), Aromatic protons: 7.42-7.44 (m, 3H, *m*-H, *p*-H), 7.67 (m, 1H, *o*-H), 7.69 (m, 1H, CH furan); Anal.calcd for $C_{17}H_{13}BrN_2O_5$: C,50.39; H,3.23 ; Br,19.72; N,6.91 ; O,19.74.

Ethyl 2-methyl-5(5-(o-toluoyl)-1,3,4-oxadiazole-2-carbonyl)furan-3-carboxylate **(36)**

Over yield: 16%. It was recrystallized from ethanol as needles; R_f: 0.68 (benzene: methanol, 10:5, v/v); m.p: 140-142°C; IR (KBr) cm^{-1}; 1715 (CO ester), 1602 (C=O),

1540 (C=N); ^{1}H-NMR ($CDCl_3$); δ: 1.34-1.36(m, 3H, CH_3 ester), 2.64(m, 6H, CH_3 furan, CH_3 tolyl), 4.32-4.33 (m, 2H, CH_2 ester), Aromatic protons: 7.25-7.29 (m, 2H, *m*-H), 7.43-7.46 (m,1H, *p*-H), 7.53(m, 1H, *o*-H), 8.04-8.06 (m,1H, CH furan); Anal.calcd for $C_{18}H_{16}N_2O_5$: C,63.52; H,4.74; N,8.23; O,23.51.

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