International Journal of Organic Chemistry, 2012, 2, 295-301
http://dx.doi.org/10.4236/ijoc.2012.223040 Published Online November 2012 (http://www.SciRP.org/journal/ijoc)

Synthesis and Trypanocidal Evaluation of Some Novel 2-(Substituted benzylidene)-5, 7-dibromo-6-hydroxy-1-benzofuran-3(2*H*)-ones

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Received August 7, 2012; revised September 17, 2012; accepted September 26, 2012

ABSTRACT

Substituted 2-benzylidene-1-benzofuran-3-ones are commonly known as aurones. This class of bioactive heterocycles belongs to flavonoid family. The article intends to put forth the rational design and synthesis of a new series of aurones using 3',5'-dibromo-2',4'-dihydroxychalcones and copper bromide in presence of DMF-water mixture (8:2, v/v) for the first time. Preliminary bioassay shows that most of compounds have good trypanocidal activity against *Trypanosoma cruzi* at 10 μg/mL. Few compounds are equally potent to the standard drugs Benznidazole and Nifurtimox. The structures of the newly synthesized products **2a-n** were established by elemental analysis, FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic studies.

Keywords: Chalcones; Aurones; *Trypanosoma cruzi*; Chagas Disease; Inhibition

1. Introduction

Substituted 2-benzylidene-1-benzofuran-3-ones are commonly known as aurones that belongs to the naturally occurring flavonoids [1,2] and are structurally isomeric to flavones. They play significant role for the pigmentation of the flowers in which they are found. Antifungal, antibacterial, antiplasmodial, antileshmanial and antiviral activities of aurones have also been reported [3-6]. In view of these observations it was devised to synthesize some novel aurones using a new methodology largely on account of their trypanocidal evaluation. Chagas disease [7-10] commonly known as American trypanosomiasis is a parasitic infection caused by the *T. cruzi*. It is a serious health issue in Latin America with withering consequences in terms of human morbidity and mortality. Due to limited existing drug therapy, poor efficacy and several side effects, there is an immediate need of novel therapeutic agents for the treatment of this disease.

Chalcones, possess a wide spectrum of biological activities [11-16], offers an unprecedented opportunity to chemists to design different sized bioactive heterocycles [17-21]. The presence of *α,β*-unsaturated carbonyl functionality in chalcone makes it a versatile substrate. In continuation of our earlier venture [22-24] to design and synthesis of novel bioactive heterocycles, we herein, report a convenient one pot conversion of 3',5'-dibromo-2',4'-dihydroxy substituted chalcones to 2-(substituted benzylidene)-5,7-dibromo-6-hydroxy-1-benzofuran-3(2*H*)-ones and their trypanocidal evaluation.

2. Results and Discussion

2.1. Chemistry

Aurones have received very limited, methods of their synthesis. The most common synthetic procedures are based on their conversion of coumaran-3-ones with benzaldehydes in the presence of sodium hydroxide to afforded *Z*-aurones. H_3PO_4 [25] and acetic anhydride [26] were also used as catalysts for this conversion. Green routes, using basic alumina [27] or alumina-KF [28] have also been reported for such conversions. Oxidative cyclization of 2'-hydroxychalcones also results aurones as one of the product. Recently aurones have been synthesized from 2'-hydroxychalcones using DMSO-$CuBr_2$ or pyridine-Hg $(OAc)_2$ [29]. To avoid the use of high boiling volatile organic solvents, more recently polyethylene

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glycol (PEG) and mercuric (II) acetate [30] were used in environmentally benign protocols for the synthesis of aurones (benzofuran-3-ones).

Presently, it is a need of more environmentally benign protocols and solvent free systems that reduces or eliminates the use of toxic or environmentally hazardous solvents. In the present study the starting 3',5'-dibromo-2', 4'-dihydroxychalcones **(1a-n)** were prepared by reacting 3,5-dibromo-2,4-dihydroxyacetophenone and variously substituted aromatic aldehydes in the presence of base by conventional Claisen-Schmidt condensation method by our laboratory team. 3',5'-dibromo-2',4'-dihydroxychalcones **(1a-n)** on refluxing (6 - 7 hr) with $CuBr_2$ in presence of DMF-water (8:2, v/v) resulted 2-(substituted benzyli-dene)-5,7-dibromo-6-hydroxy-1-benzofuran-3(2*H*)-ones (**2a-n)** for the first time as shown in **Scheme 1**, with 63% - 73% yields. The purity of the compounds was checked by TLC and structures of the synthesized products were confirmed by their spectral and elemental analysis.

The FTIR spectrum of all the products delineated absorption bands at 1699 - 1713 due to >C=O stretching of aurones. The ^{1}H NMR spectra showed a characteristic singlet near at δ 6.77 - 6.89 due to 1H of benzylidine proton while other aromatic and aliphatic protons were observed at expected regions, ^{13}C NMR spectroscopy further confirms the assigned formation of aurones. The chemical shift values in the range δ 186.49 - 192.29 (C=O), 110.15 - 117.41 (CH=CH) and were in conformity with the assigned literature values for aurones [28]. The mass spectra of the compounds showed molecular ion peak corresponding to their molecular formula. Besides this compounds showed appropriate isotopic abundances which confirmed the presence of halo groups in respective compounds. Finally the identity of synthesized aurones was established by m.p. with samples prepared by reported methods [29] and superimposable IR spectra. All newly synthesized compounds were also evaluated for their *in-vitro* trypanocidal evaluation.

2.2. *In Vitro* Trypanocidal Evaluation

The trypanocidal activity of compounds was evaluated by the colorimetric method based on reduction of the substrate chlorophenolred-β-d-galactopyranoside (CPRG) for β-galactosidase resulting from the expression of the gene for *T. cruzi* (Tulahuen C4) [31]. The assay was realised in 96 wells plates containing monolayer VERO cells which were infected with 5×10^4 trypomastigotes (Tulahuen C4). We grew the parasite using VERO cells that are infected with *T. cruzi* trypomastigotes. The parasite is in the trypomastigote stage before it infects the cells. Once it infects the Vero cells, it enters an amastigotes stage and begins to reproduce as amastigotes. When it is released from the cells, it returns to the original trypomastigote stage to infect new cells. All the active compounds showed anti-trypanocidal activity, passed through a second test for determining the inhibitory concentration of 50% growth of the parasites (IC_{50}). These compounds were evaluated at 10, 2, 0.4, 0.8 and 0.16 μg/mL and incubated for 5 days at 37˚C, relative humidity 95% and 5% CO_2.

The intensity of colour resulting from the cleavage of CPRG by *T. cruzi* (Tulahuen C4) β-galactosidase was measured at 570 nm using a reader boards VersaMax Micro™ microplate reader. The IC_{50} of the compound were calculated by logarithmic regression of the values of OD obtained, compared with the untreated control. Those samples showing IC_{50} values < 50 μg/mL, have been further tested for cytotoxicity. Nifurtimox (Bayer) was used as a control at concentrations of 0.1, 1 and 10 μg/mL. Negative Control was comprised of 50 uL of a solution containing DMSO, equivalent to the DMSO contained in samples (working dilution).

2.3. Biological Evaluation of the Synthesized Compounds

All the synthesized 2-(substituted benzylidene)-5,7-dibromo-6-hydroxy-1-benzofuran-3(2*H*)-ones have been biologically evaluated against *T. cruzi* wherein two compounds **2b** and **2k** showed highest percentage Growth Inhibition (GI) 54.37 and 68.03 respectively. The IC_{50} value appeared as 8.37 (μg/mL) and 5.06 (μg/mL) for compounds **2b** and **2k** respectively with the standard drugs Nifurtimox and Benznidazole which were used to validate the assay. Cytotoxicity of compounds **2b (**25 μg/mL) and **2k** (37 μg/mL) were also tested. The results are shown in **Tables 1** and **2**.

3. Experimental

3.1. General

All melting points (m.ps.) were determined in open capillaries on Veego (VMP-PM) melting point apparatus and are uncorrected. The purity of the compounds was routinely checked by thin layer chomatography (TLC) with Silica Gel-G (Merck). The instruments used for spectroscopic data are: IR-FTIR spectrophotometer Bruker, ^{1}H NMR and ^{13}C NMR ($CDCl_3$) on 500 MHz FT-NMR spectrometer Bruker AV III, GC-MS (EI-MS fragment) performed on JEOL GC Mass spectrometer and elemental analysis was carried out on a Carlo Erba 1108 analyzer and were within the ±0.5% of the theoretical values.

3.2. General Procedure for the Synthesis of 2-(Substituted benzylidene)-5,7-dibromo-6-hydroxyl-1-benzofuran-3(2*H*)-ones (2a-n)

$CuBr_2$ (10 - 15 mg) was dissolved in DMF-water mixture

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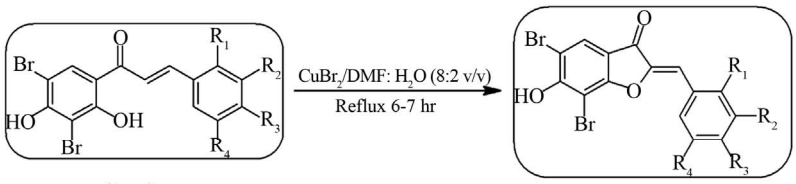

ENtry	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	2m	2n
R_1	H	Cl	H	Cl	H	H	H	H	OH	CH_3	H	H	H	H
R_2	H	H	H	H	OH	OCH_3	OCH_3	OCH_3	H	H	H	H	H	NO_2
R_3	H	H	Cl	Cl	OCH_3	OCH_3	OCH_3	OH	H	H	Br	F	OCH_3	H
R_4	H	H	H	H	H	H	OCH_3	Br	Br	H	H	H	H	H

Scheme 1. Synthesis of the title compounds (2a-n). A novel series of some 2-(substituted benzylidene)-5,7-dibromo-6-hydroxy-1-benzofuran-3(2*H*)-ones 2a-n was been synthesized by the oxidative cyclization of variously substituted chalcones using copper bromide in the presence of DMF-water mixture (8:2, v/v).

Table 1. Biological evaluation of 2-(substituted benzylidene)-5,7-dibromo-6-hydroxyl-1-benzofuran-3(2*H*)-ones against *Trypanosoma cruzi*; % Growth inhibition.

Entry	Concentration used	% Growth Inhibition	Entry	Concentration Used	% Growth Inhibition
2a	10 ug/mL	15.72	**2i**	10 ug/mL	3.25
2b	10 ug/mL	54.37	**2j**	10 ug/mL	24.71
2c	10 ug/mL	20.18	**2k**	10 ug/mL	68.03
2d	10 ug/mL	23.74	**2l**	10 ug/mL	19.63
2e	10 ug/mL	27.70	**2m**	10 ug/mL	7.77
2f	10 ug/mL	16.15	**2n**	10 ug/mL	3.86
2g	10 ug/mL	32.99	**Nifurtimox**	10 ug/mL	68.50
2h	10 ug/mL	4.12	**Benznidazole**	10 ug/mL	86.77

*Each value is the mean of three experiments.

Table 2. Biological evaluation of active samples against *Trypanosoma cruzi*; IC_{50} and Cytotoxicity.

Entry	Concentration used	% Growth Inhibition	*[a]IC_{50} (ug/mL)	[b]Cytotoxicity (ug/mL)
2b	10 ug/mL	54.37	8.37	25
2k	10 ug/mL	68.03	5.06	37
Nifurtimox	10 ug/mL	68.50	0.47	27
Benznidazole	10 ug/mL	86.77	0.81	>50

*[a]IC_{50}: concentration that produces 50% inhibitory effect, [b]cytotoxicity: dose required to produce of 50% cell LLCMK2.

(8:2, v/v) and to this substituted 3',5'-dibromo-2',4'-dihydroxychalcones **1a-n** (0.02 mol) were added. The resulted solution was refluxed for 6 - 7 hr. After the completion of reaction (monitored by TLC) the reaction mixture was cooled, and diluted with 50% ice cold water. The product obtained was filtered and purified by re-crystallization from ethanol afforded pure samples of **2a-n**. We tried different DMF: water mixture ratio (5:5 v/v, 6:4 v/v, 7:3 v/v, 8:2 v/v) and finally the ratio 8:2 v/v was found most suitable with improved yield (63% - 73%).

Characterizations of the synthesized products are as follows:

(2*Z*)-2-benzylidene-5,7-dibromo-6-hydroxy-1-benzofuran-3(2*H*)-one (2a): Light brown solid; yield, 63%; mp 90˚C - 91˚C; IR spectrum, *v*, cm^{-1}: 3377 (Ar-OH), 3071, 3009 (Ar-H), 1699 (-C=O), 1642 (-C=CH), 862 (C-Br), 754 (-C-O-C). ^1H NMR spectrum (500 MHz,

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$CDCl_3$), δ, ppm, (*J*, Hz): 9.93 (s, 1H, Ar-OH), 7.95 (s, 1H, Ar-H), 7.42 - 7.08 (m, 5H, Ar-H), 6.77 (s, 1H, =CHPh). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 190.27, 157.91, 152.93, 147.99, 137.43, 135.21, 130.28, 129.82, 126.05, 114.62, 110.15, 105.62, 78.22. MS, *m/z*: 395.80 (M^+). Anal. Calcd For $C_{15}H_8Br_2O_3$: Found, %: C, 45.52; H, 2.10. Calculated, %: C, 45.48; H, 2.02.

(2*Z*)-5,7-dibromo-2-(2-chlorobenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one (2b): Light brown solid; yield, 65%; mp 193˚C - 194˚C; IR spectrum, *v*, cm^{-1}: 3374 (Ar-OH), 3084, 3005 (Ar-H), 1701 (-C=O), 1641 (-C=CH), 862 (C-Br), 753 (C-Cl), 758 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm, (*J*, Hz): 9.89 (s, 1H, Ar-OH), 7.89 (s, 1H, Ar-H), 7.48 - 7.17 (m, 4H, Ar-H), 6.77 (s, 1H, =CHPh). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 188.49, 159.26, 155.66, 139.16, 135.21, 130.28, 129.60, 125.37, 114.68, 103.62, 79.19, 76.15. MS, *m/z*: 430.30 (M^+). Anal. Calcd For $C_{15}H_7Br_2O_3Cl$: Found, %: C, 41.87; H, 1.70. Calculated, %: C, 41.83; H, 1.62.

(2*Z*)-5,7-dibromo-2-(4-chlorobenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one (2c): Brown solid; yield, 64%; mp 99˚C - 100˚C; IR spectrum, *v*, cm^{-1}: 3364 (Ar-OH), 3083, 3013 (Ar-H), 1705 (-C=O), 1646 (-C=CH), 862 (C-Br), 763 (-C-O-C), 753 (C-Cl). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm, (*J*, Hz): 9.91 (s, 1H, Ar-OH), 7.73 (s, 1H, Ar-H), 7.78 - 7.27 (m, 4H, Ar-H), 6.89 (s, 1H, =CHPh). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 186.49, 158.26, 156.61, 137.16, 134.21, 130.38, 123.37, 114.81, 105.62, 78.19, 76.77, 64.19. MS, *m/z*: 430.30 (M^+). Anal. Calcd For $C_{15}H_7Br_2O_3Cl$: Found, %: C, 41.78; H, 1.67. Calculated, %: C, 41.83; H, 1.62.

(2*Z*)-5,7-dibromo-2-(2,4-dichlorobenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one (2d): Brown yellow solid; yield, 69%; mp 219˚C - 220˚C; IR spectrum, *v*, cm^{-1}: 3390 (Ar-OH), 3078, 3005 (Ar-H), 1699 (-C=O), 1648 (-C=CH), 862 (C-Br), 783,753 (C-Cl), 778 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm, (*J*, Hz): 9.97 (s, 1H, Ar-OH), 7.91 (s, 1H, Ar-H), 7.78 - 7.07 (m, 3H, Ar-H), 6.83 (s, 1H, =CHPh). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 188.49, 157.26, 155.61, 135.16, 130.08, 125.37, 112.81, 104.62, 81.19, 76.77. MS, *m/z*: 464.80 (M^+). Anal. Calcd For $C_{15}H_6Br_2O_3Cl_2$: Found, %: C, 38.80; H, 1.35. Calculated, %: C, 38.73; H, 1.29.

*(***2*Z*)-5,7-dibromo-6-hydroxy-2-(3-hydroxy-4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (2e):** Light brown solid; yield, 65%; mp 200˚C - 201˚C; IR spectrum, ν, cm^{-1}: 3364 (Ar-OH), 3089, 3009 (Ar-H), 1707 (-C=O), 1638 (-C=CH), 1034 (-OCH_3), 862 (C-Br), 767 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm, (*J*, Hz): 10.12 (s, 1H, Ar-OH), 7.88 - 7.27 (m, 4H, Ar-H), 7.61 (s, 1H, Ar-H), 6.85 (s, 1H, =CHPh), 3.73 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 189.49, 155.26, 152.31, 139.96, 134.78, 115.37, 111.27, 80.39, 77.27, 56.19. MS, *m/z*: 441.80 (M^+). Anal. Calcd. for $C_{16}H_{10}Br_2O_5$: Found, %: C, 43.93; H, 3.69. Calculated, %: C, 43.83; H, 3.62.

(2*Z*)-5,7-dibromo-2-(3,4-dimethoxybenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one (2f): Brown solid; yield, 70%; mp 129˚C - 130˚C; IR spectrum, *v*, cm^{-1}: 3389 (Ar-OH), 3069, 3012 (Ar-H), 1711 (-C=O), 1648 (-C=CH), 862 (C-Br), 754 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm, (*J*, Hz): 9.85 (s, 1H, Ar-OH), 7.98 - 7.41 (m, 3H, Ar-H), 7.84 (s, 1H, Ar-H), 6.87 (s, 1H, =CHPh), 3.86 (s, 6H, Ar-OCH_3). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 189.21, 153.38, 149.31, 137.86, 134.70, 116.49, 107.74, 79.31, 76.76, 57.74. MS, *m/z*: 455.80 (M^+). Anal. Calcd. for $C_{17}H_{12}Br_2O_5$: Found, %: C, 44.87; H, 2.58. Calculated, %: C, 44.76; H, 2.63.

(2*Z*)-5,7-dibromo-6-hydroxy-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (2g): Light yellow solid; yield, 71%; mp 149˚C - 150˚C; IR spectrum, ν, cm^{-1}: 3399 (Ar-OH), 3059, 3005 (Ar-H), 1706 (-C=O), 1649 (-C=CH), 862 (C-Br), 786 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm, (*J*, Hz): 9.87 (s, 1H, Ar-OH), 7.98 - 7.35 (d, 2H, Ar-H), 7.89 (s, 1H, Ar-H), 6.83 (s, 1H, =CHPh), 3.83 (s, 9H, Ar-OCH_3). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 189.29, 152.39, 148.51, 138.86, 135.70, 117.41, 108.74, 79.31, 77.76, 55.44. MS, *m/z*: 485.80 (M^+). Anal. Calcd. for $C_{18}H_{14}Br_2O_6$: Found, %: C, 44.55; H, 2.76. Calculated, %: C, 44.46; H, 2.88.

(2*Z*)-5,7-dibromo-2-(3-bromo-4-hydroxy-5-methoxybenzylidene)-6-hydroxy-1-benzofura-3(2*H*)-one (2h): Light brown solid; yield, 68%; mp 169˚C - 170˚C; IR spectrum, ν, cm^{-1}: 3392 (Ar-OH), 3059, 3006 (Ar-H), 2848 (-OCH_3), 1709 (-C=O), 1643 (-C=CH), 862 (C-Br), 783 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm, (*J*, Hz): 9.93, 9.86 (2s, 2H, 2 × Ar-OH), 7.91 (s, 1H, Ar-H), 7.82 - 7.87 (d, 2H, Ar-H), 6.83 (s, 1H, =CHPh), 3.83 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 189.29, 155.19, 148.53, 141.11, 128.90, 115.41, 107.74, 81.92, 77.01, 55.44. MS, *m/z*: 520.70 (M^+). Anal. Calcd. for $C_{16}H_9Br_3O_5$: Found, %: C, 36.94; H, 1.79. Calculated, %: C, 36.87; H, 1.73.

(2*Z*)-5,7-dibromo-2-(5-bromo-2-hydroxybenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one (2i): Brown solid; yield, 70%; mp 182˚C - 183˚C; IR spectrum, ν, cm^{-1}: 3394 (Ar-OH), 3054, 3009 (Ar-H), 1701 (-C=O), 1641 (-C=CH), 862 (C-Br), 786 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm, (*J*, Hz): 9.91, 9.78 (2s, 2H, Ar-OH), 7.93 (s, 1H, Ar-H), 7.89 - 7.91 (m, 3H, Ar-H), 6.82 (s, 1H, =CHPh). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 192.29, 156.57, 149.53, 137.11, 130.32, 114.34, 107.74, 76.76. MS, *m/z*: 490.70 (M^+). Anal. Calcd. for $C_{15}H_7Br_3O_4$: Found, %: C, 36.74; H, 1.48. Calculated, %: C, 36.68; H, 1.42.

*(***2*Z*)-5,7-dibromo-6-hydroxy-2-(2-methylbenzylidene)-1-benzofuran-3(2*H*)-one (2j):** Brown solid; yield,

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69%; mp 139˚C - 140˚C; IR spectrum, ν, cm^{-1}: 3392 (Ar-OH), 3061, 3007 (Ar-H), 1699 (-C=O), 1644 (-C=CH), 862 (C-Br), 783 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm, (*J*, Hz): 9.97 (s, 1H, Ar-OH), 7.96 (s, 1H, Ar-H), 7.89 - 7.18 (m, 4H, Ar-H), 6.87 (s, 1H, =CHPh), 2.68 (s, 3H, $-CH_3$). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 190.29, 152.39, 149.51, 137.82, 129.90, 114.41, 106.74, 79.92, 76.77, 29.23. MS, *m/z*: 409.80 (M^+). Anal. Calcd. for $C_{16}H_{10}Br_2O_3$: Found, %: C, 46.90; H, 2.50. Calculated, %: C, 46.85; H, 2.44.

(2*Z*)-5,7-dibromo-2-(4-bromobenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one (2k): Light brown solid; yield, 68%; mp 225˚C - 226˚C; IR spectrum, ν, cm^{-1}: 3406 (Ar-OH), 3061, 3007 (Ar-H), 1711 (-C=O), 1648 (-C=CH), 862 (C-Br), 781 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), *δ*, ppm, (*J*, Hz): 9.93 (s, 1H, Ar-OH), 7.96-7.31 (m, 4H, Ar-H), 7.93 (s, 1H, Ar-H), 6.89 (s, 1H, =CHPh). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 191.19, 156.39, 149.51, 141.81, 129.90, 116.41, 108.74, 81.92, 78.72. MS, *m/z*: 474.70 (M^+). Anal. Calcd For $C_{15}H_7Br_3O_3$: Found, %: C, 37.97; H, 1.54. Calculated, %: C, 37.92; H, 1.47.

(2*Z*)-5,7-dibromo-2-(4fluorobenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one (2l): Light brown solid; yield, 73%; mp 180˚C - 181˚C; IR spectrum, ν, cm^{-1}: 3491 (Ar-OH), 3083, 3013 (Ar-H), 1705 (-C=O), 1649 (-C=CH), 1244 (C-F), 862 (C-Br), 763 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), *δ*, ppm, (*J*, Hz): 9.83 (s, 1H, Ar-OH), 7.89 (s, 1H, Ar-H), 7.78 - 7.34 (m, 4H, Ar-H), 6.79 (s, 1H, = CHPh). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 191.29, 154.26, 149.31, 137.86, 134.70, 116.49, 108.85, 79.31, 76.77, 56.14. MS, *m/z*: 413.80 (M^+). Anal. Calcd For $C_{15}H_7Br_2O_3F$: Found, %: C, 43.57; H, 1.62. Calculated, %: C, 43.50; H, 1.69.

(2*Z*)-5,7-dibromo-6-hydroxy-2-(4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (2m): Brown solid; yield, 69%; mp 87˚C - 88˚C; IR spectrum, ν, cm^{-1}: 3402 (Ar-OH), 3059, 3005 (Ar-H), 1713 (-C=O), 1649 (-C=CH), 859 (C-Br), 781 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), *δ*, ppm, (*J*, Hz): 9.90 (s, 1H, Ar-OH), 7.93 (s, 1H, Ar-H), 7.84 - 7.28 (m, 4H, Ar-H), 6.84 (s, 1H, =CHPh), 3.88 (s, 3H, $-OCH_3$). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 189.27, 157.93, 148.02, 137.47, 128.59, 115.19, 107.73, 79.03, 78.37, 55.17. MS, *m/z*: 425.80 (M^+). Anal. Calcd For $C_{16}H_{10}Br_2O_4$: Found, %: C, 45.15; H, 2.42. Calculated, %: C, 45.09; H, 2.35.

(2*Z*)-5,7-dibromo-6-hydroxy-2-(3-nitrobenzylidene)-1-benzofuran-3(2*H*)-one (2n): Brown solid; yield, 71%; mp 182˚C - 183˚C; IR spectrum, ν, cm^{-1}: 3390 (Ar-OH), 3061, 3006 (Ar-H), 1708 (-C=O), 1639 (-C=CH), 1531 (Asy Ar-NO_2), 1350 (Sym Ar-NO_2), 862 (C-Br), 786 (-C-O-C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), *δ*, ppm, (*J*, Hz): 9.91 (1s, 1H, Ar-OH), 7.97 (s, 1H, Ar-H), 7.87 - 7.34 (m, 4H, Ar-H), 6.89 (s, 1H, =CHPh). ^{13}C NMR (500 MHz, $CDCl_3$) ppm: 192.19, 163.27, 156.85, 147.25, 137.73, 130.34, 127.87, 122.28, 114.50, 108.95, 79.26, 77.29. MS, *m/z*: 440.80 (M^+). Anal. Calcd For $C_{15}H_7Br_2O_5N$: Found, %: C, 40.90; H, 1.63; N, 3.13. Calculated, %: C, 40.83; H, 1.58; N, 3.17.

4. Conclusion

Two noteworthy have emerged. Firstly, a novel series of 2-(substituted benzylidene)-5,7-dibromo-6-hydroxy-1-benzofuran-3(2*H*)-ones have been synthesized from corresponding chalcones using environmentally benign protocols. Secondly, it was observed from the results obtained by the trypanocidal evaluation that Compounds **2b** and 2**k** were the more potent, showing good % GI and considered as an active and selected for second level biological evaluation IC_{50}. Compounds **2b** and 2**k** were also tested for cytotoxicity and the results obtained are appreciable in accordance with standard drugs Nifurtimox and Benznidazole. These preliminary results of biological assay of the tested compounds are encouraging which may lead to the discovery of potent trypanocidal drug.

5. Acknowledgements

The authors are thankful to Dr. Sunil Jhakhoria, Dean, FASC, MITS University for his constant encouragement during this work. Authors are also thankful to the Head, Sophisticated Analytical Instrument Facility, Indian Institute of Technology, Madras for spectral analysis.

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