IJPSR (2021), Volume 12, Issue 3 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 17 March 2020; received in revised form, 18 June 2020; accepted, 25 June 2020; published 01 March 2021

SYNTHESIS OF 2-(2-(2-(BIS (2-CHLOROETHYL) AMINO) ETHOXY) BENZYLIDENE) BENZOFURAN - 3(2H) - ONE DERIVATIVES ON BASIS OF BENZALDEHYDES AND ACETOPHENONES FOR ITS CYTOTOXIC ACTIVITY

Agasa Ramu Mahesh * and Vedigounder Murugan

Department of Pharmaceutical Chemistry, College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru - 560078, Karnataka, India.

Keywords:

Benzofuranone, Nitrogen mustard, Acetophenone, MTT, Cytotoxicity

Correspondence to Author:
Agasa Ramu Mahesh

Assistant Professor,
Department of Pharmaceutical Chemistry, College of Pharmaceutical Sciences,
Dayananda Sagar University,
Bengaluru - 560078, Karnataka, India.

E-mail: mahesh-sps@dsu.edu.in

ABSTRACT: Benzofuranones and nitrogen mustards have been reported as highly potential alkylating agents; with this evidence, the synthesis of some benzofuranones fused with nitrogen mustards was planned and was subjected to *in-vitro* cytotoxic studies. Substituted benzofuranones were synthesized by condensation of 2-hydroxy benzaldehydes and substituted 2-hydroxy acetophenones and further fused with nitrogen mustards gave high yields of target compounds 2 - (2 - (2 - (Bis (2 - chloroethyl) amino) ethoxy) benzylidene) benzofuran-3(2H)-one derivative. The derivatives synthesized had various halo substitutions such as chloro, bromo, fluro and methyl chloro derivatives. These synthesized compounds were characterized by FTIR, ^{1}H NMR and LCMS spectral studies. Further, the synthesized compounds were subjected to 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide assay on human lung carcinoma cells, A-549 and breast cancer cells, MCF-7 for its *in-vitro* cytotoxic activity. All the synthesized compounds showed promising cytotoxic activity in which AN – O - 04, (Z) - 2 - (2 - (2 - (bis (2 -chloroethyl) amino) ethoxy) benzylidene) -5 - chloro - 6-methylbenzofuran-3(2H)-oneshowed minimum CTC-50 of 119.32 ± 8.98 and 82.18 ± 6.23 for A-549 and M-549 cell lines respectively which indicates the potency of the synthesized compounds against A-549 and MCF-7 cell lines.

INTRODUCTION: 2-Hydroxy benzaldehydes and 2-Hyroxy acetophenones are economical and readily available reagents for organic synthesis; an effective method for the preparation of benzofuranone derivatives have been reported on the basis of fusing of benzaldehydes and acetophenones [1, 2]. Aurones, a class of flavonoids compound signifies some of the less studied secondary metabolites of natural compounds, which are known to parades a wide range of biological activity [3-6].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(3).1723-28

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(3).1723-28

Based on our former investigation regarding the synthetic potential of chalcones by condensation of benzaldehydes with acetophenones, we designed the synthesis of 2-(2-(2-(Bis (2-chloroethyl) amino) ethoxy) benzylidene) benzofuran - 3 (2H) - one derivatives [7]. Aurones and their derivatives signify a group of heterocyclic compounds which are claimed to contain widespread applications in the field of drug discovery containing benzofuranone moiety.

A number of Aurones are isolated from several natural sources, such as Cyperaceae and *Cyperus capitatus* family [8-9]. These derivatives are reported for their persuasive Anti-neoplastic, antidiabetic and anti-inflammatory activities. Alkylating neoplastic agents such as nitrogen mustards interfere with cellular proliferation [10-12]. In the current work, we report the synthesis of a series of

substituted 2-(2-(2-(Bis (2-chloroethyl) amino) ethoxy) benzylidene) benzofuran-3(2H)-one derivative from 2-Hydroxy benzaldehydes and 2-Hydroxy acetophenones as the starting material to synthesize chalcones which on cyclizing using mercuric acetate gave benzofuranone's and further attaching of nitrogen mustards to the synthesized benzofuranone's. The synthesized compounds were subjected to *In-vitro* cytotoxic activity by MTT assay procedure using A-549 and MCF-7 Cell lines [13, 14].

MATERIALS AND METHODS: The chemicals and the solvents used in the present project work were purchased from Sigma Aldrich and Merck India.

Thin Layer Chromatography (TLC): Purity of the synthesized compounds and progress of reactions were monitored by Thin layer chromatography using silica gel-G as stationary phase and various mobile phases were used such as n-Hexane: Ethyl acetate (2:1), CH_2Cl_2: MeOH (9:1), Hexane: Acetic acid (9:1), Hexane: Ethyl acetate: Acetic acid (various ratio's like 5:4:1, 4:4:2, 3:6:1, 2:7:1), Chloroform: Ethyl acetate: Acetic acid (5:4:1). The spots resolved were visualized using UV and Iodine chamber.

IR Spectra: The IR spectra of the synthesized compounds were recorded on a Fourier Transform IR spectrometer (model Shimadzu 8400S) in the range of 400-4000 by KBr pellet method, and the values of V max are reported in cm^{-1}.

^{1}H NMR Spectra: Nuclear magnetic resonance spectra were obtained on 400 MHz Bruker Supercon using DMSO. The chemical shifts (δ) are reported in parts per million downfield from standard internal reference Tetramethyl silane (TMS).

Mass Spectra: Mass spectra were recorded on an LCMS 2010, Shimadzu, Japan using Auto spectra ionization negative ion mode. General scheme for the synthesis of Compound 1; tri (2-chloroethyl) amine hydrochloride. To a stirred solution of compound 1 (1 eq) in $SOCl_2$ (10 Vol), DMF (Catalyst) was added at 0 °C and slowly increased the temperature to 80 °C and allowed to stir for 8 h. After completion of the reaction, which was confirmed by TLC, the reaction mixture was evaporated under reduced pressure to obtain crude precipitate [2]. The precipitate thus obtained was taken for the next step without further purification. Scheme showed as in **Fig. 1.**

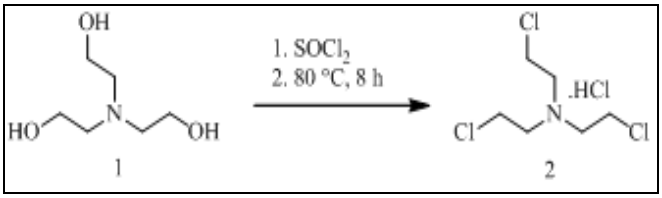

FIG. 1: GENERAL SCHEME FOR SYNTHESIS OF TRIS (2 - CHLOROETHYL) AMINE HYDROCHLORIDE (SCHEME-1)

General procedure for the synthesis of compound (4); 2-(2- (Bis (2-chloroethyl) amino) ethoxy) benzaldehyde. To a stirred solution of compound 3 (1 eq) in ACN, K_2CO_3 (4 eq) was added at 0 °C and stirred for 10 minutes, added compound 2 (2 eq) then the reaction mixture was allowed to stir at 60 °C for 4 h. After completion of the reaction was confirmed by TLC, the reaction mixture was quenched with ice water, extracted with EtOAc. The combined organic layer was washed with brine solution, dried over sodium sulphate, filtered, and evaporated under reduced pressure to obtain a crude product. The crude product thus obtained was purified by column chromatography using silica gel (100-200 mesh) eluted with 8-10% EtOAc in hexane to afford compound 4 as yellow solid. The scheme is shown as in **Fig. 2.**

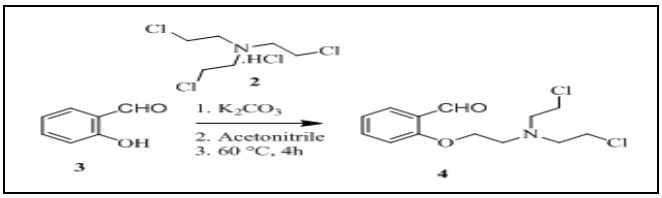

FIG. 2: SYNTHESIS OF COMPOUND (4), 2 - (2- (BIS (2-CHLOROETHYL) AMINO) ETHOXY) BENZALDEHYDE

General procedure for the synthesis of compound (6); Derivatives of 3 - (2 - (2 - (Bis (2 -chloroethyl) amino) ethoxy) phenyl) - 1 - (2 -hydroxyphenyl) prop - 2 - en - 1 – one. To the suspension of compound 4 (1.0 eq) in ethanol, compound 5 (1.0 eq) was added at 0 °C and allowed to stir for 15 min. Then $SOCl_2$ (0.5 V) was added dropwise, and the reaction mixture was allowed to stir at room temperature for 16 h. After completion of the reaction was confirmed by TLC, the reaction mixture was evaporated to dryness, diluted with water, and extracted with EtOAc; the combined organic layer was washed with saturated brine

solution, dried over sodium sulphate and evaporated under reduced pressure to get crude precipitate. The precipitate thus obtained was purified by column chromatography using silica gel (100-200 mesh) eluted with EtOAc in hexane to afford compound 6. Scheme shown as in **Fig. 3**.

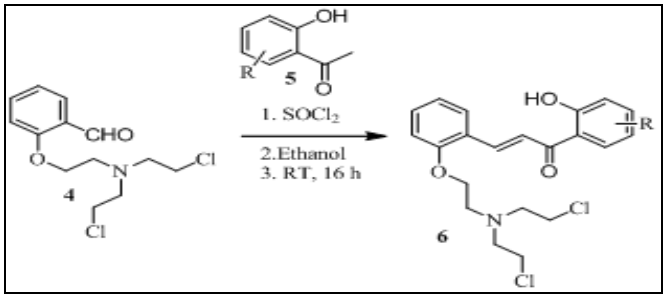

FIG. 3: SYNTHESIS OF COMPOUND (6); DERIVATIVES OF 3 - (2 - (2 - (BIS (2 -CHLOROETHYL) AMINO) ETHOXY) PHENYL)-1-(2 HYDROXYPHENYL) P ROP-2-EN-1-ONE

General procedure for the synthesis of compound (7); Derivatives of 2-(2-(2-(Bis (2-chloroethyl) amino) ethoxy) benzylidene) benzofuran-3(2H)-one. To a stirred solution of compound 6 (1 eq) in polyethylene glycol at room temperature was added mercury acetate (1 eq), and the reaction mixture was allowed to stir at 120 °C for 4 h. After completion of the reaction was confirmed by TLC, the reaction mixture was quenched with ice water, extracted with EtOAc. The combined organic layer was washed with brine solution, dried over sodium sulphate, filtered, and evaporated under reduced pressure to obtain crude residue. The crude thus obtained was purified by column chromatography using silica gel (100-200 mesh) eluted with 8-10% EtOAc in hexane to afford compound 7 as yellow solid. Scheme shown as in **Fig. 4.**

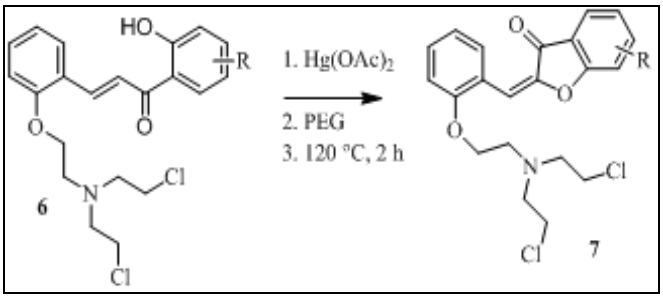

FIG. 4: SYNTHESIS OF COMPOUND (7); DERIVATIVES OF 2 - (2 - (2 - (BIS (2 - CHLOROETHYL) AMINO) ETHOXY) BENZYLIDENE) BENZOFURAN-3 (2H)-ONE

***In-vitro* Cytotoxic Studies:** 3 - (4, 5-dimethylthiazol - 2 - yl) - 2, 5 - diphenyl tetrazolium bromide (MTT) with Batch No. 0000228429 was purchased from Hi-media.

The following equipment's were used for the study, Biosafety cabinet (Ascesension, India), CO_2 incubator (NUAIRE, USA), Inverted microscope (Motic, China), automated microplate reader (Biotek, USA) and -20 ºC (Vest frost). The *in-vitro* cytotoxicity was performed for test substance on Human Lung carcinoma cell line A-549 to find a toxic concentration of the test substances by MTT assay.

Preparation of Test Solution: 10 mg of the test substance was separately dissolved in 100 µl of DMSO, and volume was made up with DMEM-HG supplemented with 2% inactivated FBS to obtain a stock solution of 1 mg/ml concentration and sterilized by 0.22 µ syringe filtration. Serial two-fold dilutions were prepared from this stock solution for further studies.

Cell line and Culture Medium: Human Lung carcinoma cells, A-549, and Breast cancer cells MCF-7 were obtained from National Centre for Cell Sciences (NCCS, Pune, India) and were cultured in DMEM-HG media supplemented with 10% inactivated Fetal Bovine Serum (FBS), penicillin (100 IU/ml), streptomycin (100 µg/ml) and amphotericin B (5 µg/ml) in a humidified atmosphere of 5% CO2 at 37 ºC until confluent. The cells were dissociated with TPVG solution (0.2% trypsin, 0.02% EDTA, 0.05% glucose in PBS). The stock cultures were grown in 25 cm^2 culture flasks, and all experiments were carried out in 96 well microtitre plates (Tarsons India Pvt. Ltd., Kolkata, India).

Cytotoxicity Studies: The monolayer cell culture was trypsinized, and the cell count was adjusted to 1.0 × 105 cells/ml using respective media *viz*., DMEM-HG containing 10% FBS. To each well of the 96 well microtitre plate, 0.1 ml of the diluted cell suspension was added.

After 24 h, when a partial monolayer was formed, the supernatant was flicked off, the monolayer was washed once with medium, and 100 µl of different concentrations of test substances were added. The plate was then incubated at 37 ºC for 72 h in 5% CO_2 atmosphere, and microscopic examination was carried out, and observations were noted for every 24 h time interval. The cell viability is assessed by MTT reduction assay.

After 72 h of incubation, the drug solutions in the wells were discarded, and 50 µl of MTT in PBS was added to each well. The plates were gently shaken and incubated for 3 hr at 37 ºC in 5% CO_2 atmosphere. The supernatant was removed, and 100 µl of DMSO was added, and the plate was gently shaken to solubilize the formed formazan. The absorbance was measured using a microplate reader at a wavelength of 540 nm. The plates were protected from light throughout the procedure. The percentage growth inhibition was calculated using the standard formula and concentration of test substances needed to inhibit the growth of the cell by 50%, *i.e*., CTC_{50} values were generated from the dose-response curves. The inhibition was expressed as the percentage relative to the cell control [15].

RESULTS AND DISCUSSION: The general structure of the synthesized compounds is as shown in **Fig. 5,** and the details of molecular weight, Yield, m/z, Melting point, Purity and the molecular formula is as given in **Table 1**. The cytotoxic effect of the test substances on A-549 cells and MCF-7 are shown in **Fig. 6** and **7,** respectively.

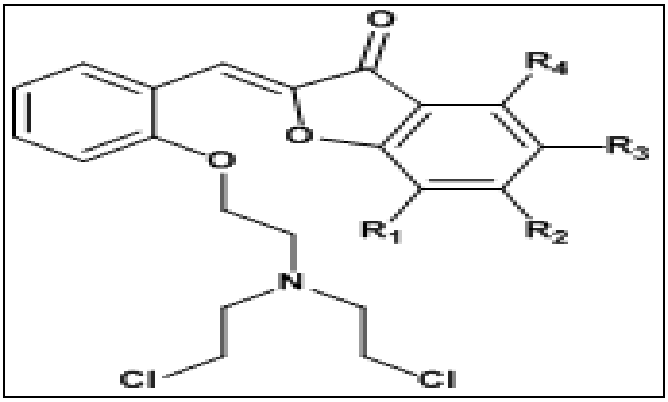

FIG. 5: SYNTHESIZED DERIVATIVES OF 2-(2-(2-(BIS (2-CHLOROETHYL) AMINO) ETHOXY) BENZYLIDENE) BENZOFURAN-3(2H)-ONE

TABLE 1: LIST OF SYNTHESIZED COMPOUNDS

S. no.	Product code	Mol formula	R_1	R_2	R_3	R_4	Mol. Wt.	Yield (mg)	m/z	Melting Point (ºC)	Purity %
1	AN-O-01	$C_{21}H_{21}Cl_2NO_3$	H	H	H	H	406	57	405.09	370-374	81.21
2	AN-O-02	$C_{21}H_{19}Cl_4NO_3$	Cl	H	Cl	H	475	26	476.1	455-459	93.88
3	AN-O-03	$C_{21}H_{20}BrCl_2NO_3$	H	H	Br	H	485	25	485	442-447	76.07
4	AN-O-04	$C_{22}H_{22}Cl_3NO_3$	H	CH_3	Cl	H	454	12	453.07	435-439	88.61
5	AN-O-05	$C_{21}H_{20}Cl_2FNO_3$	H	H	F	H	424	21	423.08	381-388	94.05

Spectral Data: AN-O-01: 2 - (2 - (2 - (Bis (2 - chloroethyl) amino) ethoxy) benzylidene) benzofuran - 3(2H) - one: Yellow Solid, IR spectrum (cm^{-1}): 3250.17 (CH-CH), 1792.92 (C=O), 1330.22 (C-O-C), 710 (C-Cl), ^{1}H NMR ($CDCl_3$): 8.29-8.31(d, J=8 Hz, ^{1}H, 7.80-7.82 (d, J=8Hz, 1H), 7.62-7.66 (t, J=8Hz,^{1}H), 7.31-7.40 (m, 3H), 7.20-7.23 (t, J=8Hz, ^{1}H), 6.92 (d, j=12Hz,^{1}H), 4.11-4.14 (t, J=4Hz,^{2}H), 3.57-3.61 (t, J=8Hz,^{4}H), 3.14-3.17 (t, J=4Hz, ^{2}H), 3.06-3.09 (t, J=8Hz, ^{4}H); m/z: 405.09. AN-O-02: 2 - (2 - (2 - (Bis (2 -chloroethyl) amino) ethoxy) benzylidene) - 5, 7 –dichlorobenzofuran - 3 (2H) - one: Yellow Solid, 3245.07 (CH-CH), 1703.02 (C=O), 1280.14 (C-O-C), 750 (C-Cl), ^{1}H NMR(CDCl3): 8.31-8.33(d, j=8 Hz, ^{1}H), 7.64-7.68 (d, j=8Hz, ^{1}H), 7.43-7.52 (t, J=8Hz,^{1}H), 7.41-7.39 (m, 3H), 7.13-7.25 (t, J=8Hz, ^{1}H), 4.12-4.15 (t, J=4Hz,^{2}H), 3.50-3.60 (t, J=8Hz,^{4}H), 3.15-3.17 (t, J=^{4}Hz, ^{2}H), 3.05-3.089 (t, J=8Hz, 4H); m/z: 476.1. AN-O-03: 2-(2-(2- (Bis(2-chloroethyl) amino) ethoxy) benzylidene) – 5 -bromobenzofuran-3(2H)-one: Yellow Sticky Solid, 3280.16 (CH-CH), 1789.11 (C=O), 1296.242 (C-O-C), 774 (C-Cl), 586 (Ar-Br), ^{1}H NMR (CDCl3): 8.24-8.26(d, J=8 Hz, 1H), 7.91-7.92 (d, J=8Hz, ^{1}H, 7.24-7.42 (m, 3H), 7.21-7.23 (t, J=8Hz, ^{1}H), 4.1-4.13 (t, J=4Hz,^{2}H), 3.50-3.60 (t, J=8Hz,4H), 3.15-3.17 (t, J=4Hz, 2H), 3.008-3.058 (t, J=8Hz, 4H); m/z: 485. AN - O - 04:2 - (2 - (2 - (Bis (2 -chloroethyl) amino) ethoxy) benzylidene) - 5 -chloro-6-methyl-benzofuran - 3(2H) - one: Yellow Solid, 3189.09 (CH-CH), 1765.05 (C=O), 1321.81 (C-O-C), 780 (C-Cl), 1H NMR(CDCl3): 8.22-8.24(d, j=8 Hz, 1H), 7.75(s, j=4Hz, ^{1}H) 7.34-7.37 (m, j=8Hz, ^{2}H) 7.21-7.24 (d, j=8Hz, ^{1}H), 7.04-7.08 (m, ^{1}H), 6.91-6.93 (t, J=8Hz, ^{1}H), 4.1-4.12 (t, J=4Hz,^{2}H), 3.55-3.59 (t, J=8Hz,4H), 3.13-3.59 (t, J=4Hz, ^{2}H), 3.058-3.076 (t, J=8Hz, ^{4}H), 2.39-2.49,(dd, J 8Hz, 3H); m/z: 453.07. AN - O - 05: 2 - (2 - (2 - (Bis (2 - chloroethyl) amino) ethoxy) benzylidene) - 5 - fluorobenzofuran-3(2H)-one: Yellow Solid, 3190.17 (CH-CH), 1689.01 (C=O), 1410 (C-O-C), 790 (C-Cl), 860 (C-F) ^{1}H NMR(CDCl3): 7.36-7.45(d, J=8 Hz, 2H), 7.33-7.54 (d, j=8Hz, 2H), 7.05-7.33 (m, 3H), 6.91-6.93 (t, J=8Hz, ^{1}H), 4.1-4.14 (t, J=4Hz,2H), 3.53-3.60 (t, J=8Hz,^{4}H), 3.14-3.17 (t, J=4Hz, 2H), 3.03-3.08 (t, J=8Hz, ^{4}H); m/z: 423.08

Cytotoxicity Studies:

TABLE 2: CYTOTOXIC PROPERTIES (MTT) OF THE TEST SUBSTANCES ON A-549 CELLS AND MCF-7 CELLS

S. no.	Test Substance	MTT (A-549)					MTT (MCF-7)				
		Test Conc (µg/ml)	% CTC	SEM (±)	CTC 50 (µg/ml)	SEM (±)	Test Conc (µg/ml)	% CTC	SEM (±)	CTC 50 (µg/ml)	SEM (±)
1	AN-O-01	1000	80.12	0.48	230.59	9.04	1000	81.44	2.23	256.70	2.67
		500	58.41	3.74			500	60.22	1.43		
		250	49.21	0.48			250	48.01	1.57		
		125	38.11	2.74			125	36.91	1.93		
		62.5	16.97	5.29			62.5	21.88	1.13		
2	AN-O-02	1000	60.25	0.56	529.10	9.10	1000	66.43	0.58	591.32	6.88
		500	41.33	0.71			500	45.63	0.36		
		250	34	2.22			250	32.81	0.77		
		125	23.1	2.88			125	20.54	0.51		
		62.5	10.21	3.98			62.5	16.76	0.42		
3	AN-O-03	1000	69.98	3.92	450.56	9.76	1000	71.63	0.53	452.12	4.32
		500	44.91	0.51			500	51.87	0.31		
		250	25.67	3.11			250	39.01	0.51		
		125	15.86	2			125	27.37	0.76		
		62.5	9.2	3.4			62.5	14.99	0.44		
4	AN-O-04	1000	80.35	5.1	119.32	8.98	1000	91.34	2.98	82.184	6.23
		500	71.2	2.98			500	87.14	1.61		
		250	59.01	2.83			250	85.21	1.28		
		125	52.61	1.9			125	72.29	1.69		
		62.5	43.23	2.54			62.5	38.73	2.09		
5	AN-O-05	1000	84.32	0.48	185.30	6.54	1000	73.92	0.54	181.33	6.21
		500	68.49	3.74			500	69.06	0.41		
		250	56.47	0.48			250	52.99	0.32		
		125	41.1	2.74			125	48.87	0.21		
		62.5	16.97	5.29			62.5	30.09	0.72		

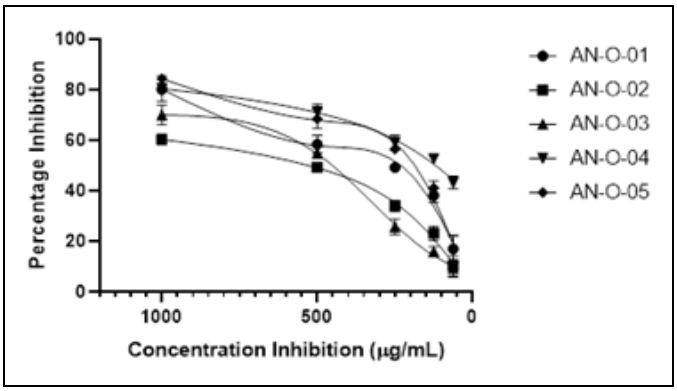

FIG. 6: CYTOTOXIC EFFECT OF THE TEST SUBSTANCES ON MCF-7 CELLS

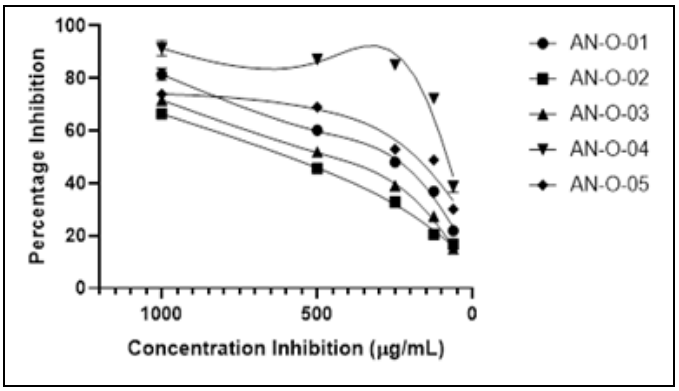

FIG. 7: CYTOTOXIC EFFECT OF THE TEST SUBSTANCES ON A-549 CELLS

CONCLUSION: A new and efficient method to synthesize 2 - (2-(2 - (Bis (2 - chloroethyl) amino) ethoxy) benzylidene) benzofuran-3 (2H) - one and its derivatives was developed. The products were obtained in good yields and acceptable purities. This scheme designed and used for the synthesis of the above-mentioned compounds suggests numerous advantages, including quite simple, time-saving, high-yielding reaction techniques. Overall, the scheme used here is effective and simple. The purity of the compounds ranged from 76 to 94%. The compounds synthesized were subjugated for the *in-vitro* cytotoxic activities through MTT assay on A-549 and MCF-7 cells. All the compounds synthesized showed mild to moderate cytotoxic activities. The test substances were exposed to different concentrations ranging from 1000 µg/ml to 62.5 µg/ml in order to determine the percentage growth inhibition on A549 cells and MCF-7. The test substances. AN-O-01, AN-O-02, AN-O-03, AN-O-04, AN-O-05has exhibited a CTC_{50} value which is 230.59±9.04, 529.10±9.10, 450.56±9.76,

119.32±8.98, 185.30±6.54 µg/ml respectively in A549 cell line and the test substances AN-O-01, AN-O-02, AN-O-03, AN-O-04, AN-O-05 has exhibited a CTC_{50} value which is256.71 ±2.67, 591.32±6.88, 452.12±4.32, 82.18±6.23 and 181.33 ±6.21 µg/ml respectively in MCF-7 cell lines, in which AN-O-04 showed minimum CTC_{50} both in A-549 and MCF-7 cell lines.

ACKNOWLEDGEMENT: The authors would oblige to thank College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru, for their support in providing the research facilities.

CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest regarding the publication of this article.

REFERENCES:

1. Hwang W: Synthesis of aurones through silver-catalyzed intramolecular cyclization from o-alkynonylphenols. Bulletin of the Korean Chem Soc 2018; 39(3): 397-400.
2. Kumar G: Synthesis and biological evaluation of quinoline basednovel aurones. Chemistry Select 2020; 5: 3539-43.
3. Mahesh AR and Murugan V: Synthesis of a biologically pertinent molecule, arones-An extensive review. European J of Biomedical and Pharmaceutical Sci 2016; 3(1): 112-6.
4. Li Y, Chen K, Zhang Y, Sun D and Ye S: N -Heterocyclic carbene-catalyzed 4+2 cyclization of α -chloroaldehydes and aurones: highly enantioselective synthesis of benzofuran fused dihydropyran-2-ones. Chinese Chemical Letters 2018; 29(8): 1209-11.
5. Rullah K: Synthesis, biological evaluation and docking studies of aurone derivatives on xanthine oxidase enzyme. Jurnal Sains Kesihatan Malaysia 2018; 16(1): 135-43.
6. Hassan G, Georgey H, George R and Mohammed E: Construction of some cytotoxic agents with aurone and furoaurone scaffolds. Futu Medi Chem 2018; 10(1): 27-52.
7. Diwaker: Synthesis, spectroscopic characterization, electronic and optical studies of (2Z)-5, 6-dimethyl-2-[(4-nitrophenyl) methylidene - 2, 3 - dihydro - 1 - benzofuran-3-one. J of Computational Science. 2015; 10: 237-46.
8. Antonina V and Popova: Aurones: synthesis and properties. Chemistry of Heterocyclic Compounds 2019; 55(4/5): 285-99.
9. Murugan V, Bhattacharjee S and Mahesh AR: Synthesis and Characterization of N-N- {Bis(2′-Chloroethylamino)-Nitroso}-2-Benzylidene-1-Benzofuran Derivatives as Antileukemic Agents. American Journal of Pharmacy & Health Research 2016; 4(7): 103-10.
10. Liew K: Assessment of the blood brain barrier permeability of potential neuroprotective aurones in parallel artificial membrane permeability assay and porcine brain endothelial cell models. Journal of Pharmaceutical Sciences 2017; 106(02): 502-10.
11. Venkateswarlu S: On water" synthesis of aurones: first synthesis of 4, 5, 3', 4', 5'-pentamethoxy-6-hydroxyaurone from Smilax riparia, Archive for Org Chem 2017; 303-14.
12. Sun H: Synthesis of 6-hydroxyaurone analogues and evaluation of their aglucosidase inhibitory and glucose consumption-promoting activity: Development of highly active 5, 6-disubstituted derivatives, Bioorganic & Medicinal Chemistry Letters 2017; 27: 3226-30.
13. Francis D and Rita L: Rapid colorimetric assay for cell growth and survival modifications to the tetrazolium dye procedure giving improved sensitivity and reliability. Journal of Immunological Methods 1986; 89: 271-77.
14. Alsayari A: Aurone a biologically attractive scaffold as anticancer agent. European Journal of Medicinal Chemistry 2019; 166: 417-31.
15. Mahesh AR and Murugan V: Synthesis of 2- (Bis (2-chloroethyl) amino) - n - (4-((3-oxobenzofuran-2(3h)-ylidene) methyl) phenyl) acetamidederivatives on basis of benzaldehydes and acetophenones as possible alkylating anticancer agents. Am J Pha Tec Res 2020; 10(3): 125-24.

How to cite this article:
Mahesh AR and Murugan V: Synthesis of 2-(2-(2 -(bis (2-chloroethyl) amino) ethoxy) benzylidene) benzofuran-3 (2h)-one derivatives on basis of benzaldehydes and acetophenones for its cytotoxic activity. Int J Pharm Sci & Res 2021; 12(3): 1723-28. doi: 10.13040/IJPSR. 0975-8232.12(3).1723-28.