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Synthesis of 5.6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one derivatives as new leads for anti-cancer activity

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ABSTRACT

Benzofuranone derivatives are of great interest in medicinal chemistry and have drawn considerable attention due to their diverse pharmacological profiles including anticancer activity. Similarly, chalcones, which are common substructures of numerous natural products belonging to the flavonoid class, feature strong anticancer properties. A novel series of 5.6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one derivatives were designed, synthesized, and characterized. In vitro antitumor activities of the newly synthesized (VA-F) were determined by using human skin cancer cell lines. Antitumor properties of all compounds were determined by 5.6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one (MTT) assay. Cell viability assay for the tested flavone compounds was performed, and the values of the compounds were calculated after 24-hour treatment. Our results indicate that the tested benzofuranone compounds show antitumor activity against human skin cancer cell lines.

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INTRODUCTION

Cancer is one of the most important clinical problems worldwide. Among the wide range of compounds approved as potential anticancer agents, derivatives with functionalities as benzofuranones have attracted great interest (Chen Y.L., 2006) Previous studies have proposed that anticancer compounds such as alkylating agents bind directly to various cellular nucleophiles, thus lacking selectivity. However, benzofuranones can be structurally modified so that they can react selectively with target nucleophiles (Ahn B.Z., 1996). Benzofuran the compounds are having 5.6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one system, also have shown a broad spectrum of biological activities including anti-inflammatory (Nowakowska, Z., 2007) antimalarial (Sivakumar P.M., 2010), anti-invasive (Adibi H., 2011), antibacterial (Shah A., 2008), and anticancer (Quintin J., 2009) activities. On the other hand, flavones are capable of inducing apoptosis (Srinivasan B., 2009). Consequently, these compounds are recognized as promising anticancer agents (Zhang H.J., 2011). A number of clinically useful anticancer drugs have genotoxic effects because of their interaction with the amino groups of nucleic acids. However, chalcones have been found not to show such undesired side effects (Sharma A., 2010). Numerous reports have been published on the interesting anti-breast cancer activity shown by flavones (Juvale K., 2012). Benzofuran derivatives are an interesting class of heterocyclic compounds. Benzofuran derivatives are of great interest in medicinal chemistry and have drawn remarkable attention due to their biological activities with chemotherapeutic properties (Basawaraj R., 2001). Some benzofurans bearing various substituents at the C-2 position are greatly distributed in nature; for example, ailanthoidol, a neolignan derivative, has been reported to have antiviral, antioxidant, and

antifungal activities. Furthermore, most of the compounds prepared from 2-acetyl benzofuran have antimicrobial, anticancer, antitumor, anti-inflammatory, and anti-tubulin activities and are also used for the treatment of cardiac arrhythmias (Rida.S.M., 2006). The use of the combinations of different pharmacological compounds in the design of new drugs may lead to finding novel drugs with interesting biological activity (Solomon.V.R., 2009). Furthermore, no studies were found in the literature evaluating the anticancer properties of benzofuran substituted chalcone derivatives. This encouraged us to synthesize benzofuran substituted chalcone compounds and to investigate anticancer properties of these compounds.

Synthesis experimental

Preparation of Phenyl (bromo) acetonitrile

11.7gm (0.1mole) was taken in 3 necked round bottomed flask in which one of the necks was connected to a flask containing bromine 17.6gm (0.1mol), to the second neck is fitted with a thermometer such that the tip was dipped in benzyl cyanide solution, the solution was heated up to 110^{o}C after preheating, third neck was fitted with a tube dipped in beaker of water to absorb excess hydrogen bromide evolved from the reaction, then slowly bromine was added drop by drop to hot benzyl cyanide until the Hydrogen bromide gas is completely evolved. Then the reaction mixture quenched into a separating funnel and washed with 5% sodium bicarbonate solution for twice, the product was extracted by ether and dried by magnesium sulphate. Finally filtered and distilled gives a crude product of phenyl (bromo) acetonitrile.

SCHEME

Preparation of 5-(2-bromo-2-phenylethanimidoyl) benzene-1,2,4-triol: A freshly vacuum dried benzene-1,2,4triol of (1.2g 0.01mol) was taken in a three-necked round-bottomed flask and 30ml of Dry ether was added then the solution was cooled to 0^{0}c then to this phenyl(bromo)acetonitrile of (2.5g 0.1mol), lewis acid $Alcl_3$ (0.5g) and then Dry Hydrochloric acid gas was passed through the solution about three hours and the reaction mixture was kept in ice chest for one day and then Dry Hydrochloric acid was again pumped in to reaction mixture for 3 hours and stored in ice chest for 3 days. After three days' reaction mixture forms a strong cake, then excess ether removed and washed with freshly distilled dry ether for two times, and obtained solid crystals dried and filtered.

Preparation of 2-bromo-2-phenyl-1-(2, 4, 5-trihydroxyphenyl) ethanone: 5-(2-bromo-2-phenylethanimidoyl) benzene-1,2,4-triol (1.0gm) was taken in a round-bottomed flask, and 0.1N of Hydrochloric acid (30 ml) was added to the reaction mixture and then refluxed for 2 hours, allowed to cool to room temperature, and then the reaction mixture was distilled excess solvent was removed, the crude mixture is extracted by dry ether and the left overnight for evaporation at room temperature. A white crystal was obtained which was dried.

Preparation of 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one:(VA): 2-bromo-2-phenyl-1-(2, 4, 5-trihydroxyphenyl) ethanone (0.8gm) was taken in a round-bottomed flask and sodium acetate (2 gm) [sodium acetate was freshly dried on Bunsen flame fine crystals were prepared] was added to the reaction mixture and dissolved in ethanol then refluxed for 10 min, ethanol was distilled and excess solvent was removed, crude was extracted by dry ether and evaporated then cream white precipitate was obtained which was filtered and dried. Thus obtained product was recrystallized by hot ethanol solution, and then T.L.C Studies were performed.

Nitration: A 5 gm (3.5ml 0.05mol) of concentrated nitric acid was placed in 250ml round-bottomed flask fitted with a thermometer, add small portions 7.4g (4 ml) of concentrated sulphuric acid the reaction mixture was kept in an ice cold bath and cooled, then 2.4g (0.01mol) of 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one (Compound VA) was added, stirred well and the temperature was controlled. A reflux condenser was fixed for the above reaction mixture and boiled up to 50-55^{o}c (care to be taken such that temperature does not increase beyond 55^{o}c) for about 1 hour and the reaction mixture was poured into 100 ml cold water and stirred and then supernatant layer of acid was discarded and the product was washed with ice-cold water for thrice until acid is completely washed out from the product, then transferred in to solution of 5% calcium chloride solution. The aqueous layer is separated in separating flask, and a trace amount of water is removed by heating on a flame. Thus obtained product was recrystallized by hot ethanol solution, and then T.L.C Studies were performed.

Dinitration: A 3.7ml of concentrated sulphuric acid was placed in 250ml round-bottomed flask fitted with a thermometer, few fragments of glazed porcelain are added then small portions 2.87gm(0.01mol) of 5,6-dihydroxy-2-(-4-nitrophenyl)-1-benzofuran-3(2*H*)-one (compound-VB) is added the reaction mixture was refluxed on a water bath for 30 minutes with

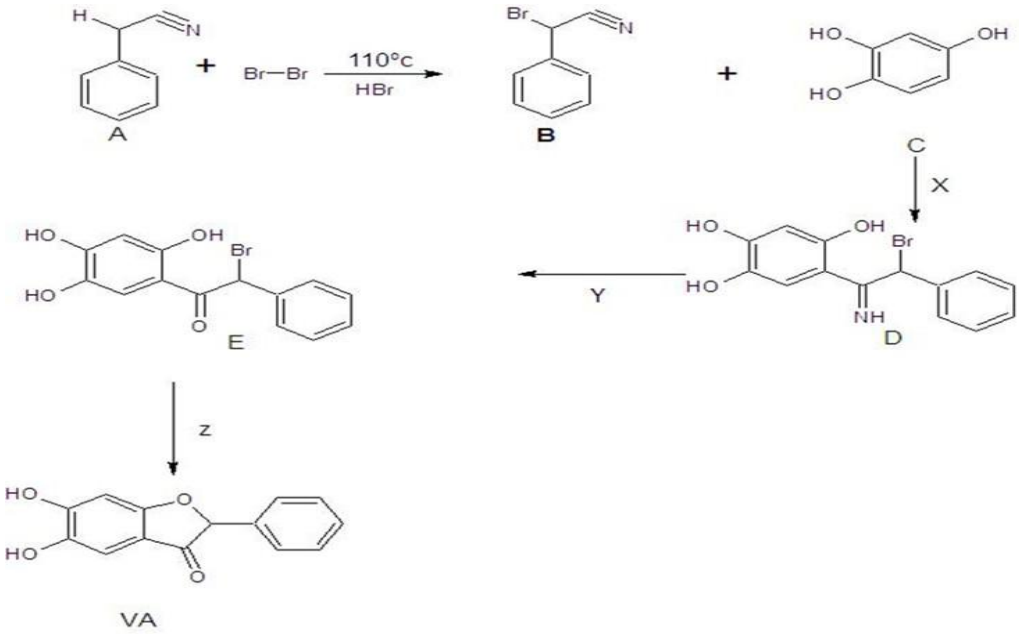


Figure 1: Scheme for Preparation of Benzofuranone derivatives: X ZnCl2, Dry HCL, Dry ether, at 0°C. Y 0.1N HCL Z Sodium acetate and ethanol. A-Phenyl acetonitrile, B-Phenyl(bromo) acetonitrile, C- benzene-1,2,4triol, D 5-(2-bromo-2-phenylethanimidoyl) benzene-1,2,4-triol, E 2-bromo-2-phenyl-1-(2, 4, 5-trihydroxyphenyl) ethanone, VA 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one

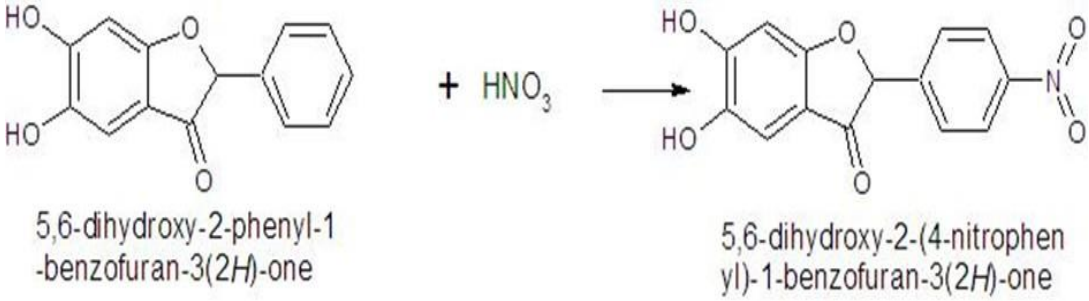


Figure 2: Preparation of 5,6-dihydroxy-2-(-4-nitrophenyl)-1-benzofuran-3(2H)-one

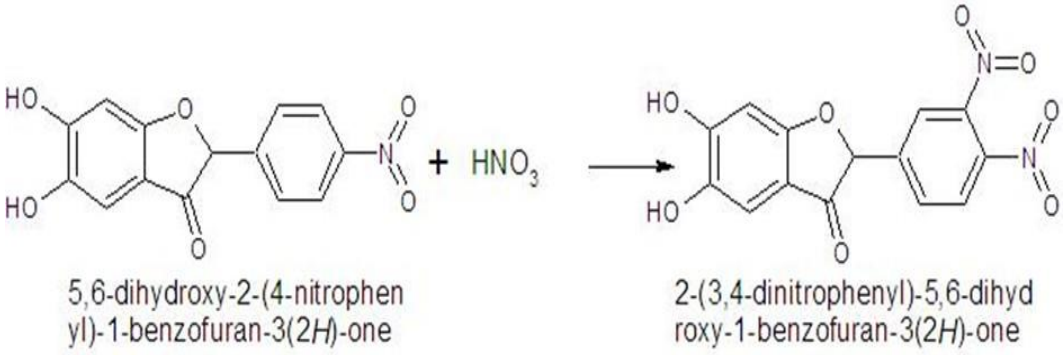


Figure 3: Preparation of 2-(-3,4-dinitrophenyl)-5,6-dihydroxy-1-benzofuran-3(2H)-one

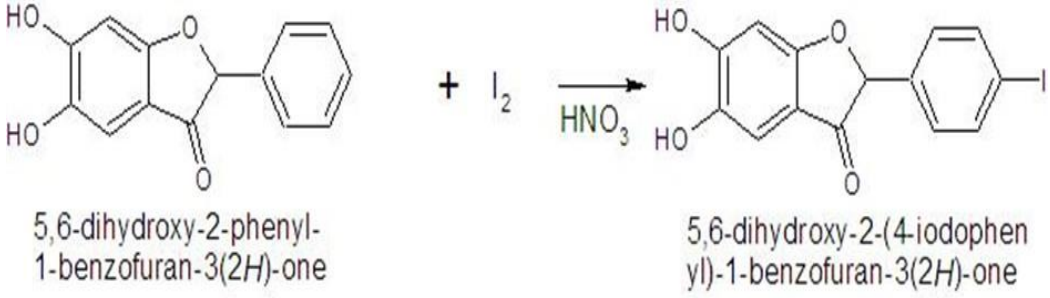
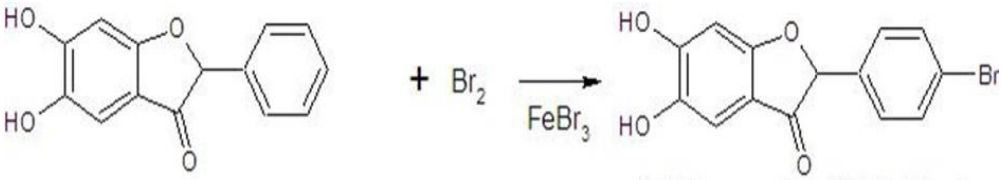


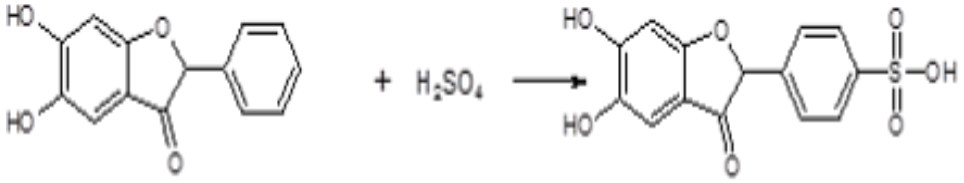
Figure 4: Preparation of 5,6-dihydroxy-2-(4-iodophenyl)-1-benzofuran-3(2H)-one



5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one

2-(4-bromophenyl)-5,6-dihydroxy-1-benzofuran-3(2*H*)-one

Figure 5: Preparation of 2-(4-bromophenyl)-5,6-dihydroxy-1-benzofuran-3(2H)-one



5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one

4-(5,6-dihydroxy-3-oxo-2,3-dihydro-1-benzofuran-2-yl)benzenesulfonic acid

Figure 6: Preparation of 4-(5,6-dihydroxy-3-oxo-2,3-dihydro-1-benzofuran-2-yl)benzene sulfonic acid

occasional stirring and the reaction mixture was poured into 100 ml cold water and stirred and vacuum filtered dried as much as possible. Thus obtained product was recrystallized by hot ethanol solution, and then T.L.C Studies were performed.

Iodination

A 2.6g (0.3mol) of 2.4g (0.01mol) of 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one (Compound VA) 2.2gm of iodine was taken in a three-necked round-bottomed flask fitted with reflux condenser and then to this add 3ml of nitric acid was added slowly through a separating funnel then the oxides of nitrogen is evolved and the temperature is raised and refluxed for about 15 minutes, and then the solution is poured in to ice cold water, washed with sodium hydroxide solution, (care has been taken such that reaction mixture is alkaline to litmus) finally washed with water and dried. Thus obtained product was recrystallized by hot ethanol solution, and then T.L.C Studies were performed.

Bromination

A 2.4g (0.01mol) of 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one (Compound VA) was taken in a three-necked round-bottomed flask fitted with reflux condenser and gas outlet tube connected to a beaker of water to collect the Hydrogen bromide gas, then to this add 3ml of pyridine (freshly dried over potassium hydroxide) then the apparatus is carefully arranged over a tripod stand with an ice cold water bath, then bromine was added with most care and then reaction started vigorously and slackens then the temperature is raised to 25^{o}C finally temperature raised to 70^{o}C and continued for 1 hour until evolution of bromine ceased (no red fumes from the reaction mixture) and then the solution is poured in to ice cold water, washed sodium hydroxide solution, (care has been taken such that reaction mixture is alkaline to litmus) finally washed with water and dried. Thus obtained product was recrystallized by hot ethanol solution, and then T.L.C Studies were performed.

Sulphonation

A 25ml of concentrated sulphuric acid was boiled in a flat bottomed flask, then added 10ml of oleum (fuming sulphuric acid) and boiled for few minutes and then a 2.4g (0.01mol) of 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one (Compound VA) was added and then refluxed for 2 hours. Then the solution was cooled and then neutralized by sodium bicarbonate and to this mixture sodium chloride was until the total solution saturated by sodium chloride, then sodium salt of a product was obtained and then extracted by absolute ethanol, the product is recovered by the evaporation of the solvent, and then T.L.C Studies were performed.

Anti-cancer activity

The sulforhodamine B (SRB) assay was developed by Skehan and colleagues to measure drug-induced cytotoxicity and cell proliferation for large-scale drug-screening applications. Its principle is based on the ability of the protein-dye sulforhodamine B to bind electrostatically. The activity is pH dependent on protein basic amino acid residues of trichloroacetic acid-fixed cells. Under mildly acidic conditions it binds to and under mild basic conditions it can be extracted from cells and solubilized for measurement. The signal-to-noise ratio is favorable, and the resolution is 1000-2000 cells/well. Its performance is similar when compared to other cytotoxicity assays such as MTT or clonogenic assay. The SRB assay possesses a colourimetric

endpoint and is nondestructive and indefinitely stable. These practical advances make the SRB assay an appropriate and sensitive assay to measure drug-induced cytotoxicity even at large-scale application.

Parameters reported: GI_{50}, TGI, and LC_{50}

GI_{50}: Growth inhibition of 50 % (GI_{50}) calculated from drug concentration resulting in a 50 % reduction in the net protein increase.TGI: Drug concentration resulting in total growth inhibition (TGI). LC_{50}: Concentration of drug resulting in a 50 % reduction in the measured protein at the end of the drug treatment (concentration of drug causing lethality to 50 % of the cells as compared to that at the beginning) indicating a net loss of cells following treatment.

RESULTS

5,6-dihydroxy-2-phenyl-1-benzofuran-3(2H)-one: (VA)

Yield: 65.62 %, Melting point 231°C, Rf Value: 0.76, Mol formula $C_{14}H_{10}O_4$ Mol Weight: 242.22; IR (Cm^{-1}) (KBr): 3370.13 (OH); 3095.24 (OH); 1624.18 (C=O); 1231.85 (C-O-C); ^{1}H NMR (400 MHz, MeOD-d_6): δ= 8.48 (s-1H CH) 8.23-8.21 (d 1H Ar-H *J*=8) 7.92-7.91 (d 1H Ar-H *J*=6) 7.57 (s 2H Ar-H) 7.42-31 (m 2H Ar-H), 7.06-7.05(d 2H Ar-H).^{13}C NMR (100 MHz, MeOD): δ= 88.06 (C-2), 152.98 (C-5), 100.91 (C-7), 115.88 (C-9), 127.41 (C-1``), 128.41 (C-2``), 129.69 (C-2```), 159.98 (C-1`), 110.17 (C-4), 160.04 (C-8), 96.51 (C-6), 197.32 (C-3). Mass m/z: 243 (M+1), 241 (M-1);

5,6-dihydroxy-2-(-4-nitrophenyl)-1-benzofuran-3(2H)-one: (VB)

Yield: 84.5%, Melting point 264°C, Rf Value: 0.68, Mol formula $C_{14}H_9NO_6$ Mol Weight: 287.22; IR (Cm^{-1}) (KBr): 3424.22 (OH); 3115.02 (OH); 1743.18 (C=O); 1280.18 (C-O-C); 1690.94 (NO2) Mass m/z: 288 (M+1), 286 (M-1);

2-(-3,4-dinitrophenyl)-5,6-dihydroxy-1-benzofuran-3(2H)-one: (VC)

Yield: 90.5%, Melting point 186°C, Rf Value: 0.51, Mol formula $C_{14}H_8N_2O_8$Mol Weight: 332.22; IR (Cm^{-1}) (KBr): 3323.37 (OH); 3224.82 (OH); 1753.06 (C=O); 1171.32 (C-O-C); 1640.58 (NO2); Mass m/z: 333 (M+1), 331 (M-1);

5,6-dihydroxy-2-(4-iodophenyl)-1-benzofuran-3(2H)-one: (VD)

Yield: 54.5%, Melting point 266°C, Rf Value: 0.64, Mol formula $C_{14}H_9IO_4$ Mol Weight: 368.12; IR (Cm^{-1}) (KBr): 3322.92 (OH); 3224.75 (OH); 1753.06 (C=O); 1171.29 (C-O-C); 634.04 (I); Mass m/z: 368 (M+1), 366 (M-1);

2-(4-bromophenyl)-5,6-dihydroxy-1-benzofuran-3(2H)-one: (VE)

Yield: 58.40%, Melting point 208°C, Rf Value: 0.58, Mol formula $C_{14}H_9O_4Br$ Mol Weight: 312.12; IR (Cm^{-1}) (KBr): 3393.63 (OH); 3279.29 (OH); 1753.06 (C=O); 1107.40 (C-O-C); 695.71 (Br); Mass m/z: 319 (M-1);

4-(5,6-dihydroxy-3-oxo-2,3-dihydro-1-benzofuran-2-yl) benzenesulfonic acid: (VF)

Yield: 62.33%, Melting point 167°C, Rf Value: 0.47, Mol formula $C_{14}H_{10}O_7S$ Br Mol Weight: 322.29; IR (Cm^{-1}) (KBr): 3395.99 (OH); 3187.57 (OH); 1601.36 (C=O); 1231.43 (C-O-C); Mass m/z: 323 (M+1), 321 (M-1);

Anti-Cancer Activity Results

Human Skin Cancer Cell Line G361, % Growth, Molar Drug Concentration

Table 1: Anti-Cancer Results Experiment – 1

	Experiment - 1			
	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M
VA	100.0	100.0	71.2	2.2
VB	100.0	100.0	100.0	21.9
VC	100.0	100.0	100.0	-61.2
VD	100.0	100.0	100.0	-61.5
VE	100.0	100.0	100.0	-36.5
VF	100.0	100.0	97.3	46.6

Table 2: Anti-Cancer Results Experiment – 2

		Experiment - 2		
	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M
VA	100.0	90.8	88.0	10.2
VB	100.0	100.0	89.5	19.9
VC	100.0	100.0	74.1	-62.9
VD	100.0	100.0	79.8	-57.0
VE	100.0	100.0	74.9	-30.0
VF	100.0	100.0	77.2	39.5

Table 3: Anti-Cancer Results Experiment – 3

		Experiment - 3		
	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M
VA	100.0	86.7	73.6	8.5
VB	100.0	100.0	86.1	15.8
VC	100.0	89.4	80.2	-63.3
VD	100.0	89.6	79.1	-64.4
VE	100.0	84.0	79.2	-37.7
VF	100.0	89.3	75.3	34.0

Table 4: Anti-Cancer Results Average Values

		Average Values		
	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M
VA	100.0	92.5	77.6	6.9
VB	100.0	100.0	91.9	19.2
VC	100.0	96.5	84.8	-62.5
VD	100.0	96.5	86.3	-61.0
VE	100.0	94.7	84.7	-34.7
VF	100.0	96.4	83.3	40.0

Table 5: Results of anti-cancer activity for LC50, TGI, G150

G361	Molar Drug Concentration		
	LC 50	TGI	G150
VA	$>10^{-4}$	$>10^{-4}$	$2.6*10^{-6}$
VB	$>10^{-4}$	$>10^{-4}$	$3.2*10^{-5}$
VC	$>10^{-4}$	$3.2*10^{-5}$	$2.02*10^{-6}$
VD	$>10^{-4}$	$3.2*10^{-5}$	$2.04*10^{-6}$
VE	$>10^{-4}$	$3.7*10^{-5}$	$2.2*10^{-6}$
VF	$>10^{-4}$	$>10^{-4}$	$3.8*10^{-5}$
ADR	$1.7*10^{-7}$	$<10^{-7}$	$<10^{-7}$

DISCUSSION AND CONCLUSION

2-Phenyl Benzofuranone

The reactants phenylacetonitrile and bromine reacted where phenyl acetonitrile was preheated 110^{o}C and bromine was added drop by drop where alpha hydrogen was replaced by bromine, and HBr gas has been evolved which was trapped in water, and after ceasing of HBr gas the reaction has been completed, then after completion of the reaction it was washed with 5% sodium bicarbonate and then extracted by Dry ether and dry ether solution also washed with magnesium sulphate and the solvent is distilled off. Thus obtained product was confirmed by the reported boiling point of 242^{o}C. And a good yield of 90.40% and IR spectrum has confirmed the existence of bromine in the molecule. Bromo(phenyl)acetonitrile was stirred in a three-necked round-bottomed flask immersed in ice-salt mixture which leads 0^{o}c for the reaction then added 30ml of a dry ether solvent, to this mixture benzene-1,2,4triol was added slowly then zinc chloride was (Lewis acid) added as a catalyst. Dry hydrochloric acid was prepared and pumped into the reaction mixture for about three hours and kept in ice-chest for three days. After three days' flask was removed from the ice chest and the supernatant ether layer was removed and then washed with dry ether and then dried. Which yielded a crude product of 86.10%. 5-(2-bromo-2-phenylethanimidoyl) benzene-1,2,4-triol (1gm) was dissolved in 0.1N hydrochloric acid and then refluxed for two hours where the imine was oxidized which converts the imine to ketone, then the reaction mixture was distilled and the crude was extracted by dry ether and evaporated which yields a fine white powder with a yield of 56.10%. 2-bromo-2-phenyl-1-(2, 4, 5-trihydroxyphenyl) ethanone (1gm) was dissolved in freshly distilled ethanol, and sodium acetate which was freshly dried on a bunsen flame 2gm is added and then refluxed for 10 min then ethanol was distilled off and the crude extract was dissolved in dry ether and evaporated yields a white cream crystals of 78.10%.

Nitration: Sulphuric acid and nitric acid was mixed in a flask and then cooled in an ice bath and then 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one and care has been taken such that temperature does not raise more than 55^{o}C such that an avoid multiple nitrations on the phenyl ring. Then slowly refluxed and the product obtained is washed ice cold water finally extracted with ether and distilled gives a yield of 84.5%

Dinitration: Sulphuric acid and nitric acid was mixed in a flask and then cooled in an ice bath and then 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one Then vigorously refluxed and dinitrate product 2-(-3,4-dinitrophenyl)-5,6-dihydroxy-1-benzofuran-3(2*H*)-one obtained is washed ice cold water finally extracted with ether and distilled gives a yield of 90.5%.

Iodination: Iodine and nitric acid were mixed in a flask and then cooled in an ice bath and then 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one Then vigorously refluxed and dinitrate product 5,6-dihydroxy-2-(4-iodophenyl)-1-benzofuran-3(2*H*)-one obtained is washed ice cold water finally extracted with ether and distilled gives a yield of 54.5%

Bromination: Bromine and pyridine was mixed in a flask and then cooled in an ice bath and then 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one Then pyridine (Freshly distilled) was added then the reaction temperature raises to 70^{o}C and HBr gas evolution from the reaction mixture is ceased indicates the completion of reaction gives product 2-(4-bromophenyl)-5,6-dihydroxy-1-benzofuran-3(2*H*)-one obtained is washed ice cold water finally extracted with ether and distilled gives a yield of 58.40%

Sulphonation: Oleum (Fuming Sulphuric acid) was mixed in a flask and then boiled in a water bath and then 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one Then vigorously refluxed gives sulphonic product 4-(5,6-dihydroxy-3-oxo-2,3-dihydro-1-benzofuran-2-yl) benzene sulfonic acid obtained is washed ice cold water finally extracted with ether and distilled gives a yield of 72.33%

Anti-cancer activity

The newly synthesized compounds were screened for their anticancer activity against Human Skin Cancer Cell Line G361 by Sulforhodamine B assay. Doxorubicin was used as a standard reference drug and the results obtained were shown in (Table:2 & 3). All compounds showed low antiproliferative activity. The % Growth inhibition of the compounds VA, VC, VD, VE, was found to be considered at a concentration of 10^{-4} M. TGI_{50} (Growth inhibition of 50 % cells, calculated from drug concentration resulting in a 50 % reduction in the net protein

increase). As 2-phenylbenzofuranone derivatives are the most active compound, it serves as a lead to further optimization in the drug discovery process.

CONCLUSION

We had successfully developed a new series of 5,6-dihydroxy-2-phenyl-1-benzofuran-3(2*H*)-one derivatives. Though benzofuranones were existed with prominent anti-cancer activity and in our developed a new series of phenyl substituted benzofuranones. These compounds are screened for antiproliferative activity against human skin cancer cell lines. The compounds VA, VC, VD, VE**, s**howed an excellent antiproliferative activity which serves as a lead to further optimization in the drug discovery process.

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