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Design, Synthesis of 4-hydroxy-2-phenyl-1-benzofuran-3(2*H*)-one derivatives as new leads for anti-cancer activity

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ABSTRACT

Benzofuranone is a bicyclic ring where a benzene ring fused with a furanone. Computation chemistry plays a major role in the development of new lead molecules. The final compounds were obtained in multistep synthesis reactions using benzofuran-3-one derivatives as starting materials which were gained in various synthetic ways. Synthetic chemistry plays a major in developing a series of potent anti-cancer agents. Benzofuranone was synthesised by reacting benzene diols, and triols with bromo phenyl acetonitrile yielded an imine derivative are converted to a ketone with treatment with hydrochloric acid then cyclised with sodium acetate. Computational tools docking, virtual screening, ADMET prediction are utilised in the identification of new lead molecules. The compounds identity and purity were confirmed by spectral and analytical methods. Benzofuranone derivatives are screened antineoplastic activity was performed against human skin cancer cell line G361 at micro molecular concentrations. The compounds, IIB, IIC was found to be with potent activity.

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INTRODUCTION

Flavonoids are secondary metabolites of plants which exhibit various biological properties that are beneficial for human health via interacting with some cellular targets in the body. They can be classified into several subclasses, and some of these subclasses are flavonols, flavones, isoflavones, flavanones, flavans, aurones and chalcones (Singh M, 2014). All classes of flavonoids exhibit a variety of biological and pharmacological activities, but among them, the chalcones and their ring analogue flavones have been considerably explored. Various natural, semi-synthetic and synthetic derivatives of these structures have been investigated and reported with a wide range of biological applications (Detsi A, 2009). Aurones, (Z)-2-benzylidenebenzofuran-3-(2H)-ones, constitute a less studied subclass of flavonoids although they are isosteres of flavones (Fan R, 2012). However, they have attracted attention with promising biological potential such as anti-microbial (Mcalpine, JB 1997), anti-cancer (Kumar R 2014), anti-leishmanial (Kayser O, 1999), anti-histaminic (Wang J, 2007), anti-inflammatory (Bandgar BP, 2010), antioxidant (Jardosh H, 2014), insect antifeedant (Morimoto M, 2007), herbicidal (Zhang M, 2012), anti-HIV (Gao X, 2012), anti-HCV (hepatitis C virus) (Meguellati A, 2014), anti-malarial (Gupta AK, 2014), ChE inhibitory, MAO inhibitory (Geldenhuys WJ, 2012) activities in the specified studies. The observed biological potential is thought to be due to the similarity of adenine of ATP and the flavonoids, consequently inhibition of the activity of ATP-dependent enzymes and proteins, which is essential for the function of enzymes and receptors. In particular, the aurones are estimated to mimic better the adenine because of the benzofuranone structure than the benzopyranone part of the corresponding

flavones. Some naturally occurring aurones maritimein, sulfuretin and aureusidin are also studied and among them sulfuretin has been known to have anti-inflammatory activity (Shin SY, 2011). Along with the identified molecular mechanisms of flavonoids as carcinogen inactivation, anti-proliferation, cell cycle arrest, induction of apoptosis and differentiation, inhibition of angiogenesis, antioxidation and reversal of multidrug resistance; a b-unsaturated carbonyl structure has been evaluated inducing anti-cancer activity with acting as an alkylating agent (Pratt WB, 1994). Considering literature findings and as a continuation of our on-going studies (Gundogdu Karaburun N, 2014), we synthesized new aurone derivatives and evaluated their anti-cancer activity.

Computational Studies

Experimental Procedure

Selection of protein: CDK is the most abundantly found in tumor cell generation. So, CDK inhibitor has been selected for Docking the lead molecules, the protein database was searched in the portal http://www.rcsb.org, the protein was searched from a group and 1GII protein was found with species of Homosapiens with X-ray method was used in determination of the protein, with lowest resolution of 2.00A^{o} and validated for the Domain completeness.

Preparation of Protein: The selected protein 1GII has been was explored in Auto dock 4.0, the bonds and atoms in the protein are optimized, missing hydrogens are added, the non-polar centre between the hydrogens were merged, and all the histidine hydrogens are protonated with +1charge. Kollaman and gastegier charges were added to the protein. All the missing atoms are repaired, and charges are applied to the protein.

Design of Ligands

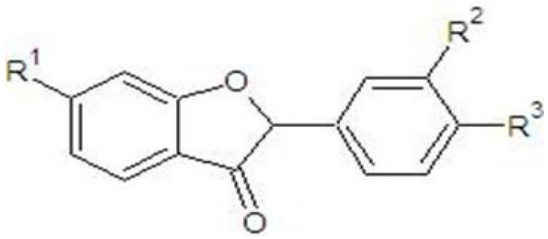

Figure 1: Basic benzofuranone

The basic benzofuranone was designed with modifications in the R^1, R^2, $R^3$of the molecule given below in figure: 1.

Preparation of Ligands

The above combinations of ligands were drawn with Chemsketch open source software obtained from http://www.acdlabs.com, as a (.mol) file in a 2D structural format. Then the ligands are undergone for energy optimization and converted (.pdb) 3D structural format by using Discovery studio visualiser 4.0 from http://accelrys.com, and the angular forces between the bonds of ligands are minimized.

Table 1: Combinations of Ligands

R^1	OH, OCH3, H	3 combinations
R^2	H, OH, OCH_3, CH_3, C_2H_5, NH_2 , NO_2 ,BR, CL	9 combinations
R^3	H, OH, OCH_3,CH_3, C_2H_5, NH_2, NO_2, BR, CL	9 combinations

Virtual screening

The optimized protein is then explored in virtual screening software, and then ligand databank of the group is also linked, and quantitative optimization is performed. Then computational parameters like an auto grid, autovina, auto dock are applied, protein is fixed in the grid box, and Virtual screening is performed.

Admet profile prediction of ligands

Ligands are preliminary are studied for Adsorption, Distribution, Metabolism, Elimination, and Toxicity for the search for best-fit ligands. Lipinski rule of 5 is the best fit parameter for prediction of ADMET of ligands, Lipinski rule of 5 parameters Log p (≤5), Molecular weight (≤500daltons), Hydrogen acceptors (≤5) and hydrogen acceptors (≤5). Molecules violate these parameters are found to be with poor bioavailability parameters. Data warrior of OSIRIS software is utilized for the prediction of the above parameters, and the best fit results are listed below. The molecules exhibiting mutagenicity, tumorigenicity, reproductive effect and irritant nature are found that molecules may be with toxicity and they are also removed from the database for the further insilico studies.

The molecules with good ADMET properties are used for insilico screening such as virtual screening and docking studies further.

Docking studies

The best fit ligands from primary filtration by virtual screening and docking are then subjected to secondary Insilco studies (Docking).

Protein and Ligand Preparation

Auto dock 4.0 open source software is utilized for the docking studies. The optimized protein file (1GII) is explored in the auto dock 4.0, then optimized ligand is fit in it, and 3D structural energy is minimized, torrisions of the ligands are verified, adjusted, and the ligand is stored as (. pdbqt) parameter.

Table 2: Virtual Screening results

S.No	Ligand	Target	Binding Energy	Date Created
1	288_uff_E=387.43	1GII	-8.3	2015.07.31 00:44:34
2	289_uff_E=317.65	1GII	-8.3	2015.07.31 00:45:14
3	293_uff_E=371.56	1GII	-8.3	2015.07.31 00:48:29
4	301_uff_E=404.03	1GII	-8.3	2015.07.31 00:55:26
5	320_uff_E=353.44	1GII	-8.3	2015.07.31 01:09:59
6	34_uff_E=456.15	1GII	-8.3	2015.07.30 20:42:23
7	38_uff_E=449.52	1GII	-8.3	2015.07.30 20:45:47
8	43_uff_E=439.26	1GII	-8.3	2015.07.30 20:50:50
9	58_uff_E=430.21	1GII	-8.3	2015.07.30 21:05:51
10	68_uff_E=377.70	1GII	-8.3	2015.07.30 21:15:32
11	79_uff_E=417.80	1GII	-8.3	2015.07.30 21:25:07
12	95_uff_E=434.62	1GII	-8.3	2015.07.30 21:38:49
13	103_uff_E=337.65	1GII	-8.2	2015.07.30 21:46:28
14	104_uff_E=315.79	1GII	-8.2	2015.07.30 21:47:26
15	105_uff_E=341.94	1GII	-8.2	2015.07.30 21:48:27
16	120_uff_E=402.72	1GII	-8.2	2015.07.30 22:01:43
17	136_uff_E=368.29	1GII	-8.2	2015.07.30 22:17:39
18	141_uff_E=446.57	1GII	-8.2	2015.07.30 22:23:25
19	142_uff_E=488.70	1GII	-8.2	2015.07.30 22:24:39
20	148_uff_E=341.73	1GII	-8.2	2015.07.30 22:29:59
21	152_uff_E=324.80	1GII	-8.2	2015.07.30 22:33:36
22	157_uff_E=341.52	1GII	-8.2	2015.07.30 22:37:44
23	16_uff_E=536.84	1GII	-8.2	2015.07.30 20:26:02
24	172_uff_E=314.29	1GII	-8.2	2015.07.30 22:51:32
25	176_uff_E=343.97	1GII	-8.2	2015.07.30 22:56:10
26	201_uff_E=409.07	1GII	-8.2	2015.07.30 23:23:29
27	212_uff_E=388.77	1GII	-8.2	2015.07.30 23:36:11
28	22_uff_E=358.49	1GII	-8.2	2015.07.30 20:31:33
29	220_uff_E=417.46	1GII	-8.2	2015.07.30 23:45:56
30	225_uff_E=401.28	1GII	-8.2	2015.07.30 23:52:31
31	229_uff_E=313.05	1GII	-8.2	2015.07.30 23:56:27
32	238_uff_E=348.14	1GII	-8.2	2015.07.31 00:05:37
33	24_uff_E=368.95	1GII	-8.2	2015.07.30 20:33:36
34	242_uff_E=332.18	1GII	-8.2	2015.07.31 00:10:10
35	243_uff_E=295.15	1GII	-8.2	2015.07.31 00:11:04
36	250_uff_E=374.33	1GII	-8.2	2015.07.31 00:15:38
37	279_uff_E=332.56	1GII	-8.2	2015.07.31 00:37:22
38	28_uff_E=298.96	1GII	-8.2	2015.07.30 20:37:14
39	280_uff_E=345.03	1GII	-8.2	2015.07.31 00:38:01
40	286_uff_E=415.64	1GII	-8.2	2015.07.31 00:43:05
41	287_uff_E=393.59	1GII	-8.2	2015.07.31 00:43:49
42	297_uff_E=329.47	1GII	-8.2	2015.07.31 00:52:01
43	304_uff_E=484.73	1GII	-8.2	2015.07.31 00:58:10
44	316_uff_E=303.67	1GII	-8.2	2015.07.31 01:07:05
45	35_uff_E=358.15	1GII	-8.2	2015.07.30 20:43:09
46	36_uff_E=356.20	1GII	-8.2	2015.07.30 20:43:57
47	37_uff_E=371.90	1GII	-8.2	2015.07.30 20:44:46
48	42_uff_E=418.04	1GII	-8.2	2015.07.30 20:49:43
49	55_uff_E=389.15	1GII	-8.2	2015.07.30 21:02:36
50	56_uff_E=448.01	1GII	-8.2	2015.07.30 21:03:45
51	57_uff_E=436.17	1GII	-8.2	2015.07.30 21:04:53
52	60_uff_E=446.57	1GII	-8.2	2015.07.30 21:08:10
53	67_uff_E=306.48	1GII	-8.2	2015.07.30 21:14:37
54	70_uff_E=420.51	1GII	-8.2	2015.07.30 21:17:25
55	76_uff_E=340.55	1GII	-8.2	2015.07.30 21:22:16

*Info: Vina

Table 2: Virtual Screening results (Contd...)

S.No	Ligand	Target	Binding Energy	Date Created
56	77_uff_E=376.29	1GII	-8.2	2015.07.30 21:23:11
57	86_uff_E=354.41	1GII	-8.2	2015.07.30 21:30:39
58	88_uff_E=380.30	1GII	-8.2	2015.07.30 21:32:26
59	102_uff_E=359.58	1GII	-8.1	2015.07.30 21:45:37
60	107_uff_E=318.88	1GII	-8.1	2015.07.30 21:50:26
61	108_uff_E=318.07	1GII	-8.1	2015.07.30 21:51:17
62	109_uff_E=321.81	1GII	-8.1	2015.07.30 21:51:59
63	110_uff_E=358.52	1GII	-8.1	2015.07.30 21:52:49
64	111_uff_E=368.29	1GII	-8.1	2015.07.30 21:53:44
65	115_uff_E=436.90	1GII	-8.1	2015.07.30 21:57:16
66	131_uff_E=379.38	1GII	-8.1	2015.07.30 22:12:40
67	133_uff_E=428.44	1GII	-8.1	2015.07.30 22:14:53
68	138_uff_E=414.69	1GII	-8.1	2015.07.30 22:19:59
69	14_uff_E=457.25	1GII	-8.1	2015.07.30 20:23:50
70	146_uff_E=337.31	1GII	-8.1	2015.07.30 22:28:16
71	153_uff_E=323.45	1GII	-8.1	2015.07.30 22:34:25
72	160_uff_E=399.54	1GII	-8.1	2015.07.30 22:40:35
73	161_uff_E=324.00	1GII	-8.1	2015.07.30 22:41:24
74	162_uff_E=322.81	1GII	-8.1	2015.07.30 22:42:13
75	166_uff_E=309.51	1GII	-8.1	2015.07.30 22:45:45
76	169_uff_E=390.56	1GII	-8.1	2015.07.30 22:48:51
77	188_uff_E=344.48	1GII	-8.1	2015.07.30 23:10:16
78	190_uff_E=295.39	1GII	-8.1	2015.07.30 23:12:15
79	192_uff_E=375.22	1GII	-8.1	2015.07.30 23:14:20
80	195_uff_E=371.72	1GII	-8.1	2015.07.30 23:17:17
81	20_uff_E=359.14	1GII	-8.1	2015.07.30 20:29:41
82	204_uff_E=400.30	1GII	-8.1	2015.07.30 23:26:58
83	222_uff_E=452.85	1GII	-8.1	2015.07.30 23:48:39
84	224_uff_E=404.49	1GII	-8.1	2015.07.30 23:51:20

*Info: Vina

Grid Alignment: The protein (1GII) is explored in 3D space, and grid box is fixed on the macromolecule protein and grid adjusted such that all binding pockets are aligned in the grid, and other parameters are fixed, and grid parameter file (. gpf) is prepared.

Docking parameters: The macromolecule and ligand are exposed then genetic algorithm search; auto dock 4.2 parameters are fixed. A Lamarckian genetic algorithm for docking (. dpf) is prepared.

Docking: The prepared grid parameter file is then docked over with standard grid path database, and grid log file (. glg) is prepared. The docking parameter file is then docked with a comparison to the standard docking path file, and the docking score are obtained. The best fit molecules with docking score are analysed.

Analysing the docking results

After performing docking, the. dlg file is then opened by using analyse parameter in the software. No of dockings performed are recorded, and then the docking results are reviewed by using play ranked by energy options Best docking result with minimum binding energy and inhibition energy are recorded The recorded results are indexed below.

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.

Table 3: ADMET results

Molecule Name	Absolute Weight	cLogP	cLogS	H-Acceptors	H-Donors	Total Surface Area	Polar Surface Area	Druglikeness	LELP from Molecule Name
1	240.079	2.849	-3.306	3	1	214	46.53	0.14141	5.2868
2	254.094	3.2646	-3.465	3	1	220	46.53	-0.0598	6.3992
3	241.074	1.8278	-3.038	4	2	210	72.55	0.3527	3.3966
4	271.048	1.2605	-3.246	6	1	225	94.27	-0.7158	2.6045
5	303.974	3.2303	-3.796	3	1	219	46.53	-1.6125	6.0114
6	260.024	3.1111	-3.698	3	1	217	46.53	0.26995	5.7935
7	256.074	2.4351	-2.98	4	1	224	55.76	0.2867	4.7899
8	272.069	2.0894	-2.684	5	2	229	75.99	0.2867	4.3291
9	286.084	2.3651	-2.998	5	1	250	64.99	0.2867	5.1488
10	270.089	2.779	-3.324	4	1	231	55.76	0.259	5.7655
11	301.059	1.1905	-3.264	7	1	224	103.5	-0.8659	2.7222
12	333.984	3.1603	-3.814	4	1	247	55.76	-1.5033	6.5736
13	290.035	3.0411	-3.716	4	1	233	55.76	0.38059	6.3296
17	242.058	2.1594	-2.666	4	2	207	66.76	0.1775	4.0475
18	258.053	1.8137	-2.37	5	3	214	86.99	0.1775	3.5906
19	272.069	2.0894	-2.684	5	2	226	75.99	0.2867	4.3568
21	256.074	2.5033	-3.01	4	2	219	66.76	0.14141	4.9619
22	287.043	0.9148	-2.95	7	2	210	114.5	-1.1006	2.0077
28	319.968	2.8846	-3.5	4	2	226	66.76	-1.6125	5.7313
30	276.019	2.7654	-3.402	4	2	222	66.76	0.26995	5.4976
38	240.079	2.849	-3.306	3	1	215	46.53	0.14141	5.3688
39	270.089	2.779	-3.324	4	1	242	55.76	0.259	5.8254
40	254.094	3.1929	-3.65	3	1	220	46.53	0.14141	6.3619
43	285.064	1.6044	-3.59	6	1	235	94.27	-3.0625	3.5392
44	274.04	3.455	-4.042	3	1	227	46.53	0.2372	6.903
46	254.094	3.2646	-3.465	3	1	237	46.53	-0.0598	6.5261
55	270.089	2.9189	-3.169	4	2	233	66.76	-0.0598	6.1454
56	284.105	3.1946	-3.483	4	1	241	55.76	0.07375	7.0658
57	268.11	3.6085	-3.809	3	1	248	46.53	-0.0598	7.6052
58	299.079	2.02	-3.749	6	1	215	94.27	-1.4335	4.6902
61	332.005	3.9898	-4.299	3	1	247	46.53	-1.8498	8.426
62	241.074	1.8278	-3.038	4	2	211	72.55	0.3527	3.4776
63	271.048	1.2605	-3.246	6	1	215	94.27	-1.4823	2.6762
64	287.043	0.9148	-2.95	7	2	225	114.5	-0.8395	2.0403
65	301.059	1.1905	-3.264	7	1	226	103.5	-0.0574	2.7829
66	285.064	1.6044	-3.59	6	1	210	94.27	-2.3225	3.5816
67	316.033	0.0159	-3.53	9	1	235	132.77	-1.2946	0.03898
70	348.959	1.9857	-4.08	6	1	214	85.03	-3.0846	4.4408
71	305.009	1.8665	-3.982	6	1	216	85.03	-1.1843	4.1761
73	303.974	3.2303	-3.796	3	1	218	46.53	-1.6125	6.1977
74	319.968	2.8846	-3.5	4	2	234	66.76	-1.6125	5.8444
75	317.989	3.5742	-4.14	3	1	237	46.53	-1.6486	7.2479
76	381.884	3.9555	-4.63	3	1	245	46.53	-1.6125	8.0347
79	260.024	3.1111	-3.698	3	1	209	46.53	0.26995	5.9919
80	276.019	2.7654	-3.402	4	2	224	66.76	0.26995	5.6243
81	290.035	3.0411	-3.716	4	1	233	55.76	0.38059	6.5132
82	274.04	3.455	-4.042	3	1	228	46.53	0.2372	7.0326
83	305.009	1.8665	-3.982	6	1	215	85.03	-0.9675	4.2042

*Mutagenic: none; Tumorigenic: none; Reproductive Effective: none; Irritant: none

Table 4: Docking results

S.no	Mole Cule No	Iupac name	Binding energy	Ic 50	Ic 50 units	No. of confirmations
1	85	6-hydroxy-2-(4-methyl phenyl) -1-benzofuran-3(2*H*)-one	-7.54	3	MM	9
2	86	2-(4-ethyl phenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-7.54	3	MM	9
3	87	2-(4-aminophenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-7.09	6.4	MM	10
4	88	6-hydroxy-2-(4-nitrophenyl) -1-benzofuran-3(2*H*)-one	-7.43	3.57	MM	8
5	89	2-(4-bromophenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-7.8	1.91	MM	8
6	90	2-(4-chlorophenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-7.67	2.38	MM	8
7	91	6-hydroxy-2-(3-methoxyphenyl) -1-benzofuran-3(2*H*)-one	-6.94	8.23	MM	6
8	92	6-hydroxy-2-(4-hydroxy-3-methoxyphenyl) -1-benzofuran-3(2*H*)-one	-7.56	2.87	MM	10
9	93	2-(3,4-dimethoxyphenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-6.98	7.66	MM	10
10	94	6-hydroxy-2-(3-methoxy-4-methylphenyl) -1-benzofuran-3(2*H*)-one	-5.51	91.05	MM	10
11	97	6-hydroxy-2-(3-methoxy-4-nitrophenyl) -1-benzofuran-3(2*H*)-one	-7.83	1.2	MM	9
12	98	2-(4-bromo-3-methoxyphenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-6.55	17.82	MM	7
13	99	2-(4-chloro-3-methoxyphenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-7.37	3.93	MM	7
16	100	6-hydroxy-2-(3-hydroxyphenyl) -1-benzofuran-3(2*H*)-one	-7.54	2.99	MM	7
17	101	2-(3,4-dihydroxyphenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-7.64	2.64	MM	8
18	102	6-hydroxy-2-(3-hydroxy-4-methoxyphenyl) -1-benzofuran-3(2*H*)-one	-6.42	19.85	MM	8
19	103	6-hydroxy-2-(3-hydroxy-4-methylphenyl) -1-benzofuran-3(2*H*)-one	-7.41	3.71	MM	9
21	106	6-hydroxy-2-(3-hydroxy-4-nitrophenyl) -1-benzofuran-3(2H)-one	-7.99	1.39	MM	8
22	107	2-(4-bromo-3-hydroxyphenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-6.75	10.68	MM	9
28	108	2-(4-chloro-3-hydroxyphenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-7.71	2.22	MM	50
30	109	6-hydroxy-2-(3-methylphenyl) -1-benzofuran-3(2*H*)-one	-7.64	2.5	MM	8
39	111	6-hydroxy-2-(4-methoxy-3-methylphenyl) -1-benzofuran-3(2*H*)-one	-6.24	24.85	MM	9
40	112	2-(3,4-dimethylphenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-6.16	10.24	MM	10
43	115	6-hydroxy-2-(3-methyl-4-nitrophenyl) -1-benzofuran-3(2*H*)-one	-7.63	2.55	MM	8
44	117	2-(4-chloro-3-methylphenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-7.59	2.64	MM	9
46	118	2-(3-ethylphenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-7.32	4.29	MM	9
55	119	2-(3-ethyl-4-hydroxyphenyl)-6-hydroxy -1-benzofuran-3(2*H*)-one	-6.43	19.34	MM	10

Table 4: Docking results (Contd….)

S.no	Mole Cule No	Iupac name	Binding energy	Ic 50	Ic 50 units	No. of confirmations
56	120	2-(3-ethyl-4-methoxyphenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-6.08	35.2	MM	10
57	121	2-(3-ethyl-4-methylphenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-6.95	8.02	MM	10
58	124	2-(3-ethyl-4-nitrophenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-8.04	1.27	MM	9
61	125	2-(4-bromo-3-ethylphenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-7.5	3.16	MM	5
62	127	2-(3-aminophenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-5.94	44.61	MM	8
63	136	6-hydroxy-2-(3-nitrophenyl) -1-benzofuran-3(2H)-one	-7.74	2.11	MM	9
64	137	6-hydroxy-2-(4-hydroxy-3-nitrophenyl) -1-benzofuran-3(2H)-one	-7.59	2.8	MM	10
65	138	6-hydroxy-2-(4-methoxy-3-nitrophenyl) -1-benzofuran-3(2H)-one	-7.46	3.38	MM	9
66	139	6-hydroxy-2-(4-methyl-3-nitrophenyl) -1-benzofuran-3(2H)-one	-7.56	2.85	MM	8
67	142	2-(3,4-dinitrophenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-9.05	232.38	NM	7
70	143	2-(4-bromo-3-nitrophenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-7.4	3.77	MM	8
71	144	2-(4-chloro-3-nitrophenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-7.03	7.02	MM	9
73	145	2-(3-bromophenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-7.12	6.06	MM	8
74	146	2-(3-bromo-4-hydroxyphenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-7.96	1.47	MM	9
75	148	2-(3-bromo-4-methylphenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-7.64	2.7	MM	10
76	152	2-(3,4-dibromophenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-6.77	10.91	MM	9
79	154	2-(3-chlorophenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-6.21	27.88	MM	10
80	155	2-(3-chloro-4-hydroxyphenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-6.12	32.65	MM	10
81	156	2-(3-chloro-4-methoxyphenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-7.32	4.3	MM	9
82	157	2-(3-chloro-4-methylphenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-7.86	1.73	MM	10
83	160	2-(3-chloro-4-nitrophenyl)-6-hydroxy -1-benzofuran-3(2H)-one	-7.48	3.27	MM	10

Scheme

Synthesis of 4-(2-bromo-2-phenylethanimidoyl) benzene-1,3-diol

A fresh vacuum dried Resorcinol of (2.2g 0.2mol) was taken in a three-necked round-bottomed flask, and 30ml of Dry ether was added then the solution was cooled to 0^0c than to this phenyl(bromo)acetonitrile of (2.5g 0.2mmol), Lewis acid $Alcl_3$ (0.5g) andthen Dry Hydrochloric acid gas was passed through the solution about three hours, and the reaction mixture was kept in an ice chest for one day and then Dry Hydrochloric acid was again pumped into the reaction mixture for 3 hours and stored in an 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.

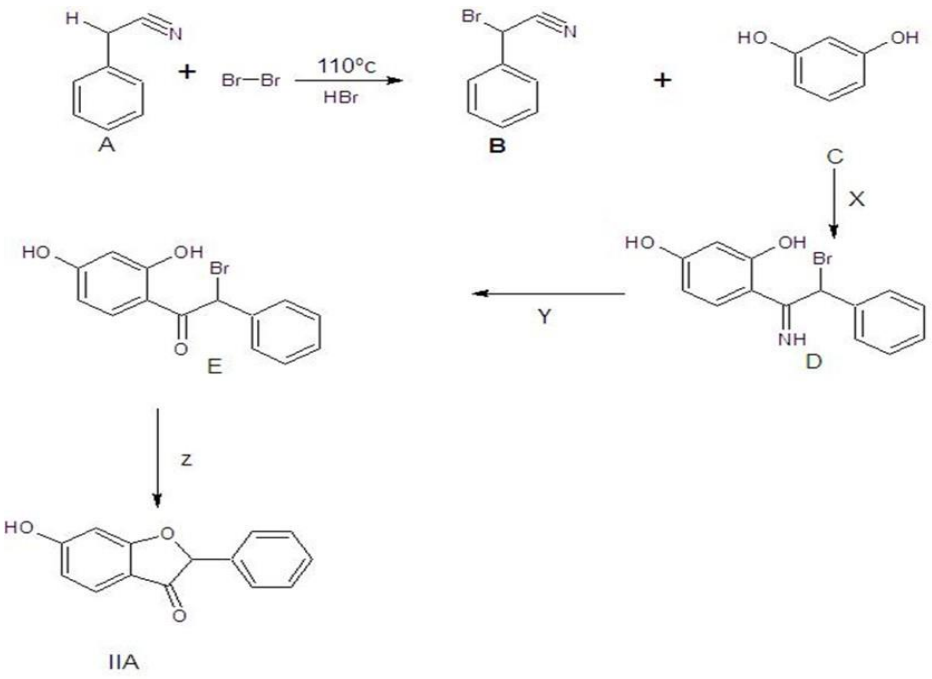

Figure 2: Scheme for Preparation of Benzofuranone derivatives: X ZnCl2, Dry HCL, Dry ether, at 0°C. Y 0.1N HCL Z Sodium acetate and ethanol. A-Phenyl acetonitrile, B-Phenyl(bromo) acetonitrile, C-Resorcinol, D 4-(2-bromo-2-phenylethanimidoyl) benzene-1,3-diol E 2-bromo-1-(2,4-dihydroxyphenyl)-2-phenylethanone,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

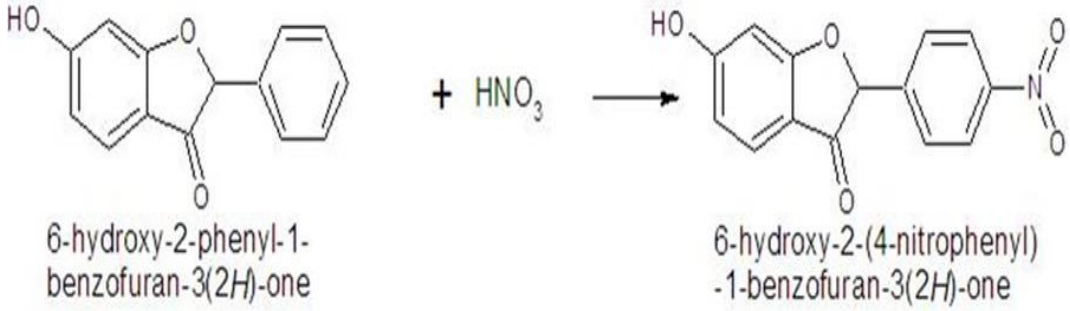

Figure 3: Preparation of 6-hydroxy-2-(-4-nitrophenyl)-1-benzofuran-3(2H)-one

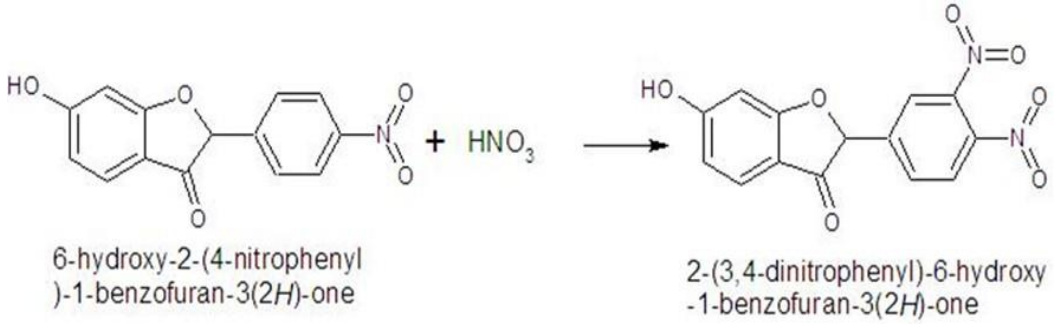

Figure 4: Preparation of 2-(-3,4-dinitrophenyl)-6-hydroxy-1-benzofuran-3(2H)-one

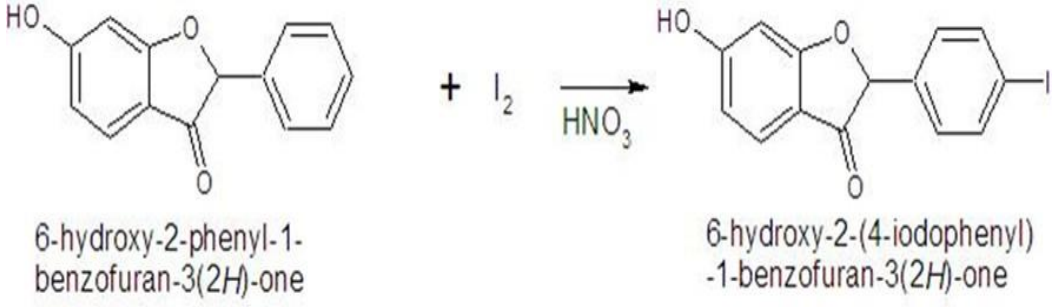

Figure 5: Preparation of 6-hydroxy-2-(4-iodophenyl)-1-benzofuran-3(2H)-one

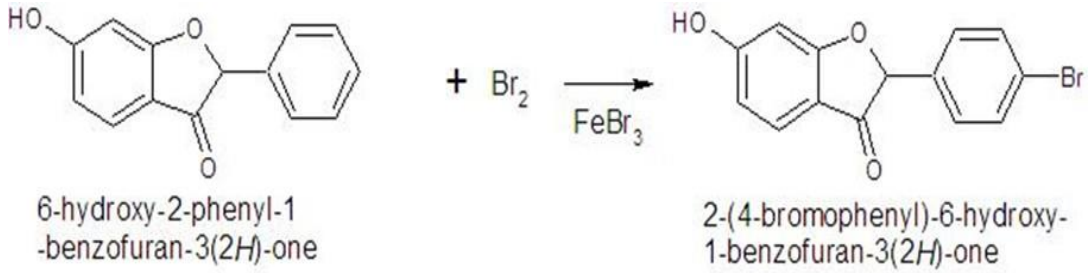

Figure 6: Preparation of 6-hydroxy-2-(4-bromophenyl)-1-benzofuran-3(2H)-one

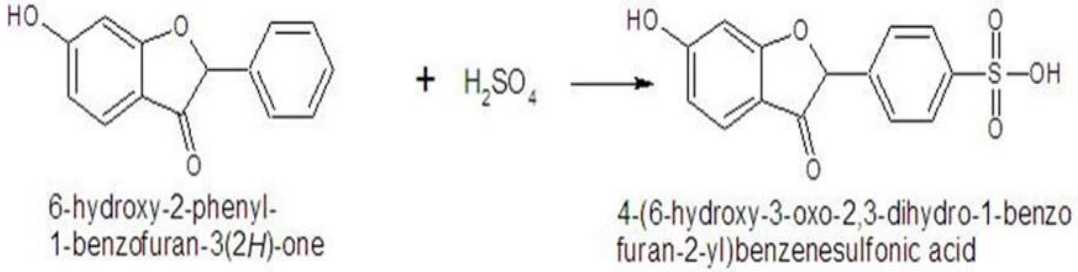

Figure 7: Preparation of 4-(6-hydroxy-3-oxo-2,3-dihydro-1-benzofuran-2-yl)benzenesulfonic acid

Preparation of Dry Hydrochloric Acid

Dry hydrochloric acid was prepared by reacting sulphuric acid with sodium chloride gives a dry HCL gas which was trapped in a flask containing sulphuric acid which absorbs traces of water in the gas. Then gas was pumped into the reaction mixture.[72]

Synthesis of 2-bromo-1-(2,4-dihydroxyphenyl)-2-phenylethanone

4-(2-bromo-2-phenylethanimidoyl) benzene-1,3-diol(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. White cream crystals were obtained which was dried.

6-hydroxy-2-phenyl-1-benzofuran-3(2*H*)-one:(IIA)

2-bromo-1-(2,4-dihydroxyphenyl)-2-phenylethanone (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 recrystallised 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 2.2g (0.02mol) of compound IIA 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 45 min, and the reaction mixture was poured into 100 ml cold water and stirred, and the 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 recrystallised by hot ethanol solution, and then T.L.C Studies were performed.

Dinitration: A 4.5ml 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 2.71gm (0.01mol) of 6-hydroxy-2-(-4-nitrophenyl)-1-benzofuran-3(2*H*)-one (compound-IIB) is added the reaction mixture was refluxed on a water bath for 30 minutes with 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 recrystallised by hot ethanol solution, and then T.L.C Studies were performed.

Iodination: A 3.1g (0.1mol) of compound IIA, 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 recrystallised by hot ethanol solution, and then T.L.C Studies were performed.

Bromination: A 2.2g (0.1mol) of compound IIA 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 recrystallised 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 1gm of compound IIA 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 product compound IIA 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 solubilised 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 colorimetric 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. [29]

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

6-hydroxy-2-phenyl-1-benzofuran-3(2H)-one: (IIA)

Yield: 75.62 %, Melting point 211 ^{o}C, Rf Value: 0.38, Mol formula $C_{14}H_{10}O_3$ Mol Weight: 226.22; IR (Cm^{-1}) (KBr): 3425.72 (OH); 1685.42 (C=O); 1158.85 (C-O-C); ^{1}H NMR (400 MHz, MeOD-d_6): δ= 8.15 (d 1H Ar-H *J*=8.4) 7.31-7.39 (m 5H Ar-H) 6.05 (d 1H Ar-H *J*= 1.6Hz), 5.49 (d 1H Ar-H *J*= 1.6Hz) 5.49 (s 1H CH) ^{13} C NMR (100 MHz, MeOD): δ= 88.06 (C-2), 109.16 (C-5), 95.91 (C-7), 112.06 (C-9), 127.41 (C-1``), 128.41 (C-2``), 129.69 (C-2```), 136.59 (C-1`), 124.36 (C-4), 170.80 (C-8), 164.88 (C-6), 197.32 (C-3). Mass m/z: 227 (M+1), 225 (M-1);

6-hydroxy-2-(-4-nitrophenyl)-1-benzofuran-3(2H)-one: (IIB)

Yield: 64.5%, Melting point 196 ^{o}C, Rf Value: 0.58, Mol formula $C_{14}H_9NO_5$ Mol Weight: 271.22; IR (Cm^{-1}) (KBr): 3424.22 (OH); 1743.18 (C=O); 1115.37 (C-O-C); 1690.94 (NO2) Mass m/z: 271 (M+1), 269 (M-1);

2-(-3,4-dinitrophenyl)-6-hydroxy-1-benzofuran-3(2H)-one: (IIC)

Yield: 74.5%, Melting point 236 ^{o}C, Rf Value: 0.36, Mol formula $C_{14}H_8N_2O_7$ Mol Weight: 316.22; IR (Cm^{-1}) (KBr): 3274.17 (OH); 1684.59 (C=O); 1150.86 (C-O-C); 1684.86 (NO2); 1616.60 (NO2); Mass m/z: 317 (M+1), 315 (M-1);

6-hydroxy-2-(4-iodophenyl)-1-benzofuran-3(2H)-one: (IID)

Yield: 84.5%, Melting point 286 ^{o}C, Rf Value: 0.54, Mol formula $C_{14}H_9IO_3$ Mol Weight: 352.12; IR (Cm^{-}

$^{-1}$) (KBr): 3423.23 (OH); 1787.96 (C=O); 1164.58 (C-O-C); 746.39 (I); Mass m/z: 352 (M+1), 350 (M-1);

2-(4-bromophenyl)-6-hydroxy-1-benzofuran-3(2H)-one: (IIE)

Yield: 76.40%, Melting point 248^{o}C, Rf Value: 0.60, Mol formula $C_{14}H_9O_3Br$ Mol Weight: 305.12; IR (Cm^{-1}) (KBr): 3441.51 (OH); 1710.71 (C=O); 1349.87 (C-O-C); 758.90 (Br); Mass m/z: 304 (M+1), 302 (M-1);

4-(6-hydroxy-3-oxo-2,3-dihydro-1-benzofuran-2-yl) benzenesulfonic acid: (IIF)

Yield: 92.33%, Melting point 198^{o}C, Rf Value: 0.46, Mol formula $C_{14}H_{10}O_6S$ Mol Weight: 306.29; IR (Cm^{-1}) (KBr): 3423.25 (OH); 1677.32 (C=O); 1230.45 (C-O-C); 1340.72 (SO2); Mass m/z: 305 (M+1), 307 (M-1);

Anti-Cancer Activity Results

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

Table 5: Anti-Cancer Results Experiment – 1

	Experiment - 1			
	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M
IIA	100.0	100.0	100.0	21.9
IIB	100.0	100.0	71.2	2.2
IIC	100.0	100.0	100.0	-20.8
IID	100.0	100.0	100.0	22.4
IIE	100.0	100.0	100.0	52.5
IIF	100.0	100.0	100.0	25.6

Table 6: Anti-Cancer Results Experiment – 2

	Experiment - 2			
	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M
IIA	100.0	100.0	89.5	19.9
IIB	100.0	90.8	88.0	10.2
IIC	100.0	100.0	100.0	-40.9
IID	100.0	100.0	100.0	9.1
IIE	100.0	100.0	100.0	41.6
IIF	100.0	100.0	86.5	15.8

Table 7: Anti-Cancer Results Experiment – 3

	Experiment - 3			
	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M
IIA	100.0	100.0	86.1	15.8
IIB	100.0	86.7	73.6	8.5
IIC	100.0	100.0	100.0	-45.2
IID	100.0	100.0	100.0	13.4
IIE	100.0	100.0	100.0	42.2
IIF	100.0	100.0	100.0	12.0

Table 8: Anti-Cancer Results Average Values

	Average Values			
	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M
IIA	100.0	100.0	91.9	19.2
IIB	100.0	92.5	77.6	6.9
IIC	100.0	100.0	100.0	-35.6
IID	100.0	100.0	100.0	15.0
IIE	100.0	100.0	100.0	45.4
IIF	100.0	100.0	95.5	17.8

Table 9: Results of anti-cancer activity for LC50, TGI, G150

G361	Molar Drug Concentration		
	LC 50	TGI	G150
IIA	$>10^{-4}$	$>10^{-4}$	$3.2*10^{-5}$
IIB	$>10^{-4}$	$>10^{-4}$	2.6*10-6
IIC	$>10^{-4}$	$>10^{-4}$	$2.3*10^{-6}$
IID	$>10^{-4}$	$>10^{-4}$	$3.2*10^{-5}$
IIE	$>10^{-4}$	$>10^{-4}$	$>10^{-4}$
IIF	$>10^{-4}$	$>10^{-4}$	$3.2*10^{-5}$
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-1,5-diol 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 supernatant ether layer was removed and then washed with dry ether and then dried. Which yielded a crude product of 86.10%. 4-(2-bromo-2-phenylethanimidoyl) benzene-1,3-diol (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 67.10%. 4-(2-bromo-2-phenylethanimidoyl) benzene-1,3-diol (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 75.62%.

Nitration: Sulphuric acid and nitric acid was mixed in a flask and then cooled in an ice bath and then 6-hydroxy-2-phenyl-1-benzofuran-3-(2*H*)-one and care have been taken such that temperature does not raise more than 55^{o}C such that a 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 64.5%

Dinitration: Sulphuric acid and nitric acid was mixed in a flask and then cooled in an ice bath and then 6-hydroxy-2-phenyl-1-benzofuran-3-(2*H*)-one Then vigorously refluxed and dinitrate product 2-(-3,4-dinitrophenyl)-6-hydroxy-1-benzofuran-3(2*H*)-one obtained is washed ice cold water finally extracted with ether and distilled gives a yield of 74.5%

Iodination: Iodine and nitric acid was mixed in a flask and then cooled in an ice bath and then 6-hydroxy-2-phenyl-1-benzofuran-3-(2*H*)-one Then vigorously refluxed and dinitrate product 6-hydroxy-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 84.5%

Bromination: Bromine and pyridine was mixed in a flask and then cooled in an ice bath and then 6-hydroxy-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)-6-hydroxy-1-benzofuran-3(2*H*)-one obtained is washed ice cold water finally extracted with ether and distilled gives a yield of 76.40%

Sulphonation: Oleum (Fuming Sulphuric acid) was mixed in a flask and then boiled in a water bath and then 6-hydroxy-2-phenyl-1-benzofuran-3-(2*H*)-one Then vigorously refluxed gives sulphonic product 4-(6-hydroxy-3-oxo-2,3-dihydro-1-benzofuran-2-yl) benzenesulfonic acid obtained is washed ice cold water finally extracted with ether and distilled gives a yield of 92.33%

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 IIB, IIC 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 6-hydroxy-2-phenyl-1-benzofuran-3(2H)-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 IIB, IIC **s**howed an excellent antiproliferative activity which serves as a lead to further optimization in the drug discovery process.

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