SYNTHESIS AND EVALUATION OF N-(5-ETHYL AMINO) -2, 5-DIHYDRO-1, 3-THIAZOL-2-YL)-3-HYDROXY-5-NITRO-1-BENZOFURAN-2 CARBOHYDRAZIDE

Prapulla Putta*, Prof (Dr) Kaushal K. Chandrul[1]
[*]Research Scholar, Mewar University, NH-79, Gangrar, Chittorgarh, Rajastan-312901, India.
[1]Research Supervisor, Dean and Professor, Department of Pharmaceutical Sciences, Mewar University, Gangrar, Chittorgarh, Rajasthan-312901, India.

Address:
Corresponding author:
*Prapulla Putta, Research Scholar,
Mewar University,
NH-79, Gangrar, Chittorgarh (Dt),
Rajasthan-312901, India.

Abstract
In the current research the title Benzofuran are synthesized from methyl-2-hydroxy benzoate which has been nitrated at 5-positon by concentrated sulphuric acid and nitric acid further prepared methyl-2-hydroxy-5-nitro benzoate. Benzofuran are synthesized from methyl-2-hydroxy benzoate which has been nitrated at 5-positon by concentrated sulphuric acid and nitric acid further prepared methyl-2-hydroxy-5-nitro benzoate. The prepared methyl-2-hydroxy-5-nitro benzoate was converted to basic environment by freshly prepared Chloroacetyl chloride to form [2-(3-hydroxy-5-nitro-1-benzofuran-2-carbabonyl) hydrazinyl] acetyl chloride which is further undergoes cyclisation and yielded N-(5-amino-2, 5-dihydro-1, 3-thiazol-2-yl)-3-hydroxy-5-nitro-1-benzofuran-2-carbohydrazide. Then it was reacted with acetaldehyde which yielded the title compound N-(5-ethylamino) -2, 5-dihydro-1, 3-thiazol-2-yl)-3-hydroxy-5- nitro-1-benzofuran-2-carbohydrazide. To prepare further derivatives the hydroxyl group in the different position has been treated with reagents which had underwent the substitution chlorine at position 3 and yielded different alkyl and aryl amine carbohydrazide derivatives.
Key Words: Benzofuran, Carbohydrazide, Heterocyclic.

I. INTRODUCTION:
Heterocyclic compounds are the cyclic organic compounds which contain at least one hetero atom, the most common heteroatoms are the nitrogen, oxygen and sulphur but heterocyclic rings containing other hetero atoms are also widely known. Carbocyclic compound a cyclic organic compound containing all carbon atoms in ring formation. Heterocyclic compounds considered one of the vital classes of organic compounds, which are used in many biological fields, due to it is activity in multiple illnesses. Biological molecules such as DNA and RNA, chlorophyll, hemoglobin, vitamins and many more contains the heterocyclic ring in major skeleton [1].
Derivatives of benzofuran-2-carbohydrazide are known for exhibiting various pharmacological activities. Such compounds were found to be selective adenosine receptor antagonists, anti-inflammatory agents, and local anaesthetics [2]. Variously substituted 2-benzofurancarbohydrazide derivatives show selective cytotoxicity against human cancer cell line [4]. On the other hand, benzofuran-2-carboxylic acids bearing (chlorometyl) indoline or benzoyl nitrogen mustard as DNA-binding group are structural subunits of synthetic analogues of some natural antitumor agents such as CC-1065, duocarmycin, dystamycin, and netropsin[5-8]. Amide derivatives of halo-benzofuran-2-carboxylic acid were found to be useful in the treatment of the diseases which are associated with the modulation of H3 receptors [9]. Moreover, 7-piperazinylbenzofuran-2-carbxylic acid amides having halogens or methoxyl groups in benzene ring were patented as partial agonists of 5-HT receptors which should be useful

in the treatment of many psychiatric disorders [10].

II. MATERIALS AND METHODS:

Reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel GF254 plates from E-Merck Co. and compounds visualized either by exposure to UV or by dipping in 10% aqueous potassium permanganate solution. Melting points were determined using open capillary tube method and are uncorrected. Infrared (IR) spectra were recorded using KBr disk on a Thermo Nicolet MX-1 FTIR spectrometer [11]. 1 H NMR spectra were recorded on Bruker AMX-400 and 101 MHz, respectively. Chemical shifts are reported in δ ppm units with respect to TMS as internal standard. Mass spectra were recorded on Autospec Mass Spectrometer under the electron impact at 70 eV. All the chemicals used were of analytical grade obtained from Himedia and SD fine chemicals [12].

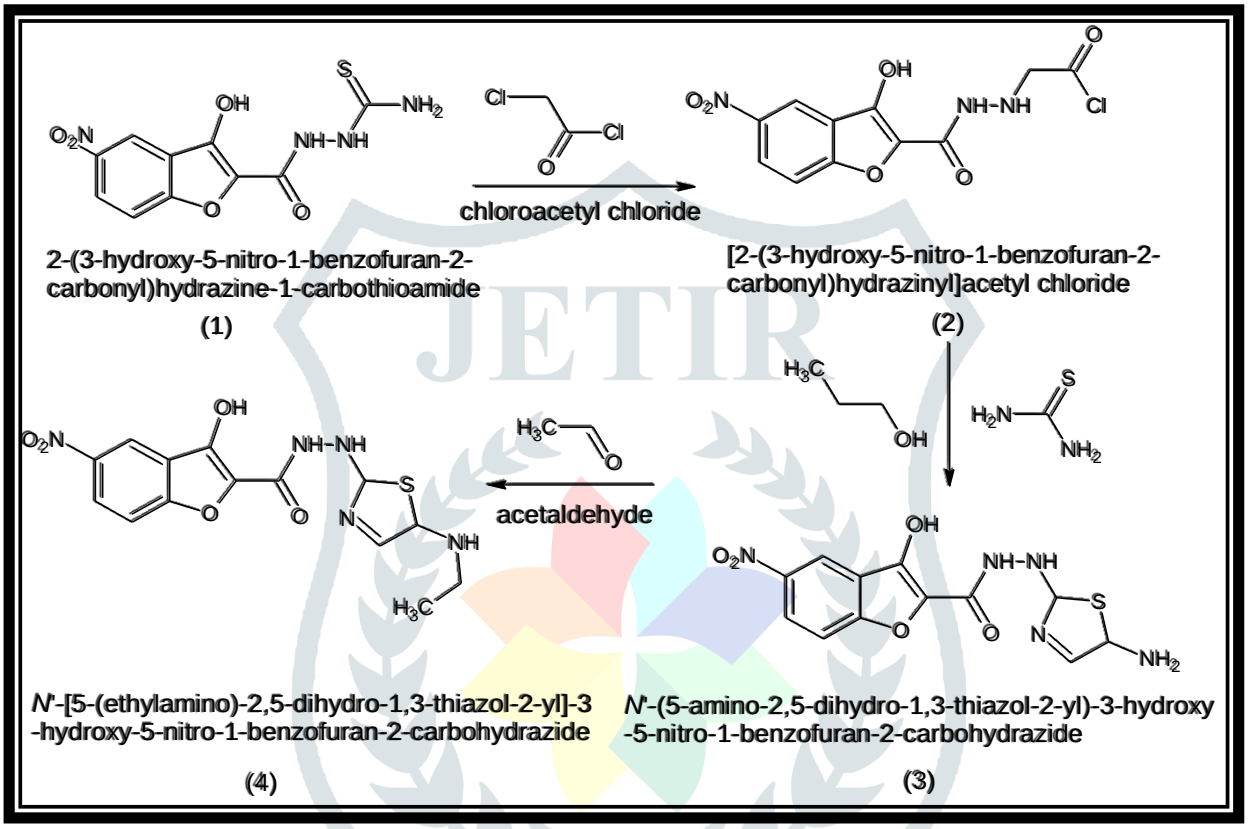

Figure 1: Experimental Schematic design for the synthesis of Benzofuran derivatives

III. RESULTS:

Synthesis of 2-(3-hydroxy-5-nitro-1-benzofuran-2-carbonyl) hydrazine-1-carbothioamide:

Procedure: A 2.3gm (0.1mol) of 3-hydroxy-5-nitro-1-benzofuran-2-carbohydrazide was dissolved freshly prepared sodium ethoxide 15 ml were taken in a round bottomed flask to which 7.3 gm of thiourea was added and refluxed at high temperature such as 80°C for about 6 hrs. Sodium ethoxide preparation 100ml of ethanol was taken in a round bottomed flask is fitted with a balloon and a 10gm of sodium metal was crunched in to small pieces added to ethanol with strong stirring. After completion reaction procedure the ethanol was distilled of from the reaction mixture then transferred in to a crushed ice. Precipitate was filtered and dried in a hot air oven. Finally obtained product was recrystalized with hot methanol T.L.C studies were performed to estimate the purity of the product. Results shown in table 1.

Table 1: Physical properties and spectral data of compound

1	**Molecular formula**	$C_{10}H_8N_4O_5S$
2	**Molecular wt**	296.22
3	**Molecular composition**	C (40.54%) H (2.72%) N (18.91%) O (27.00%) S (10.82%)
4	**Melting point (°C)**	264
5	**Colour**	Light brown
6	**State**	Solid

7	**Rf Value**	0.64
8	**Percentage yield**	64.5
9	**Solubility**	Methanol
10	**Mass data Mass** m/z **:**	297(M+1),
11	**IR data IR (Cm^{-1}) (KBr):**	3441.51 (NH); 2924.35 (CH3); 1631.47 (C=O); 1349.87 (C-O-C); 1602.71 (NO2) 1383.14 (C-N);
12	**1HNMR data**	δ 7.83 (1H, dd, *J* = 8.8, 0.5 Hz), 8.28 (1H, dd, *J* = 8.8, 1.8 Hz), 8.81 (1H, dd, *J* = 1.8, 0.5 Hz).
13	**13CNMR data**	δ 113.0 (1C, s), 114.8 (1C, s), 119.3 (1C, s), 125.8 (1C, s), 145.3 (1C, s), 152.5 (1C, s), 154.2 (1C, s), 154.6 (1C, s), 157.2 (1C, s), 181.7 (1C, s).

Synthesis of 2-(3-hydroxy-5-nitro-1-benzofuran-2-carbonyl) hydrazinyl] acetyl chloride:

Procedure: A 2.96 gm (0.1mol) of 2-(3-hydroxy-5-ntro-1-enzofura-2-carbonyl) hydrazine-1-carothioamide was taken I a round bottomed flask to which thionyl chloride (30ml) were added and then 1.12 gm (0.1mol) of chloro acetyl chloride was mixed to the reaction mixture and boiled at 110^{o}C for 24 hrs. Excess thionyl chloride was distilled and removed and then the reaction mixture was quenched to ice cold water then pure crystals were obtained washed twice with water to remove the excess acid present in the product and finally dried over flame to remove the moisture. Finally obtained product was recrystalized with hot ethanol T.L.C studies were performed to estimate the purity of the product. Results shown in table 2.

Table 2: Physical properties and spectral data of compound

1	**Molecular formula**	$C_{11}H_8ClN_3O_6$
2	**Molecular wt**	313.65
3	**Molecular composition**	C (42.12%) H (2.57%) Cl (11.30%) N (13.40%) O (30.61%)
4	**Melting point (^{O}C)**	284
5	**Colour**	Brown
6	**State**	Solid
7	**Rf Value**	0.72
8	**Percentage yield**	74.5
9	**Solubility**	Methanol
10	**Mass data** Mass m/z	314(M+1),
11	**IR data IR (Cm^{-1})** (KBr):	3441.51 (NH); 2924.35 (CH3); 1631.47 (C=O); 1349.87 (C-O-C); 1602.71 (NO2) 1383.14 (C-N);
12	**1HNMR data**	δ 3.66 (2H, s), 7.83 (1H, dd, *J* = 8.8, 0.5 Hz), 8.28 (1H, dd, *J* = 8.8, 1.8 Hz), 8.81 (1H, dd, *J* = 1.8, 0.5 Hz).
13	**13CNMR data**	δ 49.1 (1C, s), 113.0 (1C, s), 114.8 (1C, s), 119.3 (1C, s), 125.8 (1C, s), 145.3 (1C, s), 152.5 (1C, s), 154.2 (1C, s), 154.6 (1C, s), 157.2 (1C, s), 166.5 (1C, s).

Synthesis of *N*'-(5-amino-2, 5-dihydro-1, 3-thiazol-2-yl)-3-hydroxy-5-nitro-1-benzofuran-2-carbohydrazide:

Procedure: A 3.13gm (0.1mol) [2-(3-hydroxy-5-nitro-1-benzofuran-2-carbonyl) hydrazinyl] acetyl chloride was dissolved in alcohol to which 0.7ml of thionyl chloride was added to the reaction mixture in a round bottomed flask then a 5ml of propanol was added to the reaction mixture. The reaction was refluxed for about 16 hrs and monitored by chromatographic studies. Excess thionyl chloride was distilled and removed and then the reaction mixture was quenched to ice cold water then pure crystals were obtained washed twice with water to remove the excess acid present in the product and finally dried over flame to remove the moisture. Finally obtained product was recrystalized with hot ethanol T.L.C studies were performed to estimate the purity of the product. Results shown in table 3.

Table 3: Physical properties and spectral data of compound

1	**Molecular formula**	$C_{12}H_{11}N_5O_5S$
2	**Molecular wt**	337.31
3	**Molecular composition**	C (42.73%) H (3.29%) N (20.76%) O (23.72%) S (9.51%)
4	**Melting point (^{O}C)**	224
5	**Colour**	Brown
6	**State**	Solid
7	**Rf Value**	0.66
8	**Percentage yield**	54.5
9	**Solubility**	Ethanol
10	**Mass data** Mass m/z	338(M+1),
11	**IR data IR (Cm^{-1})** (KBr):	3441.51 (NH); 2924.35 (CH3); 1631.47 (C=O); 1349.87 (C-O-C); 1602.71 (NO2) 1383.14 (C-N);
12	**1HNMR data**	δ 5.54 (1H, d, *J* = 2.4 Hz), 5.71 (1H, s), 7.83 (1H, dd, *J* = 8.8, 0.5 Hz), 8.28 (1H, dd, *J* = 8.8, 1.8 Hz), 8.46 (1H, d, *J* = 2.4 Hz), 8.81 (1H, dd, *J* = 1.8, 0.5 Hz).
13	**13CNMR data**	δ 65.2 (1C, s), 71.7 (1C, s), 113.0 (1C, s), 114.8 (1C, s), 119.3 (1C, s), 125.8 (1C, s), 143.2 (1C, s), 145.3 (1C, s), 152.5 (1C, s), 154.2 (1C, s), 154.6 (1C, s), 157.2 (1C, s).

Synthesis of *N*'-[5-(ethyl amino)-2, 5-dihydro-1, 3-thiazol-2-yl]-3-hydroxy-5-nitro-1-benzofuran-2-carbohydrazide:

Procedure: A 8.13gm (0.1mol) N'-(5-amino-2,5-dihydro-1,3-thiazol-2-yl)-3-hydroxy-5-nitro-1-benzofuran-2-carbohydrazide was dissolved in alcohol to which 3.5 ml of acetaldehyde was added to the reaction mixture in a round bottomed flask. The reaction was refluxed for about 6hrs and monitored by chromatographic studies. Excess ethanol was distilled and removed and then the reaction mixture was quenched to ice cold water then pure crystals were obtained washed twice with water to remove the excess acid present in the product and finally dried over flame to remove the moisture. Finally obtained product was recrystalized with hot ethanol T.L.C studies were performed to estimate the purity of the product. Results shown in table 4.

Table 4: Physical properties and spectral data of compound

1	**Molecular formula**	$C_{14}H_{15}N_5O_5S$
2	**Molecular wt**	365.36
3	**Molecular composition**	C (46.02%) H (4.14%) N (19.17%) O (21.90%) S (8.78%)
4	**Melting point (^{O}C)**	288
5	**Colour**	Light Yellow
6	**State**	Solid
7	**Rf Value**	0.72
8	**Percentage yield**	66.7
9	**Solubility**	Methanol
10	**Mass data Mass** m/z	366 (M+1),
11	**IR data IR (Cm^{-1}) (KBr):**	3441.51 (NH); 2924.35 (CH3); 1631.47 (C=O); 1349.87 (C-O-C); 1602.71 (NO2) 1383.14 (C-N);
12	**1HNMR data**	δ 1.11 (3H, t, *J* = 7.3 Hz), 2.65-2.77 (2H, 2.71 (q, *J* = 7.3 Hz), 2.71 (q, *J* = 7.3 Hz)), 5.16 (1H, d, *J* = 3.1 Hz), 5.65 (1H, s), 7.83 (1H, dd, *J* = 8.8, 0.5 Hz), 8.28 (1H, dd, *J* = 8.8, 1.8 Hz), 8.52 (1H, d, *J* = 3.1 Hz), 8.81 (1H, dd, *J* = 1.8, 0.5 Hz).
13	**13CNMR data**	δ 14.9 (1C, s), 37.6 (1C, s), 65.2 (1C, s), 71.7 (1C, s), 113.0 (1C, s), 114.8 (1C, s), 119.3 (1C, s), 125.8 (1C, s), 143.2 (1C, s), 145.3 (1C, s), 152.5 (1C, s), 154.2 (1C, s), 154.6 (1C, s), 157.2 (1C, s).

Synthesis of 3-hydroxy-5-nitro-*N*'-[5-(propylamino)-2, 5-dihydro-1, 3-thiazol-2-yl]-1-benzofuran-2-carbohydrazide:

Procedure: A 8.13gm (0.1mol) N'-(5-amino-2,5-dihydro-1,3-thiazol-2-yl)-3-hydroxy-5-nitro-1-benzofuran-2-carbohydrazide was dissolved in alcohol to which 3.5 ml of propanal was added to the reaction mixture in a round bottomed flask. The reaction was refluxed for about 8 hrs and monitored by chromatographic studies. Excess ethanol was distilled and removed and then the reaction mixture was quenched to ice cold water then pure crystals were obtained washed twice with water to remove the excess acid present in the product and finally dried over flame to remove the moisture. Finally obtained product was recrystalized with hot ethanol T.L.C studies were performed to estimate the purity of the product. Results shown in table 5.

Table 5: Physical properties and spectral data of compound

1	**Molecular formula**	$C_{15}H_{17}N_5O_5S$
2	**Molecular wt**	379.39
3	**Molecular composition**	C (47.49%) H (4.52%) N (18.46%) O (21.09%) S (8.45%)
4	**Melting point (^{O}C)**	158
5	**Colour**	Light Yellow
6	**State**	Solid
7	**Rf Value**	0.72
8	**Percentage yield**	64.5
9	**Solubility**	Methanol
10	**Mass data Mass** m/z	380 (M+1),
11	**IR data IR (Cm^{-1}) (KBr):**	3441.51 (NH); 2924.35 (CH3); 1631.47 (C=O); 1349.87 (C-O-C); 1602.71 (NO2) 1383.14 (C-N);
12	**1HNMR data**	^{1}δ 0.92 (3H, t, *J* = 7.5 Hz), 1.49-1.62 (2H, 1.56 (qt, *J* = 7.5, 5.7 Hz), 1.56 (qt, *J* = 7.5, 5.7 Hz)), 2.61-2.72 (2H, 2.67 (t, *J* = 5.7 Hz), 2.67 (t, *J* = 5.7 Hz)), 5.16 (1H, d, *J* = 3.7 Hz), 5.66 (1H, s), 7.83 (1H, dd, *J* = 8.8, 0.5 Hz), 8.28 (1H, dd, *J* = 8.8, 1.8 Hz), 8.52 (1H, d, *J* = 3.7 Hz), 8.81 (1H, dd, *J* = 1.8, 0.5 Hz).
13	**13CNMR data**	δ 11.4 (1C, s), 22.8 (1C, s), 41.6 (1C, s), 65.2 (1C, s), 71.7 (1C, s), 113.0 (1C, s), 114.8 (1C, s), 119.3 (1C, s), 125.8 (1C, s), 143.2 (1C, s), 145.3 (1C, s), 152.5 (1C, s), 154.2 (1C, s), 154.6 (1C, s), 157.2 (1C, s).

Synthesis of 3-hydroxy-*N*'-{5-[(2-methylpropyl) amino]-2, 5-di hydro-1, 3-thiazol-2-yl}-5-nitro-1-benzofuran-2-carbohydrazide:

Procedure: A 8.13gm (0.1mol) N'-(5-amino-2, 5-dihydro-1,3-thiazol-2-yl)-3-hydroxy-5-nitro-1-benzofuran-2-carbohydrazide was dissolved in alcohol to which 3.5 ml of 2-methylpropanal was added to the reaction mixture in a round bottomed flask. The reaction was refluxed for about 4 hrs and monitored by chromatographic studies. Excess ethanol was distilled and removed and then the reaction mixture was quenched to ice cold water then pure crystals were obtained washed twice with water to remove the excess acid present in the product and finally dried over flame to remove the moisture. Finally obtained product was recrystalized with hot ethanol T.L.C studies were performed to estimate the purity of the product. Results shown in table 6.

Table 6: Physical properties and spectral data of compound

1	**Molecular formula**	$C_{16}H_{19}N_5O_5S$
2	**Molecular wt**	393.41
3	**Molecular composition**	C (48.85%) H (4.87%) N (17.80%) O (20.33%) S (8.15%)
4	**Melting point (^{O}C)**	264
5	**Colour**	Light brown
6	**State**	Solid
7	**Rf Value**	0.72
8	**Percentage yield**	74.5
9	**Solubility**	Methanol

10	**Mass data Mass** m/z	394(M+1),
11	**IR data IR (Cm^{-1}) (KBr):**	3441.51 (NH); 2924.35 (CH3); 1631.47 (C=O); 1349.87 (C-O-C); 1602.71 (NO2) 1383.14 (C-N);
12	**1HNMR data**	δ 0.81-0.93 (6H, 0.87 (d, *J* = 6.6 Hz), 0.87 (d, *J* = 6.6 Hz)), 1.76 (1H, tsept, *J* = 7.3, 6.6 Hz), 2.65-2.77 (2H, 2.71 (d, *J* = 7.3 Hz), 2.71 (d, *J* = 7.3 Hz)), 5.16 (1H, d, *J* = 3.7 Hz), 5.72 (1H, s), 7.83 (1H, dd, *J* = 8.8, 0.5 Hz), 8.28 (1H, dd, *J* = 8.8, 1.8 Hz), 8.53 (1H, d, *J* = 3.7 Hz), 8.81 (1H, dd, *J* = 1.8, 0.5 Hz).
13	**^{13}C NMR data**	δ 11.4 (1C, s), 22.8 (1C, s), 41.6 (1C, s), 65.2 (1C, s), 71.7 (1C, s), 113.0 (1C, s), 114.8 (1C, s), 119.3 (1C, s), 125.8 (1C, s), 143.2 (1C, s), 145.3 (1C, s), 152.5 (1C, s), 154.2 (1C, s), 154.6 (1C, s), 157.2 (1C, s).

IV. DISCUSSION:

The synthesis of N-(5-ethylamino) -2, 5-dihydro-1, 3-thiazol-2-yl)-3-hydroxy-5- nitro-1-benzofuran-2-carbohydrazide was synthesized using the appropriate synthetic procedures.

Benzofuran are synthesized from methyl-2-hydroxy benzoate which has been nitrated at 5-positon by concentrated sulphuric acid and nitric acid further prepared methyl-2-hydroxy-5-nitro benzoate. The prepared methyl-2-hydroxy-5-nitro benzoate was converted to basic environment by freshly prepared Chloroacetyl chloride to form [2-(3-hydroxy-5-nitro-1-benzofuran-2-carbabonyl) hydrazinyl] acetyl chloride which is further undergoes cyclisation and yielded N-(5-amino-2, 5-dihydro-1, 3-thiazol-2-yl)-3-hydroxy-5-nitro-1-benzofuran-2-carbohydrazide. Then it was reacted with acetaldehyde which yielded the title compound N-(5-ethylamino) -2, 5-dihydro-1, 3-thiazol-2-yl)-3-hydroxy-5- nitro-1-benzofuran-2-carbohydrazide. To prepare further derivatives the hydroxyl group in the different position has been treated with reagents which had underwent the substitution chlorine at position 3 and yielded different alkyl and aryl amine carbohydrazide derivatives.

V. CONCLUSION:

N-(5-ethyl amino) -2, 5-dihydro-1, 3-thiazol-2-yl)-3-hydroxy-5- nitro-1-benzofuran-2-carbohydrazide synthesized. The title compounds in good yields. An optimized method with prominent conditions for the schematic synthesis of the compounds listed as per the title. Synthesized compounds structures were confirmed with spectroscopic data such as mass spectrum, NMR spectrum and Infra red spectrum. Synthesized compound physical properties such as Molecular formula, Molecular weight were developed and recorded.

VI. REFERENCES:

[1] Saku O, Saki M, Kurokawa M, et al. Synthetic studies on selective adenosine A2A receptor antagonists: synthesis and structure-activity relationships of novel benzofuran derivatives. Bioorga and Med Chem Let. 2010; 20(3):1090–1093.

[2] Mane BY, Agasimundin YS, and Shivakumar B. Synthesis of benzofuran analogs of fenamates as non-steroidal antiinflammatory agents. Ind J Chem. 2010; 49(2): 264–269.

[3] Kossakowski J, Zawadowski T. Synthesis of some amides of benzofurane-2-carboxylic and benzofurane-3-carboxylic acids with potential antidepressant activity. Acta Poloniae Pharmaceutica. 1987; 44(6): 497–502.

[4] Kossakowski J, Ostrowska K, Hejchman E, Wolska I. Synthesis and structural characterization of derivatives of 2- and 3-benzo[b]furan carboxylic acids with potential cytotoxic activity. Farmaco. 2005; 60(6):519–527.

[5] Prapulla Putta, Sridhar Babu Gummadi. Design, synthesis and evaluation of 3- (dimethyl amino)-5-methyl-2-(4-methylphenyl) quinazolin-4(3h)-one derivatives as potent biological agents. Int J Rese Analy Rev. 2019; 6(1): 637-643.

[6] Baraldi PG, Romagnoli R, Beria I et al. Synthesis and antitumor activity of new benzoheterocyclic derivatives of distamycin. A. J Med Chem. 2000; 43(14): 2675–2684.

[7] Wang Y, Li L, Ye W et al. CC-1065 analogues bearing different DNA-binding subunits: synthesis, antitumor activity, and preliminary toxicity study. J Med Chem. 2003; 46(4): 634–637.

[8] El-Messery, SM., Hassan, GS. Nagi, MN. Habib, ESE. Al-Rashood, ST., El-Subbagh, HI. Synthesis, biological evaluation and molecular modeling study ofsome new methoxylated 2-benzylthio-quinazoline-4(3H)-ones as nonclassicalantifolates. Bioorg. Med. Chem. Lett. 2016; 26: 4815–4823.

[9] Prapulla Putta, Sridhar Babu Gummadi. Synthesis of 2-{4-[(z) (benzylidene) amino]

phenyl}-3-[(dimethylamino) methyl] quinazolin-4(*3h*)-one derivatives as anti cancer agents. J Emerg Techn Inno Rese. 2019; 6(2): 615-1619.

[10] Baraldi PG, Romagnoli R, Bianchi N, Gambari R. Benzoyl nitrogen mustard derivatives of benzoheterocyclic analogues of netropsin: synthesis and biological activity. Bioorg Med Chem. 2003; 11(11): 2381–2388.

[11] Mohr P, Nettekoven M, Plancher J et al. Benzofuran and benzothiophene-2-carboxylic acids amide derivatives. US Pat. 0029976 A1, 2009.

[12] Andersson JH, Gybäck H, Johansson A et al. 2-Carboxamide-7-piperazinyl-benzofuran derivatives. 774 US Pat. 0331341 A1, 2010.