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SYNTHESIS AND COMPUTATIONAL STYDY OF 7-METHOXY-2-[4-METHOXYPHENYL]-1-BENZOFURAN-5-CARBOXALDEHYDE AND SYNTHESIS OF ITS SCHIFF BASES

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Abstract:
Vanillin undergoes sequence of reaction forming phosphonium salt through dimethyaminomethyl derivative (Mannich reaction). The synthesis of phosphonium salt can be achieved by sequence of three steps which was condense with 4-methoxybenzoyl chlorides by refluxing in toluene in presence of triethylamine forming 7-Methoxy-2-[4-methoxyphenyl]-l-benzofuran-5-carboxaldehyde (**1**). Computational study of (**1**) such as Binding energy, density of state, HOMO, LUMO, charge density and reactivity is done by using density functional theory. The aldehyde (**1**) is condensed with series of hydrazides (**4a-e**) forming schiff bases (**5a-e**). The acid hydrazide was synthesized from corresponding carboxylic acid (**2a-e**). The schiff bases (**5a-e**) are characterized by IR, NMR and mass spectra.

Key Words: Benzofuran, Schiff bases, Hydrazide, DFT, DOS, HOMO-LUMO.

Introduction:

Heterocyclic compounds plays very important role in the biological system. Many heterocyclic compounds are of natural origin with useful medicinal properties have served as lead compound in the designing of synthetic drugs. Heterocyclic compounds[I,II] bearing benzofuran moieties constitute the structure of number of pharmacological and biologically active interesting compounds. 7-Methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**1**) was synthesized by known literature method[III]. 7-Methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**1**) contain aldehyde functional group at benzofuran skeleton which will be condensed with various primary and secondary aliphatic or aromatic amines forming imines (Schiff bases) or iminium salt in mild acidic conditions.

Schiff base was first reported by Hugo Schiff [IV] in 1864. The compounds containing azomethine (-C=N-) group are know as Schiff bases, are formed by the condensation of a primary amines with a carbonyl compounds such as aldehydes or ketones in different reaction conditions and in different solvents with elimination of water molecule. The common general formula of Schiff base is RR'C=NR'', where R, R' and R'' are alkyl, aryl, cycloalkyl, heterocyclic, etc groups which may be substituted by other groups. Schiff bases are characterized by the –N=CH– (imine)

group which is important in elucidating the mechanism of transamination and racemisation reactions in biological systems[V,VI].

The nitrogen atom amine or aniline shows nucleophilic attack on the carbonyl carbon atom of the carbonyl group of the aldehyde or ketone forming carbinol amine which is further undergoes dehydration in presence of mild acidic conditions or dehydrating agent forming imine or Schiff base. The strong acidic and basic conditions are not recommended for the Schiff base formation because, carbinol amine does not further undergoes dehydration to imine or reaction can be stopped at carbinol amine. Also in strong acidic condition, amine or aniline get protonated and not showing nucleophilic attack on the carbonyl group of aldehyde or ketone.

The common feature of the Schiff base [RR'C=NR''] is the presence of azomethine group. The presence of lone pair of lectrons on the sp^2 hybridized orbital of the nitrogen atom of azomethine group is of considerable chemical importance and impart excellent chelating ability especially when used in the combination with one or more donor atoms close to the azomethine group.

Acid hydrazides are synthesized by condensing ester with hydrazine in presence of acid catalyst. The remarkable biological activity of acid hydrazides R-CO-NH-NH_2, a class of Schiff base, their corresponding aroylhydrazones, R-CO-NH-N=CH-R' and the dependence of their mode of chelation with transition metal ions present in the living system have been of significant interest in the past[VII-X]. The coordination compounds of aroylhydrazones have been reported to act as enzyme inhibitors and are useful due to their pharmacological applications[XI-XIII].

Schiff bases of primary amines and the carbonyl compounds are involved in many metabolic processes. Numerous products of further fragmentation and cross linking are responsible for the color, favor and taste of foods and drinks[XIV]. The chelating ability of the Schiff bases combined with the ease of the preparation and flexibility in the varying chemical environment above –C=N< groups make it interesting ligand in co-ordination chemistry.

Computational approaches[XV-XVI] put a handle on such imprecise but important concepts as steric hindrance, electrostatics, partial charges, strain, aromaticity and others. One of the most powerful ways to use computational chemistry methods for the elucidation of reaction mechanisms is the direct matching of computed and spectroscopic data. This involves comparison of optimised structures with experimental structural data keeping in mind that different experimental and theoretical methods give different averaged values for the geometrical parameters of molecules.

Experimental Work

7-Methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**1**) contain aldehyde functional group at benzofuran skeleton which will be condensed with various aromatic hydrazides (**4a-e**) forming imines (Schiff bases) (**5a-e)** in mild acidic conditions.

The 7-methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde (**1**) was synthesized by known literature method[III]. Mannich reaction of vanillin for the synthesis of 5-dimethylaminomethyl-4-hydroxy-3-methoxybenzaldehyde by using dimethylamine and paraformaldehyde in methanol was carried out at room temperature. The Mannich base was then acetylated by refluxing it with acetic anhydride for about 24 hrs and the volatile material was distilled out under reduced pressure to give crude diacetate. It is not purified further and directly treated with conc. Hydrochloric acid to gives 2-hydroxy-5-formylbenzyl chloride derivative in good yield. This benzyl chloride derivative on reaction with triphenyl phosphine in dry benzene under reflux condition forming phosphonium salt (Wittig reagent) m.p. 254^0C (decompose) which was the condensation with 4-(methoxy)benzoyl chloride in presence of base

(intramolecular Wittig reaction) forming 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**1**).

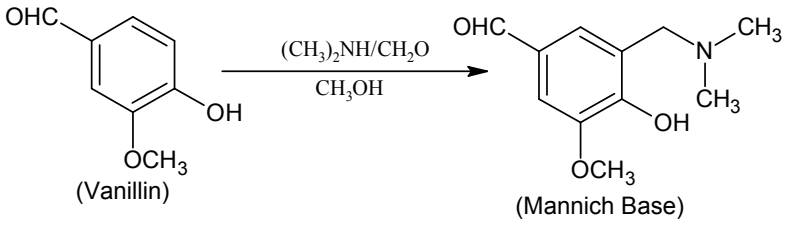
Acid hydrazide (**4a-e**) was synthesized by known literature method. The carboxylic acid (**2a-e**) in ethanol in round bottom flask in presence of concentrated sulfuric acid with constant stirring at room temperature and then reflux the resulting reaction mixture to 4-5 hrs (till all solid acid get dissolve, to obtain clear solution). Cool the resulting reaction mixture in ice bath and poured into crushed ice and the solution make alkaline by adding ammonia. Extract the ester product (**3a-e**) by 2 x petroleum ether. Ester (**3a-e**) was further treated with hydrazine hydrate in presence of acid catalyst forming solid product (acid hydrazide) (**4a-e**).

The hydrazides (**4a-e**) were treated with aldehyde (**1**) in alcohol in presence of acid catalyst forming schiff bases (**5a-e**). The formation of the products and its structure has been confirmed from the analytical data, FT-IR (KBr), NMR and mass spectroscopy.

2.1. Synthesis of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (1) :

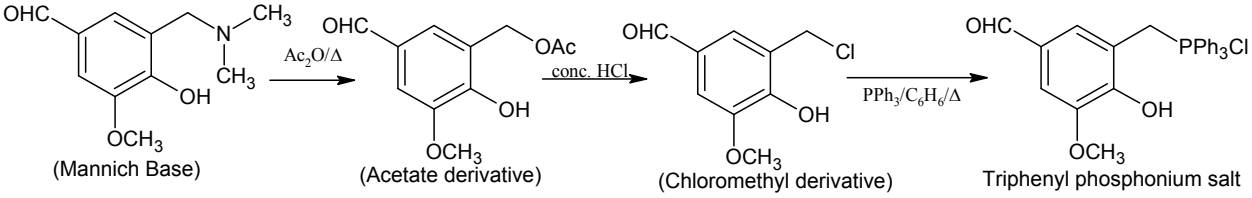
2.1.1. Preparation of 5-dimethylaminomethyl-4-hydroxy-3-methoxybenzaldehyde:

Vanillin (76 g, 0.5 mol) was added to a well stirred solution of 37% aqueous paraformaldehyde (60 g, 0.75 mol) and 38% aqueous dimethylamine (90 g, 0.75 mol) in methanol (450 ml). The reaction mixture was refluxed for 30 min and the stirred at ambient temperature for 8 hrs. It was then cooled to 5^0C and the white granular solid formed was filtered, washed with ice cold acetone (50 ml) and dried under vaccum to give 5-dimethylaminomethyl-4-hydroxy-3-methoxybenzaldehyde as a crystalline solid (92 g, 88%) m.p. 140-141^{0}C (lit 139-141^{0}C).



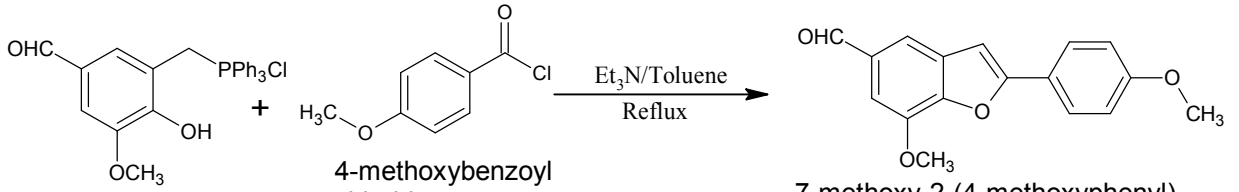
2.1.2. Preparation of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride:

A solution of 5-dimethylaminomethyl-4-hydroxy-3-methoxybenzaldehyde (10 g, 0.047 mol) in acetic anhydride (50 g, 0.49 mol) was refluxed for 24 hrs. The volatile material was removed by distillation under reduced pressure. The residue crude acetate was cooled and add concentrated hydrochloric acid (45 ml, 0,53 mol) to it gradually. The reaction mixture was stirred at about 1.5 hours at ambient temperature. The chloromethyl derivative formed was extracted by using benzene (2 x 75 ml). The combined benzene layer was washed with water (2 x 50 ml), dried over Na_2SO_4 and evaporate to gives a solid. The solid compound dissolves in benzene (125 ml) and triphenylphosphine (8 g, 0.03 mol) was added to it. The reaction mixture was heated under reflux for 6 hrs. The solid separated was filtered, washed with hot benzene (25 ml) and dried to gives (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (17.50 g, 79%), m.p. 254^{0}C (decomp).



2.1.3. Synthesis of 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (1):

A mixture of (2-hydroxy-3-methoxy-5-formylbenzyl) triphenylphosphonium chloride (3.5 g, 7.5 mmol), 4-methoxybenzoyl chloride (1.34 g, 7.8 mmol) and triethylamine (1.6 g, 16 mmol), in toluene (70 ml) was heated under reflux for 6 hrs. The reaction mixture was cooled to room temperature and water (50 ml) was added to it. Separate the organic layer by separating funnel and wash it by water (2 x 50 ml) and dried over Na_2SO_4. Toluene was distilled out under reduced pressure and the residue obtained was purified by using silica column chromatography (100-200 mesh, Eluent 40% ethyl acetate in hexane), from the 7-methoxy-2-[4-(methoxy)phenyl]-l-benzofuran-5-carboxaldehyde (**1**) (1.385 g, 62%) as a Faint Yellow crystalline solid, m.p. 170^0C.



(1)

FT-IR (KBr): 3010, 2977, 2935, 2709, 1693, 1612, 1598, 1513, 1228, 1133, 1024, 836 cm^{-1}.

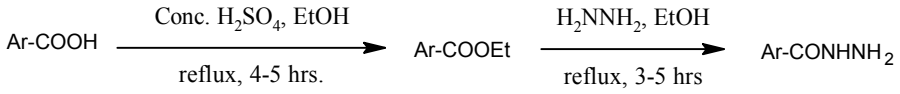
NMR (300 MHz) (DMSO-D6; δ ppm) $C_{17}H_{14}O_4$ (mol wt: 282.290 g/mol): 10.01 (s, 1H, -CHO), 7.86 – 7.891 (m, 3H, 3 Aromatic protons), 7.42 (dd, 2H, Aromatic protons), 7.09 (m, 2H, Aromatic protons), 4.046 (s, 3H, $-OCH_3$), 3.831 (s, 3H, $-OCH_3$).

2.2. General procedure for the synthesis of Schiff bases:

2.2.1. Synthesis of Hydrazides (4a-d):

Dissolve 0.01 equivalent of carboxylic acid (**2a-d**) 5 ml of ethanol in round bottom flask and add 1.78 ml of concentrated sulfuric acid into it slowly with constant stirring at room temperature. Reflux the resulting reaction mixture to 4-5 hrs (till all solid acid get dissolve, to obtain clear solution). Cool the resulting reaction mixture in ice bath and poured into 16.50 g crushed ice and the solution make alkaline by adding ammonia. Extract the ester product (**3a-d**) by 2 x 4.50 ml petroleum ether. Combine the organic layer and dried it by anhydrous sodium salphate. Distilled out ether under reduced pressure to obtain crude ester (**3a-d**) which is purified by recrystallisation or distillation.

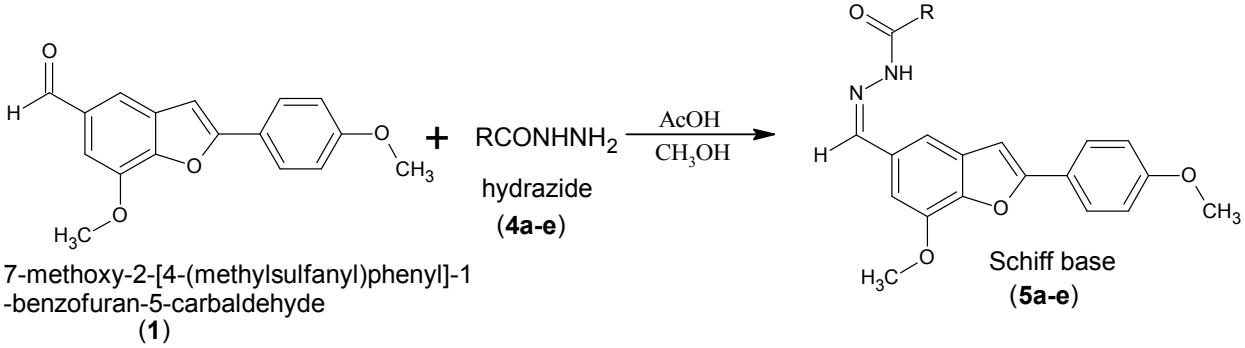
Dissolve 0.01 equivalent of ester (**3a-d**) in 5 ml of ethanol in round bottom flask. Add 0.011 equivalent of hydrazine hydrate slowly with constant stirring and reflux the reaction mixture to 3-5 hrs. Cool the reaction mixture and filter the solid product (acid hydrazide) (**4a-d**). The product was characterized by FT-IR and NMR spectroscopy.



2.2.2. Schiff bases of hydrazides (5a-e):

Dissolve 75 mg (0.25 mmol) of 7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-carbaldehyde (**1**) in 5 ml of methanol in round bottom flask. Add (0.27 mmol) of carbohydrazide (**4a-e**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 80-90 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in water bath & filter it on suction pump. The yield of *N*'-[(*E*)-{7-

methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]ary/alkyl carbohydrazide (**5a-e**) and m.p. of the product and characterized by using IR, NMR and Mass spectroscopy.



7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-carbaldehyde
(**1**)

2.3. Synthesis of various hydrazides:

2.3.1. Synthesis of 3-methypyridine-4-carbohydrazide (4a):

Dissolve 0.1 mole of 3-methylpyridine-4-carboxylic acid (**2a**) in 41 ml of ethanol in round bottom flask and add 18 ml of concentrated sulfuric acid into it slowly with constant stirring at room temperature. Reflux the resulting reaction mixture to 5 hrs (till all solid acid get dissolve, to obtain clear solution). Cool the resulting reaction mixture in ice bath and poured into 165 g crushed ice and the solution make alkaline by adding ammonia. Extract the ester product (**3a**) by 2 x 45 ml petroleum ether. Combine the organic layer and dried it by anhydrous sodium salphate. Distilled out ether under reduced pressure to obtain crude ester which is purified by recrystallisation with ethanol.

Dissolve 0.05 mole of ethyl 3-methylpyridine-4-carboxylate (**3a**) in 20 ml of ethanol in round bottom flask. Add 0.06 mole of hydrazine hydrate slowly with constant stirring and reflux the reaction mixture to 4 hrs. Cool the reaction mixture and filter the solid product (3-methylpyridine-4-carbohydrazide) (**4a**). The product was characterized by FT-IR spectroscopy.

Yield : 78 %; **M.P.**: 186 ^{0}C; **Molecular formula**: $C_7H_9N_2O$.

FT-IR (in KBr) : 3315, 3266, 3054, 1644, 1598, 1548, 1344, 1164, 968, 827, 707 cm^{-1}.

2.3.2. Synthesis of heptanehydrazide (4b):

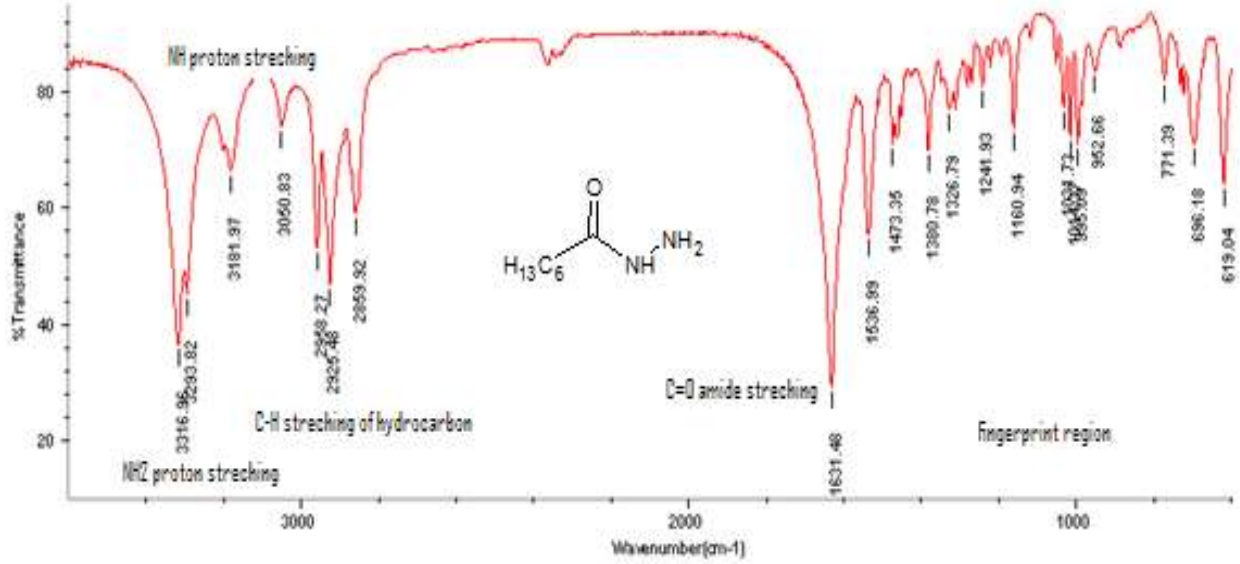
Dissolve 0.1 mole of heptanoic acid (**2b**) in 41 ml of ethanol in round bottom flask and add 18 ml of concentrated sulfuric acid into it slowly with constant stirring at room temperature. Reflux the resulting reaction mixture to 4 hrs (till all solid acid get dissolve, to obtain clear solution). Cool the resulting reaction mixture in ice bath and poured into 165 g crushed ice and the solution make alkaline by adding ammonia. Extract the ester product (**3b**) by 2 x 45 ml petroleum ether. Combine the organic layer and dried it by anhydrous sodium salphate. Distilled out ether under reduced pressure to obtain crude ester which is purified by recrystallisation with ethanol.

Dissolve 0.05 mole of ethyl heptanoate (**3b**) in 20 ml of ethanol in round bottom flask. Add 0.06 mole of hydrazine hydrate slowly with constant stirring and reflux the reaction mixture to 3 hrs. Cool the reaction mixture and filter the solid product (heptanahydrazide) (**4b**). The product was characterized by FT-IR spectroscopy.

Yield : 72 %; **M.P**.: 142 ^{0}C; **Molecular formula**: $C_7H_{16}N_2O$.

FT-IR (in KBr) : 3316, 3293, 3181, 3050, 2925, 1631, 1536, 1380, 1160 cm^{-1}.

Fig 01: FT-IR spectra of heptanehydrazide (4b)



2.3.3. Synthesis of pyridine-4-carbohydrazide (isonazide) (4c):

Dissolve 0.1 mole of pyridine-4-carboxylic acid (**2c**) in 41 ml of ethanol in round bottom flask and add 18 ml of concentrated sulfuric acid into it slowly with constant stirring at room temperature. Reflux the resulting reaction mixture to 5 hrs (till all solid acid get dissolve, to obtain clear solution). Cool the resulting reaction mixture in ice bath and poured into 165 g crushed ice and the solution make alkaline by adding ammonia. Extract the ester product (**3c**) by 2 x 45 ml petroleum ether. Combine the organic layer and dried it by anhydrous sodium sulphate. Distilled out ether under reduced pressure to obtain crude ester which is purified by recrystallisation with ethanol.

Dissolve 0.05 mole of ethyl pyridine-4-carboxylate (**3c**) in 20 ml of ethanol in round bottom flask. Add 0.06 mole of hydrazine hydrate slowly with constant stirring and reflux the reaction mixture to 3 hrs. Cool the reaction mixture and filter the solid product (pyridine-4-carbohydrazide or isonazide) (**4c**). The product was characterized by FT-IR spectroscopy.

Yield : 81 %; **M.P.**: 175^{0}C; **Molecular formula**: $C_6H_7N_2O$.

FT-IR (in KBr) : 3305, 3112, 3052, 2867, 1660, 1635, 1558, 1413, 1334, 1222, 1141, 995, 844, 676 cm^{-1}.

2.3.4. Synthesis of 2,2,2-trifluoroacetohydrazide (4d):

Dissolve 0.1 mole of 2,2,2-trifluoroacetic acid (**2d**) in 41 ml of ethanol in round bottom flask and add 18 ml of concentrated sulfuric acid into it slowly with constant stirring at room temperature. Reflux the resulting reaction mixture to 4 hrs (till all solid acid get dissolve, to obtain clear solution). Cool the resulting reaction mixture in ice bath and poured into 165 g crushed ice and the solution make alkaline by adding ammonia. Extract the ester product (**3d**) by 2 x 45 ml petroleum ether. Combine the organic layer and dried it by anhydrous sodium salphate. Distilled out ether under reduced pressure to obtain crude ester which is purified by recrystallisation with ethanol.

Dissolve 0.05 mole of ethyl 2,2,2-trifluoroacetate (**3d**) in 20 ml of ethanol in round bottom flask. Add 0.06 mole of hydrazine hydrate slowly with constant stirring and reflux the reaction mixture to 3 hrs. Cool the reaction mixture and filter the solid product (2,2,2-trifluoroacetohydrazide) (**4d**). The product was characterized by FT-IR spectroscopy.

Yield : 68 %; **M.P.**: 125 ^{0}C; **Molecular formula**: $C_2H_3N_2OF_3$.

FT-IR (in KBr) : 3349, 3297, 3147, 2875, 1685, 1612, 1205, 1141, 970 cm^{-1}.

2.4. Schiff bases of 7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-carbaldehyde and hydrazides (5a-e):

2.4.1. Synthesis of 3-methyl-*N*'-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-4-carbohydrazide (5a):

Dissolve 71 mg (0.25 mmol) of 7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-carbaldehyde (**1**) in 5 ml of methanol in round bottom flask. Add 38 mg (0.27 mmol) of 3-methypyridine-4-carbohydrazide (**4a**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 85 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in water bath & filter it on suction pump. The yield and m.p. of 3-methyl-*N*'-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-4-carbohydrazide (**5a**) was recorded.

Yield : 70 %; **M.P.** : 248^{0}C turns black; **Mol. Formula** : $C_{24}H_{21}N_3O_4$.

FT-IR (in KBr) : 3191, 3062, 2869, 1648, 1616, 1590, 1563, 1467, 1382, 1255, 1214, 1159, 1116, 1062, 1020, 971, 910, 833, 709 cm^{-1}.

NMR (DMSO; δ in ppm) : 11.954 (s, 1H, CO-NH); 8.873 (s, 1H, CH=N); 8.604 (s, 1H, -OH); 8.492 (s, 1H, py-H); 8.074 (s, 1H, py-H); 7.850 (dd, 2H, Ar-H); 7.600 (m, 1H, py-H); 7.508 (s, 1H, Ar-H); 7.331 (s, 1H, Ar-H); 7.313 (s, 1H, Furan-H); 7.060 (dd, 2H, Ar-H); 4.036 (s, 3H, OCH_3); 3.817 (s, 3H, OCH_3); 2.389 (s, 3H, Ar-CH_3).

Mass Spectra (molecular ion peak): 416.32 (M + 1).

2.4.2. Synthesis of *N*'-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]heptanehydrazide (5b):

Dissolve 71 mg (0.25 mmol) of 7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-carbaldehyde (**1**) in 5 ml of methanol in round bottom flask. Add 36 mg (0.27 mmol) of heptanehydrazide (**4b**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 85 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in water bath & filter it on suction pump. Record the yield and m.p. of *N*'-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]heptanehydrazide (**5b**) and is characterised by using IR, NMR and Mass spectroscopy.

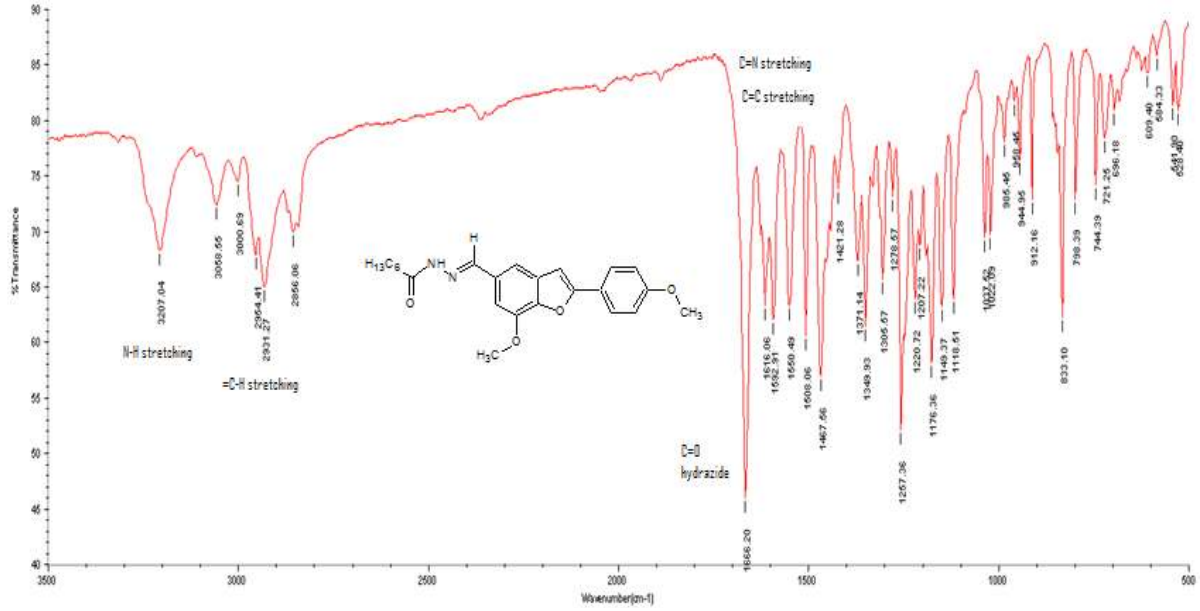
Yield : 72 %; **M.P.** : 244 ^{0}C; **Mol. Formula** : $C_{24}H_{28}N_2O_4$.

FT-IR (in KBr) : 3207, 3058, 2856, 1666, 1616, 1592, 1550, 1467, 1349, 1257, 1176, 1149, 1118, 912, 833, 798, 744 cm^{-1}.

NMR (DMSO; δ in ppm) : 11.285 and 11.180 (s, 1H, CO-NH); 8.209 (s, 1H, CH=N); 8.017 (s, 1H, N=COH); 7.846 – 7.821 (dd, 2H, Ar-H); 7.420 (dd, 1H, Ar-H); 7.277 (dd, 1H, Ar-H); 7.222 (s, 1H, Furan-H); 7.060 (dd, 2H, Ar-H); 4.042 (s, 1H, OCH_3); 3.813 (s, 3H, OCH_3); 2.210 (t, 2H, CO-CH_2); 1.572 (m, 2H); 1.268 (m, 6H); 0.854 (t, 3H).

Mass Spectra (molecular ion peak): 409.40 (M + 1).

Fig 03c: FT-IR spectra of *N*'-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]heptanehydrazide (5b):



2.4.3. Synthesis of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-4-carbohydrazide (5c):

Dissolve 71 mg (0.25 mmol) of 7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-carbaldehyde (**1**) in 5 ml of methanol in round bottom flask. Add 35 mg (0.27 mmol) of pyridine-4-carbohydrazide (**4c**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 90 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in water bath & filter it on suction pump. Record the yield and m.p. of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-4-carbohydrazide (**5c**) and characterised by using IR, NMR and Mass spectroscopy.

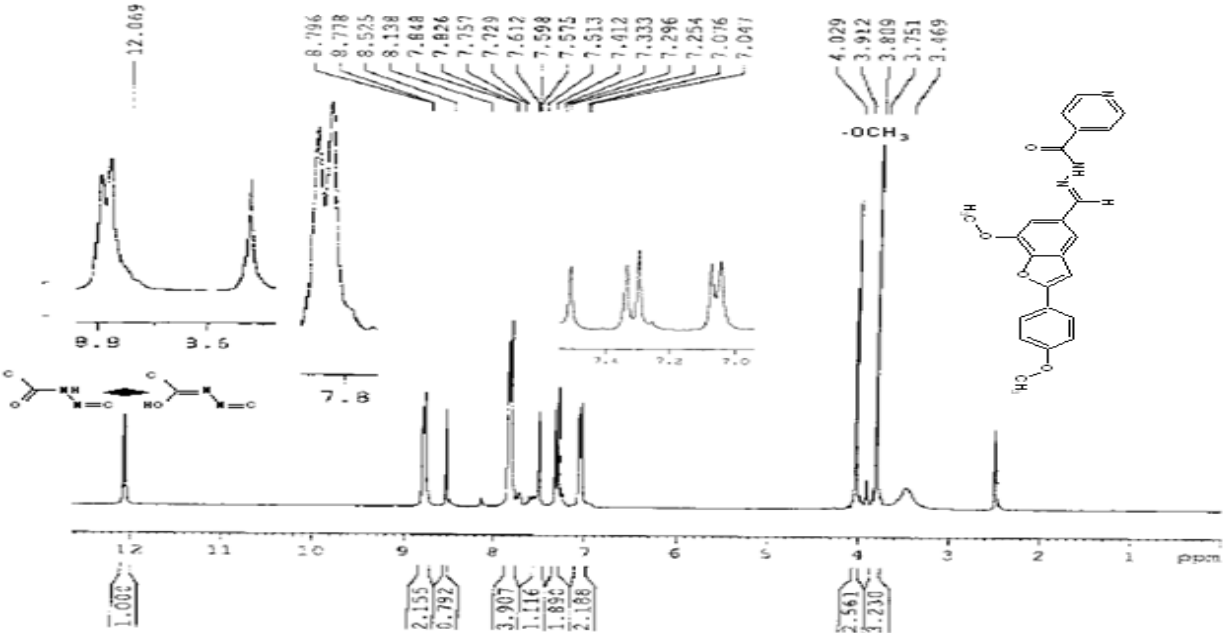
Yield : 82 %; **M.P.** : Decompose above 260 ^{0}C; **Mol. Formula**: $C_{23}H_{19}N_3O_4$.

FT-IR (in KBr) : 3199, 3045, 2958, 2840, 1654, 1616, 1590, 1473, 1259, 836 cm^{-1}.

NMR (DMSO; δ in ppm): 12.069 (s, 1H, CO=NH); 8.780 (dd, 2H, py-H); 8.525 (s, 1H, CH=N); 7.848 – 7.826 (m, 4H, Ar-H); 7.513 (s, 1H, Ar-H); 7.339 (s, 1H, Ar-H); 7.296 (s, 1H, furan-H); 7.050 (dd, 2H, Ar-H); 4.029 (s, 3H, OCH_3);3.809 (s, 3H, OCH_3).

Mass Spectra (molecular ion peak): 402 (M + 1).

Fig 02: NMR spectra of *N*'-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-4-carbohydrazide (5a)



2.4.4. Synthesis of 2,2,2-trifluoro-*N*'-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]acetohydrazide (5d):

Dissolve 71 mg (0.25 mmol) of 7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-carbaldehyde (**1**) in 5 ml of methanol in round bottom flask. Add 32 mg (0.27 mmol) of 2,2,2-trifluoroacetohydrazide (**4d**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 90 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in water bath & filter it on suction pump. Record the yield and m.p. of 2,2,2-trifluoro-*N*'-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]acetohydrazide (**5d**) and characterised by using IR, NMR and Mass spectroscopy.

Yield : 82 %; **M.P.** : Decompose above 240 ^{0}C; **Mol. Formula** : $C_{19}H_{15}F_3N_2O_4$.

FT-IR (in KBr): 3087, 3004, 2840, 1625, 1610, 1596, 1508, 1467, 1351, 1265, 1147, 1022, 833, 744 cm^{-1}.

NMR (DMSO; δ in ppm): 12.761 (s, 1H, CO-NH); 8.820 (s, 1H, N=CH); 8.548 (s, 1H, N=C-OH); 7.841 (dd, 2H, Ar-H); 7.712 (s, 1H, Ar-H); 7.592 (s, 1H, Ar-H); 7.282 (s, 1H, furan-H); 7.078 (dd, 2H, Ar-H); 4.021 (s, 3H, OCH_3); 3.821 (s, 3H, OCH_3).

Mass Spectra (molecular ion peak): 393.36 (M + 1)

2.4.5. Synthesis of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-3-carbohydrazide (5e):

Dissolve 71 mg (0.25 mmol) of 7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-carbaldehyde (**1**) in 5 ml of methanol in round bottom flask. Add 35 mg (0.27 mmol) of pyridine-3-carbohydrazide (**4e**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 80 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in water bath & filter it on suction pump. Record the yield and m.p. of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-

yl}methylidene]pyridine-3-carbohydrazide (**5e**) and characterised by using IR, NMR and Mass spectroscopy.

Yield : 82 %; **M.P.** : 234 ^{0}C; **Mol. Formula**: $C_{23}H_{19}N_3O_4$.

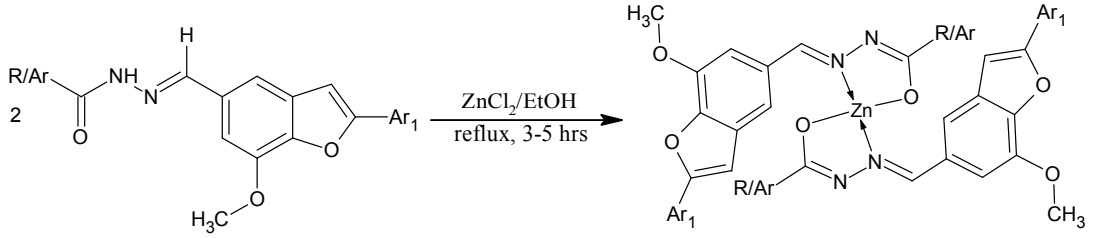
FT-IR (in KBr) : 3191, 3056, 2865, 1650, 1616, 1590, 1560, 1469, 1346, 1311, 1257, 1168, 1147, 1118, 1018, 970, 835, 707 cm^{-1}.

NMR (DMSO; δ in ppm): 11.997 (s, 1H, CO-NH): 9.071 (s, 1H, py-H); 8.768 (dd, 1H, py-H); 8.501 (s, 1H, CH=N); 8.250 (dd, 1H, py-H); 7.850 (dd, 2H, Ar-H); 7.560 (m, 1H, py-H); 7.517 (s, 1H, Ar-H); 7.337 (s, 1H, Ar-H); 7.311 (s, 1H, furan-H); 7.07 (dd, 2H, Ar-H); 4.035 (s, 3H, OCH_3); 3.815 (s, 3H, OCH_3).

Mass Spectra (molecular ion peak): 402.26 (M + 1).

2.5. Synthesis of Zinc (II) complex of 2-aryl-7-methoxybenzofuran-5-carboxaldehyde and hydrazides:

Dissolve 0.1 mmol of *N*'-[(*E*)-{7-methoxy-2-[aryl]-1-benzofuran-5-yl}methylidene]aryl/alkyl carbohydrazide and 0.05 mmol of zinc chloride in 5 ml ethanol. Add 0.1 mmol of potassium hydroxide in the above solution and reflux it for about 3-5 hours in boiling water bath. Cool the reaction mixture and filter the solid product. Record the yield, m.p and FT-IR spectra.



Ar_1 ≡ 4-(methylsulfanyl)phenyl & 4-(methoxy)phenyl.

2.5.1. Zn (II) complex of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-3-carbohydrazide:

Dissolve 0.1 mmol of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-3-carbohydrazide (**5e**) and 0.05 mmol of zinc chloride in 5 ml ethanol. Add 0.1 mmol of potassium hydroxide in the above solution and reflux it for about 3-5 hours in boiling water bath. Cool the reaction mixture and filter the faint yellow solid product. Record the yield and FT-IR spectra.

Yield : 89 %.

FT-IR (in KBr): 3467, 3218, 1656, 1616, 1560, 1509, 1471, 1255, 1164, 1025, 827 cm^{-1}.

Fig 04: FT-IR spectra of Zn (II) complex of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-3-carbohydrazide (5e):

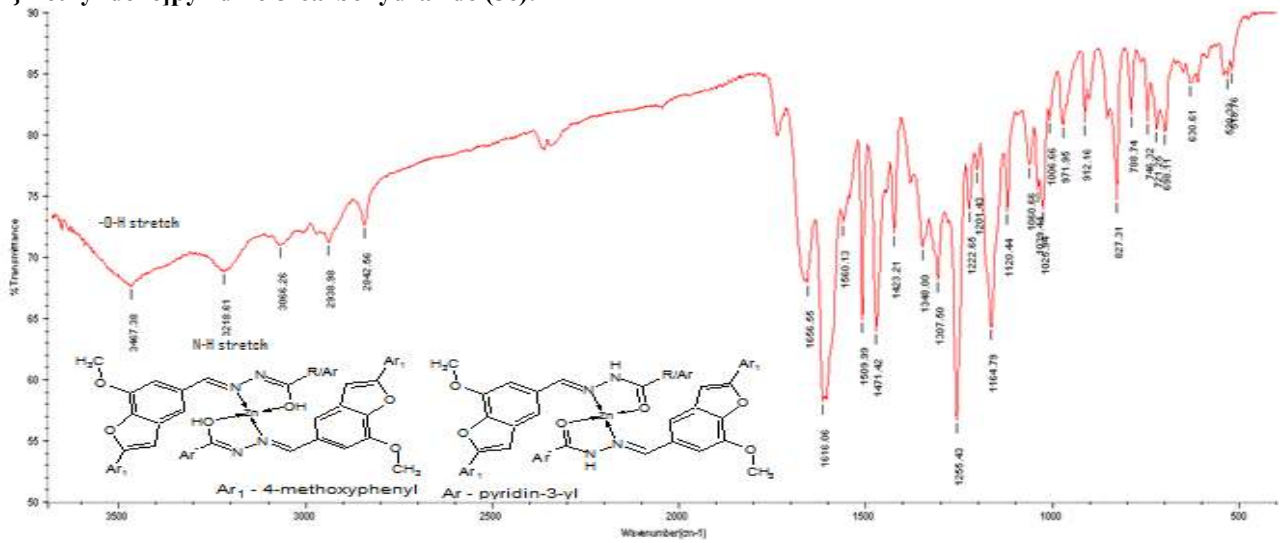
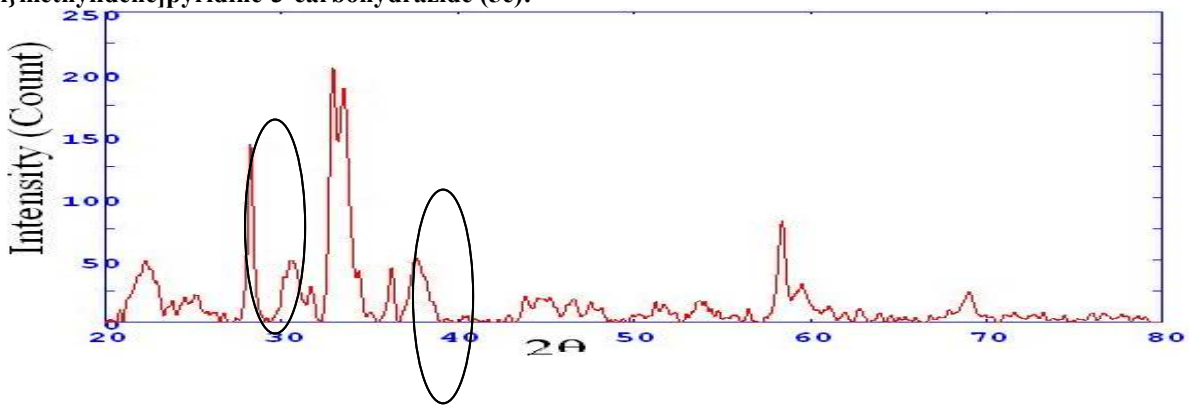


Fig 05: XRD spectra of Zn (II) complex of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-3-carbohydrazide (5e):



3.7.2. Zn (II) complex of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-4-carbohydrazide:

Dissolve 0.1 mmol of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-3-carbohydrazide (**5c**) and 0.05 mmol of zinc chloride in 5 ml ethanol. Add 0.1 mmol of potassium hydroxide in the above solution and reflux it for about 3-5 hours in boiling water bath. Cool the reaction mixture and filter the faint yellow solid product. Record the yield and FT-IR spectra.

Yield : 81 %.

FT-IR (in KBr): 3471, 3428, 1619, 1604, 1564, 1509, 1465, 1263, 1149, 1033, 912, 836 cm^{-1}.

Fig 06: FT-IR spectra of Zn (II) complex of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-4-carbohydrazide (5c):

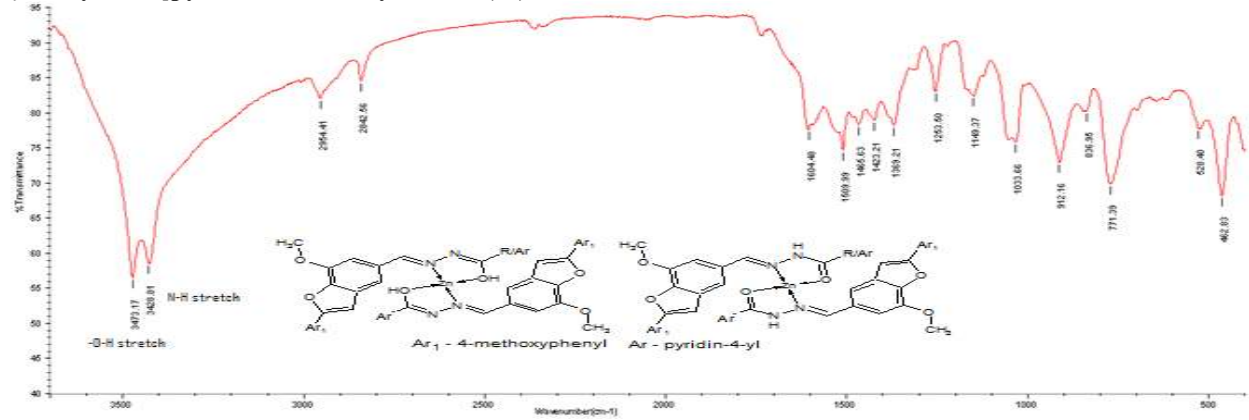
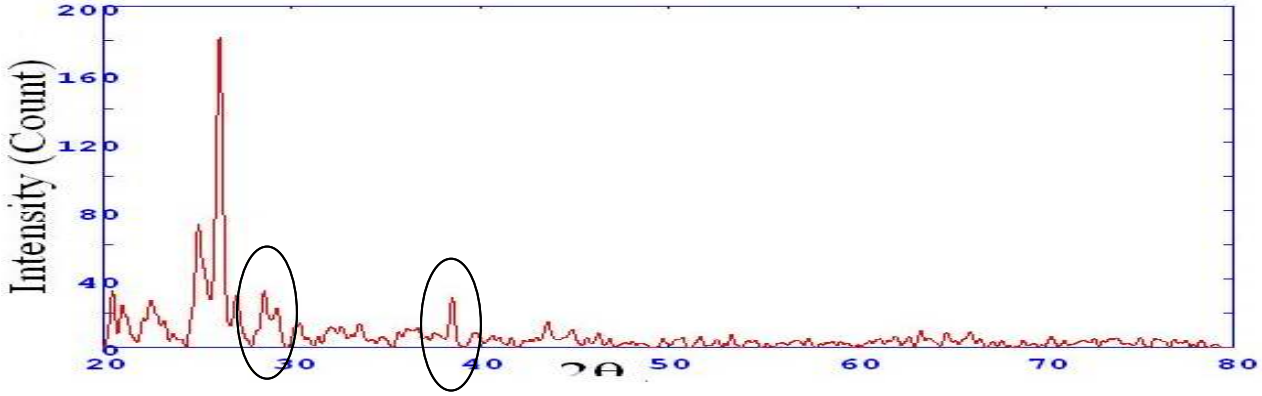


Fig 07: FT-IR spectra of Zn (II) complex of *N'*-[(*E*)-{7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-4-carbohydrazide (5c):



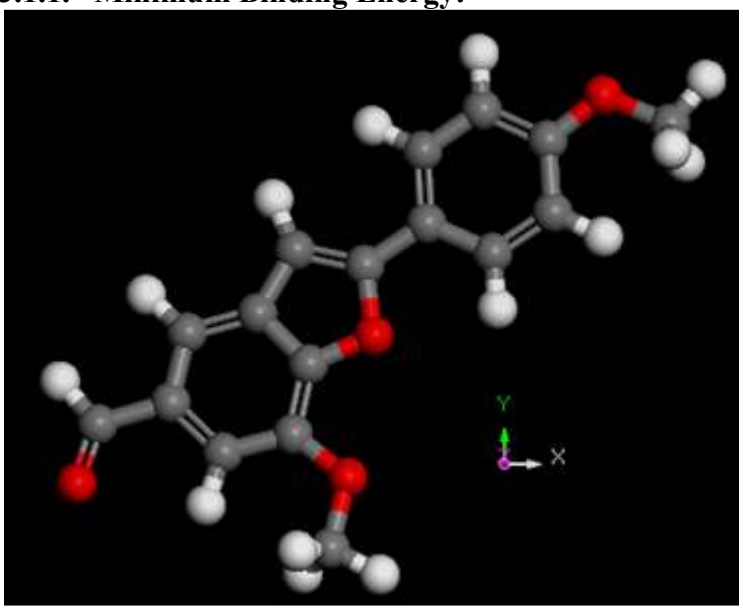
3. Computational study:

The quote by Schleyer that "computational chemistry is to model all aspects of chemistry by calculation rather than experiment" tells us that practically every mechanistic question can be tackled by computational methods. This can be doing with lowest energy pathway between the various stationary points by using DFT. The main objective of density functional theory (DFT) is to replace the many-body electronic wave function with the electron density as a simpler quantity to deal with. HK theorem proved the direct relationship between the ground state electron density and the ground state electronic wave function of a many-particle system, that DFT is used for chemistry as well. The Kohn–Sham method which reduces the intractable many-body problem of interacting electrons in a static external potential to a tractable problem of non-interacting electrons moving in an effective potential. The effective potential includes the external potential and the effects of Coulombic interactions between the electrons.

When spectroscopic accuracy is desired, the effort is magnified and the theoretical treatment can become very elaborate. It is pleasing to see that the organic chemist's standard evidence for structural identification such as NMR and IR spectral data can be computed quite accurately.

3.1. Study of Binding energy, density of state, HOMO, LUMO, charge density and reactivity with electrophile and nucleophile of 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde:

3.1.1. Minimum Binding Energy:



It is the structure of 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde obtained at minimum binding energy. The white colour ball indicate presence of hydrogen, red ball indicates presence of oxygen and gray colour ball is carbon. The minimum binding energy of the molecule is calculated from the HOMO-LUMO energy gap (from density of states) or given directly.

3.1.2. Density of states:

It is the function used to calculate band gap between HOMO [Highest Occupied Molecular Orbital] and LUMO [Lowest Unoccupied Molecular Orbital] of the organic and inorganic molecules. It is also used to determine the electrical conduction nature (conductivity property) form the conduction band with reference to Fermi energy. The density of state (DOS) of 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde shows conduction band indicates the molecule has electrical conductivity property. The DOS is also used to calculate minimum energy required for the excitation of electrons from HOMO to LUMO (for electronic transition) which will confirm from the UV-spectra of the molecule. The DOS of the molecule also shows HOMO of the molecule is partially filled as shown in fig. The energy of HOMO is 0.0206Ha (0.0558 eV) and that of LUMO is 0.0791 Ha (0.2145 eV).

Fig. 08: HOMO and LUMO of 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde

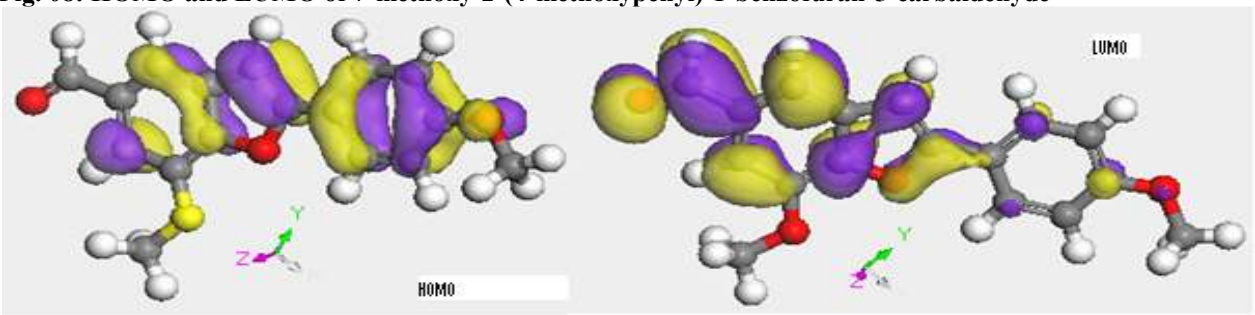
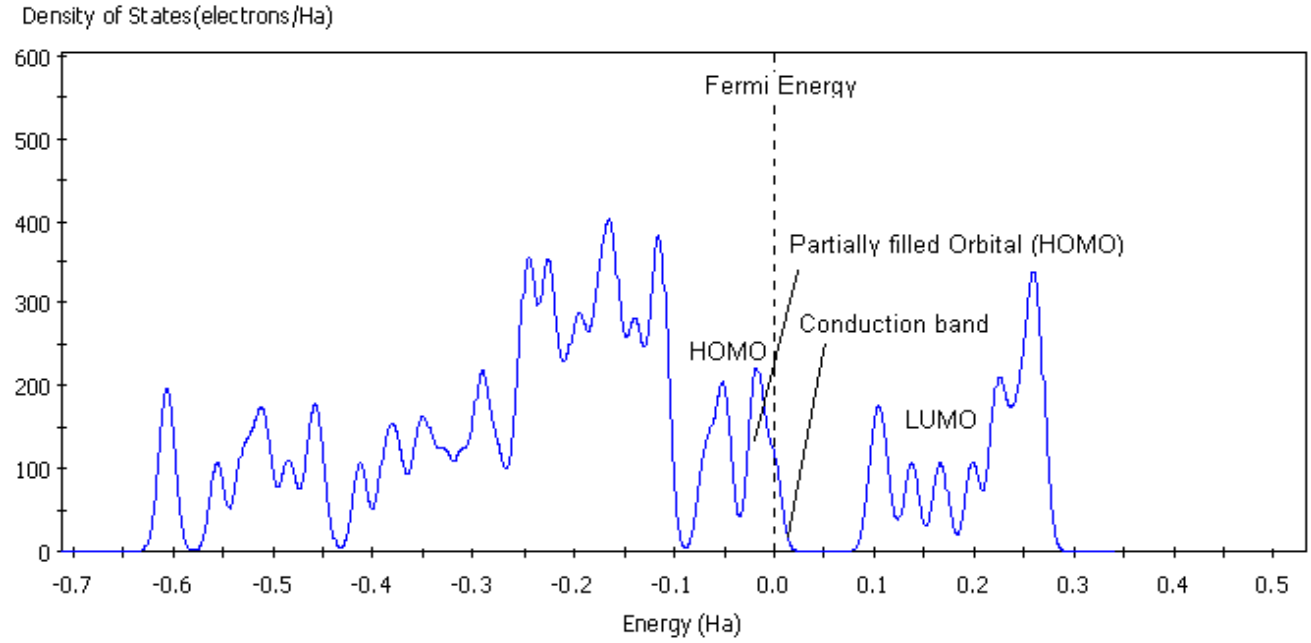


Fig. 09: DOS of 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde



3.1.3. Electron density:

The following diagrams explain the electron density present around the atom/skeleton of 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde. The molecule containing two –OCH_3 groups which gives two different singlets in its NMR spectrum, one at 4.046 (s, 3H, -OCH_3) and second at 3.831 (s, 3H, -OCH_3). This can be explaining with the help of electron density distribution diagram. The oxygen atom of –OCH_3 (-0.458e) group attached to benzofuran ring at 7-position having more electron charge than oxygen atom –OCH_3 (-0.445e) of 4-methoxyphenyl attached to 2-position of benzofuran ring. Therefore –CH_3 protons of methoxy group present at 7-position of benzofuran ring is shielded as compared to other and shows singlet at 3.831 ppm while that of 4-methoxypenyl group shows singlet at 4.046 ppm. This can be explain with the help of following resonance structures. The electron density of the C_7–carbon atom also increased by the +R effect of furan oxygen i.e. electron rich furan ring increase the electron density of C_7–carbon to some extent which further increase electron density of oxygen of C_7–OCH_3 group. The lone pair of oxygen of –OCH_3 group of 4-methoxyphenyl group attached to 2-position of benzofuran ring is shifted towards benzofuran ring, but such stabilization disturbed aromatic character of the phenyl ring and furan ring of benzofuran skeleton therefore this effect is very weak as compared to the resonance stabilization present when such groups are attached to the same ring. The aldehydic group shows strong -R effect so that electron density of benzene ring of benzofuran skeleton is decreased. The –OCH_3 group (present meta position to aldehydic group) attached at C_7 carbon of benzofuran ring shows weaker -+I effect (strong +R effect because of presence of two lone pair of electrons on it) because its electronegativity, therefore the electronic charge (electron density) of the oxygen of C_7–OCH_3 group is higher than that of oxygen of –OCH_3 group of 4-methoxyphenyl group. The electron density of benzofuran ring oxygen and aldehydic group oxygen is less than methoxy oxygen because they are attached to more electronegative carbon atoms (sp^2 hybridized carbon atoms, ring carbon). The furan ring is has more electron density than the remaining two phenyl rings because of presence of six electrons around five ring atoms (the average electron density

around each atom is > 1). The furan oxygen shares its two electrons for the completion of aromatic sextet, explaining decrease electron density around it. This electron density distribution can also explain shielding of furan ring hydrogen.

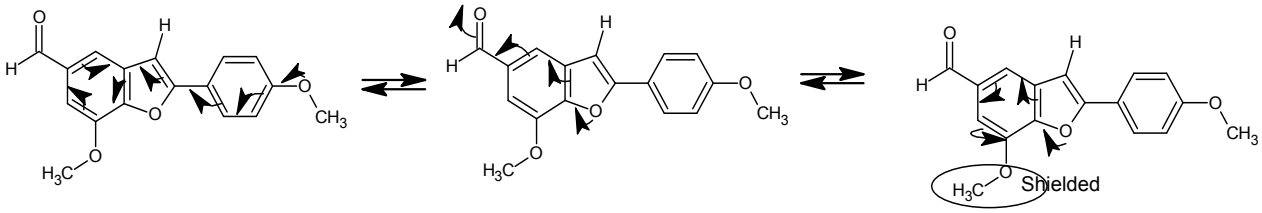
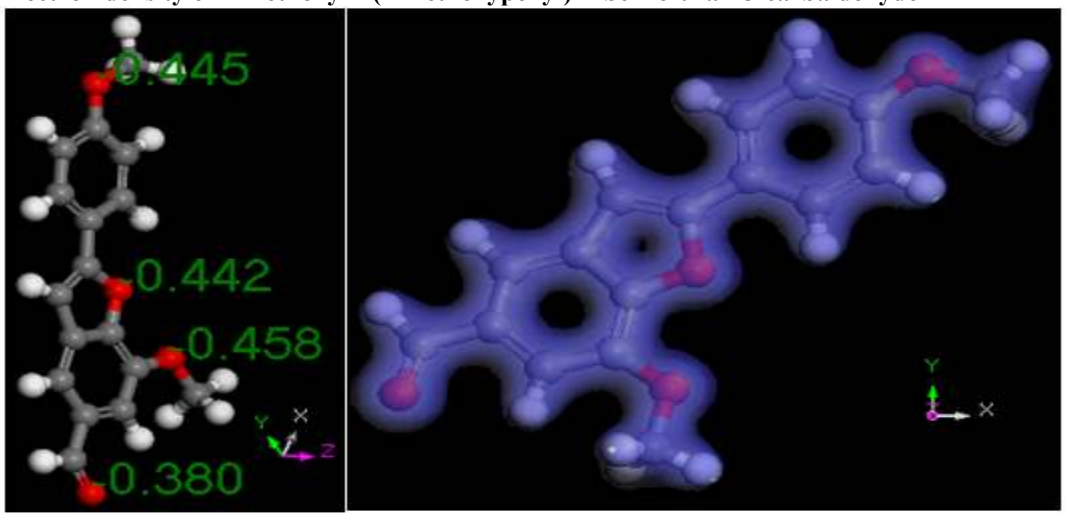
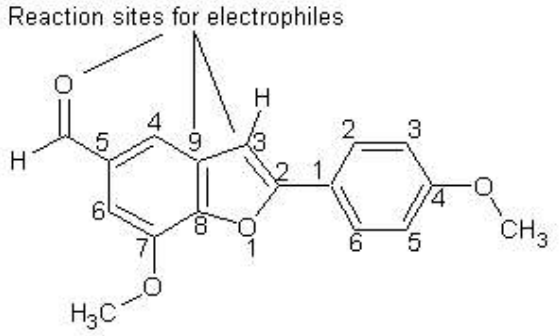


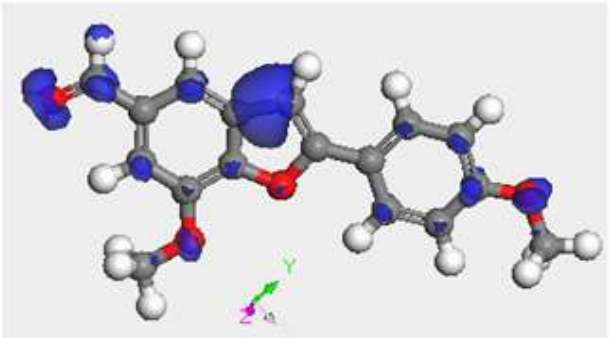
Fig. 10: Electron density of 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde



3.1.4. Reactivity of 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde with electrophile and nucleophile:

The 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde has two aromatic nucleus, two methoxy groups and one aldehyde functional group. Out of two aromatic nucleuses, one is substituted benzofuran skeleton and another is substituted phenyl ring. The furan ring (heterocyclic ring) of benzofuran skeleton is electron rich than fused benzene ring therefore reactivity of all ring carbons are different. The methoxy group (ether functionality) is less reactive as compared to others. The reactivity of 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde molecule against electrophile and nucleophile was studied which shows following results.

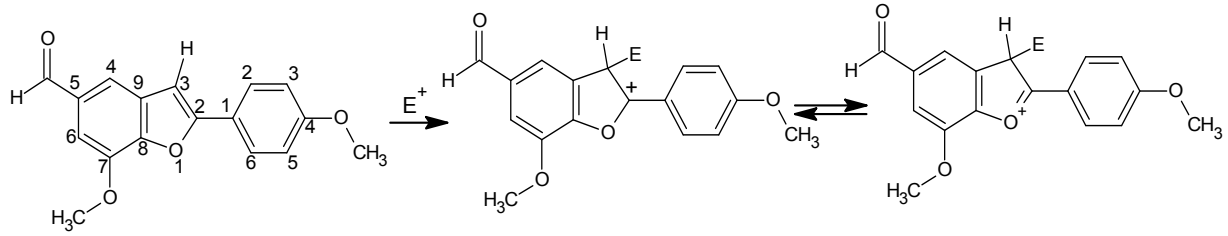




The furan ring of benzofuran skeleton is electron rich as compared to other rings, therefore more reactive towards electrophile along with electron rich oxygen atoms of aldehyde and methoxy

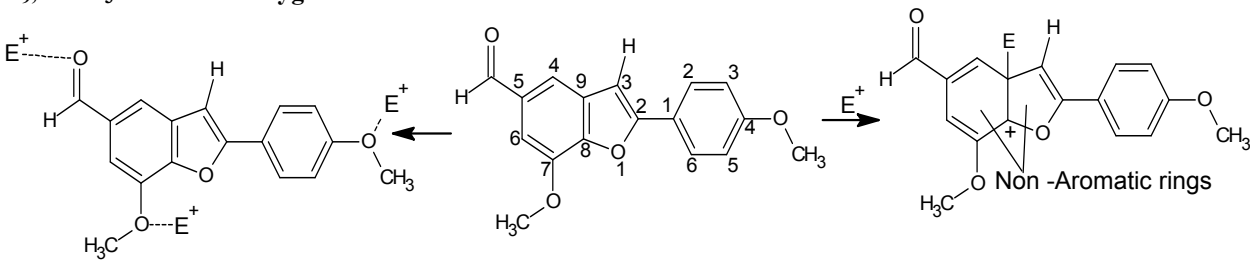
groups. The methoxy groups do not have good leaving group or multiple bonds therefore not shows good activity against electrophile for either substitution or addition reaction. The oxygen atom of furan ring share its electron pair into aromatic sextet therefore not donate electrons toward electrophile. The oxygen atom of aldehyde functional group is electron rich (has two lone pair of electrons and pi-bond) therefore reacts with electrophile via addition reaction. The C_3 and C_9 carbon atom of furan ring are reactive towards electrophile.

Scheme 1: Reaction of Electrophile with 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde at C_3:

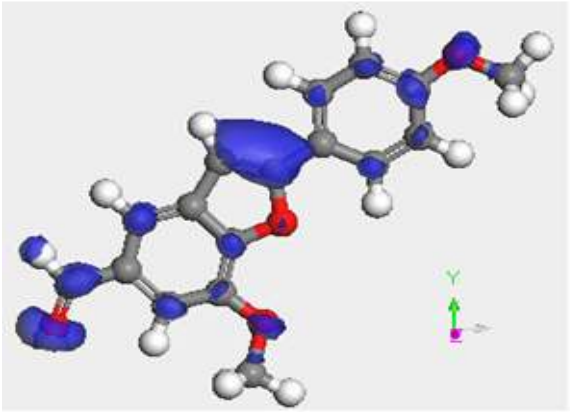


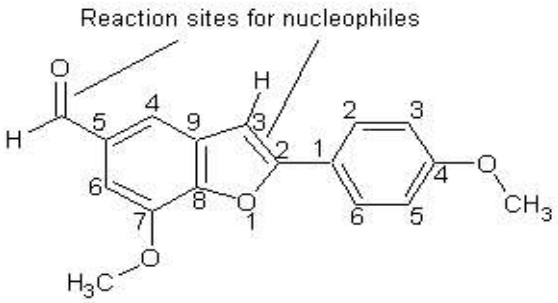
The C_3 carbon react with electrophile via electrophilic substitution reaction rather than addition reaction because it bearing hydrogen which is act as leaving group in acidic medium. The intermediates formed by electrophilic substitution at C_3 carbon was stabilized by two resonance structures without disturbing aromatic character of fused benzene ring. But when electrophile reacts at C_9, it forming addition product rather than substitution because it does not bearing any leaving group. This addition reaction disturbed aromatic character of benzofuran skeleton therefore such addition is highly energetic and not observed. *The C_3 carbon is preferred position for the electrophilic substitution.*

Scheme 2: Interaction of Electrophile with 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde at C_9, OCH_3 and –CHO oxygen:



The nucleophiles are electron rich sources and reacts with electron deficient centers. The oxygen atom of the furan ring is electronegative therefore attract the electron density towards itself (by strong –I effect) make the ring electron deficient.

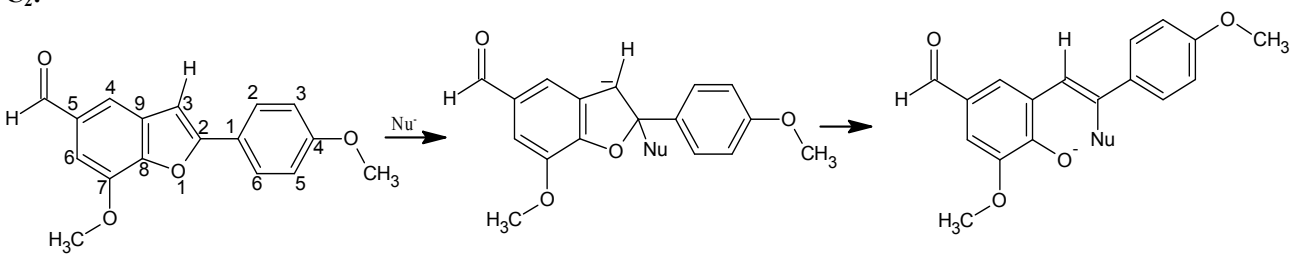




The electron density of the C_2-carbon and C_8-carbon was decreased due to strong –I effect of furan ring oxygen and therefore nuclephiles shows attack at these positions preferentially as

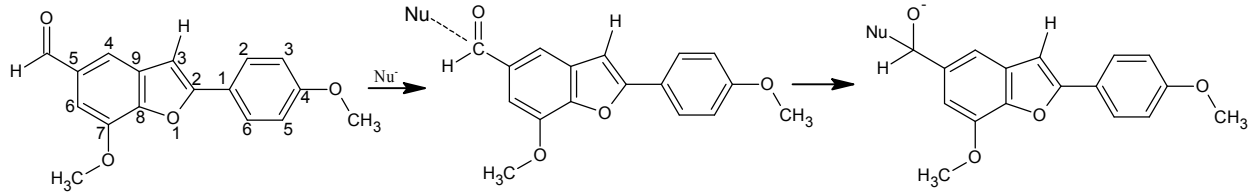
shown in fig. The attack at C_8-carbon is highly energetic because of electronic repulsion between attacking nucleophile and electron rich oxygen of $–OCH_3$ group and furan ring. The nucleophile reacts at C_2-carbon and undergoes addition reaction with lose of aromatic character of benzofuran skeleton but when reacts with ring opening of furan ring without disturbing aromatic character of fused benzene ring is less energetic. *Therefore nucleophile preferentially reacts at C_2-carbon with ring opening of furan ring*.

Scheme 3: Interaction of Nucleophile with 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde at C_2:



The aldehydic carbon is more electrophilic therefore nucleophile reacts to it with breaking of C-O pi-bond i.e. nucleophile reacts to aldehydic carbon via addition reaction or condensation reaction.

Scheme 4: Interaction of Nucleophile with 7-methoxy-2-(4-methoxypenyl)-1-benzofuran-5-carbaldehyde at C of -CHO:



4. Result and Discussion:

The 4-(methoxy)phenyl substitution at 2-position of benzofuran ring and –CHO functionality present at 5-position has been confirmed by FT-IR, NMR and mass spectra. The formation of aldehyde group has been confirm by silver mirror and 2,4-DNP test.

The various hydrazides used for the synthesis of Schiff bases of (**1**) are synthesized by known literature method from corresponding carboxylic acids (**2a-d**) and **4e** is available in laboratory. The formation of hydrazides has been confirmed by FT-IR spectroscopy. The NH_2 and N-H group present in the form of CO–NH-NH_2 of hydrazide shows strong absorption band in the region 3050 – 3350 cm^{-1}. The carbonyl group of hydrazides CO–NH-NH_2 shows strong absorption in the region 1685 – 1640 cm^{-1} depending on the nature substituents. The $–CF_3$ and pyridine ring of the **4d**, **4a** and **4c** are deactivating the carbonyl group therefore it shows absorption at higher wave number side as compared to **4b**.

The 7-methoxy-2-[4-(methoxy)phenyl]-1-benzofuran-5-carbaldehyde (**1**) was the treated with hydrazides **4a-e** in methanol in presence of acetic acid catalyst forming corresponding Schiff bases **5a-e** under reflux conditions. The formation of product has been confirmed by various analytical techniques including FT-IR, NMR and Mass spectroscopy. The Schiff bases **5a-e** shows two proton signals in its NMR spectra at the region 8.50 – 8.90 ppm (due to NH-C=O proton) and 11.00 – 12.80 ppm (due to N=C-OH proton) is due to keto-enol tautomerism of N-H proton. The amide carbonyl group of the Schiff bases **5a-c** and **5e** shows absorption in 1640 – 1650 cm^{-1} except **5d** in their FT-IR spectra. The amide carbonyl group of **5d** shows absorption at 1625 cm^{-1}. The imine bond (>C=N-) shows strong absorption band in the region 1610 – 1590

cm^{-1} in **5a-e**. The XRD spectrum of **5c** and **5e** shows the formation of square planar complex with Zn(II).

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