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SYNTHESIS OF SCHIFF BASES OF 7-METHOXY-2-[4-(METHYLSULFANYL)PHENYL]-1-BENZOFURAN-5-CARBOXALDEHYDE AND ANIMES AND HYDRAZIDE

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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-methylsulfanylbenzoyl chlorides by refluxing in toluene in presence of triethylamine forming 7-Methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde (**1**). It is condensed with series of hydrazides (**3a-e**) and amines (**4a-f**) forming schiff bases (**5a-e, 6a-f**). The acid hydrazide was synthesized from corresponding carboxylic acid. The schiff bases are characterized by IR, NMR and mass spectra.

Key Words: Benzofuran, Schiff bases, Hydrazide, Heterocyclic compounds, imines.

1. 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-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde (**1**) was synthesized by known literature method[III]. 7-Methoxy-2-[4-(methylsulfanyl)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.

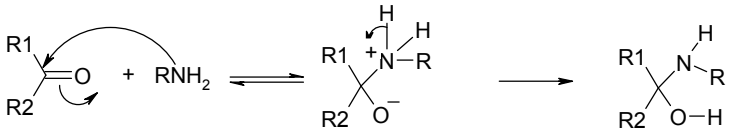
Schiff base was first reported by Hugo Schiff[IV] in 1864. The compounds containing azomethine (-C=N-) group are know as Schiff bases, are formed by the condensation of a primary amines with a carbonyl compounds such as aldehydes or ketones in different reaction conditions and in different solvents with 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].

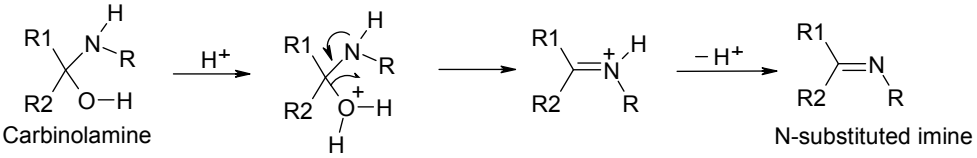
The nitrogen atom amine or aniline shows nucleophilic attack on the carbonyl carbon atom of the carbonyl group of the aldehyde or ketone forming carbinol amine which is further undergoes dehydration in presence of mild acidic conditions or dehydrating agent forming imine or Schiff base. The strong acidic 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.

Mechanism:

Step I: Formation of carbinol amine:



Step II: Dehydration of carbinol amine (Formation of imine):



The electron withdrawing group (showing –I or –R electronic effect) attached to amine or aniline, decreases the electron density of nitrogen atom of $–NH_2$ group so that amino group does not easily shows nucleophilic attack on carbonyl group. For such amines or anilines, more drastic conditions are required for the formation of Schiff bases. The electron donating group (showing +I or +R electronic effect) attached to amine or aniline are easily undergoes Schiff base formation even at room temperature. The electrophilic character of carbonyl carbon atom also plays important role in the formation of Schiff bases. As electrophilic character (increases by the electron withdrawing group) of the carbonyl group increases, rate of formation of Schiff bases increases even at room temperature on stirring.

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.

2. Experimental Work

7-Methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde (**1**) contain aldehyde functional group at benzofuran skeleton which will be condensed with various aromatic hydrazides (**3a-e**) and amines (**4a-f**) forming imines (Schiff bases) (**5a-e, 6a-f**) 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-(methylsulfanyl)benzoyl chloride in presence of base (intramolecular Wittig reaction) forming 7-methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde (**1**).

Acid hydrazide was synthesized by known literature method. The carboxylic acid 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 (**2a-d**) by 2 x petroleum ether. Ester (**2a-d**) was further treated with hydrazine hydrate in presence of acid catalyst forming solid product (acid hydrazide) (**3a-d**).

The formation of the products and its structure has been confirmed from the analytical data, FT-IR (KBr), NMR and mass spectroscopy.

2.1. General procedure for the synthesis of Schiff bases:

2.1.1. Synthesis of Hydrazides (3a-d):

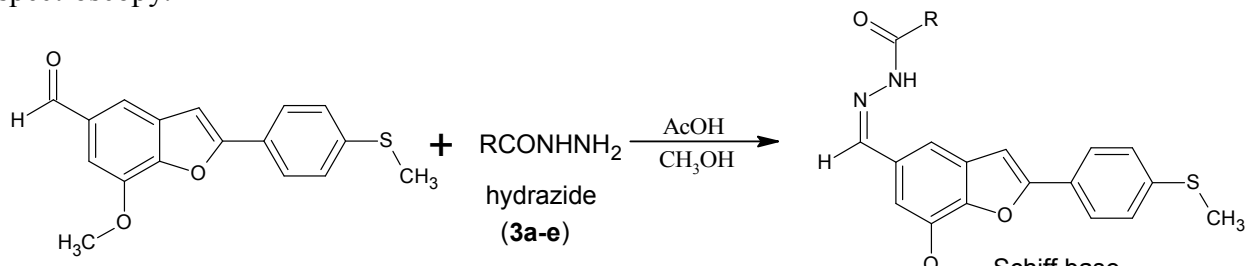
Dissolve 0.01 equivalent of carboxylic acid 5 ml of ethanol in round bottom flask and add 1.78 ml of concentrated sulfuric acid into it slowly with constant stirring at room temperature. Reflux the resulting reaction mixture to 4-5 hrs (till all solid acid get dissolve, to obtain clear solution). Cool 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 (**2a-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 (**2a-d**) which is purified by recrystallisation or distillation.

Dissolve 0.01 equivalent of ester (**2a-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) (**3a-d**). The product was characterized by FT-IR and NMR spectroscopy.

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

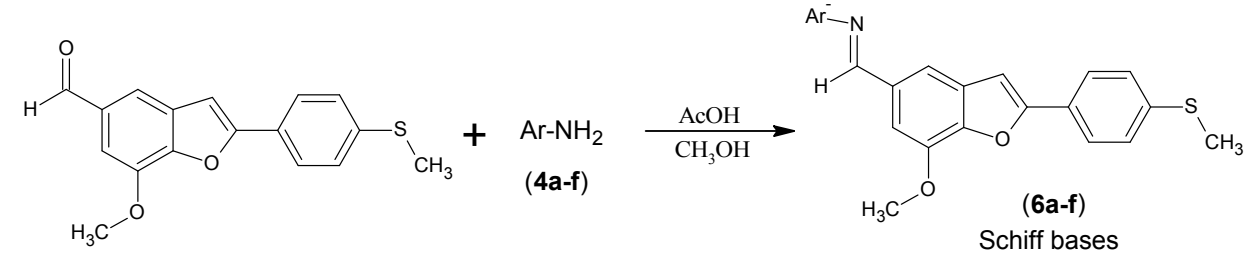
Dissolve 75 mg (0.25 mmol) of 7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-carbaldehyde (**1**) in 5 ml of methanol in round bottom flask. Add (0.27 mmol) of carbohydrazide (**3a-e**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at 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-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]ary/alkyl carbo hydrazide (**5a-e**) and m.p. of the product and characterised by using IR, NMR and Mass spectroscopy.



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

2.1.3. Schiff bases of amines (6a-f):

Dissolve 75 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 0.27 mmol of amine (**4a-f**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 60 – 90 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in ice bath & filter solid schiff base product (**6a-f**) on suction pump. Record the yield and m.p. of the product and characterised by using IR, NMR and Mass.



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

2.2. Synthesis of various hydrazides:

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

Dissolve 0.1 mole of 3-methylpyridine-4-carboxylic acid 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

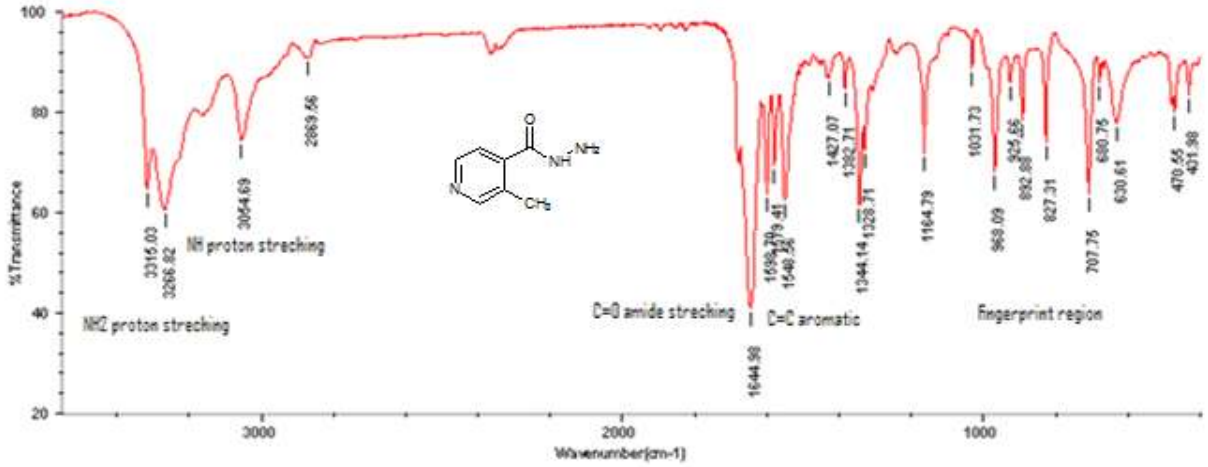
obtain clear solution). Cool the resulting reaction mixture in ice bath and poured into 165 g crushed ice and the solution make alkaline by adding ammonia. Extract the ester product by 2 x 45 ml petroleum ether. Combine the organic layer and dried it by anhydrous sodium salphate. Distilled out ether under reduced pressure to obtain crude ester which is purified by recrystallisation with ethanol.

Dissolve 0.05 mole of ethyl 3-methylpyridine-4-carboxylate (**2a**) 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) (**3a**). 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}.

Fig 01: FT-IR spectra of 3-methypyridine-4-carbohydrazide (3a)



2.2.2. Synthesis of heptanehydrazide (3b):

Dissolve 0.1 mole of heptanoic acid 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 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 (**2b**) 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) (**3b**). 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}.

2.2.3. Synthesis of pyridine-4-carbohydrazide (isonazide) (3c):

Dissolve 0.1 mole of pyridine-4-carboxylic acid 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 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 (**2c**) 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) (**3c**). 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}.

2.2.4. Synthesis of 2,2,2-trifluoroacetohydrazide (3d):

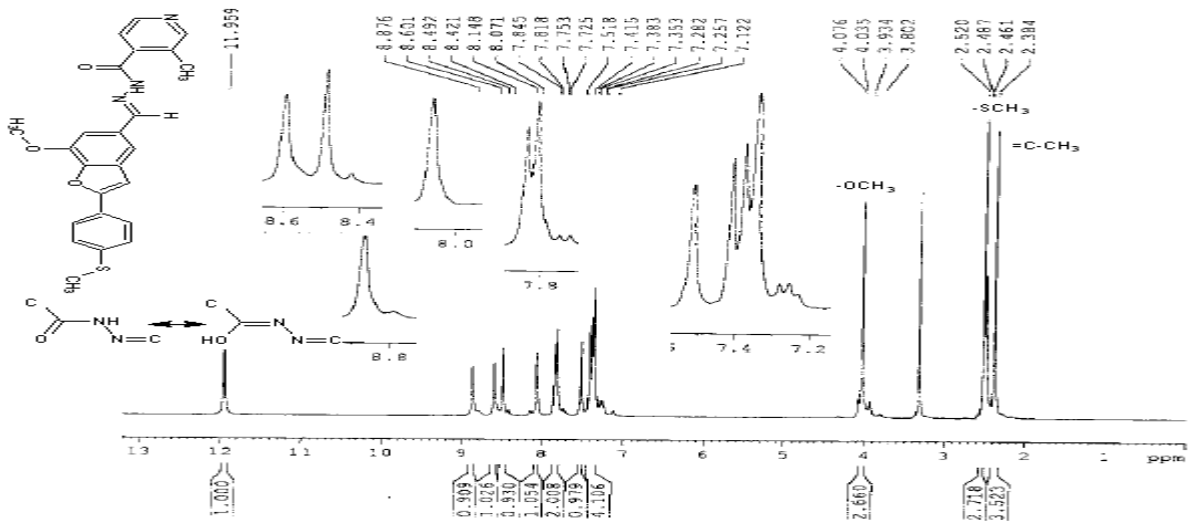
Dissolve 0.1 mole of 2,2,2-trifluoroacetic acid in 41 ml of ethanol in round bottom flask and add 18 ml of concentrated sulfuric acid into it slowly with constant stirring at room temperature. Reflux the resulting reaction mixture to 4 hrs (till all solid acid get dissolve, to obtain clear solution). 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 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 (**2d**) 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) (**3d**). 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}.

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

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

Dissolve 75 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 38 mg (0.27 mmol) of 3-methypyridine-4-carbohydrazide (**3a**) 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. The yield and m.p. of 3-methyl-*N*'-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-4-carbohydrazide (**5a**) was recorded.
Yield : 72 %; **M.P.** : Decomposed above 251 ^{0}C; **Mol. Formula** : $C_{24}H_{21}N_3O_3S$.
FT-IR (in KBr) : 3187, 3064, 2956, 1646, 1590, 1565, 1469, 1348, 1214, 1095, 910, 836 cm^{-1}.
NMR (DMSO; δ in ppm) : 11.959 (s, 1H, CO-NH); 8.876 (s, 1H, CH=N); 8.601 (s, 1H, -OH); 8.460 (d, 1H, py-H); 8.100 (d, 1H, py-H); 7.780 (dd, 2H, Ar-H); 7.518 (s, 1H, Ar-H); 7.415-7.257 (m, 4H, Ar-H); 7.122 (s, 1H, Furan-H); 4.035 (s, 3H, OCH_3); 2.487 (s, 3H, SCH_3); 2.384 (s, 3H, Ar-CH_3).
Mass Spectra (molecular ion peak): 432 (M + 1).

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



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

Dissolve 75 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 36 mg (0.27 mmol) of heptanehydrazide (**3b**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 75 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-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]heptanehydrazide (**5b**) and is characterised by using IR, NMR and Mass spectroscopy.

Yield : 88 %; **M.P.** : 206 ^{0}C; **Mol. Formula** : $C_{24}H_{28}N_2O_3S$.

FT-IR (in KBr) : 3207, 3054, 2931, 1666, 1592, 1546, 1467, 1349, 1220, 1095, 912, 823 cm^{-1}.

NMR (DMSO; δ in ppm) : 11.295 and 11.183 (s, 1H, CO-NH); 8.21 (s, 1H, CH=N); 8.017 (s, 1H, N=COH); 7.824 – 7.794 (dd, 2H, Ar-H); 7.443 (s, 1H, Ar-H); 7.350 (m, 3H, Ar-H); 7.272 (s, 1H, Furan-H); 3.996 (s, 1H, OCH_3); 2.626 (s, 3H, SCH_3); 2.173 (t, 2H, $CO\text{-}CH_2$); 1.57 (m, 2H); 1.260 (m, 6H); 0.845 (t, 3H).

Mass Spectra (molecular ion peak) : 425 (M + 1).

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

Dissolve 75 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-4-carbohydrazide (**3c**) 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-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-4-carbohydrazide (**5c**) and characterised by using IR, NMR and Mass spectroscopy.

Yield : 83 %; **M.P.** : 254 ^{0}C; **Mol. Formula** : $C_{23}H_{19}N_3O_3S$.

FT-IR (in KBr) : 3193, 3045, 2919, 2854, 1650, 1590, 1542, 1346, 1214, 1095, 908, 840, 742 cm^{-1}.

NMR (DMSO; δ in ppm) : 2.466 (s, 3H, SCH_3); 4.040 (s, 3H, OCH_3); 7.260 (s, 1H, furan-H); 7.406 – 7.358 (m, 4H, Ar-H); 7.533 (s, 1H, Ar-H); 7.843 – 7.829 (m, 4H, Ar-H); 8.527 (s, 1H, N=C-OH); 8.789 (bs, 2H, Ar-H & N=CH); 12.060 (s, 1H, CO-NH).

Mass Spectra (molecular ion peak) : 418.20 (M + 1)

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

Dissolve 75 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 32 mg (0.27 mmol) of 2,2,2-trifluoroacetohydrazide (**3d**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 75 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-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]acetohydrazide (**5d**) and characterised by using IR, NMR and Mass spectroscopy.

Yield : 90 %; **M.P.** : Decomposed above 235 ^{0}C; **Mol. Formula** : $C_{19}H_{15}F_3N_2O_3S$.

FT-IR (in KBr) : 3230, 3087, 2938, 1716, 1627, 1596, 1467, 1349, 1213, 1149, 910, 825, 744 cm^{-1}.

NMR (DMSO; δ in ppm) : 2.539 (s, 3H, SCH_3); 4.035 (s, 3H, OCH_3); 7.280 (s, 1H, furan-H); 7.579 – 7.378 (m, 3H, Ar-H); 7.712 (s, 1H, Ar-H); 7.957 – 7.930 (t, 2H, Ar-H); 8.556 (s, 1H, N=C-OH); 8.837 (s, 1H, N=CH); 12.775 (s, 1H, CO-NH).

Mass Spectra (molecular ion peak) : 409 (M + 1).

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

Dissolve 75 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 (**3e**) 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-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]pyridine-3-carbohydrazide (**5e**) and characterised by using IR, NMR and Mass spectroscopy.

Yield : 80 %; **M.P.** : 249 ^{0}C; **Mol. Formula**: $C_{23}H_{19}N_3O_3S$.

FT-IR (in KBr) : 3199, 3058, 1650, 1594, 1563, 1469, 1349, 1218, 1095, 912, 835 cm^{-1}.

NMR (DMSO; δ in ppm): 2.538 (s, 3H, SCH_3); 4.051 (s, 3H, OCH_3); 7.274 (s, 1H, furan-H); 7.446 – 7.317 (m, 4H, Ar-H); 7.604 – 7.553 (m, 2H, Ar-H); 7.868 – 7.841 (d, 2H, Ar-H); 8.281 – 8.255 (d, 1H, py-H); 8.518 (s, 1H, N=C-OH); 8.770 (s, 1H, N=CH); 9.080 (s, 1H, py-H); 12.016 (s, 1H, CO-NH).

Mass Spectra (molecular ion peak) : 418 (M + 1).

2.4. Schiff bases of 7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-carbaldehyde and aromatic amines (6a-f):

2.4.1. Synthesis of 3,4-dichloro-*N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]aniline (6a):

Dissolve 75 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 44 mg (0.27 mmol) of 3,4-

dichloroaniline (**4a**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 50 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in ice bath & filter it on suction pump. Record the yield and m.p. of the 3,4-dichloro-*N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]aniline (**6a**) and characterised by using IR, NMR and Mass.

Yield : 84 %; **M.P.** : 164 ^{0}C; **Mol. Formula :** $C_{23}H_{17}Cl_2NO_2S$.

FT-IR (in KBr) : 2893, 2826, 1629, 1596, 1554, 1471, 1353, 1218, 910, 815 cm^{-1}.

NMR (DMSO; δ in ppm) : 8.705 (s, 1H, imine CH); 7.858 – 7.831 (d, 2H, Ar-H); 7.758 (s, 1H, Ar-H); 7.676 – 7.647 (d, 1H, Ar-H); 7.572 – 7.552 (d, 2H, Ar-H); 7.495 (s, 1H, Furan-H); 7.396 – 7.369 (d, 2H, Ar-H); 7.301 – 7.274 (d, 1H, Ar-H); 4.043 (s, 3H, OCH_3); 2.533 – 2.499 (s, 3H, SCH_3).

Mass Spectra (molecular ion peak): 443 (M + 1).

2.4.2. Synthesis of 3,5-difluoro-*N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]aniline (6b):

Dissolve 75 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 3,5-difluoroaniline (**4b**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 45 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in ice bath & filter it on suction pump. Record the yield and m.p. of the 3,5-difluoro-*N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]aniline (**6b**) and characterised by using IR, NMR and Mass.

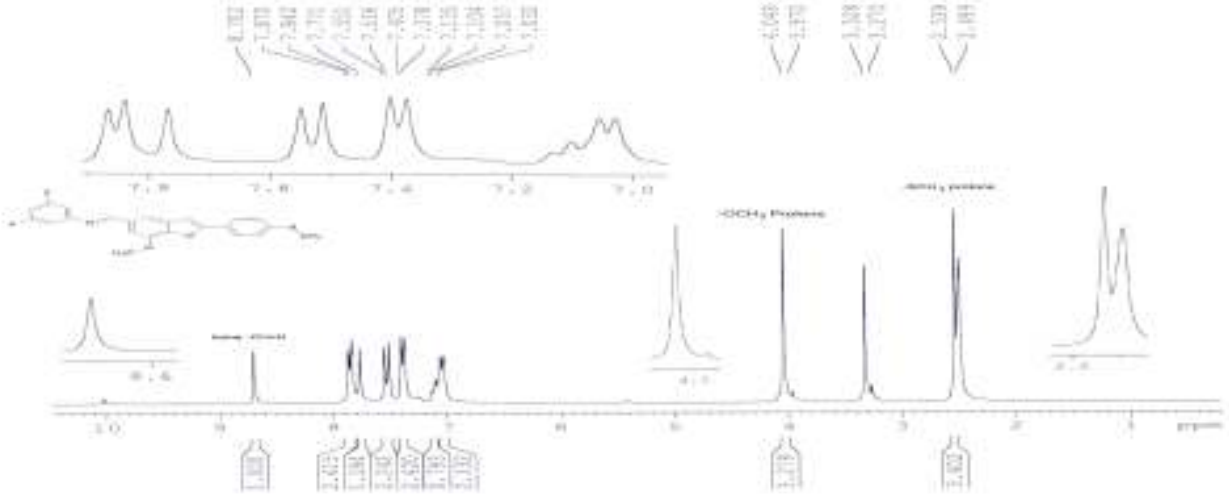
Yield : 88 %; **M.P.** : 169 ^{0}C; **Mol. Formula :** $C_{23}H_{17}F_2NO_2S$

FT-IR (in KBr) : 3081, 2929, 1614, 1590, 1473, 1390, 1218, 971, 912, 821 cm^{-1}.

NMR (DMSO; δ in ppm) : 8.702 (s, 1H, imine CH); 7.87 – 7.84 (d, 2H, Ar-H); 7.771 (s, 1H, furan-H); 7.551 – 7.516 (d, 2H, Ar-H); 7.405 – 7.378 (d, 2H, Ar-H); 7.135 – 7.104 (d, 1H, Ar-H); 7.057 – 7.032 (d, 2H, Ar-H); 4.048 (s, 3H, OCH_3); 2.539 – 2.499 (d, 3H, SCH_3).

Mass Spectra (molecular ion peak): 410 (M + 1).

Fig 3: PMR spectra of 3,5-difluoro-*N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]aniline (6b):



2.4.3. Synthesis of 4-fluoro-*N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]-2-methylaniline (6c):

Dissolve 75 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 34 mg (0.27 mmol) of 4-fluoro-2-methylaniline (**4c**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 75 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in ice bath & filter it on suction pump. Record the yield and m.p. of the 4-fluoro-*N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]-2-methylaniline (**6c**) and characterised by using IR, NMR and Mass.

Yield : 80 %; **M.P.** : 149 ^{0}C; **Mol. Formula** : $C_{24}H_{20}FNO_2S$

FT-IR (in KBr) : 2923, 2861, 1623, 1596, 1490, 1388, 1351, 1270, 914, 808 cm^{-1}.

NMR (DMSO; δ in ppm) : 8.563 (s, 1H, imine CH); 7.873 – 7.846 (d, 2H, Ar-H); 7.766 (s, 1H, furan-H); 7.588 (s, 1H, Ar-H); 7.505 (s, 1H, Ar-H); 7.407 – 7.379 (d, 2H, Ar-H); 7.145 – 7.034 (m, 3H, Ar-H); 4.051 (s, 3H, OCH_3); 2.539 – 2.499 (d, 3H, SCH_3); 2.346 (s, 3H, Ar-CH_3)

Mass Spectra (molecular ion peak): 406 (M + 1).

2.4.4. Synthesis of 4-bromo-2-fluoro-*N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]aniline (6d):

Dissolve 75 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 51 mg (0.27 mmol) of 4-bromo-2-fluoroaniline (**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 ice bath & filter it on suction pump. Record the yield and m.p. of the 4-bromo-2-fluoro-*N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]aniline (**6d**) and characterised by using IR, NMR and Mass.

Yield : 82 %; **M.P.** : 116 ^{0}C; **Mol. Formula :** $C_{23}H_{17}BrFNO_2S$

FT-IR (in KBr) : 2973, 2937, 1631, 1592, 1473, 1344, 1218, 1141, 910 cm^{-1}.

NMR (DMSO; δ in ppm) : 8.712 (s, 1H, N=CH); 7.950 (d, 1H, Ar-H); 7.887 – 7.857 (m, 3H, Ar-H); 7.652 (s, 1H, Ar-H); 7.625 (d, 1H, Ar-H); 7.576 (s, 1H, Ar-H); 7.414 – 7.387 (m, 3H, furan-H & Ar-H); 4.051 (s, 3H, OCH_3); 2.541 (s, 3H, SCH_3).

Mass Spectra (molecular ion peak): 471.35 (M + 1).

2.4.5. Synthesis of 4-chloro-*N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]aniline (6e):

Dissolve 75 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 4-chloroaniline (**4e**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 50 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in ice bath & filter it on suction pump. Record the yield and m.p. of the 4-chloro-*N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]aniline (**6e**) and characterised by using IR, NMR and Mass.

Yield : 86 %; **M.P.** : 159 ^{0}C; **Mol. Formula** : $C_{23}H_{18}ClNO_2S$

FT-IR (in KBr) : 2973, 2869, 1625, 1594, 1492, 1349, 1216, 910, 813 cm^{-1}.

NMR (DMSO; δ in ppm) : 8.666 (s, 1H, imine CH); 7.862 – 7.835 (d, 2H, Ar-H); 7.751 (s, 1H, furan-H); 7.562 (s, 1H, Ar-H); 7.487 – 7.457 (m, 3H, Ar-H); 7.398 – 7.370 (d, 2H, Ar-H); 7.319 – 7.291 (d, 2H, Ar-H); 4.046 (s, 3H, OCH_3); 2.534 – 2.498 (d, 3H, SCH_3).

Mass Spectra (molecular ion peak) : 409 (M + 1).

2.4.6. Synthesis of *N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]-3-trifluoromethylaniline (6f):

Dissolve 75 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 44 mg (0.27 mmol) of 3-trifluoromethylaniline (**4f**) in above solution with stirring and catalytic amount of acetic acid. Reflux the reaction mixture in water at about 45 minutes. Check the completion of reaction time to time by monitoring TLC. Cool the reaction mixture in ice bath & filter it on suction pump. Record the yield and m.p. of the *N*-[(*E*)-{7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-yl}methylidene]-3-trifluoromethylaniline (**6f**) and characterised by using IR, NMR and Mass.

Yield : 86 %; **M.P.** : 130 ^{0}C; **Mol. Formula** : $C_{24}H_{18}F_3NO_2S$

FT-IR (in KBr) : 2979, 2869, 1631, 1614, 1590, 1469, 1328, 908, 802 cm^{-1}.

NMR (DMSO; δ in ppm) : 8.757 (s, 1H, imine CH); 7.879 – 7.851 (d, 2H, Ar-H); 7.808 (s, 1H, furan-H); 7.588 (s, 1H, Ar-H); 7.670 – 7.601 (m, 5H, Ar-H); 7.526 (s, 1H, Ar-H); 7.410 – 7.383 (d, 2H, Ar-H); 4.058 (s, 3H, OCH_3); 2.541 – 2.500 (d, 3H, SCH_3).

Mass Spectra (molecular ion peak) : 442 (M + 1).

3. Result and Discussion:

The FT-IR spectra of the 7-methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde (**1**) was recorded by using KBr pallet. The weak band in the IR-spectra at 2973, 2938 and 2834 cm^{-1} are due to the υ C-H (aromatic) stretching vibrations of both aromatic and heterocyclic ring. These bands are weak due to small change in dipole moment due to vibrations. The weak band at 2723 cm^{-1} and strong band at 1691 cm^{-1} is due to aldehydic υ C-H and aldehydic υ C=O group vibrations. The carbonyl vibration of aldehydic group is shifted to the lower wave number is due to the conjugation with active aromatic ring. The band due to carbonyl vibration is strong and sharp band because of large change in dipole moment due to stretching. The presence of aromatic C=C bond has been confirmed by the absorption bands in the region 1640-1500 cm^{-1}. The absorption band at 1218 cm^{-1} is due to the stretching vibrations of C-O bond of ether group of the ligand.

The NMR spectra of 7-methoxy-2-[4-(methylsulfanyl)phenyl]-l-benzofuran-5-carboxaldehyde **(1)** was recorded in deuterated DMSO as solvent, TMS as reference and in 300 MHz instrument. The singlet at 2.532 of three protons is due to thiomethyl group attached to aromatic ring. The chemical shift value indicates that, methyl protons are deshielded due to – I effect of sulphur atom. The singlet at 4.089 is due to three protons of methyl group attached to oxygen atom i.e. methoxy protons. The aromatic protons shows chemical shift in the region of 7.04 – 7.78 ppm. The proton of C_3-H of furan ring shows singlet at 7.040. The aldehydic proton shows singlet at 9.997 ppm. It is highly deshielded due to anisotropic effect of aldehydic carbonyl (C=O) group and – I effect of aldehydic oxygen atom. In mass spectrum, it shows (M + 1) peak at 298.94 and (M + 2) peak at 299.92 with 1/3rd intensity indicates presence of one sulphur atom in the compound.

The 7-methoxy-2-[4-(methylsulfanyl)phenyl]-1-benzofuran-5-carbaldehyde (**1**) was the treated with various haloanilines **4a-f** in methanol in presence of acetic acid catalyst forming corresponding Schiff bases **6a-f** under reflux conditions. The haloanilines used for the synthesis are recrystallized or distilled out (under reduced pressure) before used. If they contain any colour impurity then it can by purified by giving charcoal treatment. The formation of Schiff bases has been confirmed from their FT-IR, NMR and mass spectra along with chemical element detection

test. The formation of CH=N bond is confirmed by FT-IR and NMR spectra. The C=N stretching vibration of **6a-f** shows absorption in the region of 1610 – 1630 cm-1 and the imine proton shows chemical shift in the region of 8.55 – 8.76 ppm. The product does not shows any absorption band in the carbonyl group region of aldehyde and not shows positive 2,4-DNP test. The aromatic protons of the Schiff bases **6a-f** shows chemical shift at the 7.03 – 7.87 ppm region.

The various hydrazides (**3a-d**) used for the synthesis of Schiff bases of **1** are synthesised by known literature method from corresponding carboxylic acids and **3e** is available in laboratory. The formation of hydrazides has been confirmed by FT-IR spectroscopy. The 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} depending on the nature of substituents. 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 **8d**, **8a** and **8c** are deactivating the carbonyl group therefore it shows absorption at higher wave number side as compared to **8b**.

The 7-methoxy-2-[4-(methylsulfanyl)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 **6a-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 **6a-e** shows two proton signals in its NMR spectra at the region 8.50 – 8.56 ppm (due to NH-C=O proton) and 12.01 – 12.80 ppm (due to N=C-OH proton) is due to keto-enol tautomerism of N-H proton. The imine proton of the Schiff bases **6a-e** shows chemical shift in the region 8.66 – 8.80 ppm. The amide carbonyl group of the Schiff bases **6a-c** and **6e** shows absorption in 1640 – 1650 cm^{-1} except **6d** in their FT-IR spectra. The amide carbonyl group of **6d** shows absorption at 1716 cm^{-1} is due to strong electron withdrawing inductive effect of $–CF_3$ group. The imine bond (>C=N-) shows strong absorption band in the region 1600 – 1590 cm^{-1} in **6a-c** and **6e** whereas that of **6d** shows band at 1627 cm^{-1}.

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