Design, Synthesis And Characterization Of Benzofuran Derivatives For Anti-Bacterial Activity - A Research Article

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ABSTRACT: Many compounds are produced by different modifications of the benzofuran moiety, and each of those molecules exhibits a wide range of biological activity. New benzofuran derivatives (M5a-M5t) were produced using various reagents and techniques. The benzofuran derivatives (M5a-M5t) were made by combining 7-chlorobenzofuran-3-yl hydrazine and 5-nitrobenzofuran-3-yl)hydrazine with various benzaldehydes, such as 2-chloro, 4-Chloro, 4-Nitro, 2-Nitro, 4-Fluoro, 3-Methoxy, 4-bromo, 3-Bromo, 3-Chloro and 3-Nitrobenzaldehyde were used. The synthesized compounds spectral analysis was done by Infrared spectroscopy (IR), ^{1}H-Nuclear magnetic resonance (^{1}HNMR) and liquid chromatography-mass spectroscopy (LCMS). The synthesized compounds were tested for bacterial activity and the activity was done by Agar well diffusion method and it has been observed that Compounds M5a, M5g has shown potent antibacterial activity at 50µg/ml against Enterococcus Faecalis whereas compound M5i, M5k, M5l has shown significant antibacterial activity at 25µg/ml against and Candiida albicans**.**

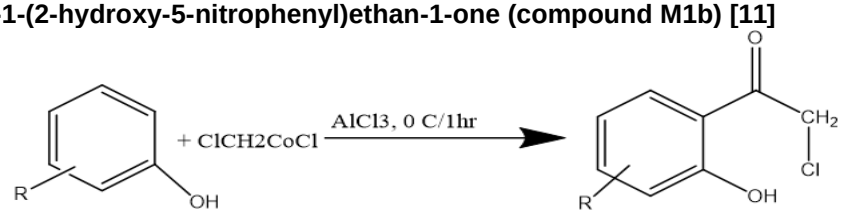
INTRODUCTION: Furan is a heterocyclic organic compound consisting of a five-membered aromatic ring with four carbon atoms and one oxygen atom **(1).** Benzofuran is formed when benzene ring is attached to furan ring. With its wide range of biological activity, the benzofuran skeleton occupies a significant place in organic chemistry and is regarded as one of the most significant heterocyclic systems**.(2)** The most abundantly occurring compounds in nature, benzofuranones, are mostly used in drug development and chemical biology; many medications are derived from natural sources and have extremely powerful biological activity**.(3)** Once it was revealed that furanones have a high level of anti-cancer action, benzofuranones have become important in medicinal chemistry. There is evidence that benzofuran has a wide range of effects, including hypnotic, analgesic, edema-inhibiting, platelet aggregation, anticonvulsant, and anti-inflammatory ones. **(4, 5, 6, 7).**.The significant interest in employing benzofuran as the building blocks of pharmacological drugs is justified by the large variety of biological features that are inherent in the benzofuran scaffold. Several of the medications with clinical approval of benzofuran derivatives are produced synthetically or naturally, some of which are combined with other heterocyclic moieties.**(8)** Among the many biological activities displayed by the benzofuran moiety is antibacterial activity. Antimicrobial agents, are compounds that either prevent or completely destroy the growth of specific microorganisms.(**9)** Today the leading cause of infections are bacterias. Bacteria are present everywhere. They are essential to protecting our living environment. The bacteria that cause disease and infection are not the majority of the bacteria on the planet. These bacterial infections have a major effect on public health. Treatment for viral illnesses is usually more complex than treatment for bacterial infections.**(10).** Many antibacterial medications have been discovered, produced, and utilized in clinical settings over the past few decades, but they do not fully address the challenges of eliminating bacterial infections completely hence in this research article new prepared benzofuran derivatives new approaches has been made or new antibacterial drugs has been prepared or used for antibacterial infections.

MATERIAL AND METHODS:

Materials: The analytical grade solvents and chemicals that were employed in the research were all procured from Central Drug House (P) Ltd. (Delhi, India) and Tokyo Chemical Industrial Co., Ltd. (Tokyo, Japan).

Synthesis:

Procedure for the preparation of 2-chloro-1-(3-chloro-2-hydroxyphenyl)ethan-1-one (compound M1a) & 2-Chloro-1-(2-hydroxy-5-nitrophenyl)ethan-1-one (compound M1b) [11]

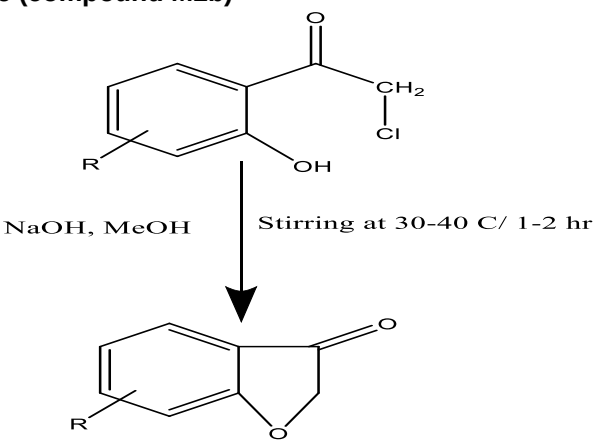


Substituted phenol
R=2-Cl, 4-NO2

2-chloro-1(-3chloro/5nitro-2hydroxyphenyl)ethan-1-one
Compound M1a & M1b

AlCl3 (10mmol) in diethyl ether (30ml) was added to substituted phenol(2-chloro and 4-nitro) **(M) (10mmol)** in round bottom flask with stirring at 0°C. The chloroacetyl chloride **(10 mmol)** in diethyl ether (10 mL) was then added to the pre-stirred mixture at 0^0C (caution: the addition procedure discussed so far should be done carefully, slowly, and in small quantities at 0 degrees Celsius because it is an exothermic reaction).Then the reaction is stirred for 4-5 hours at 30^0C.TLC analysis was done on the reaction's outcome. Afterwards, the ether-based solvent was distilled, and the resulting residue was quenched with dil. HCl (20 mL). Dichloromethane (2 x 50 mL) was used to extract the mixture, and the combined organic extracts were dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. The resulting solid was recrystallized from ethanol to give 2-chloro-1-(3-chloro-2-hydroxyphenyl)ethan-1-one **(M1a)** & 2-Chloro-1-(2-hydroxy-5-nitrophenyl)ethan-1-one **(M1b)**

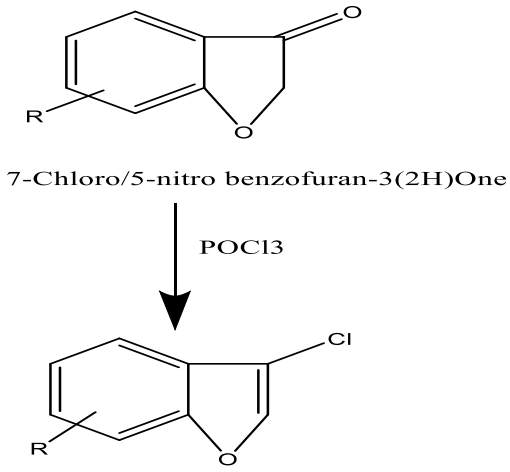
Procedure for the preparation of 7-chlorobenzofuran-3(2H)-one (compound M2a) & 5-nitrobenzofuran-3(2H)-one (compound M2b)



7-Chloro/5-nitrobenzofuran-3(2H)One
M2a & M2b

2-chloro-1-(3-chloro-2-hydroxyphenyl) ethan-1-one and 2-chloro-1-(2-hydroxy-5-nitrophenyl) ethan-1-one **(compound M1a & M1b)(3mmol)** was added in 10ml of methanol with continuous stirring followed by the addition of NaOH (3mmol of NaOH dissolved in 5 ml of water) and stirred at 30^0C for 1-2 hr. After the reaction was finished ethanol was distilled off and the solid residue which was left was thoroughly washed with plentiful amount of water. The crude product that is 7-chlorobenzofuran-3(2H)-one **(compound M2a) &** 5-nitrobenzofuran-3(2H)-one **(compound M2b)** is obtained, dried and recrystallized from ethanol.

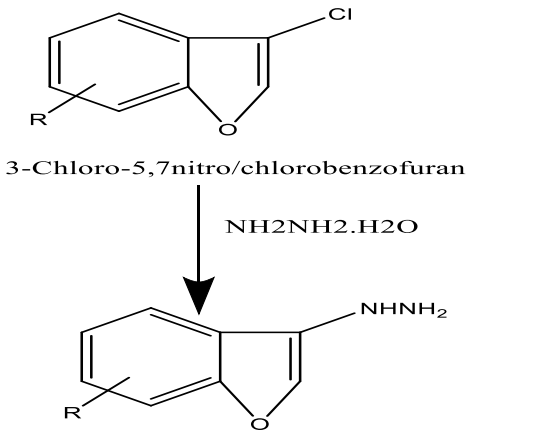
Procedure for the synthesis of 3,7-dichlorobenzofuran (compound M3a) & 3-chloro-5-nitrobenzofuran (compound M3b) [12]



Compound M3a & M3b

7-chlorobenzofuran-3(2H)-one **(compound M2a) &**5-nitrobenzofuran-3(2H)-one **(compound M2b) (0.01 mol)** with phosphorous pentachloride (0.01 mol) in phosphorous oxychloride (20 ml) was heated on a steam bath for approximately 3 hours. The resulting product was poured on crushed ice. The solid which is obtained was filtered and recrystallized from methanol to obtain compound 3, 7-dichlorobenzofuran **(compoundM3a) &** 3-chloro-5-nitrobenzofuran **(compound M3b)**

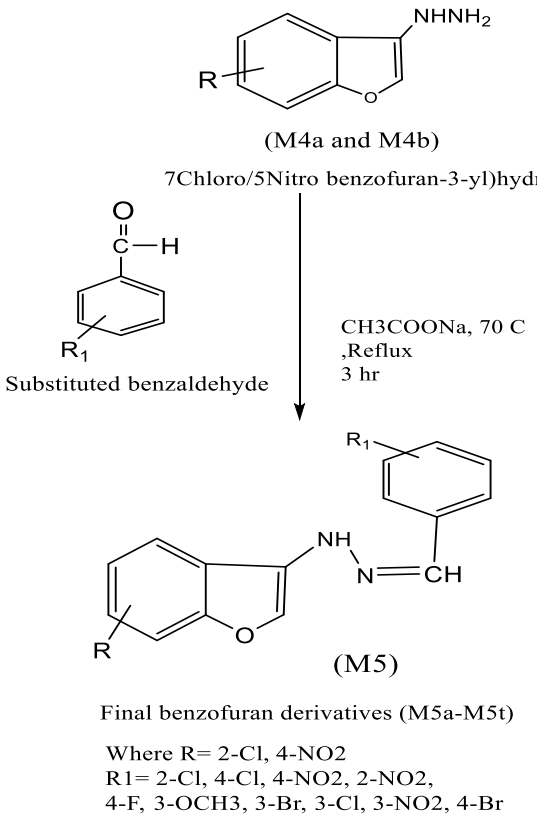
Procedure for the synthesis of 7-chlorobenzofuran-3-yl)hydrazine (compound M4a) & 5-nitrobenzofuran-3-yl)hydrazine (compound M4b)



Compound M4a & M4b

A mixture of compound **(compound M3a)** i.e. 3, 7-dichlorobenzofuran (0.01mol) & 3-chloro-5-nitrobenzofuran **(compound M3b)** is taken with hydrazine hydrate (98%, 0.01 mol) in ethanol (20ml) and heated under reflux for 6 hrs. The resulting product i.e. (7-chlorobenzofuran-3-yl)hydrazine **(compound M4a) &** 5-nitrobenzofuran-3-yl)hydrazine **(compound M4b)** was obtained from which the excess of solvent is removed and the product is filtered and washed with ethanol and recrystallized from methanol .

Procedure for the preparation of final benzofuran derivative (M5a-M5t): (14)



Final benzofuran derivatives (M5a-M5t)

Where R= 2-Cl, 4-NO2
R1= 2-Cl, 4-Cl, 4-NO2, 2-NO2,
4-F, 3-OCH3, 3-Br, 3-Cl, 3-NO2, 4-Br

A (1.0 mmol) of (7-chlorobenzofuran-3-yl) hydrazine (CompoundM4a) and 5-nitrobenzofuran-3-yl)hydrazine **(**compound M4b**)** and sodium acetate (1.0mmol, 0.137g)(buffering agent) was dissolved in 15ml of ethanol and mixed with 0.104ml of substituted benzaldehyde. Now all the mixture of the solutions was transferred in a round bottom flask of 100ml and the reaction is refluxed for 3 hours at 70-75^{0}C and the reaction is allowed to cool overnight. Finally the precipitate of final benzofuran derivatives**(M5a-M5t)** is obtained by filtration process, washed with ethanol and allowed to air dry.

ANTIBACTERIAL ACTIVITY:

Antibacterial activity by Agar well diffusion method

To test the anti-bacterial activity Enterococcus Faecalis and Candida Albicans was used for Agar well diffusion experiment.For agar well diffusion method the following procedures are utilized:

- Assessment of anti-bacterial activity samples were determined by agar well diffusion method
- Inoculums of E.faecalis and C.albicans bacterial strains were plated using sterile swabs into petridishes containing approximately 25 ml of Nutrient agar media, where 6mm wells were made and filled with different concentrations 25, 50µl/ml of samples and as a standard Chlorobiocin 20µl/ml.
- The petri dishes were pre-incubated for 3 hr at room temperature, allowing the complete diffusion of the samples and then,
- Incubated at 37+1^{0}C for 24 hr.

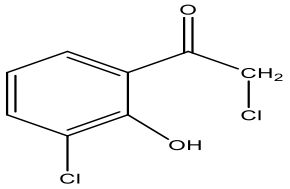
Further antibacterial activity of the above prepared derivatives were determined by measuring the zone of inhibition millimeters (mm) according to the standard clinical parameters

Result and discussion: In this research, all the benzofuran derivatives are synthesized according to synthetic root. The data of 5 synthesized benzofuran derivatives (M5a, M5g, M5i, M5k, M5l) are shown in **Table 1.** All the synthesized compounds was established by the interpretation of NMR, IR, LCMS .In this research work Agar well diffusion method is used for synthesized compounds to perform antibacterial activity

TABLE 1: PHYSIOCHEMICAL CHARACTERISTICS OF NEWLY PREPARED DERIVATIVES WITH IUPAC NAME AND MOLECULAR MASS (M5a, M5g, M5i, M5k, M5l)

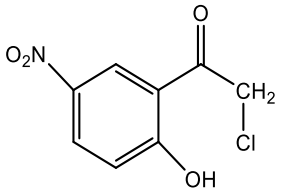
Derivative Name	Chemical formula	IUPAC Name	Molecular mass
M5a	C15H10Cl2N2O	1-(7-chlorobenzofuran-3-yl)-2-(2-chlorobenzylidene hydrazine	305.16
M5g	C15H10BrClN2O	1-(4-bromobenzylidene)-2-(7-chlorobenzofuran-3-yl)hydrazine	349.61
M5i	C15H10Cl2N2O	1-(7-chlorobenzofuran-3-yl)-2-(3-chlorobenzylidene)hydrazine	305.16
M5k	C15H10ClN3O3	(E)-1-(2-chlorobenzylidene)-2-(5-nitrobenzofuran-3-yl)hydrazine	315.04
M5l	C15H10ClN3O3	1-(4-chlorobenzylidene)-2-(5-nitrobenzofuran-3-yl)hydrazine	315.71

Interpretation of Intermediate, 2-chloro-1-(3-chloro-2-hydroxyphenyl)ethan-1-one (Compound M1a):

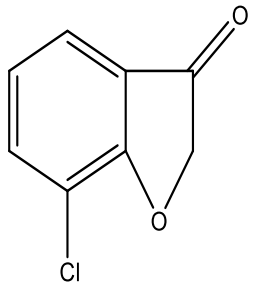
Code of synthesized compound	Details of synthesized compound	Spectral analysis data
M1a	 Intermediate,2-chloro-1-(3-chloro-2-hydroxyphenyl)ethan-1-one	**^{1}H-NMR interpretation** **^{1}H-NMR (400MHz, DMSO)** δ 2.5 (1H, s, Ar-OH), 3.4 (2H, s, -CH2-) and 7.3-7.6 (H, m, Ar-H) **FT-IR Intepretation** IR (KBr): 3194 cm-1 (stretching, O-H), 2987 cm-1 (stretching, Ar-H), 1624 cm-1(stretching, C=O), 1450 cm-1 (bending, C-H) and 709 cm-1(stretching, C-Cl) **LCMS Interpretation** Mass (ESI-MS): m/z 206.02 (M+H)

Intermediate, 2-Chloro-1-(2-hydroxy-5-nitrophenyl)ethan-1-one (Compound M1b)

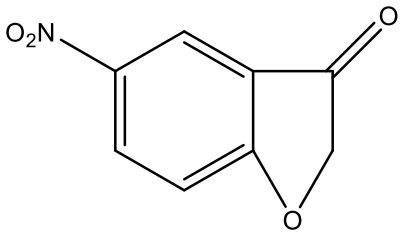
Code of compound	Detail of synthesized compounds	Spectral analysis data

M1b	 Intermediate 2-chloro-1-(2-hydroxy-5-nitrophenyl)ethan-1-one	**^{1}H-NMR interpretation** **^{1}H-NMR (400MHz, DMSO)** δ 2.5 (1H, s, Ar-OH), 3.3(2H, s, -CH2-) and 6.9-7.5 (H, m, Ar-H) **FT-IR Intepretation** IR (KBr): 3198 cm-1 (stretching, O-H), 2490 cm-1 (stretching, Ar-H), 1624 cm-1(stretching, C=O), 1610 cm-1 (bending, Ar-NO2) and 1460 cm-1(bending, C-H) and 711cm-1(stretching, C-Cl) **LCMS Interpretation** Mass (ESI-MS): m/z 216.94 (M+H)

Intermediate, 7-chlorobenzofuran-3(2H)-one (M2a)

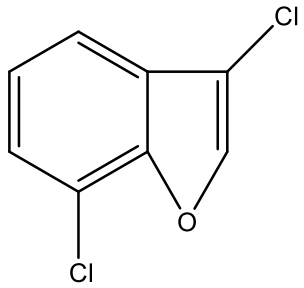
M2a	 Intermediate, 7-chlorobenzofuran-3(2*H*)-one	**^{1}H-NMR interpretation** **^{1}H-NMR (400MHz, DMSO)** δ 3.4 (2H, s, -CH2-), and 7.6 (H, m, Ar-H) **FT-IR Intepretation** IR (KBr): 3416 cm-1 (stretching, Ar-H), 1591 cm-1 (stretching, C=O), 1342 cm-1(bending C-H), and 758 cm-1 (stretching, C-Cl) **LCMS Interpretation** Mass (ESI-MS): m/z 169 (M+H)

Intermediate, 5-nitrobenzofuran-3(2H)-one (M2b)

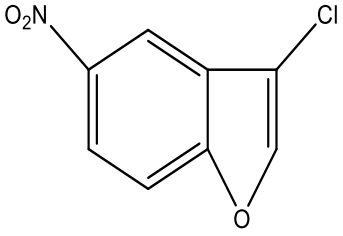
Code of compound	Detail of synthesized compound	Spectral analysis data
M2b	 Intermediate, 5-nitrobenzofuran-3(2*H*)-one	**^{1}H-NMR interpretation** **^{1}H-NMR (400MHz, DMSO)** δ 3.3 (2H, s, -CH2-), and 6.7-6.8 (H, m, Ar-H) **FT-IR Intepretation** IR (KBr): 3303 cm-1 (stretching, Ar-H), 1724 cm-1 (stretching, C=O), 1591 cm-1(stretching, Ar-NO2), and 1342 cm-1 (bending, C-H) **LCMS Interpretation** Mass (ESI-MS): m/z 180.02 (M+H)

Intermediate, 3,7-dichlorobenzofuran (M3a)

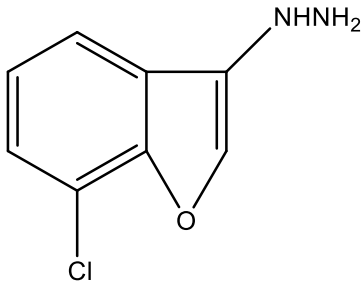
Code of compound	Detail of synthesized compound	Spectral analysis data

M3a	 Intermediate, 3,7-dichlorobenzofuran	**^{1}H-NMR interpretation** **^{1}H-NMR (400MHz, DMSO)** δ 6.8 (H,S=CH-), and 7.8 (H, Ar-H) **FT-IR Intepretation** IR (KBr): 3327 cm-1 (stretching, Ar-H) and 742 cm-1 (stretching, C=Cl), **LCMS Interpretation** Mass (ESI-MS): m/z 188(M+H)

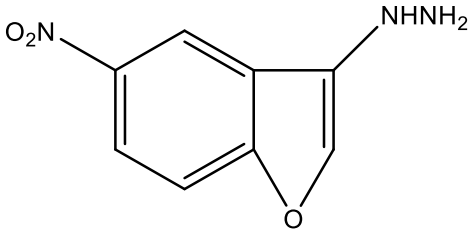
Intermediate, 3-chloro-5-nitrobenzofuran (M3b)

Code of compound	Detail of synthesized compound	Spectral analusis data
M3b	 Intermediate, 3-chloro-5-nitrobenzofuran	**^{1}H-NMR interpretation** **^{1}H-NMR (400MHz, DMSO)** δ 5.1 (H,s=CH-), and 6.9-7.4 (H, Ar-H) **FT-IR Intepretation** IR (KBr): 2928 cm-1 (stretching, Ar-H) and 1629 cm-1 (stretching, Ar-NO2) and 553vcm-1 (stretching, C-Cl) **LCMS Interpretation** Mass (ESI-MS): m/z 198.01(M+H)

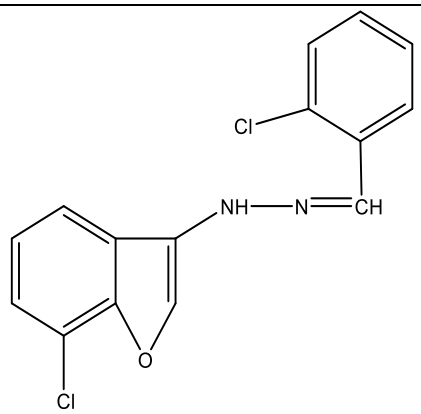
Intermediate, 7-chlorobenzofuran-3-yl)hydrazine (M4a)

Code of compound	Detail of synthesized compound	Spectral analysis data
M4a	 (7-chlorobenzofuran-3-yl)hydrazine	**^{1}H-NMR interpretation** **^{1}H-NMR (400MHz, DMSO)** δ 2.5 (H,s,-NH-), 7.2-7.4 (H, Ar-H) and 8.8 (H,s-NH2) **FT-IR Intepretation** IR (KBr): 3244 cm-1 (stretching, -NH-) and 3142 cm-1 (stretching, Ar-H) and 964 cm-1 (stretching, C-Cl) **LCMS Interpretation** Mass (ESI-MS): m/z 183 (M+H)

Intermediate, 5-nitrobenzofuran-3-yl)hydrazine (M4b)

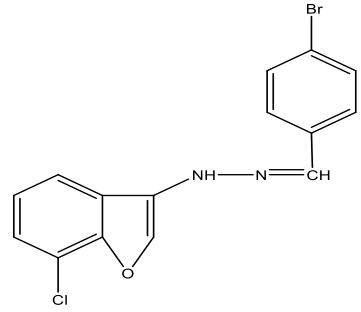
Code of the compound	Detail of synthesized compound	Spectral analysis data
M4b	 (5-nitrobenzofuran-3-yl)hydrazine	**^{1}H-NMR interpretation** **^{1}H-NMR (400MHz, DMSO)** δ 2.5 (H,s,-NH-), 6.9 (H, Ar-H) and 8.1 (H,s-NH2) **FT-IR Intepretation** IR (KBr): 3244 cm-1 (stretching, -NH-), 3093 cm-1 (stretching, Ar-H) and 1624 cm-1 (stretching, Ar-NO_2) **LCMS Interpretation** Mass (ESI-MS): m/z 194.01 (M+H)

Final derivative, 1-(7-chlorobenzofuran-3-yl)-2-(2-chlorobenzylidene)hydrazine (M5a)

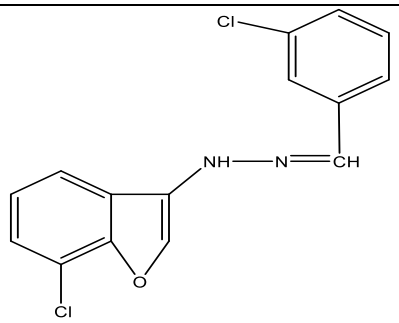
Code of compound	Details of synthesized compound	Spectral analysis data
M5a	 1-(7-chlorobenzofuran-3-yl)-2-(2-chlorobenzylidene)hydrazine	**^{1}H-NMR interpretation** **^{1}H-NMR (400MHz, DMSO)** δ 1.8 (H,s,-NH-), 3.3 (H,s, -CH-) , 7.1 (H,S,-N=CH-)and 7.3-8.1 (H, m, Ar-H) **FT-IR Intepretation** IR (KBr): 3514 cm-1 (stretching, -NH-), 3068 cm-1 (stretching, Ar-H), 1616 cm-1 (stretching, C=-N-),and 750 cm-1(Stretching,C-Cl) **LCMS Interpretation** Mass (ESI-MS): m/z306.16 (M+H

Final derivative, 1-(4-bromobenzylidene)-2-(7-chlorobenzofuran-3-yl)hydrazine (M5g)

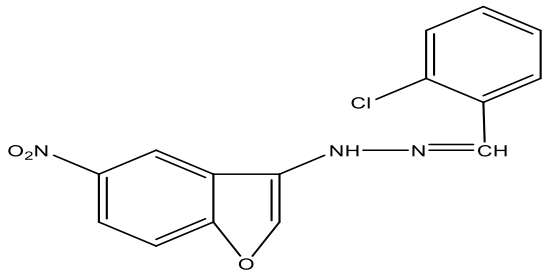
Code of synthesized compound	Detail of synthesized compound	Data of spectral analysis
M5g		**^{1}H-NMR interpretation** **^{1}H-NMR (400MHz, DMSO)** δ 1.6 (H,s,-NH-), 7.7 (H,S,-N=CH), and 7.8 (H, Ar-H) **FT-IR Intepretation** IR (KBr): 3421 cm-1 (stretching, -NH-), 2929 cm-1 (stretching, Ar-H), 1639 cm-1 (stretching, C=-N-), and 704 cm-1(stretching, C-Cl), 644 cm-1 (stretching, C-Br)

	 1-(4-bromobenzylidene)-2-(7-chlorobenzofuran-3-yl)hydrazine	**LCMS Interpretation** Mass (ESI-MS): m/z 350.61 (M+H)

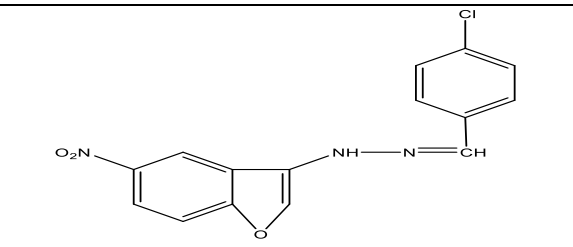
Final derivative, 1-(7-chlorobenzofuran-3-yl)-2-(3-chlorobenzylidene)hydrazine (M5i)

Code of the compound	Detail of synthesized compound	Data of spectral analysis
M5i	 1-(7-chlorobenzofuran-3-yl)-2-(3-chlorobenzylidene)hydrazine	**^{1}H-NMR interpretation** **^{1}H-NMR (400MHz, DMSO)** δ 1.6 (H,s,-NH-), 3.3 (H,s, -CH-), 7.5 (H, S, -N=CH-) and 7.6-8.3 (H, m, Ar-H) **FT-IR Intepretation** IR (KBr): 3441 cm-1 (stretching, -NH-), 2929 cm-1 (stretching, Ar-H), 1641 cm-1 (stretching, C=-N-), and 748 cm-1(stretching, C-Cl) **LCMS Interpretation** Mass (ESI-MS): m/z 306 (M+H)

Final derivative, 1-(2-chlorobenzylidene)-2-(5-nitrobenzofuran-3-yl)hydrazine (M5k)

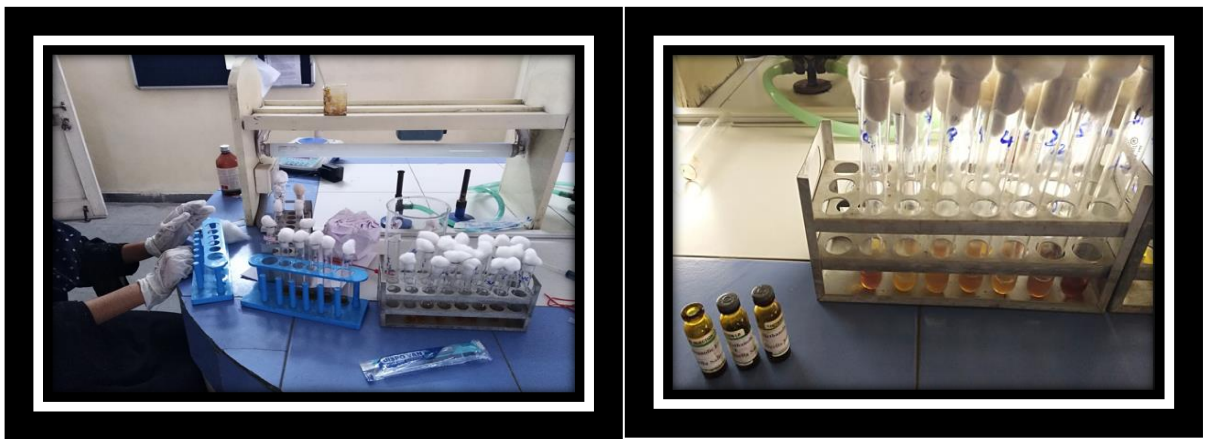
Code of the compound	Detail of synthesized compound	Data of spectral analysis
M5k	 1-(2-chlorobenzylidene)-2-(5-nitrobenzofuran-3-yl)hydrazine Molecular Weight: 315.71 Compound- M5k	**^{1}H-NMR interpretation** ^{1}H NMR (400 MHz, DMSO) δ 1.6 (H,s, -NH-), 7.1 (H, S, -N=CH-) and 7.2-7.6 (H, m, Ar-H) **FT-IR Intepretation** IR (KBr): 3402 cm-1 (stretching, -NH-), 2359 cm-1 (stretching, Ar-H), 1629 cm-1 (stretching, C=-N-), 1521 cm-1 (stretching, Ar-NO_2), and 736 cm-1 (stretching, C-Cl) **LCMS Interpretation** Mass (ESI-MS): m/z 316.71 (M+H)

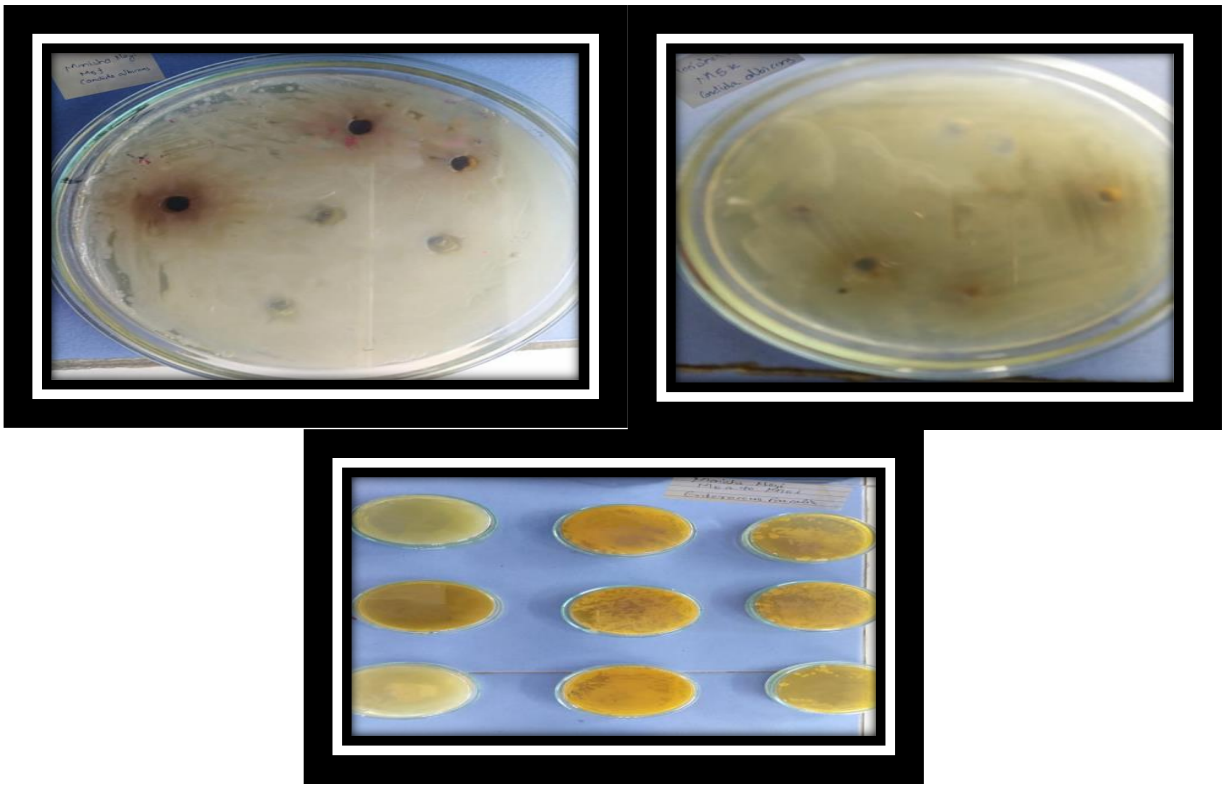
Final derivative, 1-(4-chlorobenzylidene)-2-(5-nitrobenzofuran-3-yl)hydrazine (M5l)

Code of compound	Detail of synthesized compound	Data of spectral analysis
M5l	 1-(4-chlorobenzylidene)-2-(5-nitrobenzofuran-3-yl)hydrazine Molecular Weight: 315.71 Compound-M5L	**^{1}H-NMR interpretation** ^{1}H NMR (400 MHz, DMSO) δ 1.8 (H,s, -NH-), 7.2 (H, S, -N=CH-) and 7.3-7.9 (H, m, Ar-H) **FT-IR Intepretation** IR (KBr): 3394 cm-1 (stretching, -NH-), 2949 cm-1 (stretching, Ar-H), 1626 cm-1 (stretching, C=-N-), 1554 cm-1 (stretching, Ar-NO_2), and 779 cm-1 (stretching, C-Cl) **LCMS Interpretation** Mass (ESI-MS): m/z 316.71 (M+H)

Anti-bacterial activity: By using Agar well diffusion method, newly synthesized derivative M5a, M5g, M5i, M5k, M5l were tested for bacterial activity and it has been observed that Compounds M5a, M5g has shown potent antibacterial activity at 50µg/ml against Enterococcus Faecalis whereas compound M5i, M5k, M5l has shown significant antibacterial activity at 25µg/ml against and Candida albicans**.**

ANTIBACTERIAL ACTIVITY DATA OF THE ABOVE SAMPLES BY MEASURING THE ZONE OF INHIBITION(MM) AGAINST ENTEROCOCCUS FAECALIS AND CANDIDA ALBICANS





Compound Name	**M5a**		**M5g**		**Chlorobiocin**	
Concentration in µl/ml	50	25	50	25	50	25
Enterococcus Faecalis	3.7	1.9	3.9	3.58	3.58	2.01
ZONE OF INHIBITION IN (mm)						

Compound Name	**M5i**		**M5k**		**M5l**		**Chlorobiocin**	
Concentration in µl/ml	50	25	50	25	50	25	50	25
Candida albicans	2.8	1.6	3.2	1.7	3.4	1.8	3.75	2.13
ZONE OF INHIBITION IN (mm)								

CONCLUSION: All the novel synthesized benzofuran derivatives (M5a, M5g, M5i, M5k, M5l) were confirmed by spectral analysis, i.e., proton nuclear magnetic resonance, infra-red spectrometry, and liquid chromatography-mass spectrometry. Compounds M5a & M5g showed potent anti-bacterial activity at 50 µg/ml against Enterococcus Faecalis and Compounds M5i, M5k, M5l has shown significant anti-bacterial activity at 50 µg/ml against bacteria Candida albicans.

CONFLICTS OF INTEREST: No conflict of interest

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