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SYNTHESIS, CHARACTERISATION AND BIOLOGICAL EVALUATION OF A NEW SERIES OF BENZOFURANS

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ABSTRACT

Present investigation deals with synthesis of a series benzofurans by using various chemicals like ethyl acetoacetate, salicylic acid, aminoguanidine, guanidine, chloro acetyl chloride, carbon disulphide, potassium hydroxide, resorcinol, acetylacetone, thionyl chloride, urea, hydrazine hydrate, hydrazine hydrochloride, thiourea, ethylacetate, methanol, potassium cardonate, thioglycollic acid. The synthesized complexes are characterised by using Melting point determination, Thin layer chromatography, Infrared spectroscopy, Nuclear magnetic resonance spectroscopy, Mass spectroscopy. The synthesised compounds were recrystallised with appropriate solvents. All the synthesised complexes are screened for their antibacterial activities.

KEYWORDS: Benzofurans, Meltingpoint, TLC, IR, Massspectroscopy, NMR, Recrystallisation.

INTRODUCTION

The area of research including synthesis and characterisation by using various chemicals is gaining increased attention of researches working in inorganic chemistry since last few years. This fact created intrest in synthetic products containing benzofuran nucleus. Kreamer and Spilker discovered benzofuran in coal tar. It was synthesised by Perkin in 1870. Natural benzofuran compounds have varied chemical structures. They exist in simple form such as a substitued benzofuran to a highly complicated molecule like morphine. Several monographs.[1-5] devoted to the study of such natural and synthetic benzofurans have appeared in literature from time to time *heterocyclic* compounds encompassing benzofuran

nucleus are widely distributed in the nature, particularly among plant kingdom. They found to posses wide range of biological and pharmacological activities such as antiviral, analeptic, antimicrobial, analgesic, and anti-inflammatory.

Benzofuran is a planner heteroaromtic molecule. As in furan, oxygen contributes 2pi electron to form a 10pi electron system. Benzofuran belongs to the group of what is known as "electron rich" or "pi-excessive" heteroaromatics. Resonance considerations of such condensed system indicate that electophilic substitution should occur at C-3. But benzofuran undergoes substitution almost exclusively at the C-2. This unusual difference in orientiation between benzofuran and benzothiazepine is realized to be associated with electronegativity of oxygen and sulphur. Since oxygen is more electronegative than sulphur[6], the unshared electrons around oxygen are held more tightly than those of sulphur.

All the synthesized complexes were screened for their in vitroantibacterial activities against bacterial pathogens such as Escherichia coli, Staphylococcus aureus, Bacillus pimilis.

MATERIALS AND METHODS

Chemicals (including solvents) used in the present studywere purchased from Liala Implex, Vijayawada. All the chemicals used were of AR grade. The purification of solvents was done by Re-crystallization as per literature.

Synthesis of benzofuran derivatives

The preparation of Benzofuran derivatives involves 3steps.

Step-1: Synthesis of Diketone

Salicylaldehyde, 0.1mole and 0.15mole of acetyl acetone were taken in a RBF. To this added 20ml of ethanol and 3gms of sodium metal and refluxed in water bath for 3hrs. The flask was removed. To this added cold water and stored in a cool place. It was extracted with ether and the solvent was evaporated. The so formed Diketone was recrystallised from ethanol. The completion of reaction was monitored byTLC.

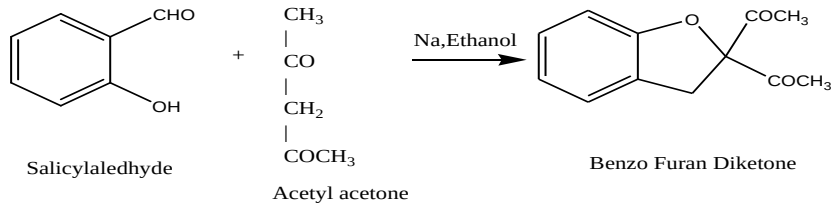
Step-2: Synthesis of Hydrazone

To the above formed Diketone 20ml of hydrazine hydrate was added and refluxed for 3hrs. To this added cold water and then stored in a cool place. It was extracted with ether and the solvent was evaporated. Hydrazone so obtained recrystallised from ethanol. The completion of reaction was monitored by TLC.

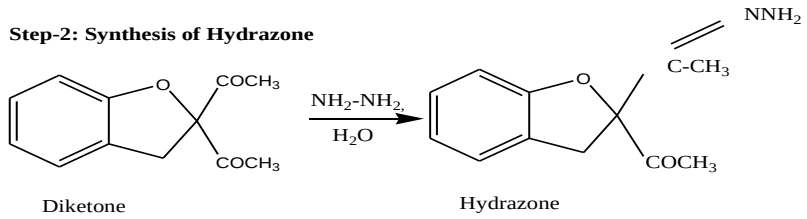
Step-3: Synthesis of Benzofuran derivatives

The hydrazone formed was allowed to react with different reagents like Ethyl acetoacetate, Chloro acetyl chloride, Thioglycollic acid, Thiosemicarbazine, O-Phenylene diamine to give different benzofuran derivatives. The obtained products are characterised by IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. The synthesised complexes were obtained in 60-65% yield. Scheme representing synthesis of co ofcomlexes is given in below in (Figure 1).

Step-1: Synthesis of Diketone



Step-2: Synthesis of Hydrazone



Step-3: Synthesis of Benzofuran derivatives

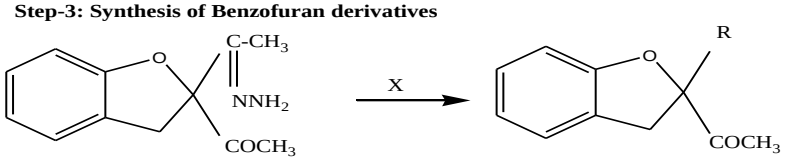


Fig 1: Schematic Diagram for the synthesis of Benzofuran derivatives, where X= Chloro acetyl chloride, Thioglycollic acid, Ethyl aceto acetate, Thiosemi carbazone, O-Phenylene diamine.

ANTIBACTERIAL ACTIVITY

Antibacterial activity was measured by Cup plate method.[17] Nutrient agar medium was prepared and sterilized by autoclaving at 15Lbs/Sq.inch for 15 minutes. It was allowed to cool below 46^{0}C and inoculated with test organism. The bacterial cultures selected was, one gram negative cultures viz. E.coli, and two gram positive cultures viz. S.aureus, B.pimilis. This preparation was then poured in sterile petri plate under aseptic condition and allowed to solidify. When media was solidified, four cups were made using sterile cork borer. Two drops of each of the test solutions as well as standard solutions and blank(DMSO) were placed in each cups seperately under aseptic condition, the petri plates were kept in the

refrigerator for 2hrs to allow the uniform diffusion of drug into the agar medium. All the petri plates were then incubated at 37^0C for 24 hours and zones of inhibition of bacterial growth around the agar cup. Results were recorded by measuring the zone of inhibition in millimeter (mm) using zone reader.

RESULTS AND DISCUSSION

The compounds synthesized were identified and characterised by following methods such as: 1) Melting point determination 2) Thin layer chromatography 3) Infra red spectroscopy 4) Nuclear magnetic resonance spectoscopy 5) Mass spectroscopy.

Melting point Determination: The determination of melting point is the most important and easy way of differentiating the physical constant of one compound from other. The melting point of organic compound was determined by Theil's capillary tube(Capiilary tube method). The melting point data for all the synthesised complexes were reported in Table 1.

Table 1: Melting point determination data of the synthesised complexes.

S.no	Proposed Molecular Formula	Calculated Molecular Weight (gm/mol)	Melting point (^{0}C)	% Yield
1.	$C_{13}H_{17}N_2O_3$	284.739	121-123	65
2.	$C_{14}H_{16}N_2O_3S$	292.353	133-135	61
3.	$C_{16}H_{18}N_2O_3$	286.326	124-126	56
4.	$C_{10}H_9N_3OS$	219.26	129-131	63
5.	$C_{18}H_{16}N_2O$	276.332	155-157	60

Thin layer Chromatography (TLC): TLC is an important method for synthetic chemistry to the formation of the compound based on the R_f values since different compound will have different R_f values. It also helps in confirming the progress of the reaction. The solvent used was Methanol:Ethyl acetate. TLC data for the synthesised complexes were reported in Table2.

Table 2: TLC data for the synthesized complexes.

S.no	Caluclated Molecular Formula	R_f
1.	$C_{13}H_{17}N_2O_3$	0.67
2.	$C_{14}H_{16}N_2O_3S$	0.59
3.	$C_{16}H_{18}N_2O_3$	0.43
4.	$C_{10}H_9N_3OS$	0.55
5.	$C_{18}H_{16}N_2O$	0.61

Infra red Spectroscopy(IR): IR is one of the most important tools for determining the various functional groups and the possible chemical structure. The important advantage of IR over the other technique is that it gives fingerprints (1300-650cm^{-1}) information about the structure (functional group, bonding with each other) of molecules easily. No two compounds have identical fingerprint region. Thus IR spectra of each and every bond will be formed. The solvent used was chloroform and ethanol. IR data for the synthesised complexes were reported in table 3.

Table 3: IR Data for the synthesised complexes.

S.no	Caluclated Molecular Formula	Functional groups	IR Ranges (Cm^{-1})	Caluclated IR Ranges
1.	$C_{13}H_{17}N_2O_3$	N-H CH-CH_2 CH-CH_3 C=O C=C C-N C-O-C C-H	3400-3500 2850-2960 2850-2960 1705-1725 1450-1600 1000-1400 1085-1150 700-850	3390.24 2974.66 2927.41 1714.41 1485.69 1233.25 1073.19 754.03
2.	$C_{14}H_{16}N_2O_3S$	N-H CH-CH_2 C=O C=C C-N C-O-C C-H	3400-3500 2850-2960 1705-1725 1450-1600 1000-1400 1085-1150 700-850	3245.61 2927.41 1708.62 1485.88 1273.75 1039.44 754.99
3.	$C_{16}H_{18}N_2O_3$	N-H CH-CH_3 C=O C=C C-N C-O-C C-H	3400-3500 2850-2960 1705-1725 1450-1600 1000-1400 1085-1150 700-850	3232.11 2927.41 1711.51 1485.88 1234.22 1034.62 754.99
4.	$C_{10}H_9N_3OS$	N-H CH-CH_3 C=N C=C N=N C=S C-O-C C-H	3400-3500 2850-2960 1630-1690 1450-1600 1575-1630 1050-1200 1085-1150 700-850	3278.22 2962.86 1619.86 1531.92 1394.23 1159.96 1000.55 847.73
5.	$C_{18}H_{16}N_2O$	C-H C-H-CH_3 C=N C=C C-N C-O-C C-H	3400-3500 2850-2960 1630-1690 1450-1600 1000-1400 1085-1150 700-850	3204.63 2973.81 1693.21 1530.54 1286.04 1080.27 754.95

Nuclear Magnetic Resonance Spectroscopy: The interaction between matter and electromagnetic forces can be observed by subjecting a substance simultaneously to 2 magnetic forces, one stationary and other varying at some radio frequency. The energy of absorption can be related to a magnetic dipolar nature of the spinning nuclei. This technique is known as Nuclear Magnetic Resonance. This technique is useful in assuming the structure of the molecule. The solvent used was Dueterated chloroform and ethanol.

Mass Spectroscopy: It is used for elucidating the chemical structures of molecules. The components of the sample are ionised by one of a variety of methods which results in the formation of charged particles (ions). Then the positive ions are then accelerated by an electric field and compute the mass-to-charge ratio (m/z) of the particles based on the details of motion of the ions as they transit through electromagnetic fields, and finally detection of the ions, which were sorted according to m/z.

Antibacterial activity: The synthesized compounds were tested for antibacterial activity by diffused assay method (bore method). The zone of inhibition observed indicated that the compounds were effective against both gram positive cultures (S.aureus, B.pimilis) & gram negative cultures (E.coli) at 250ug/ml & 500ug/ml. Hence can be potential candidate to be antibacterial agents against the bacterial pathogens studied in present investigation. Results obtained from antibacterial study are represented in Table 4, zone of inhibition and bar graphs are represented in fig no:4 and 4a,b & c.

Table 4: Antibacterial activity Recorded for all the synthesized complexes.

S.no	Complexes	E.coli		B.pimilis		S.aureus	
		250ug/ml	500ug/ml	250ug/ml	500ug/ml	250ug/ml	500ug/ml
1.	$C_{13}H_{17}N_2O_3$	5	8	6	10	11	14
2.	$C_{14}H_{16}N_2O_3S$	7	11	-	-	14	18
3.	$C_{16}H_{18}N_2O_3$	12	15	4	11	13	16
4.	$C_{10}H_9N_3OS$	-	-	11	15	9	14
5.	$C_{18}H_{16}N_2O$	9	13	10	15	10	15

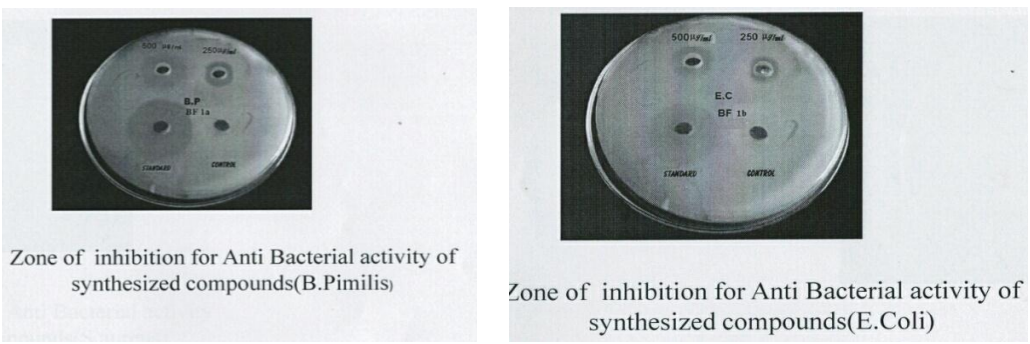


Fig- 4: Zone of inhibition for antibacterial activities

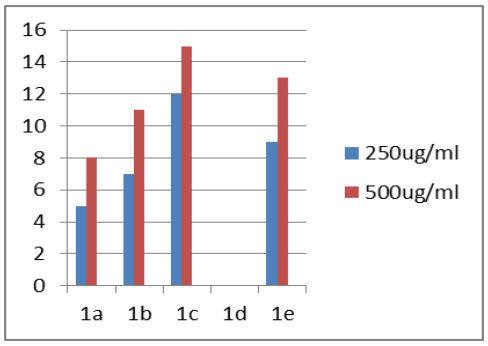


Fig 4a

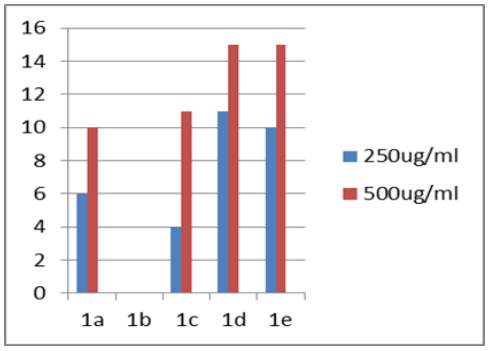


Fig 4b

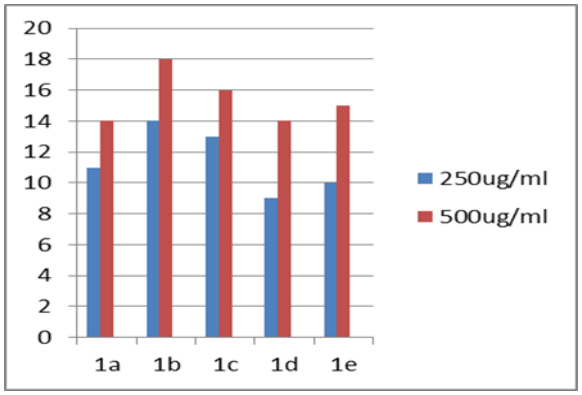


Fig 4c

Fig 4 a,b and c -Zone of inhibition for Antibacterial activity of synthesized compounds on E.coli, B.pimilis and S.aureus respectively. On x-axis Compound code & on y-axis Zone of Inhibition.

CONCLUSION

The synthesized complexes are characterised using melting point determination, TLC, IR, NMR, Antibacterial activity. Based on the results obtained that has been proposed for all the synthesized complexes.

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