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SYNTHESIS AND BIOLOGICAL CHARACTERISATION OF HYDRAZIDE DERIVATIVES OF 2-ACETYLBENZOFURAN

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ABSTRACT

2-Acetylbenzofuran was synthesized by refluxing salicyladehyde and dry chloroacetone in acetone in presence of anhydrous potassium carbonate. The product formed (characterized by TLC, NMR and mass spectroscopy) was treated with hydrazines and hydrazones derivatives in methanol in presence of catalytic amount of sodium acetate (in case of hydrochloride) or acetic acid forming Schiff base which were characterized by Mass, NMR and DSC analysis and were screened for their biological studies. These compounds does not shows any activity against Escherichia coli 113D and Staphylococcus aureus 6538.

Key words: *2-Acetylbenzofuran, Schiff base, salicyladehyde, hydrazones, hydrazines.*

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INTRODUCTION

2-Acetylbenzofuran[1-3] is also known as 2-benzofurylmethyl ketone (common name) was also named as 1-(benzofuryl-2-yl)ethanone by using IUPAC system. Due to wide spectrum of activities shown by benzofuran moiety, various substituted benzofurans with various substituents at different positions have been synthesized. It has been employed successfully as starting material for the production of biologically active compounds[4]. Treatment of 2-acetylbenzofuran with 2-aminoethanol hydrochloride gave the corresponding oxime product[5]. 2-Acetylbenzofuran on treatment with phenyl hydrazine[6], ethylhydrazine carboxylate[7] and thisemicarbazide[8] in ethanol containing acetic acid under reflux conditions gave the corresponding condensation product in good yield to excellent yields. 2-Acetylbenzofuran on Mannich reaction with various amines followed by reduction with NaBH4 gives corresponding secondary amines[9]. Two moles of 2-acetylbenzofuran reacts with one mole of guanidine forming 4,6-di(benzofuran-2-yl)-6-methyl-1,6-dihydropyrimidine-2-amine[10]. Schiff bases of 2-acetylbenzofuran/ benzofuran carbaldehyde with various aromatic amines are formed which on treatment with chloroacetyl chloride in dioxane forming azetidinones[6]. It forming oxime by the

reaction with hydroxylamine hydrochloride in presence of sodium acetate[11].

Heterocyclic compounds plays important role in biological system. Many heterocyclic compounds of natural origin with useful medicinal properties have served as lead compounds in designing synthetic drugs. Heterocyclic bearing with benzofuran moieties constitutes the structure of a number of biological and pharmacological active interesting compounds. Benzofuran compounds has immense important in pharmaceutical, pharmacological and other various fields such as agriculture, photography, textile and paper industries[12], etc. Most of the benzofuran derivatives possess antimicrobial, sedative and hypnotic, antitumor[30-31], anti-inflammatory, fungicidal and anticonvulsant activities[13-16]. Benzofuran ring system incorporated with different heterocyclic moieties has wide spectrum of anticancer against different types of carcinoma[18-23]. The ability of many compounds containing pyridine moiety (as substituent) exhibits antitumor activity[24-28]. A potent inhibitor of ClC-K chloride channels 3-phenyl-1-benzofuran-2-carboxylic acids were synthesized from different 2-hydroxybenzophenones & ethyl bromomalonates[29].

The hydrazone derivatives of 2-acetylbenzofuran is formed by the treatment with hydrazine in presence of hydrochloric acid catalyst which is treated further with various aldehydes[17]. In the present work, 2-acetylbenzofuran was synthesized from salicyladehyde and chloroacetone which is further treated with various hydrazine and hydrazones forming new hydrazine derivatives which are not showing any biological activities against Escherichia coli 113D and Staphylococcus aureus 6538.

EXPERIMENTAL WORK:

All melting points of final products are determined by DSC analysis method and are uncorrected. The IR spectra were recorded by using KBr discs on a Lambda spectrophotometer. The PMR spectra were recorded in $CDCl_3$ on Varian Mercury 300 spectrometers using TMS as an internal standard (chemical shift in δ ppm). MS were run on a Corona mass spectrophotometer. The reactions were monitored by Thin-layer chromatography on silica gel-protected aluminum sheets (type 60 F254, Merck), and the spots were detected by exposure to a UV lamp at 230-600 nm range for few seconds. All the chemicals and reagents required are purchased from Sigma-Aldrich and used without purification.

Salicylaldehyde was treated with chloroacetone in presence of anhydrous potassium carbonate in anhydrous acetone. The crude product was purified by recrystalization in ethanol. The resulting 2-acetylbenzofuran was treated with various hydrazines forming final hydrazine derivatives.

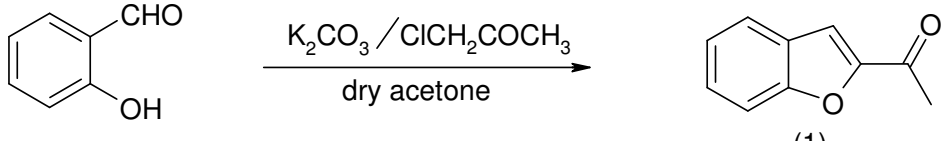
a. Preparation of 2-acetyl benzofuran (1):

Salicylaldehyde (0.1 mole) was taken in 50 ml of absolute ethanol. To this, KOH (0.1 mole) crystals were added and the reaction mixture was stirred for 5 minutes in ice bath. To this reaction mixture chloroacetone (0.1 mole) was added drop by drop from dropping funnel about 10 minutes. Further whole reaction mixture was allowed to stir for another 20 minutes with catalytic amount of potassium iodide (KI). The resultant solution was poured into the crushed ice, the solid obtained was filtered and recrystallised from ethanol to produce 2-acetyl benzofuran(32) and was used directly for the next step. 90-95% yield, Melting Point (M.P.) 74-76^{0}C, R_f Value: 0.57

IR: 3023, 1660 and 1588 cm^{-1}.

PMR (in ppm): 2.30 (s, 3H, CH_3); 6.83-7.25 (m, 5H).

Mass Spectra (molecular ion peak): 160.

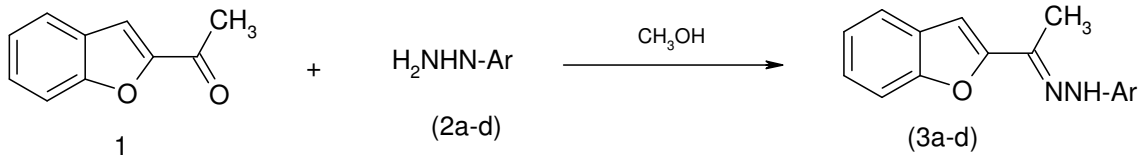


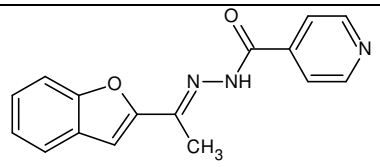
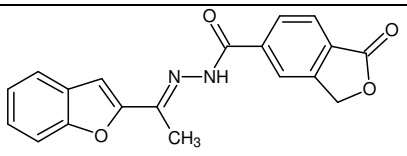
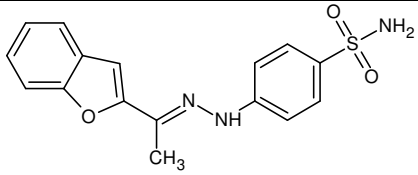
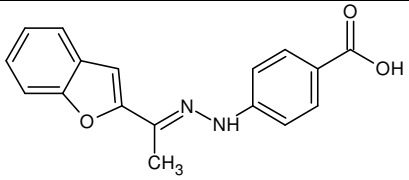
(1)

b. Synthesis of Hydrazine derivatives of 2-acetyl benzofuran (3a-d):

A solution of 2-acetyl benzofuran (1) (0.160 g, 1 mmol), hydrazine hydrochloride and sodium acetate in methanol (15 ml) were refluxed for 4-6 hrs. Saturated the reaction mixture by distillating excess solvent and cooled it in ice bath, the resulting solid is filtered and wash with cold ethanol. The compound was recrystallized from ethanol. Record the yield, m.p. and characterized by NMR, Mass and DSC study.

A solution of 2-acetyl benzofuran (0.160 g, 1 mmol), hydrazone and catalytic amount of acetic acid in methanol (10 ml) were refluxed for 4-6 hrs. Saturated the reaction mixture by distillating excess solvent and cooled it in ice bath, the resulting solid is filtered and wash with cold ethanol. The compound was recrystallized from ethanol. Record the yield, m.p. and characterized by NMR, Mass and DSC study.



3a	 *N*-[(1*E*)-1-(1-benzofuran-2-yl)ethylidene] pyridine-4-carbohydrazide	**Mol. Formula: $C_{16}H_{13}O_2N_3$** 2.422 (s, 3H); 7.489-7.294 (m, 3H); 7.807-7.699 (m, 4H); 8.768 (m, 2H); 11.113 (bs, NH/OH). Base ion peak = 280.12, 281.09, 282.09 m.p. (^{0}C) = 237.77	83 %
3b	 *N*-[(1*E*)-1-(1-benzofuran-2-yl)ethylidene]-1-oxo -1,3-dihydro-2-benzofuran-5-carbohydrazide	**Mol. Formula: $C_{19}H_{14}O_4N_2$** 2.362 (s, 3H); 4.663 (s, 2H); 7.290 (s, 1H); 7.75-7.31 (m, 5H); 7.84-7.81 (d, 1H); 8.13 (s, 1H); 9.65 (bs, NH); 10.469 (bs, OH). Base ion peak = 334, 317. m.p. (^{0}C) = 217.19	72 %
3c	 4-{(2*E*)-2-[1-(1-benzofuran-2-yl)ethylidene] hydrazinyl}benzenesulfonamide	**Mol. Formula: $C_{16}H_{15}O_3N_3S$** 2.326 (s, 3H); 7.123 (bs, 2H, NH_2); 7.379 – 7.255 (m, 5H); 7.724 – 7. 608 (m, 4H); 9.976 (bs, NH). Base ion peak = 330.07, 331.10, 332.07 m.p. (^{0}C) = 232.08	89 %
3d	 4-{(2*E*)-2-[1-(1-benzofuran-2-yl)ethylidene] hydrazinyl}benzoic acid	**Mol. Formula: $C_{16}H_{15}O_3N_3S$** 2.326 (s, 3H); 7.333 – 7.249 (m, 5H); 7.657 – 7.610 (t, 2H), 7.867 – 7.839 (t, 2H); 9.965 (bs, NH); 12.355 (bs, OH). Base ion peak =295.01, 296.06. m.p. (^{0}C) = 284.04	86 %

BIOLOGICAL ACTIVITY:

Biological activities were studied by subjecting the compounds to pharmacological screening by standard procedures (IP, 1996; Maroliwala et al., 2010). All the compounds synthesized in the present investigation were tested for their antimicrobial activity. The antibacterial activities were tested on nutrient medium against

Microorganisms: Strains of Escherichia coli 113D and Staphylococcus aureus 6538. Media employed: Muller-Hinton's agar Concentration used: 1000 ppm, 500 ppm, 250 ppm and 100 ppm. No zone of inhibition was observed for all the four compounds for both the microorganisms.

RESULT AND DISCUSSION:

Salicylaldehyde reacts with chloroacetone forming 2-acetylbenzofuran in acetone in presence of anhydrous potassium carbonate. The formation of product can be confirmed by NMR spectra, The acetyl methyl group shows signal at 2.30 singlet for three proton and not any broad signal for –OH and for aldehyde protons. All the five aromatic protons shows maltiplates in the region 6.83-7.25. The formation of new hydrazines (Schiff bases) from 2-acetylbenzofuran and hydrazine/hydrozone derivatives was confirmed by NMR and Mass spectra.

The microorganisms are resistant to the given compounds viz., **3a-d**. It does not show any antimicrobial activity. The compounds are not effective against any microorganism and hence cannot be used as antimicrobial agents

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