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Synthesis and Biological Evaluation of Some Novel Benzofuran Containing Carbamide Derivatives

Panchabhai V.B.[1*], Budhwani S.N.[2], Jagtap S.S.[2], Zambare Y.B.[2], Kalyane N.Y.[2]

[1]Department of Pharmaceutical Chemistry, Channabasweshwar Pharmacy College, Latur-413512.
[2]Department of Pharmaceutical Chemistry, B L D E A'S College of Pharmacy, Bijapur-586103.

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***Corresponding author:**

E-mail: onlyp_torrent@yahoo.com
Phone: +91-9423714528

ABSTRACT

The Synthesized 5-Nitrobenzofuran-2-carboxyhydrazide (4) on treatment with acetic acid, 1, 4-diaxone and sodium nitrite resulted in 5-nitro benzofuran-2-carboxyazide (5). The corresponding compound (5) on treatment with substituted aromatic amines undergoes Curtius rearrangement to give substituted-5-nitro benzofuran-2yl-carbamides.The characterization of synthesized compounds was identified on the basis of IR, NMR, MASS and elemental analysis. The compounds have been evaluated for anti-microbial and anti-inflammatory activity.

INTRODUCTION

The need of new anti-microbial agents is justified because more microorganisms are being resistance to the present drugs available in the market. Word wide researchers are trying to synthesize new drugs with better pharmacokinetic and pharmacodynamic properties with less adverse effects. The literature survey suggests that the benzofuran have proved to be good bioactive molecules. Benzofuran are the heterocyclic compounds of immense importance in pharmaceutical fields and various other fields as agriculture, photography etc. Benzofuran derivatives have been reported to posses wide variety of biological activities such as antibacterial, antifungal, anti-inflammatory, anti-depressant, analgesic, insecticidal, CNS stimulants effects etc[1-6]. Therefore in the view of all this observations we thought it is interest to undertake the synthesis & biologically evaluation of some new benzofuran derivatives. in present course of research work, we planned to synthesize some substituted novel benzofuran derivatives & their biological activities. different alcohols, phenols and appropriate amines were reacted with substituted benzofuran moiety to give different derivatives. The structures of the final compounds were confirmed by IR and 1H-NMR Spectra. The proposed compounds were screened for their antimicrobial activity and anti-inflammatory activity with the standard drugs in the well-equipped microbiology and pharmacology lab by using standard methods.

MATERIALS AND METHODS

Melting point were determined in capillary tubes and are uncorrected. IR spectra in KBr were recorded on SHIMADZU FT-IR 8400S and 300 MHz PMR spectra of synthesized compound were recorded on FT-NMR BRUCKER spectrometer at frequency in DMSO using TMS as internal standard.

Preparation of 5-Nitrosalicylaldehyde (2): salicylaldehyde (1) (25.0 gm, 0.2 mol) in 100 ml of glacial acetic acid. Added gradually 48.3 gm of calcium nitrate tetra hydrate (48.3gm, 0.2 mol) allowed to dissolve. Heated gradually to reflux on hot plate with continuous stirring. Heated under reflux for 3 hours. Cooled to room temperature, poured into 500 ml ice cold water contained in 1L beaker with continuous stirring. The solid precipitated was filtered under vacuum and dried in air. The solid dissolved in ethyl acetate and the insoluble were filtered under vacuum. The ethyl acetate filtrate was dried over sodium sulphate and evaporated under reduced pressure to get yellow colored solid. Melting point is 123-124ºC; the yield is 72.3%.

Preparation of Ethyl 5-nitrobenzofuran-2-carboxylate (3) [7]: 5-nitrosalicylaldehyde (2) (3.0 gm, 0.017 mol) was dissolved in 40ml of acetone, added potassium carbonate (6 gm) and diethyl bromomalonate (4.47 gm,0.017 mol) in a 100 ml round bottom flask. Heated to reflux on water bath and maintained for 12 hours. The reaction was monitored by TLC. When complete, cooled to room temperature, reaction mixture is filtered and potassium salts were washed with dry ether. The dry salt was suspended in water and cooled thoroughly in ice cold water. The suspension was carefully acidified with dilute hydrochloric acid and the Ethyl 5-nitrobenzofuran-2- carboxylate solids was separated and collected by filtration. The product was recrystallized from methanol to get pure compound 3 obtained as yellow crystal. Melting point is 145-147ºC; the yield is 52%.

Synthesis of 5-Nitro benzofuran-2-carbohydrazide (4)[8-10]: Ethyl 5-nitrobenzofuran-2-carboxylate (3) (1.0gm, 0.004 mole) was dissolved in 5-ml methanol, added Hydrazine hydrate (0.25gm, 0.004 mol). Heated to reflux and maintained for 2

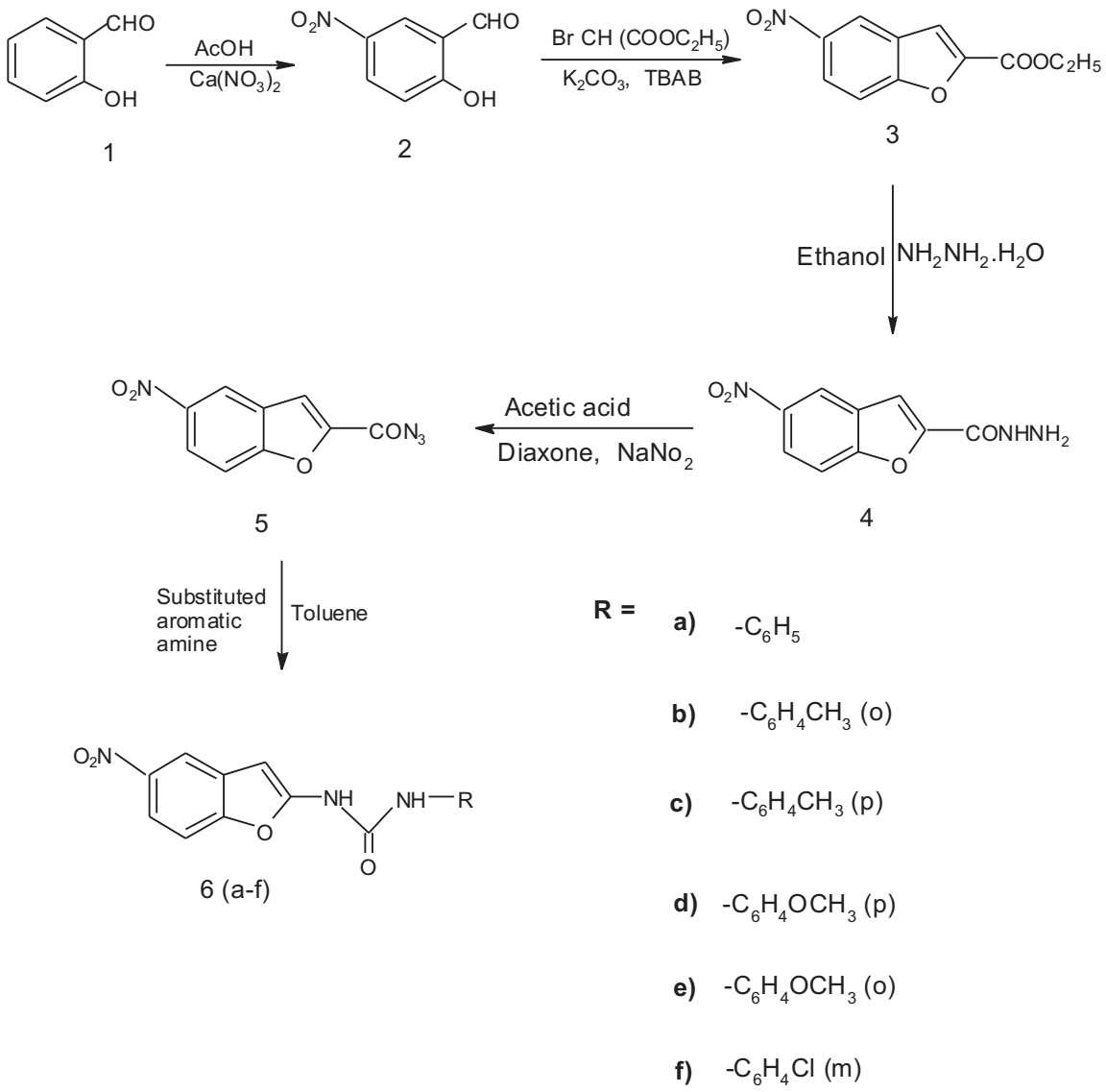

Table No.1: Physicochemical parameters of Benzofuran derivatives 6(a-f)

Compound	Molecular formula	Molecular weight	Melting point (^{0})	% Yield	CHN analysis C %	H %	N %
6a	$C_{15}H_{11}N_30_4$	298	230-233	63.4	60.57	3.74	14.16
6b	$C_{16}H_{13}N_30_4$	312	240-242	71.1	61.72	4.25	13.54
6c	$C_{16}H_{13}N_30_4$	312	283-285	74.3	61.76	4.18	13.49
6d	$C_{16}H_{13}N_30_5$	327	250-251	68.4	58.73	3.98	12.86
6e	$C_{16}H_{13}N_30_5$	327	220-223	69.4	58.69	4.03	12.83
6f	$C_{15}H_{10}ClN_30_4$	331.5	222-224	78.3	54.29	3.06	10.71

hours. The solid product was insoluble in methanol starts precipitating. The reaction was monitored by TLC. Evaporate the solvent to get a solid product, added water to remove excess hydrazine hydrate and extracted with ethyl acetate. Ethyl acetate layer washed with water and dried over sodium sulphate and evaporated to get solid product. Melting point is 252-254^{0}C; the yield is 60.63%.

Synthesis of 5-Nitrobenzofuran-2-carboxyazide (5) [8-10]:5-Nitrobenzofuran-2-carboxyhydrazide (4) (5.0 gm, 0.02 mole) was dissolved in a mixture of 30 ml of acetic acid and 30 ml of 1,4-dioxane and cool to 0^{0}C using ice salt bath. An ice cold solution of sodium nitrite (1.6 gm, 0.02 mole) in water (10 ml) was introduced in small portions with vigorous stirring while temperature of the mixture was maintained below 2ºC. After addition was completed, the reaction mixture was allowed to stay at room temperature for 30 min and then cream colour solid that precipitate was collected, washed with cold water. Solid was dried in desiccators and used immediately in next reaction. Melting point is 95-97ºC; the yield is 57.25%.

Table No.2: Spectral data of Benzofuran derivatives 6(a-f)

Compound	IR Bands (cm^{-1})	Types of Vibrations	δ ppm	Proton nature
6a	3360,1715, 1430, 2910	(-NH-),(>C=O), (-C=C-), Aromatic ring	—	——
6b	3290,1650, 1470, 3080	(-NH-),(>C=O), (-C=N-), Aromatic ring	9.05, 8.90, 6.6-8.4, 2.3	1H, NH 1H, NH 7H, Ar-H 3H, CH_3
6c	3280,1670, 1450, 3060	(-NH-),(>C=O), (-C=N-), Aromatic ring	9.1, 9.0, 6.9-8.7, 2.1	1H, NH 1H, NH 7H, Ar-H 3H, CH_3
6d	3410,1640, 1470, 3080	(-NH-),(>C=O), Ar-(C=C), Aromatic ring	—	—
6e	3420,1620, 1530, 3130	(-NH-),(>C=O), Ar-(C=C), Aromatic ring	—	—
6f	3380,1720, 1430, 3030	(-NH-),(>C=O), Ar-(C=C), Aromatic ring	—	—

General procedure for the preparation of aryl-5-nitrobenzofuran -2- carbamides. 6(a-f) [8-10]:A mixture of 5-Nitrobenzofuran-2-carboxyazide (5) (0.3 gm, 0.0013 mole) and appropriate amine (0.0013 mole) in anhydrous toluene (15 ml) was heated under gentle reflux (120º) in an oil bath for 4 hour. Reaction was monitored by TLC. The crystalline product that separated out from the reaction mixture was collected and washed with toluene and petroleum ether. The analytical sample was obtained by crystallization from ethanol to get pure compound. Physicochemical parameter and analytical data of the compound thus prepared are listed in Table-1 and Table-2.

Antimicrobial Activity: All the compounds were tested in-vitro for their antimicrobial activity against two microorganisms viz. Escherichia coli (NCTC 10418), and Staphylococcus aureus (NCTC 6571) by cup-plate method [11] using DMSO as the solvent control and ampicillin as a reference standard. The zone of inhibition after 24 h of incubation at 370 was compared with that of standard at a concentration of 500 ug/ml. only 6-d, 6-e and 6-f derivatives showed appreciable zone of inhibition against gram positive bacteria only as compared to that of standard drug Ampicillin. The results are reported in Table-3.

Anti-inflammatory Activity: The anti-inflammatory activity of the synthesized compounds was evaluated by carrageenan induced rat paw edema method. Thereby measuring the carrageenan induced inflammation by plethysmometer using DMSO as the solvent control and Ibuprofen 20mg/kg as a reference standard. only 6-d & 6-f showed significant anti-inflammatory activity when they possess P value <0.01, when compared with control group. The results are reported in Table-4.

Table No.3: Antimicrobial activity data of synthesized Benzofuran derivatives 6(a-f)

Compound (500 µg/ml)	S.Aureus	E.coli
6 a	08	11
6 b	09	10
6 c	10	12
6 d	19	09
6 e	17	10
6 f	14	20
Ampicillin (500 µg/ml)	24	32

Zone of inhibition of synthesized Benzofuran derivatives

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Table No.4: Antimicrobial activity statistical data of synthesized benzofuran derivative 6(a-f) by ANOVA method

Group	Test Material (dose)	Mean increase in paw volume ± Standard deviation and % inhibition		
		1 hr.	2 hr.	3 hr.
1.	Control	1.61±0.013	1.83 ± 0.02	1.98 ± 0.03
2.	Standard (Ibuprofen 20mg/kg)	0.74 ± 0.070** (54.03%)	0.70± 0.008** (61.74%)	0.76 ± 0.02** (61.6%)
3.	Derivative **6-a** (20mg/kg)	1.17 ± 0.04* (27.32 %)	1.35 ± 0.03* (26.22%)	1.56± 0.016* (21.21%)
4.	Derivative **6-b** (20mg/kg)	1.05± 0.042* (34.78%)	1.24 ± 0.03* (32.24%)	1.38 ± 0.09* (30.30 %)
5.	Derivative **6-c** (20mg/kg)	1.16 ± 0.031* (27.95%)	1.27± 0.03* (30.60%)	1.48 ± 0.009* (25.25%)
6.	Derivative **6-d** (20mg/kg	0.77 ± 0.074** (52.17%)	0.73 ± .009** (60.10%)	0.71±0.05** (64.14%)
7.	Derivative **6-e** (20mg/kg)	1.24 ± 0.04* (22.98%)	1.33 ± 0.037* (27.32%)	1.42 ± 0.014* (28.28 %)
8.	Derivative **6-f** (20mg/kg)	0.75 ±0.03** (53.41%)	0.74 ± 0.009** (59.56%)	0.72 ± 0.01** (63.63%)

N=6 (*P<0.05, ** P<0.01, ***P<0.001)

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