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Synthesis, Characterization, Antibacterial and Antifungal Screening of Various 5-Bromo-7-Methoxy-Benzofuran Schiff Bases

Manjunatha Harihara Mathada, H. M.Naveenakumari, and K. M.Basavaraja*

Department of Chemistry/Ind.Chemistry, Vijayanagara Sri Krishnadevaraya University, Ballari,Karnataka-583105, **INDIA**

Email: kmbasavaraja@gmail.com

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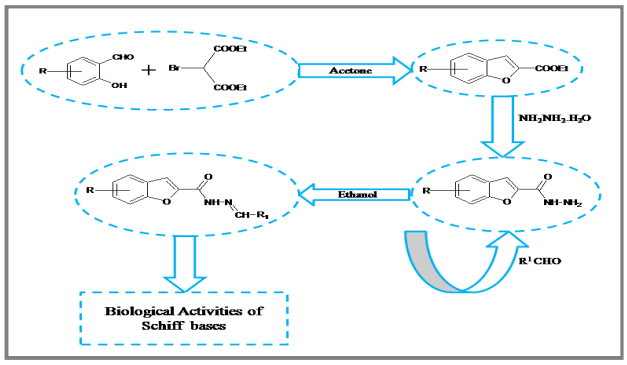
ABSTRACT

Encouraged by the pharmaceutical properties of benzofuran compounds and the Schiff's bases, in continuation of our synthetic work on pharmacologically active benzofurans, we now report the synthesis of benzofuran linked Schiff's bases. The starting compound 5-bromo-7-methoxysalicylaldehyde was synthesized by bromination of o-vanillin. The key intermediates 5-bromo-7-methoxy benzofuran-2-ethyl carboxylate ***(1)*** *was obtained by condensing with diethylbromomelonate in the presence of dry acetone and anhydrous potassium carbonate. The ester* ***(1)*** *was converted into hydrazide* ***(2)*** *by treating with hydrazine hydrate, which was then converted into Schiff bases* ***3(a-f)*** *by condensing with various aldehydes. All the compounds synthesized during the present investigation were in agreement with the assigned structure which was supported by spectral and analytical data.*

Graphical Abstract



Keywords: Benzofuran, Schiff bases, Antibacterial, Antifungal.

INTRODUCTION

Recent studies indicated that, modern medicine has taken commendable strides due to advance technology, also synthesis of fused heterocyclic compounds and their pharmacological activities gave

progressive and effective results in the last few decades [**1**]. Today a number of biologically active Benzofuran compounds, with potential therapeutic effect, are being developed. These molecules obtained either from semi-synthetic or by synthetic routes. In synthetic routes, relatively simple benzofuran molecules are used to build up structurally complex pharmacologically active compounds. Today chemists route is perhaps the widely used method to obtain pharmacologically are equipped with a large number of innovative synthetic techniques for designing and synthesizing biologically active benzofurans molecules synthetic active benzofuran compounds.

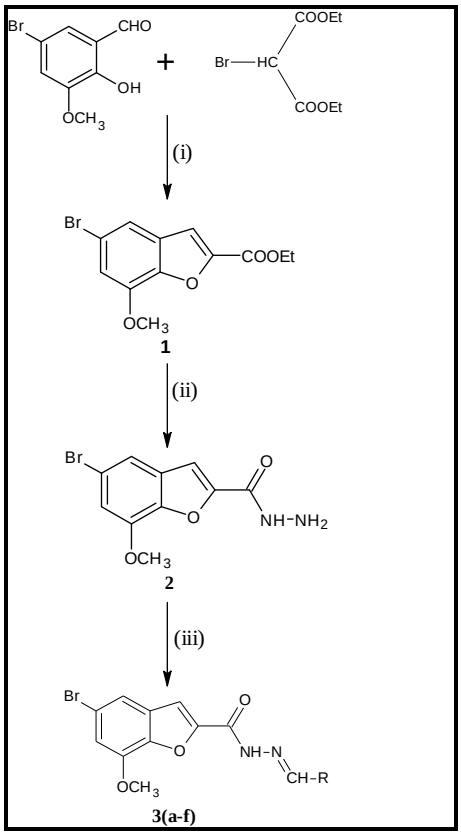
Various 2-azetidione derivatives from chalcones of 4-hydroxy coumarin were synthesized by Pawar *et al* [**2**]. All the compounds were screened in vitro for their antimicrobial activity against a variety of bacterial strains such as *S.aureus*, Salmonella paratyphi, and *E. Coli*. The antimicrobial data of the compounds revealed that compounds having the methoxy group i.e. 5-(4-methoxyphenyl)-N-[(3-chloro-2-oxo-4-phenylazetidin-1ylamino)acetyl]-3-[2H-4-hydro- xy-2oxo-benzopyron-3-yl]-4,5-dihydropyrazoles showed most significance activity. Desai et al., [**3**] have synthesized some azetidin-2-ones derivatives by both microwave and conventional condensation method. The synthesized derivatives were screened for their in vitro antibacterial activity and antifungal activity. A series of 3-chloro-4-(3-methoxy-4-acetyloxyphenyl)-1-[3-oxo-3-(phenylamino) propanamido] azetidin-2-ones were developed by Halve *et al* [**4**]. All the azetidin-2-ones were screened for their growth inhibitory activity against pathogenic microorganisms. A series of various 2-{2-[3-cholro-4 (aryl)-2-oxoazetidin-1-ylaminio]-acetylamino} benzothiazole-6-carboxylic acid have been synthesized and screened for their antibacterial activity against four microorganisms *S. Aureus*, *B. Subtilis*, *P. aeruginosa* and *E. Coli*. They were found good moderate antibacterial activity [**5**]. Bhat *et al*. Have the tested compounds, the nitro-substituted at the para position of the phenyl ring on C-4 of 2-azetidinone found to be most potent [**6**]. Kagthara *et al.,* have synthesized some 2-azetidionone derivatives which showed a potential antitubercular activity [**7**]. The synthesized compounds were tested in vitro for their antitubercular activity against Mycobacterium tuberculosis H37RV. Antitubercular activity of some 2-(6-methoxynaphthyl) propionamido azetidine-2-ones showed significant activity which is synthesized by Udipi *et al* [**8**]. Trivedi *et al* [**9**] have prepared several 1,3,7,9-tetrabromo-10[a-(4-aryl-3-chloro-2-oxo-1-azetidinyl amino)acetyl-10H-phenothiazine] derivatives. The compound with 3, 4-dimethoxyphenyl substitution showed highest percent of inhibition and also various 2-azetidinone bearing (b) thiophene nucleus act as potential antitubercular agent [**10**]. In the recent years the results were shown that 1,2,4-triazoles derivatives exhibit as effective drugs in the treatment of various diseases, these also shows considerable anti microbial and antiviral activities[**11, 12**]

MATERIALS AND METHODS

All the chemicals were used as of analytical grade. Melting points was determined in open capillary tubes and were incorrect. IR spectra were recorded on Perkin Elmer instrument. H^1NMR were recorded on Brucker 400MHz Spectrometer in DMSO and $CDCl_3$. Chemical shift were recorded in parts per million.

5-Bromo-7-methoxy salicylaldehyde: O-Vanillin (0.4 mol) to 100 mL of acetic acid was taken in an RB flask. To this bromine (0.4 mol) in 20 mL acetic acid was added drop wise with stirring for 2 h. The solid separated was filtered. The filtrate was again poured into water to get more 5-bromo-7-methoxy-salicylaldehyde the compound was recrystallized from ethanol (Scheme 1).

5-Bromo-7-methoxy-benzofuran-2-carboxylic acid ethyl ester (1): A solution of 5-Bromo-7-methoxy salicylaldehyde (0.01 mol) and diethyl bromomalonate (0.013 mol) in acetone (40 mL) was treated with anhydrous potassium carbonate (10 g). The reaction mixture was refluxed for 10 h on the steam bath. The solvent was distilled off under reduced pressure and the residual salts were dissolved in about 200 mL ice water and carefully acidified with dil.HCl. The obtained product was recrystallized from ethanol.



Scheme 1. Synthesis of Schiff's bases.

Experimental Condition: (i) $CH_3CH_2COCH_3$/ Anhydrous K_2CO_3,Reflux for 10 hours; (ii) $NH_2NH_2.H_2O/C_2H_5OH$, Reflux for 4 hours; (iii) R-CHO/C_2H_5OHReflux for 5 hours; **R: a**=C_6H_5,**b**= $C_6H_5NO_2$(p),**c**= C_6H_5Cl (O),**d**= C_6H_5Cl (m),**e**= C_6H_5OH (O),**f**= C_6H_5OH (P).

5-Bromo-7-methoxy-benzofuran-2-carboxylic acid hydrazide (2): To a solution of 5-Bromo-7-methoxy-benzofuran-2-carboxylic acid ethyl ester **(1) (**0.01 mol**)** in ethanol (30 mL), hydrazine hydrate (5 mL) was added and the mixture was heated under reflux for 4h on a water bath. Excess of ethanol was removed under reduced pressure and then diluted with water. The separated carbohydrazide **(3)** was collected and recrystallized from ethanol.

5-Bromo-7-methoxy-benzofuran-2-carboxylic acid hydrazide (substituted benzylidine) hydrazide (3a-f): 5-Bromo-7-methoxy-benzofuran-2-carboxylic acid hydrazide **(2)** (0.01 mol) and benzaldehyde/ substituted benzaldehyde (0.01 mol) dissolved in ethanol (30 mL) were refluxed for 5h. The excess of solvent was distilled off under reduced pressure. The product obtained was filtered and washed with a little sodium bisulfate solution to remove the unreacted aldehydes and then washed with dil. HCl and water, the product was dried and crystallized from the suitable solvent.

Table 1. Physical data of compounds 1, 2 and 3(a-f)

Sample Code	Yield %	MP ^{0}C	MF
1	89	98	$C_{12}H_{11}BrO_4$
2	88	224	$C_{10}H_9BrN_2O_3$
3a	79	212	$C_{17}H_{13}BrN_2O_3$
3b	80	202	$C_{17}H_{12}BrN_3O_5$
3c	71	183	$C_{17}H_{12}BrClN_2O_3$
3d	73	218	$C_{17}H_{12}BrClN_2O_3$
3e	85	175	$C_{17}H_{13}BrN_2O_4$
3f	82	205	$C_{17}H_{13}BrN_2O_4$

RESULTS AND DISCUSSION

1: IR (KBr) *v* cm^{-1}; 1712(C=O), 2924(OCH_3); ^{1}H-NMR (400 MHz, DMSO-d6): δ 1.34 (t, J = -7.20 Hz, 3H), 3.99 (s, 3H), 4.36 (q, J = 7.20 Hz, 2H), 7.28 (d, J = 1.60 Hz, 1H), 7.57 (d, J = 2.00 Hz, 1H), 7.70 (s, 1H)

2: IR (KBr) *v* cm^{-1}; 3318(NHNH), 1632(C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.97 (d, J = 25.60 Hz, 2H), 7.00 (d, J = 13.20 Hz, 1H), 7.40 (d, J = 7.60 Hz, 1H)

3a: IR (KBr) *v* cm^{-1}:3434(NH), 1587(CN), 1656(C=O); ^{1H}-NMR (400 MHz, CDC_{l3}): δ 3.78 (s, 3H), 7.19 (s, 1H), 7.05 (q, J = 4.00 Hz, 2H), 7.49 (s, 1H), 8.43 (s, 1H)

3b: IR (KBr) *v* cm^{-1} ; 3426(NH,) 1585(CN), 1635(C=O);^{1}H-NMR(400 MHz, $CDCl_3$): δ 3.96 (s, 3H), 7.00 (s, 1H), 7.19 (s, 1H), 7.39 (s, 1H), 7.55 (s, 1H), 7.91 (d, J = 8.00 Hz, 2H), 8.22 (d, J = 8.00 Hz, 2H), 8.42 (s, 1H)

3c: IR (KBr) *v* cm^{-1} ; 3406(NH,) 1585(CN), 1655(C=O);^{1}H-NMR(400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 7.00 (s, 1H), (s, 1H), 7.45 (s, 1H), 7.61 (d, J = 8.00 Hz, 2H), 8.21 (d, J = 4.00 Hz, 2H), 8.80 (s, 1H)

3d: IR (KBr) *v* cm^{-1} ; 3444(NH,) 1585(CN), 1661(C=O);^{1}H-NMR(400 MHz, CDCl3): δ 4.03 (s, 3H), 7.26 (s, 1H), 7.49 (t, J = 8.00 Hz, 3H), 7.65 (d, J = 8.00 Hz, 2H), 7.84 (s, 1H), 7.81 (s, 1H), 7.86 (s, 1H), 8.30 (s, 1H)

3e: IR (KBr) *v* cm^{-1} ; 3428(NH,) 1580(CN), 1664(C=O);^{1}H-NMR(400 MHz, $CDCl_3$): δ 3.95 (s, 3H), 7.19 (s, 1H), 7.08 (q, J = 4.00 Hz, 2H), 7.26 (t, J = -8.00 Hz, 2H), (s, 1H), 7.49 (s, 1H), 8.43 (s, 1H)

3f: IR (KBr) *v* cm^{-1}; 3432(NH,) 1585(CN), 1635(C=O); ^{1H}-NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 6.88 (d, J = 0.00 Hz, 1H), 7.03 (q, J = 4.00 Hz, 2H), 7.48 (s, 1H), 8.42 (s, 1H)

APPLICATION

The cup plate method was used for the screening of antibacterial activity. The results revealed that **3f** and **1** exhibited good antibacterial activity (Table 1). Considerable zone of inhibition was observed for **3d** against *Staphylococcus aureus*, *Staphylococcus albus* and *Klebsiella pneumoniae* when compared to the other compounds. All the compounds were compared with standard drug Aazithromycin. Antifungal activity of synthesized compounds were screened against two fungal organism namely *Candida albiacans* and *Aspergillus niger* by MIC method. The compound **1** and **2** gives excellent results and compound **3c** shows good activity (Table 2).

Table 2. Antibacterial activities of compounds 1, 2 and 3(a-f)

Synthetic Compounds	Diameter of Zone of inhibition (mm)		
	Staphylococcus aureus	*Staphylococcus albus*	*Klebsiella pneumoniae*
DMSO	-	-	-
1	12	08	12
2	14	10	-
3a	-	06	10
3b	12	-	-
3c	-	14	12
3d	14	16	20
3e	10	09	10
3f	16	12	14
Azithromycin (10µg well^{-1})	**20**	**25**	**30**

Table 03. Antifungal activities of compounds 1, 2 and 3(a-f)

Synthetic Compounds	Fungal Strain	
	Candida albiacans	*Aspergillus niger*
DMSO	-	-
1	12	12
2	12	12
3a	6.25	6.25
3b	6.25	6.25
3c	10.50	10.50
3d	6.25	6.25
3e	4.00	4.00
3f	6.00	6.00
fluconazole	12.5	12.5

CONCLUSION

The synthesized benzofuran Schiff's bases were identified by spectral data IR and ^{1}H NMR and these synthesized compounds were performed antifungal and antibacterial activity, some of these compounds shown excellent activities and some gives considerable activities.

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