International Journal of Pharmacy and Biological Sciences-IJPBS™ (2019) 9 (4): 343-349
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved

Synthesis and Evaluation of Benzofuran Derivatives for Antibacterial Activity

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Received: 10 Jul 2019 / Accepted: 12 Aug 2019 / Published online: 1 Oct 2019
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Abstract

Infectious microbial diseases remain pressing problems worldwide, because resistance to a number of antimicrobial agents among variety of clinically significant species of micro-organisms, like Methicillin-Resistant *Staphylococcus aureus* (MRSA) has become an important global health problem. Hence, furan derivatives have been widely used as antimicrobial agents. Prompted by these observations and as part of synthetic effort directed towards the synthesis of antimicrobial agents, various new substituted furans are being synthesized and evaluated. It is one of the most important classes of fused ring heterocyclic compounds. The benzofuran derivatives are naturally occurring and possess many biological applications. Numerous synthesized benzofuran derivatives were found to be biologically active. Now-a-days many synthetic benzofurans are used as good inhibitor, antimicrobial, anti-inflammatory, antibacterial, antiviral, antioxidant, antitumour, antiproliferative and antialzheimer.

Keywords

Antimicrobial, Antiproliferative, Antioxidant, Anti-alzheimer.

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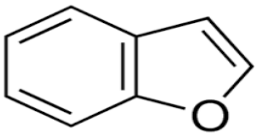
INTRODUCTION

The introduction of antimicrobial agents into general clinical use represents one of the landmark medical advances of modern medicine. In the last half of 20th century, a number of new antimicrobials came into clinical use, presenting with an array of choices when treating many types of infectious diseases. The issue of microbial resistance that has been a concern ever since the beginning of antimicrobial era has become more important in recent times. Clinicians are witnessing increasing rates of *in vitro* resistance among previously susceptible organisms and emergence of intrinsically resistant organisms as pathogens in immunocompromised hosts. The spread of resistance has in turn limited the treatment options for some serious and life threatening diseases. To curtail development and spread of antimicrobial resistance, there is an urgent need to acquire both preservation of currently available antimicrobials through their appropriate use, as well as the discovery and development of new agents. Infectious microbial diseases remain pressing problems worldwide, because resistance to a number of antimicrobial agents among variety of clinically significant species of micro-organisms, like Methicillin-Resistant *Staphylococcus aureus* (MRSA) has become an important global health problem. Hence, furan derivatives have been widely used as

antimicrobial agents. Prompted by these observations and as part of synthetic effort directed towards the synthesis of antimicrobial agents, various new substituted furans are being synthesized and evaluated.

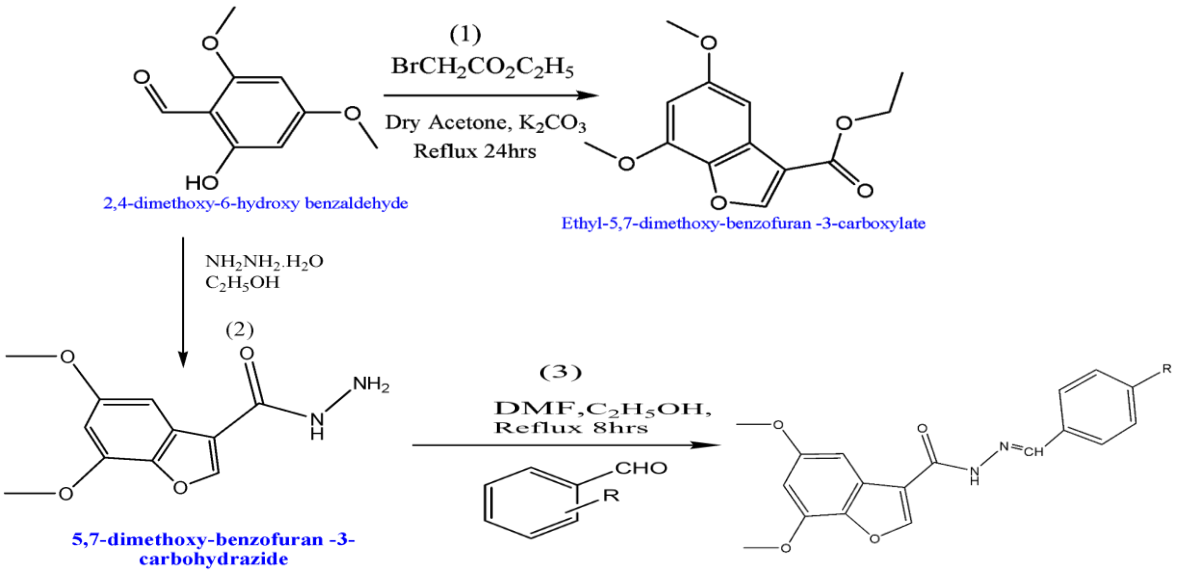


Benzofuran

Benzofuran: It is one of the most important classes of fused ring heterocyclic compounds. The bezofuran derivatives are naturally occurring and possess many biological applications. Angelicin, psoralen and bergapten are the examples of naturally occurring benzofuran derivatives with biological applications. The isolation of benzofuran derivatives from natural sources is laborious and time consuming. So the synthetic chemists are interested in synthesizing the benzofuran derivatives. Numerous synthesized benzofuran derivatives were found to be biologically active. Now-a-days many synthetic benzofurans are used as good inhibitor, antimicrobial, anti-inflammatory, antiviral, antioxidant, antitumour, antiproliferative and antialzheimer.

Antibacterial agents: Antibacterial drugs are derived from bacteria or molds. Technically, "antibiotic" refers only to antimicrobials derived from bacteria or molds but is often used synonymously with "antibacterial drug". Antibiotics have many mechanisms of action, including inhibiting cell wall synthesis, increasing cell membrane permeability and interfering with protein synthesis, nucleic acid metabolism and other metabolic processes (eg, folic acid synthesis). Antibiotics sometimes interact with other drugs, raising or lowering serum levels of other drugs by increasing or decreasing their metabolism or by various other mechanisms. The most clinically important interactions involve drugs with a low therapeutic ratio (ie, toxic levels are close to therapeutic levels). Also, other drugs can increase or decrease levels of antibiotics. Many antibiotics are chemically related and are thus grouped into classes. Although drugs within each class share structural and functional similarities, they often have different pharmacology and spectra of activity.

Scheme:



Procedure:

Step-1:

Synthesis of Ethyl 5,7-dimethoxy benzofuran -3-carboxylate:

A mixture of 2,4-dimethoxy-6-hydroxy benzaldehyde (1g), ethyl bromoacetate(1ml), anhydrous potassium carbonate (1g), dry acetone (50ml) was taken in RB flask and heated under reflux for 24 h. The reaction mixture was filtered and potassium carbonate was washed with acetone. Evaporation of the solvent from the filtrate yielded the product, which was recrystallised from ethanol to get crystalline product.

Step-2:

Synthesis of 5, 7-dimethoxy benzofuran-3-carbohydrazide:

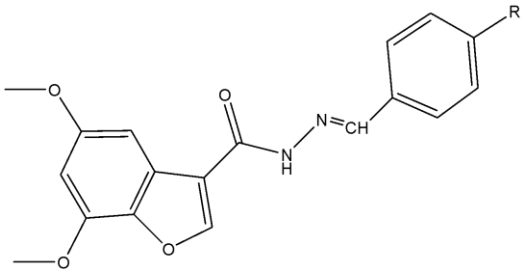
A mixture of ethyl 5,7-dimethoxy benzofuran-3-carboxylate (1g), hydrazine hydrate (0.2ml) and ethanol (25ml) was heated under reflux for 18 h. Excess ethanol was distilled off and the solid which separated out was collected by filtration, dried and recrystallised from ethanol.

Step-3:

Synthesis of Benzofuran derivatives:

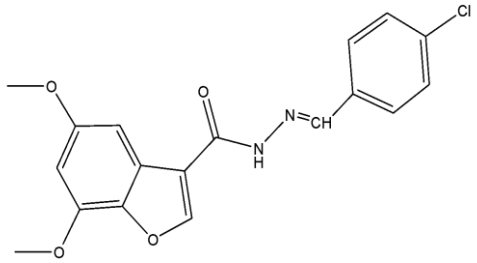
A solution of various substituted aldehydes (0.001m) in ethanol (15ml) was added to a solution of benzofuran-3-carbohydrazide (0.001m) in DMF (20ml). The reaction mixture was heated under reflux for 6-8 h, cooled to room temperature and poured into crushed ice to yield the product. The crude product that separated out was filtered and recrystallised from ethanol.

Table 1: Physical data of Benzofuran derivatives

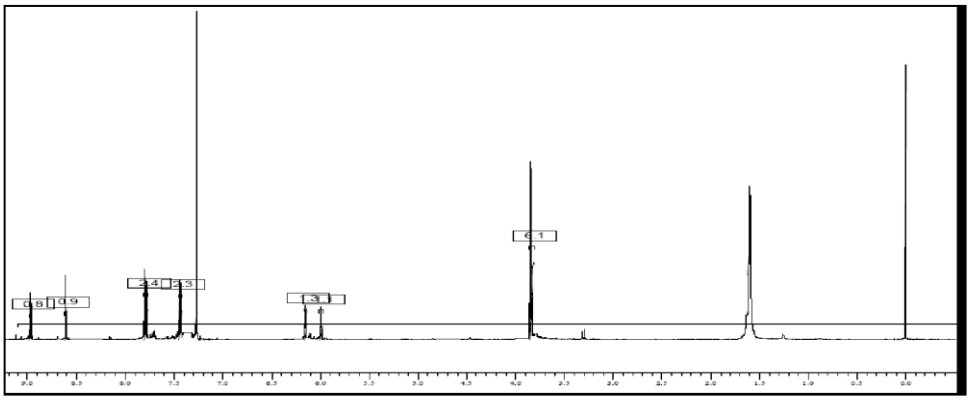


S.No	Product code	R	Molecular formula	Melting Point (°C)	% Yield
1	13a	Physical data of Benzofuran derivatives: -Cl	$C_{16}O_4H_{15}N_2Cl$	222-224	46
2	13b	-CN	$C_{16}O_4H_{15}N_2CN$	215-218	58
3	13c	-OCH3	$C_{17}O_5H_{18}$	218-220	47
4	13d	-F	$C_{16}O_4H_{15}N_2F$	138-140	56
5	13e	3-Pyridine carboxaldehye	$C_{25}O_4H_{37}N_3$	140-143	36
6	13f	Furfuraldehyde	$C_{26}O_4H_{37}N_2F$	120-122	38

NMR spectrum of compound 13a:

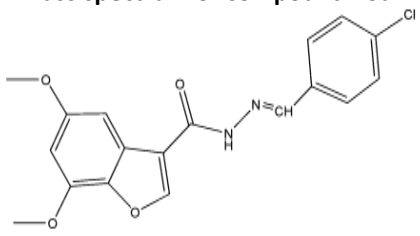


N-(4-chlorobenzylidene)-5,7-dimethoxybenzofuran-3-carbohydrazide

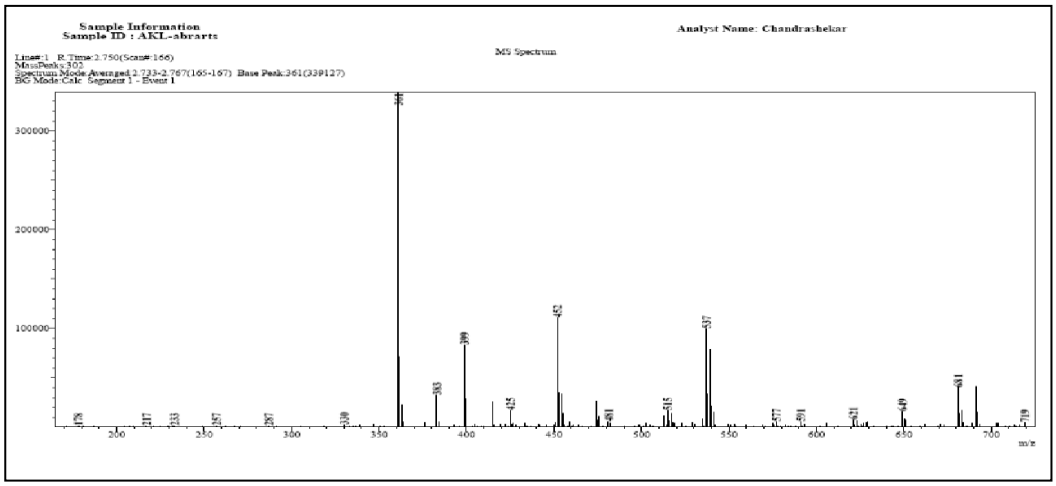


H NMR (CDCl₃, ppm): 7.3 (d,2H, Ar-H); 7.6 (d, 2H, Ar-H); 6.5 (d, 2H, Ar-H); 3.73 (m, 6 H, Ar-OCH_3); 8.5(s, 1-H, N-H) ;9(s, 1H, CH

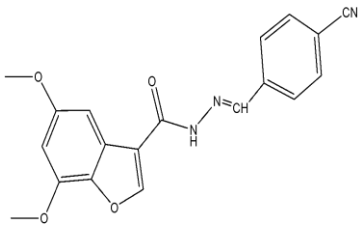
Mass spectrum of compound 13a:



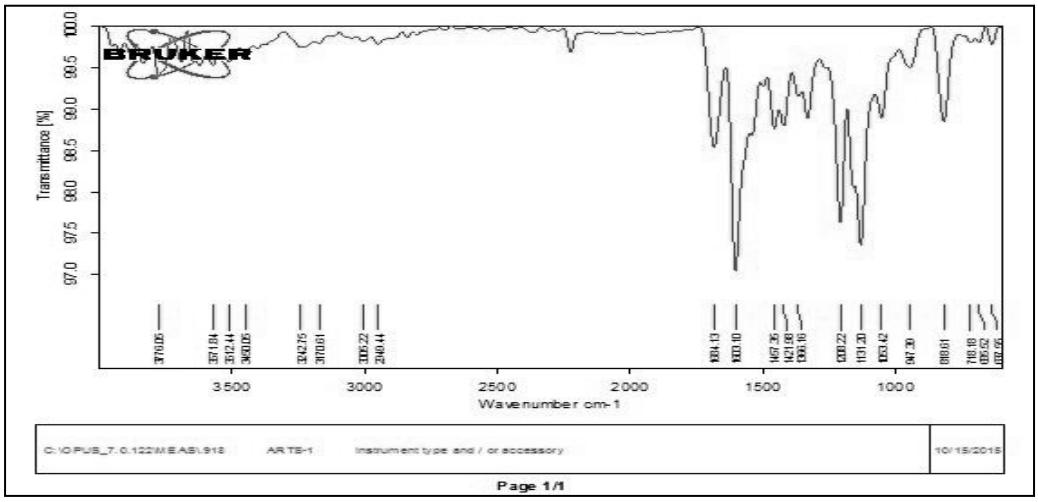
N-(4-chlorobenzylidene)-5,7-dimethoxybenzofuran-3-carbohydrazide



IR spectrum of Compound 13b:



N(4-Cyano benzylidene) 5,7-dimethoxy benzofuran -3-carbohydrazide



IR (KBR, cm^{-1}): -CN(2250cm^{-1}); =C-H(3170cm^{-1}); C=0(1603cm^{-1})

Biological Evaluation:

CUP-PLATE AGAR DIFFUSION METHOD:

Materials:

- Nutrient Broth medium
- Nutrient Agar medium
- Dimethyl Sulfoxide (DMSO)
- Ciprofloxacin
- Distilled Water

Required Equipment:

- Laminar air flow cabin
- Incubator
- Refrigerator
- Micropipettes
- Culture plates
- Boiling tubes
- Eppendorf tubes
- Aerosol resistant tips

Bacterial Organisms used:

Gram-positive bacteria:

- *Satphylococcus aureus*
- *Bacillus subtilis*

Gram-negative bacteria:

- *Pseudomonas aureginosa.*
- *Escherichia coli*

BACTERIALCULTURE MEDIA:

Nutrient Broth medium:

Composition:

- Peptone 5gm
- Sodium chloride 5gm
- Beef extract 1.5gm
- Yeast extract 1.5gm
- Distilled water up to 1000ml
- pH 7.4±0.2

The nutrient broth medium is sterilized by autoclaving at 121 ^{0}C (15 lb/sq. inches) for 15 min before sub culturing of bacterial organisms.

Nutrient Agar medium:

Composition:

- Peptone 5gm
- Sodium chloride 5gm
- Beef extract 1.5gm
- Yeast extract 1.5gm
- Agar 1.5gm
- Distilled water up to 1000ml
- pH 7.4±0.2

The nutrient agar medium is sterilized by autoclaving at 121 ^{0}C (15 lb/sq. inches) for 15 min.

Description: It is evident from the literature that Benzofuran derivatives exhibit antimicrobial activity. Therefore, it has been felt worthwhile to screen the synthesized benzofuran derivatives for antibacterial activity. For testing the antibacterial activity of benzofuran derivatives Cup-plate Agar diffusion method was done.

Antibacterial activity:

Four bacterial test organisms such as E. coli (Gram –ve), P.aureginosa (Gram –ve), S.aureus (Gram +ve) B.subtilis (Gram +ve) were selected and obtained. Cultures of test organisms were maintained on Nutrient Agar slants and were subcultered in Petri dishes prior to testing. The media used was Nutrient Agar, Nutrient Broth procured from Himedia Laboratories, Mumbai.

Six Benzofuran derivatives were synthesized as described earlier. Stock solutions of synthesized compounds were prepared in different concentrations, (i.e) 400 µg/ml, 200 µg/ml, 100 µg/ml and 50 µg/ml ug/ml using (DMSO) Dimethyl Sulfoxide as solvent for antibacterial activity.

RESULTS & DISCUSSIONS

All the synthesized compounds were screened for antibacterial activity studies at a concentration of 1mg/ml using DMSO as a control against *E. coli, S. aureus, B. substilis and P. aeruginosa* by cup-plate method on nutrient agar media. Ciproflaxicin 100 µg /ml used as standard. From the antibacterial screening, it was found that synthesized compounds showed significant and moderate activity. Compound 13a benzofuran moiety may be largely responsible for the marked bactericidal activity. The above results establish the fact that the substituted benzofuran can be studied further to search for new antimicrobial compounds. All the proposed compounds were synthesized and characterized.

Table 2: Antibacterial activity of Benzofuran derivatives

Sample Code	R	Zone of Inhibition			
		E. coli **400µg/ml**	***S.aureus*** **200µg/ml**	***B.subtilis*** **100µg/ml**	***P.aureginosa*** **50µg/ml**
13a	-Cl	10mm	6mm	4mm	2mm
13b	-CN	8mm	5mm	2mm	4mm
13c	-OCH3	4mm	6mm	3mm	6mm
13d	-F	5mm	3mm	2mm	1mm
13e	3-Pyridinecarboxaldehyde	3mm	2mm	NA	NA
13f	Furfuraldehyde	3mm	1mm	NA	NA
Ciproflaxicin		14mm	10mm	8mm	1mm
DMSO		1mm	1mm	1mm	1mm

NA-Not Active

CONCLUSIONS

The Chemistry of these systems involves considerable biological interest as Benzofuran has pharmacological properties. The following conclusions have been drawn from the results of these investigations. Synthetic work of these studies has positively undergone as per the plan and as such all the reactions carried, the proposed compounds were obtained. Synthesized Benzofuran derivatives gave satisfactory results for various evaluations like TLC, melting point, spectral data and antibacterial activity. The reactions were confirmed by TLC by using suitable solvents. Six Benzofuran derivatives were synthesized and analysed by physical and spectral data (IR,1H NMR and Mass) spectra. All the derivatives were screened for antibacterial activity and the results are compared with standard drug Ciprofloxacin. All the compounds of the series showed significant activity. Among them compound 13a had been found to be most active among all the test compounds.

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