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Synthesis, Characterization and Antimicrobial Screening of 5-Bromo-Benzofuranyl Aryl Triazoles

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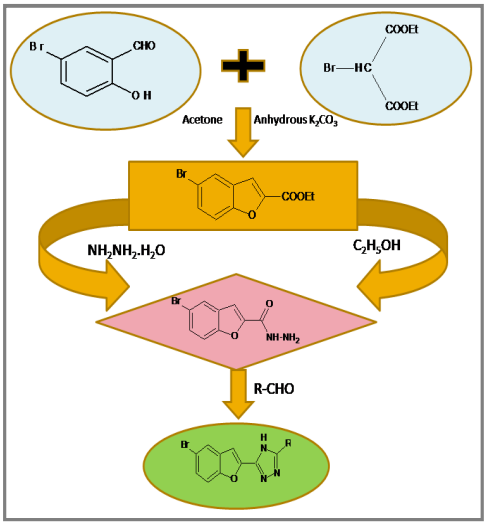
ABSTRACT

*The key intermediate 5-bromosalicylaldehyde was prepared by brominating salicylaldehyde. The benzofuran ring was constructed by treating 5-bromosalicylaldehyde with diethylbromomalonate in the presence of anhydrous acetone and anhydrous potassium carbonate to obtain 2-ethyl-5-bromo benzofuran carboxylate **(1)**. The obtained ester **(1)** was converted into corresponding hydrazide **(2)** by treating with hydrazine hydrate, which was then converted into bezofuranyl aryl triazoles **(3)**. All the compounds synthesized during the present investigation were in agreement with the assigned structure, which were supported by spectral and analytical data. The compounds synthesized were screened for their anti bacterial and antifungal activity, some of them have shown appreciable activity.*

Graphical Abstract



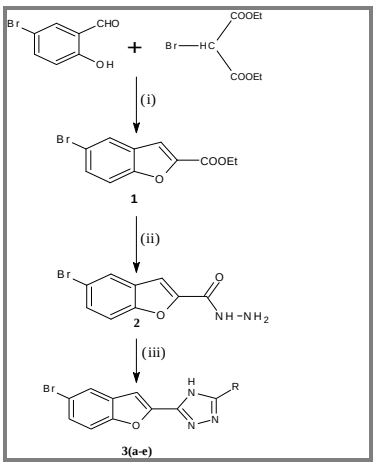
Keywords: Benzofuran, Triazoles, Antibacterial, Antifungal activity.

INTRODUCTION

Heterocycles are largest classical divisions of organic compound and play very important role in pharmaceuticals, biologically active agrochemicals and industrial applications ranging from cosmetics, reprography to plastics. For more than century, heterocycles have constituted one the largest areas of research in organic chemistry. They have contributed in greater extent for the development of society from a biological and industrial point of view. Among 20 million chemical compounds identified by the end of the second millennium, approximately half are heterocyclic compounds [**1**]. Synthetic heterocycles with heteroatoms such as oxygen [**2**], phosphorous [**3**] appears along with nitrogen have wide spread therapeutic uses such as antibacterial antifungal, anti-HIV activity, anti-tubercular, anti-malarial, anti-inflammatory, muscle relaxants, anticancer, antidepressant and insecticidal agents [**4-8**]. Among the heterocycles, fused heterocyclic benzofuran moiety constitutes the core of several interesting biologically active natural products such as Cicerfuran, Conocarpan and Ailanthoidol. Cicerfuran, an antifungal benzofuran derivative, was first obtained from the roots of wild species of *Cicerbijumgu*. The conocarpan exhibited insecticidal, antifungal and anti-trypanosomal activity [**9**]. Many Benzofuran derivatives were synthesized and screened for their antibacterial and antifungal activities which exhibited favorable activities [**10**]. In the recent days, benzofuranyl triazoles plays an important role, the special property of triazole which is responsible for binding bimolecular targets and to increase the solubility of the compound is due to its capability of forming hydrogen bond. Triazoles could connect two pharmacophores to form a bifunctional drug and they have become important in constructing bioactive and functional molecules. It is important to note that the bio-isosteric replacement between the triazole moiety and its bio-isostericbenzofuran has received considerable attention in medicinal chemistry, which has become efficient concept for the discovery and development of novel triazole drugs [**11, 12**]. 1,2,4-Triazoles were reported to possess significant activities such as anti-bacterial, anti-fungal anthelmintic[**13**], anti-microbial [**14**], anti-tubercular [**15**] activities. Promoted by these observations, as part of our research program aimed at developing new biologically active nitrogen containing heterocycles, we report the synthesis of some new benzofuranyl triazoles.

MATERIALS AND METHODS

All reagents and solvents were used as of analytical grade. ^{1}H NMR(400MHZ) were obtained by Bruker spectrometer in the appropriate ($CDCl_3$) solvent. IR spectra were recorded on Perkin-Elmer Spectrum Two spectrophotometer Instrument. Melting points were determined in open capillary tubes and were uncorrected.



(i). $CH_3CH_2COCH_3$/Anhydrous K_2CO_3, Reflux for 10 hrs; (ii). $NH_2NH_2.H_2O/C_2H_5OH$, Reflux for 4 h; (iii). R-CHO/CH_3COONH_4/CH_3COOH stirred for 24hrs at room temperature; **R:a**=C_6H_5, **b**= $C_6H_5NO_2$(p), **c**=$C_6H_4OCH_3$(p), **d**=C_6H_4Cl(m), e= C_6H_4OH(p)

Scheme. Synthesis of 5-bromobenzofuranylaryl triazoles.

General procedure

5-Bromo-Slicylaldehyde: Salicylaldehyde (50 mL, 0.4 mol) in 100 mL of acetic acid was taken in a round bottom flask. To this bromine (22 mL, 0.4) in 15ml 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 of 5-bromo salicylaldehyde. The compound was recrystallised from ethanol (Yield:79%, Mp:105°C).

5-Bromo benzofuran-2-carboxylic acid ethyl ester (1): A solution of 5-Bromo-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 steam bath, solvent was distilled off under reduced pressure and the residual salts were dissolved in about 200 mL of ice water and carefully acidified with dilute hydrochloric acid. The obtained product recrystallized from ethanol.

5-Bromo benzofuran-2-carboxylic acid hydrazide (2): To the solution of 5-Bromo 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 4 hours on the water bath, excess of ethanol was removed under the reduced pressure and then diluted with water. The separated carbohydrazide was collected and recrystallized from ethanol as colorless needles.

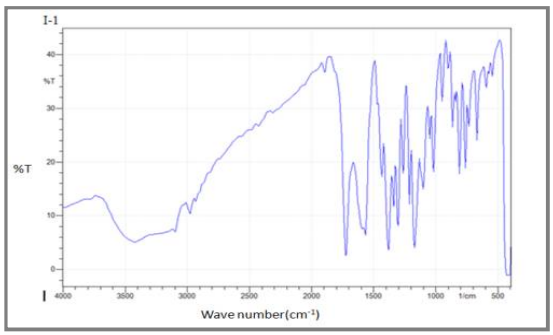
3-(5-Bromo-benzofuran -2-yl)-5-aryl-4H-[1,2,4] triazoles (3a-e): To a solution of 5-Bromo benzofuran-2-carboxylic acid hydrazide 2,(0.01 mol) in acetic acid (20 mL) was added a pinch of ammonium acetate followed by the addition of benzaldehyde/substituted benzaldehyde (0.01) and the mixture was stirred 24 h at room temperature. The reaction mixture was then neutralized with ammonia solution and the solid separated was filtered, washed with water and crystallized from suitable solvent. Yields and melting points are summarized I table 1.

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

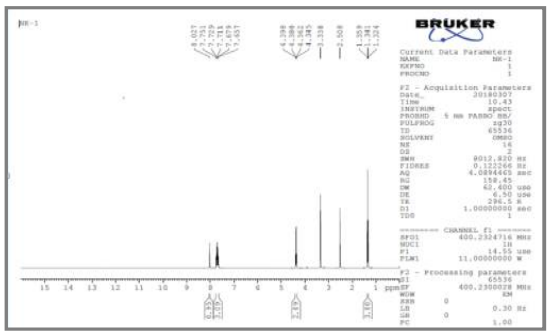
Compounds	Yield %	MP°C	MF
1	85	68	$C_{11}H_9$
2	90	210	$C_9H_6BrN_2O_2$
3a	75	215	$C_{16}H_{10}BrN_3O$
3b	72	190	$C_{16}H_9BrN_4O_3$
3c	68	200	$C_{17}H_{12}BrN_3O_2$
3d	74	185	$C_{16}H_9BrClN_3O$
3e	80	180	$C_{10}H_{10}BrN_3O_3$

RESULTS AND DISCUSSION

5-Bromo benzofuran-2-carboxylic acid ethyl ester (1): IR(KBr);vcm-1;1728(-CO), **^{1}HNMR (400 MHz, DMSO-d6**): δ 1.34 (s, 3H), 4.37 (q, J = 6.80 Hz, 2H), 7.66-7.68 (m, 3H), 8.03 (s,1H), .MS m/z;270.

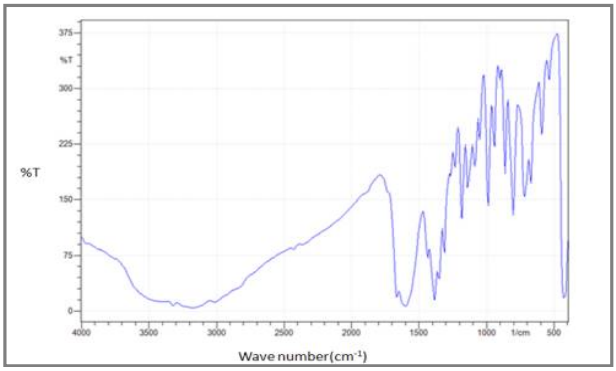


IR spectrum of compound I-1

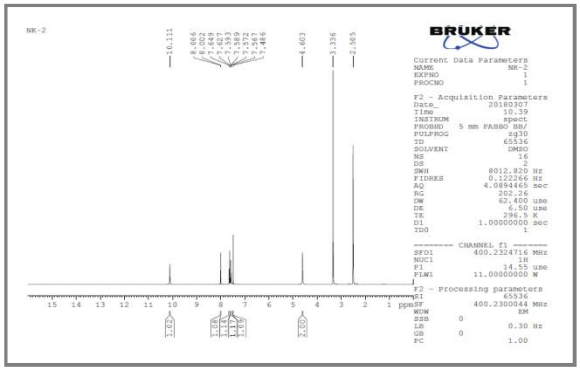


^{1}H NMR spectrum of compound I-1

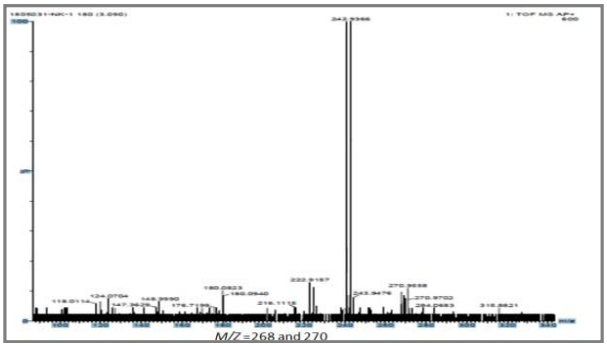
5-Bromo benzofuran-2-carboxylic acid hydrazide (2): IR(KBr);vcm^{-}1; 3402($NHNH_2$), **^{1}HNMR (400 MHz, DMSO-d6)**: δ 4.60 (s, 2H), 7.49 (s, 1H), 7.57 (d, J = 2.00 Hz, 2H), 7.59 (d, J = 1.60 Hz, 1H), 7.63 (s, 1H), 7.65 (s, 1H), 8.00 (d, J = 1.60 Hz, 1H), 10.11 (s, 1H), .MS m/z;256.



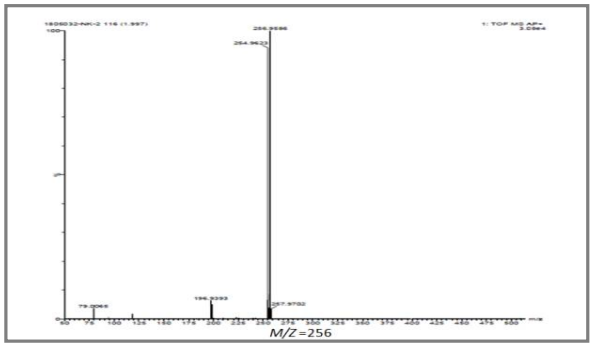
IR spectrum of compound I-2



^{1}H NMR spectrum of compound I-2



Mass spectrum of compound I-1

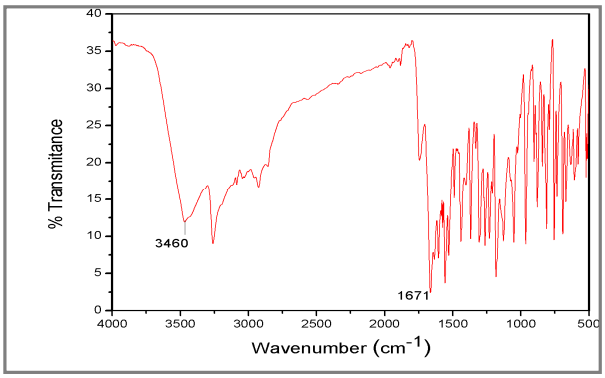


Mass spectrum of compound I-2

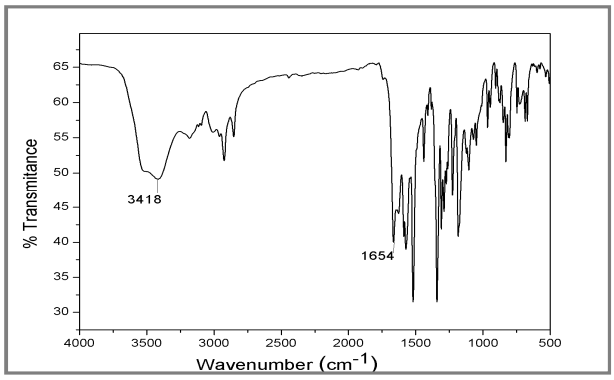
3-(5-Bromo-benzofuran -2-yl)-5-aryl-4H-[1,2,4] triazoles (3a-e): 3a: IR(KBr);vcm^{-}1;3460(-NH),1671(-C=N), **^{1}HNMR(400 MHz, CDCl3):** δ 7.26 (s, 4H), 7.43 (t, J = 7.20 Hz, 2H), 7.74 (s, 3H), 7.83 (d, J = -14.00 Hz, 3H), 7.85 (s, 3H), 7.94 (s, 1H), 8.35 (s, 1H), 9.52 (s, 1H), 9.62 (s, 1H), .

3b: IR(KBr);vcm^{-}1; 3418 (-NH),1654(-C=N).

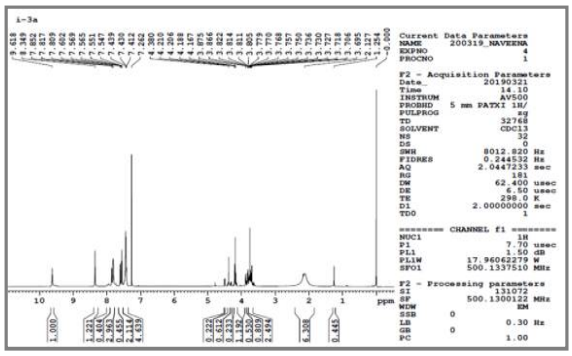
3c: IR(KBr);vcm^{-}1;3448 (-NH),1669(-C=N), **^{1}HNMR(400 MHz, CDCl3)**: δ 1.25 (s, 1H), 1.66 (s, 0H), 3.86 (s, 4H), 6.95 (d, J = 6.80 Hz, 3H), 7.26 (s, H), 7.40 (d, J = -1.60 Hz, 1H), 7.76 (d, J = 6.80 Hz, 2H), 7.85 (s, 1H), 8.27 (s, 1H), .



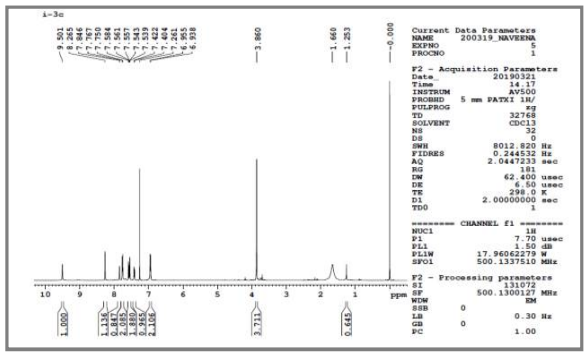
IR spectrum of compound I-3a



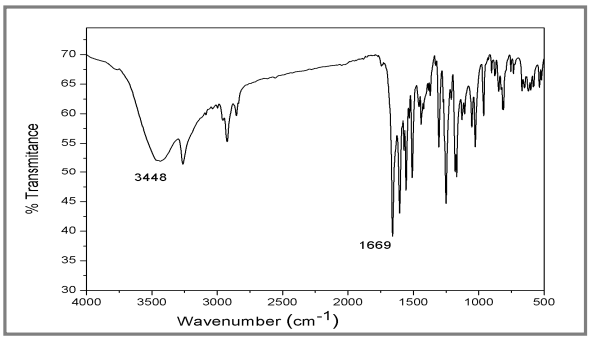
IR spectrum of compound I-3b



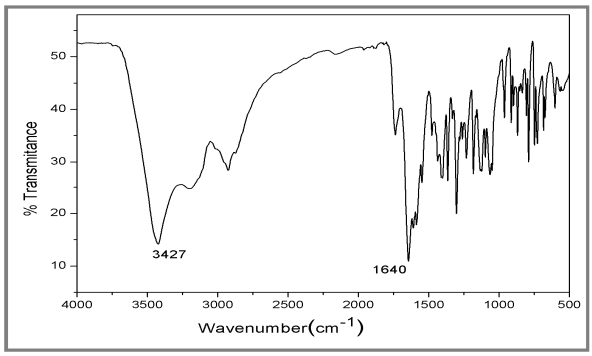
^{1}HNMR spectrum of compound I-3a



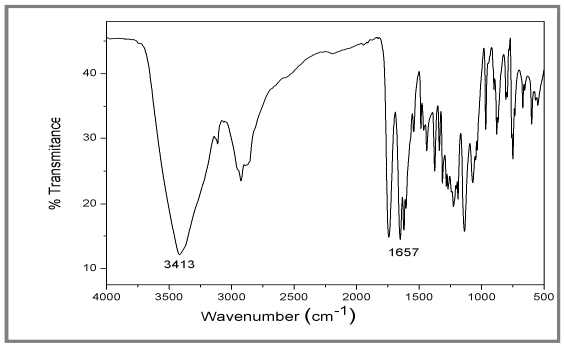
^{1}H NMR spectrum of compound I-3C



IR spectrum of compound I-3c



IR spectrum of compound I-3d



IR spectrum of compound I-3e

3d: IR(KBr);vcm¯1; 3418 (-NH),1654(-C=N).

3e: IR(KBr);vcm¯1; 3418 (-NH),1654(-C=N).

APPLICATION

The synthesized compounds were screened for antibacterial activity against the bacteria: *S. aureus*, *E. coli*, and *P. aureginosa by* cup -plate method and the data is tabulated in table 2 (Figure 1). Among all the compounds screened, compounds I-**2, I-3c**, in figure 2 (Table 2) **I-3b, I-3d** are showing considerably good antibacterial activity with reference to standard drug Pencillin and Streptomycin. The antifungal activity of the compounds was performed against the following standard fungal strains C*andida albiacans* and *Aspergillus niger* in DMF by using cup plate method shown in figure 3 (Table 3). The compounds **3d** and **3e** and in figure 4 (Table 3) **I-3b** and **I-3d** exhibited good antifungal activity with reference to the standard drug Griseofulvin.

Table 2. Antibacterial Activity

Compound	Zone of inhibition (mm)					
	S. aureus		*E.coli*		*P. aureginosa*	
	50 µg mL^{-1}	100 µg mL^{-1}	50 µg mL^{-1}	100 µg mL^{-1}	50 µg mL^{-1}	100 µg mL^{-1}
I - 1	12	15	13	16	14	17
I - 2	14	17	14	18	13	18
I – 3a	13	16	12	17	14	19
I – 3b	14	19	13	17	12	17
I – 3c	15	19	11	15	11	16
I – 3d	11	16	10	14	13	18
I – 3e	13	17	12	16	14	20
Pencillin	15	22	--	--	--	--
Streptomycin	--	--	21	28	22	27
D.M.F. (Control)	Nil	Nil	Nil	Nil	Nil	Nil

Table 3. Antifungal Activity

Compound	Zone of inhibition (in mm)			
	Candida albiacans		*Aspergillus niger*	
	50 µg mL^{-1}	100 µg mL^{-1}	50 µg mL^{-1}	100 µg mL^{-1}
I - 1	09	14	10	15
I - 2	12	15	10	14
I – 3a	10	15	11	14
I – 3b	12	18	11	17
I – 3c	10	17	10	16
I – 3d	12	18	13	17
I – 3e	11	16	12	15
Griseofulvin	23	27	23	28
D.M.F. (Control)	Nil	Nil	Nil	Nil

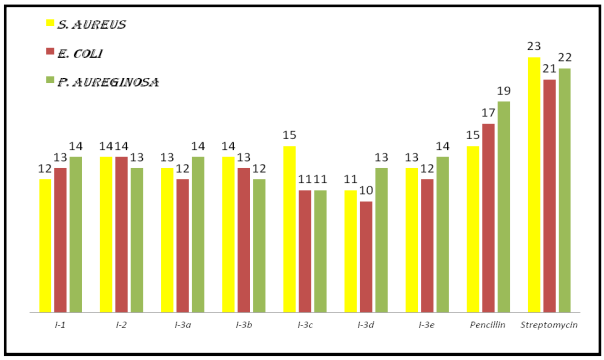


Figure 1. Antibacterial activity of the compounds (I-1 to I-3e) in 50µg mL^{-1}

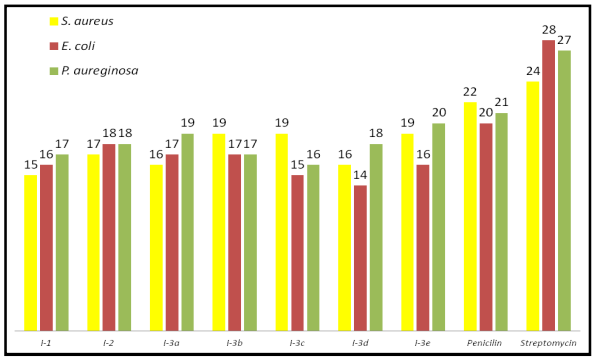


Figure 2. Antibacterial activity of the compounds (I-1 to I-3e) in 100 µg mL^{-1}

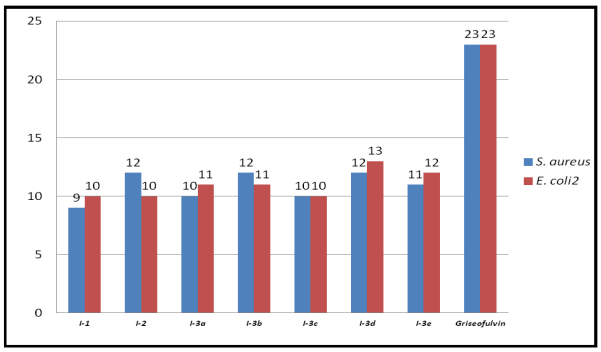


Figure 3. Antifungal activity of the compounds(I-1 to I-3e) in **50** µg mL^{-1}

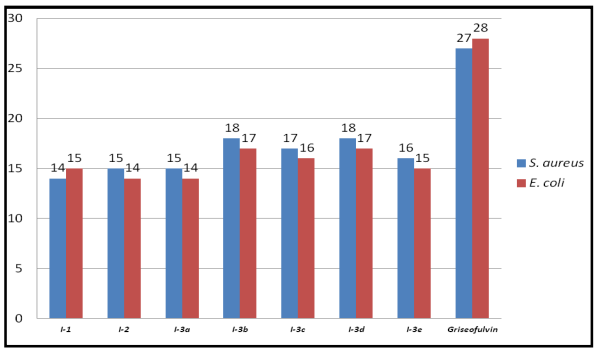


Figure 4. Antifungal activity of the compounds(I-1 to I-3e) in 100 µg mL^{-1}

CONCLUSION

The newly synthesised compounds were confirmed by IR and ^{1}HNMR Spectral data and they have shown good antibacterial and antifungal activity against the various organisms and which are compared with standard drugs penicillin and Griseofulvin.

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