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ANTIBACTERIAL ACTIVITY OF 2, 3 –DIMETHYL -6, 7, 8, 9 - TETRAHYDRO BENZOCYCLO HEPTEN-5-ONE AND ITS DERIVATIVES

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ABSTRACT

Heterocyclic compounds are known for their biological activities like cardiovascular, vasodilator, anti-arrhythmic, hemodynamic effects, anti-ulcer activity, Calcium antagonistic, spasmolytic activities and angio-tensive converting enzyme inhibition etc. Benzosuberones are a class of heterocyclic compounds which exhibit antimicrobial activity against a variety of bacteria and fungi. In the present study, 2, 3 – dimethyl - 6, 7, 8, 9 - tetrahydro benzocyclohepten-5-one and its derivatives 6-Arylidene -2,3-dimethyl- 6,7,8,9 -tetrahydro- 5H- benzocyclo –hepten -5-one and 2,3 -dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one thiosemi-carbazone are tested for their efficiency as antibacterial agents. Ten bacterial cultures *viz*. the Gram positive *Staphylococcus aureus* and Methicillin Resistant *Staphylococcus aureus* and the Gram negative *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter divergens*, *Shigella flexneri*, *Salmonella paratyphi* A, *Salmonella paratyphi* B, *Proteus mirabilis* and *Pseudomonas aeruginosa*, isolated from clinical samples were obtained from SVS Medical College, Mahabubnagar, Telangana State, India. The three compounds exhibited antibacterial activity against all the bacteria at different concentrations tested, with Compound 1 showing greater activity against *E. coli*, *Citrobacter divergens*, *Shigella flexneri*, *Salmonella paratyphi* A, *Salmonella paratyphi* B and *Pseudomonas aeruginosa* compared to other two compounds. Similarly, Compound 2 has shown more activity on Methicillin Resistant *Staphylococcus aureus* than other two compounds and Compound 3 has shown greater activity on *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Proteus mirabilis* than other two compounds. The activity varied with the type of the bacterium and the compound. The Activity Index and Relative Percentage inhibition of the compounds were also estimated.

Keywords: Benzosuberones, antibacterial activity, clinical isolates, activity index, relative percentage inhibition.

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INTRODUCTION

Heterocyclic compounds are very important compounds which are essential in our life.

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They exhibit wide range of pharmacological activity [1]. Heterocyclic compounds containing nitrogen, oxygen and sulphur are reported to show significant biological activity. Many of these compounds in the earlier years have laid a firm foundation for the development of medicinal chemistry. The earlier concept, the structure - activity relationship, chemical and biological forms of active molecules and other considerations such as the lead from the natural products were the strengthening guidelines of a medicinal chemist,

in the development of new molecules. During the last two decades or so, much emphasis is made on the biological activity and mode of action of drugs and their pharmaco-kinetic studies in the development of new drugs. Prompted by these observations, we have synthesized and analyzed some heterocyclic compounds derived from benzocyclo hepten-5- ones and tested for their antibacterial activity on a spectrum of organisms.

Heterocyclic compounds have wide range of bio activities like cardiovascular [2], vasodilator [3] [4] and anti-arrhythmic [5], hemodynamic effects [6], anti-ulcer activity [7] [8], Calcium antagonistic and spasmolytic activities [9-13], angio tensive converting enzyme inhibition [14] [15] etc. Benzosuberones and their derivatives have shown antibacterial activity [16] and stimulated the invention of various synthetic procedures for their preparation and chemical transformations. Hence in continuation of our interest in the design and synthesis of biologically active fused heterocyclic compounds, we have synthesized Benzosuberones and their derivatives to test their biological activities. The required starting compound used in this study is 2, 3-dimethyl-6, 7, 8, 9-tetra hydro benzocyclo-hepten-5 one (Compound 1).

MATERIALS AND METHODS

a. Melting points were determined using Gallankamp apparatus and are Uncorrected. IR spectra were recorded on a FT – IR 1605 Perken Elmer; ^{1}H NMR in $CDCl_3$ on AVANCE 300 MH NMR spectrometer with TMS as an internal standard; and mass spectra on a VG – micro mass 7070 H mass spectrometer. TLC was run on silica gel G coated plates and iodine vapour as visualizing agent.

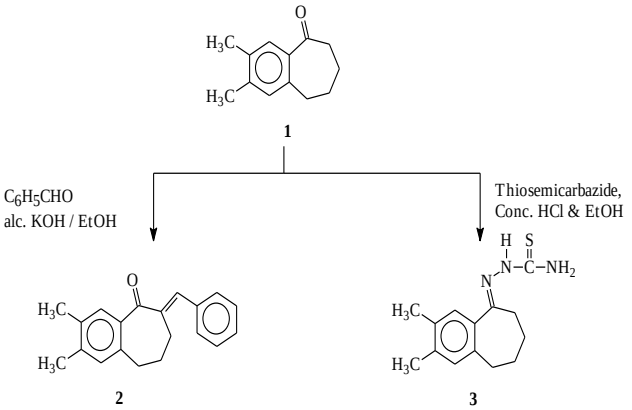
b. Compound 1: The starting compound **2, 3 – dimethyl - 6, 7, 8, 9 - tetrahydro benzocyclohepten-5-one** was prepared from 2, 3 – dimethyl benzene [17] [18].

c. Compound 2: 6-Arylidene-2, 3-dimethyl-6, 7, 8, 9-tetrahydro-5H-benzo cyclo-hepten-5-one

A mixture of 2, 3 – dimethyl - 6, 7, 8, 9 - tetrahydro benzocyclohepten-5-one (Compound 1) (0.35g, 2mMol), Benzaldehyde (0.20g, 2mMol) in ethanolic potassium hydroxide was stirred at room temperature for 0.5 hr. During this time the product was formed. The reaction mixture was neutralized with acetic acid and diluted with water. The solid thus obtained was filtered and washed thoroughly with water and dried. Recrystallization from methanol gave the product (Compound 2) Yield 94%, colourless needle like crystals, M.P. 112-113^{0}C; IR (KBr): 1661 (CO chelated) and 1601 (C=C) cm^{-1}; Anal. Found: C, 87.00; H, 6.80. $C_{19}H_{18}O$ requires C, 87.02: H, 6.80% [18].

d. Compound 3: 2, 3-dimethyl-6, 7, 8, 9-tetrahydrobenzocyclohepten-5-one thiosemi-carbazone

A mixture of 2, 3-di-methyl-6, 7, 8, 9-tetrahydrobenzocyclohepten-5-one (Compound I) (1.0 mMol), thiosemicarbazide (1.0 mMol) and 0.4 mL of Concentrated HCl in absolute ethanol (10.0 mL) was stirred at room temperature for 3hrs. It was poured into ice-cooled water, the solid thus obtained was filtered, dried and recrystallized from ethanol to furnish Compound 3: yield 95%, m.p. 180-182°C. IR (KBr): 3416, 3200, 3142 (NH & NH_2), 1168 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.60-1.80 (4H, m, 7&8-CH_2), 2.25 (6H, s, 2&3-CH_3), 2.65-2.80 (4H, m, 6&9-CH_2), 6.80 (1H, s, 1-CH), and 7.22 (1H, s, 4-CH). Anal. Found: C, 64.26; H, 7.03; N, 15.98. $C_{14}H_{19}N_3S$ requires C, 64.36; H, 7.27; N, 16.09 % [17].



e. Preparation of the bacterial culture:

Ten bacterial cultures, *viz*. the Gram positive *Staphylococcus aureus* and Methicillin Resistant *Staphylococcus aureus* and the Gram negative *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter divergens*, *Shigella flexneri*, *Salmonella paratyphi* A, *Salmonella paratyphi* B, *Proteus mirabilis* and *Pseudomonas aeruginosa*, isolated from clinical samples were obtained from SVS Medical College, Mahabubnagar, Telangana State, India. Conventional bacteriological methods such as colony morphology, Gram staining and biochemical tests were used for identification of isolates [19]. The test organisms were inoculated in Mueller Hinton broth (pH 7.4.) for 8 hours. The concentration of the suspensions was adjusted to 0.5 Mc Farland standard [20] to reach an optical density of 0.08 – 0.10 at 625 nm by adding sterile distilled water. This gives a bacterial suspension containing 1.5 x 10^8 CFU/ml [21]. Isolates were seeded on Mueller Hinton agar plates by using sterilized cotton swabs.

f. Antibacterial Sensitivity Testing:

Antimicrobial sensitivity testing was done by Agar well diffusion method. Mueller Hinton agar plates were prepared and wells of diameter 2 mm were cut. The bacterial culture was spread with a sterilized cotton swab and 50 µl of various concentrations of the compound viz.

75, 150, 300 and 600 µg/well were added to the wells. Streptomycin at a concentration of 300 mcg was used as a control antibiotic. The values of antimicrobial activity of the compounds were expressed as mean ± standard deviation (n= 3) for each sample.

g. Determination of Activity Index (AI):

Activity index of all the compounds was calculated using the following formula [22]

$$Activity\ Index(AI) = \frac{Inhibition\ Zone\ of\ the\ sample}{Inhibition\ Zone\ of\ the\ Standard}$$

h. Determination of relative percentage inhibition (RPI):

The relative percentage inhibition of all the test compounds with respect to the positive control was calculated by using the following formula [23].

$$RPI = \frac{100(X-Y)}{(Z-Y)}$$

Where X= Total area of inhibition of the test compound; Y= Total area of inhibition of the solvent and Z= Total area of inhibition of the standard drug. The total area of the inhibition was calculated by using the area = πr^2; where r = radius of the zone of inhibition.

RESULTS AND DISCUSSION

The structures of the compounds were confirmed based on spectral analysis. 6-Arylidene -2, 3 –dimethyl -6, 7, 8, 9 -tetra hydro benzocyclohepten-5-one (Compound 2) was confirmed by the ^{1}HNMR spectra, which displayed a signal at δ 7.80 characteristic peak of –C=CH. Mass & IR spectra also confirms its structure. Another derivative 2, 3 -di methyl -6, 7, 8, 9 -tetrahydro benzo cyclo hepten-5-one thiosemi-carbazone (Compound 3) was also confirmed from its spectra. IR spectrum of compound 3 showed absorption peaks at 3419, 3245, 3142 and 1192 cm^{-1} attributing to NH, NH_2 and C=S functional groups. Presence of a peak at 1592 cm^{-1} & absence of carbonyl peak also indicates the formation of C=N group. It also confirms from its ^{1}HNMR & Mass spectra.

The three compounds used in the present study, 2, 3 –dimethyl -6, 7, 8, 9 -tetrahydro benzocyclo hepten-5-one and its derivatives arylidene derivative and thiosemi carbazone have shown antibacterial activity. The results of antibacterial activity of these compounds are explained as below.

Staphylococcus aureus is sensitive to all the 3 compounds at all concentrations tested (Fig.1). Compound 3 has shown greater inhibitory activity against *Staphylococcus aureus* at all concentrations tested except at 300 µg/well, with a maximum inhibitory zone of 15.67 mm at 600 µg/well, whereas compound 2 exhibited least activity against the bacterium at all concentrations tested. Compound 1 has shown more activity than other two at a concentration of 300 µg/well (inhibitory zone of 12 mm). Compound 1 and 3 have shown increasing inhibitory effect with increasing concentrations on Methicillin Resistant *Staphylococcus aureus* (MRSA), but compound 3 is more active than compound 1 upto 300 µg/well (Fig. 2).The bacterium is resistant to compound 2 at a concentration of 75 µg/well, but became more sensitive to increasing concentrations of the compound (with a maximum inhibitory zone of 16.67 mm) compared to other 2 compounds.

Escherichia coli is resistant to compound 3 at a concentration of 75 µg/well, but is sensitive to increasing concentrations of the compound (Fig.3). Compound 1 and 2 have shown same inhibitory effect at a concentration of 75 µg/well, but with increasing concentrations, compound 1 has exhibited more inhibitory activity (22 mm zone of inhibition at 600 µg/well) compared to compound 1. All the 3 compounds tested showed similar inhibitory effect on *Klebsiella pneumoniae* at a concentration of 75 µg/well, whereas, compound 3 has shown greater inhibitory activity (12 mm zone of inhibition at 600 µg/well) with increasing concentrations compared to other 2 compounds with compound 2 exhibiting least activity (Fig. 4).

Fig. 5 shows that *Citrobacter divergens* is resistant to compound 2 and 3 at concentrations 75 and 150 µg/well, whereas it is sensitive to increasing concentrations of the 2 compounds. Compound 1 exhibited more inhibitory activity at all concentrations compared to other 2 compounds with a maximun of 18 mm zone of inhibition at 600 µg/well. *Shigella flexneri* is resistant to compound 3 at concentrations 75 and 150 µg/well, but is sensitive to increasing concentrations of the compound (Fig. 6). The bacterium is sensitive to compound 1 and 2 at all concentrations tested. Compound 2 is more active against the bacterium compared to other 2 with a maximum zone of inhibition 19.33 mm at 600 µg/well.

Salmonella paratyphi A is resistant to compound 2 and 3 at a concentration of 75 µg/well, but sensitive to higher concentrations of the compounds (Fig. 7). Compound 1 exhibited greater inhibitory activity on the bacterium at all concentrations tested compared to other 2 compounds with a maximum inhibitory zone of 14.67 mm at 600 µg/well. Similarly, *Salmonella paratyphi* B is resistant to compound 2 at a concentration of 75 µg/well and compound 3 at concentrations 75 and 150 µg/well (Fig. 8). The compounds have shown increasing inhibitory activity with increasing concentrations. Compound 1 exhibited more activty against the bacterium with a maximum of 16.67 mm inhibitory zone at a concentration of 600 µg/well.

Pseudomonas aeruginosa is sensitive to all the 3 compounds at all concentrations tested (Fig. 9). Of the 3 compounds, compound 1 exhibited more inhibitory effect

than other 2 with a maximum inhibitory zone of 15.67 mm at a concentration of 600 µg/well. On the other hand, *Proteus mirabilis* is resistant to compound 2 at all concentrations except 600 µg/well (Fig. 10). Compound 3 exhibited greater inhibitory activity against the bacterium compared to compound 1 at all concentrations tested with a maximum inhibitory zone of 12.33 mm at a concentration of 600 µg/well.

In general, the inhibitory effect of the compound depended upon the bacterium and the concentration and type of the compound. Similar antibacterial activity was reported with Benzothiazepenes on *Staphylococcus aureus* with inhibitory zones ranging from 6.25 - 25 mm whereas *Pseudomonas aeruginosa* was found to be resistant to benzothiozepenes [24]. On the other hand, Benzazepines were found to be active against *Pseudomonas* with inhibitory zones ranging from 18 - 20 mm [25] which is in coincidence with the activity of Benzosuberone and its derivatives in the present study. *Staphylococcus aureus* was found to be resistant to some Benzazepines [25] and sensitive to other Benzazepines [26]. In another study, some Benzocycloheptenes were found to be active against *E.coli* with maximum inhibitory zone diameters of 20 mm and others have shown activity on both *Staphylococcus aureus* and *E.coli* with inhibitory zones of 10 -15 mm [27].

Activity indices (AI) of the compounds were calculated and the values depicted in tables 1, 2 and 3. With Gram positive bacteria, Compound 1 exhibited a minimum AI of 0.115 for MRSA at a concentration of 75 µg/well and a maximum of 0.682 for *Staphylococcus aureus* at a concentration of 600 µg/well (Table 1). Whereas, with Gram negative bacteria the minimum AI was found to be 0.1 for both *E.coli* and *Klebsiella pneumoniae* at a concentration of 75 µg/well and a maximum of 0.733 at a concentration of 600 µg/well for *E.coli*. Table 2 indicates the values for Activity Index of compound 2. The minimum AI for Gram positive bacteria was found to be 0.142 at a concentration of 75 µg/well and a maximum of 0.650 at a concentration of 600 µg/well for *Staphylococcus aureus*. With Gram negative bacteria, a minimum of 0.1 for *E.coli* and *Klebsiella pneumoniae* at a concentration of 75 µg/well and a maximum of 0.648 at a concentration of 600 µg/well AI was noted.

With Gram positive bacteria, Compound 3 has shown a minimum Activity Index of 0.186 for MRSA at a concentration of 75 µg/well and a maximum of 0.447 for *Staphylococcus aureus* at a concentration of 600 µg/well (Table 3). With Gram negative bacteria the minimum AI was found to be 0.094 for *Klebsiella pneumoniae* at a concentration of 75 µg/well and a maximum of 0.613 for *Shigella flexneri* at a concentration of 600 µg/well.

Relative Percentage Inhibition (RPI) of the compounds was calculated and the results are depicted in Tables 4, 5 and 6. The control antibiotic used was Streptomycin (300 mcg) and the solvent used was ethanol. With compound 1, for Gram positive bacteria, the minimum RPI was found to be 0.51 at 75 µg/well for MRSA and a maximum of 41.85 at 600 µg/well for *Staphylococcus aureus* (Table 4). For Gram negative bacteria, the compound exhibited a minimum RPI of 0.11 at 300 µg/well for *Klebsiella pneumoniae* and a maximum of 103.95 at 600 µg/well for *Shigella flexneri*, which shows that this compound is more efficient antibacterial agent.

Table 5 shows the RPI of compound 2. At a concentration of 75 µg/well, compound 2 has shown negative values for all the bacteria except *Shigella flexneri*. With Gram positive bacteria, the minimum RPI was found to be 5.66 at a concentration of 150 µg/well for *Staphylococcus aureus* and maximum RPI of 39.20 at a concentration of 600 µg/well for MRSA. The minimum RPI for Gram negative bacteria was found to be 0.45 at a concentration of 300 µg/well for *Klebsiella pneumoniae* and a maximum RPI of 35.73 for *Shigella flexneri* at a concentration of 600 µg/well.

Table 1. Activity Index of Compound -1

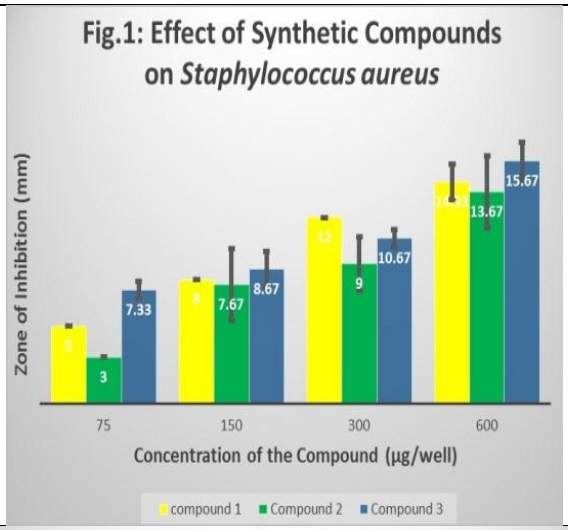
Concentration / Bacterium	75 µg/well	150 µg/well	300 µg/well	600 µg/well	Streptomycin (Control) Inhibitory zone (mm)
Gram Positive Bacteria					
Staphylococcus aureus	0.238	0.380	0.571	0.682	21.0 ± 0.0
MRSA	0.115	0.192	0.295	0.397	26.0 ± 00
Gram Negative Bacteria					
Escherichia coli	0.100	0.300	0.500	0.733	30.00 ± 0.0
Klebsiella pneumoniae	0.100	0.177	0.222	0.333	30.00 ± 0.0
Citrobacter divergens	0.266	0.380	0.438	0.514	35.00 ± 0.0
Shigella flexneri	0.456	0.614	0.736	1.017	19.00 ± 0.0
Salmonella paratyphi A	0.206	0.350	0.371	0.453	32.33 ± 0.58
Salmonella paratyphi B	0.204	0.234	0.377	0.510	32.67 ± 2.30
Pseudomonas aeruginosa	0.260	0.521	0.637	0.681	23.00 ± 0.00
Proteus mirabilis	0.160	0.200	0.346	0.386	25.00 ± 0.00

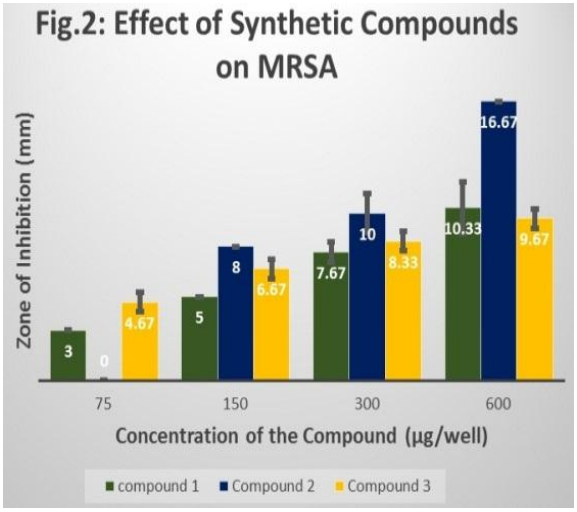
Table 2. Activity Index of Compound 2					
Concentration / Bacterium	75 µg/well	150 µg/well	300 µg/well	600 µg/well	Streptomycin (Control) Inhibitory zone (mm)
Gram Positive Bacteria					
Staphylococcus aureus	0.142	0.365	0.428	0.650	21.0 ± 0.0
MRSA	0	0.307	0.384	0.641	26.0 ± 00
Gram Negative Bacteria					
Escherichia coli	0.100	0.222	0.266	0.433	30.00 ± 0.0
Klebsiella pneumoniae	0.100	0.166	0.200	0.266	30.00 ± 0.0
Citrobacter divergens	0	0	0.162	0.257	35.00 ± 0.0
Shigella flexneri	0.263	0.421	0.508	0.648	19.00 ± 0.0
Salmonella paratyphi A	0	0.092	0.278	0.309	32.33 ± 0.58
Salmonella paratyphi B	0	0.122	0.275	0.336	32.67 ± 2.30
Pseudomonas aeruginosa	0.173	0.318	0.405	0.463	23.00 ± 0.00
Proteus mirabilis	0	0	0	0.120	25.00 ± 0.00

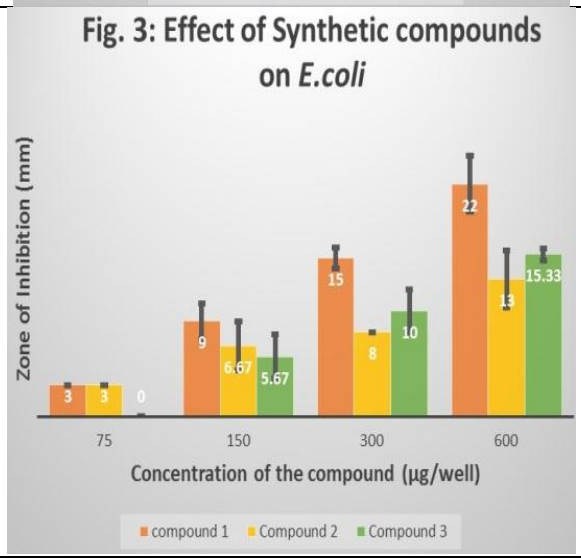
Table 3. Activity Index of Compound 3					
Concentration / Bacterium	75 µg/well	150 µg/well	300 µg/well	600 µg/well	Streptomycin (Control) Inhibitory zone (mm)
Gram Positive Bacteria					
Staphylococcus aureus	0.209	0.247	0.304	0.447	35.00 ± 0.00
MRSA	0.186	0.266	0.333	0.386	25.00 ± 0.00
Gram Negative Bacteria					
Escherichia coli	0	0.193	0.340	0.500	29.33 ± 1.15
Klebsiella pneumoniae	0.094	0.210	0.284	0.378	31.67 ± 1.53
Citrobacter divergens	0	0	0.185	0.279	28.67 ± 1.15
Shigella flexneri	0	0	0.454	0.613	14.67 ± 2.89
Salmonella paratyphi A	0	0.166	0.155	0.222	30.00 ± 0.00
Salmonella paratyphi B	0	0	0.133	0.211	30.00 ± 0.00
Pseudomonas aeruginosa	0.235	0.250	0.470	0.485	22.67 ± 0.58
Proteus mirabilis	0.213	0.280	0.373	0.493	25.00 ± 0.00

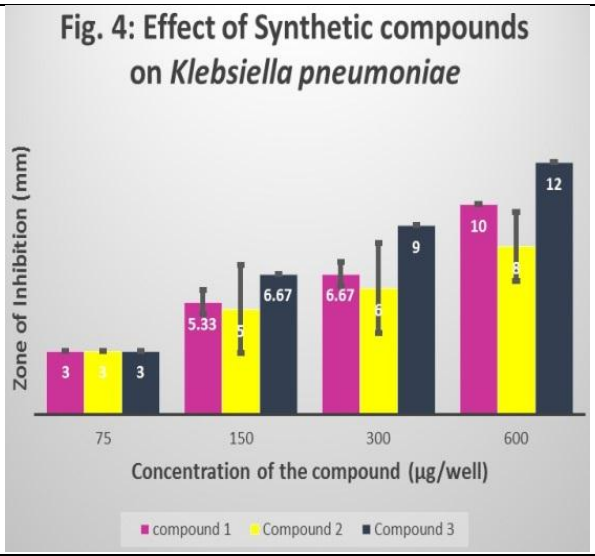
Table 4. Relative Percentage Inhibition of Compound I						
Concentration	75 µg/well	150 µg/well	300 µg/well	600 µg/well	Inhibitory zone diameter (mm)	
Bacterium					Streptomycin (Control)	Ethanol (Solvent)
Gram Positive Bacteria						
Staphylococcus aureus	- 2.73	6.91	26.66	41.85	21.0 ± 0.0	6.0 ± 0.00
MRSA	- 1.93	0.51	5.70	13.02	26.0 ± 00	4.67 ± 0.58
Gram Negative Bacteria						
Escherichia coli	- 4.16	5.20	21.87	51.85	30.00 ± 0.0	6.0 ± 0.00
Klebsiella pneumoniae	- 2.65	- 0.08	0.11	7.83	30.00 ± 0.0	5.67 ± 0.58
Citrobacter divergens	5.88	13.38	18.12	25.47	35.00 ± 0.0	4.0 ± 0.00
Shigella flexneri	12.07	30.86	49.22	103.95	19.00 ± 0.0	6.0 ± 0.00
Salmonella paratyphi A	1.92	10.15	11.67	18.67	32.33 ± 0.58	5.0 ± 0.00
Salmonella paratyphi B	1.88	3.26	12.21	24.29	32.67 ± 2.30	5.0 ± 0.00
Pseudomonas aeruginosa	- 3.76	18.96	33.98	40.37	23.00 ± 0.00	7.33 ± 1.15
Proteus mirabilis	- 4.89	- 3.34	5.31	8.47	25.00 ± 0.00	6.67 ± 0.58

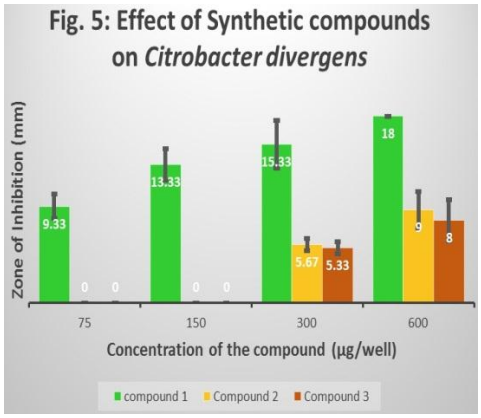
Table 6. Relative Percentage Inhibition of Compound 3						
Concentration	75 µg/well	150 µg/well	300 µg/well	600 µg/well	Inhibitory zone diameter (mm)	
Bacterium					Streptomycin (Control)	Ethanol (Solvent)
Gram Positive Bacteria						
Staphylococcus aureus	1.51	3.30	6.56	17.64	35.00 ± 0.00	6.0 ± 0.00
MRSA	0.04	3.78	7.93	11.93	25.00 ± 0.00	4.67 ± 0.58
Gram Negative Bacteria						
Escherichia coli	- 4.37	0.48	7.76	24.15	29.33 ± 1.15	6.0 ± 0.00
Klebsiella pneumoniae	- 2.38	1.27	5.04	11.52	31.67 ± 1.53	5.67 ± 0.58
Citrobacter divergens	- 1.99	- 1.99	1.54	5.95	28.67 ± 1.15	4.0 ± 0.00
Shigella flexneri	- 20.08	- 20.08	4.68	25.08	14.67 ± 2.89	6.0 ± 0.00
Salmonella paratyphi A	- 2.85	- 0.35	0.01	2.23	30.00 ± 0.00	5.0 ± 0.00
Salmonella paratyphi B	- 2.85	- 2.85	- 1.02	2.23	30.00 ± 0.00	5.0 ± 0.00
Pseudomonas aeruginosa	- 5.51	- 4.73	13.06	14.59	22.67 ± 0.58	7.33 ± 1.15
Proteus mirabilis	- 2.75	0.79	7.36	18.56	25.00 ± 0.00	6.67 ± 0.58

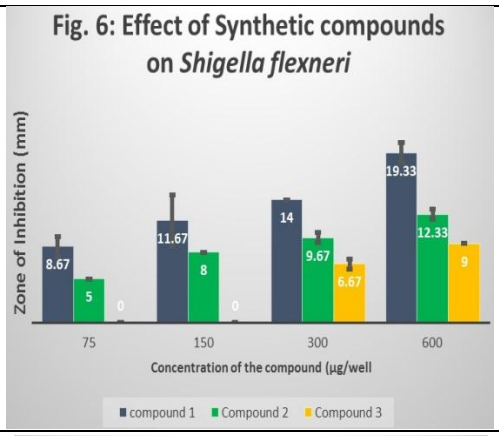


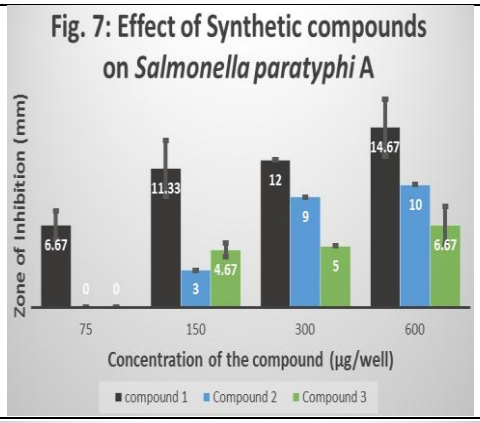


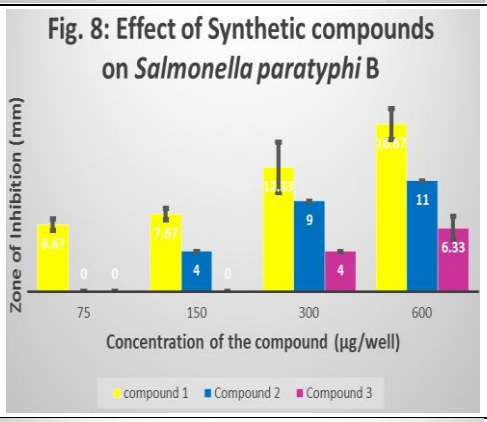


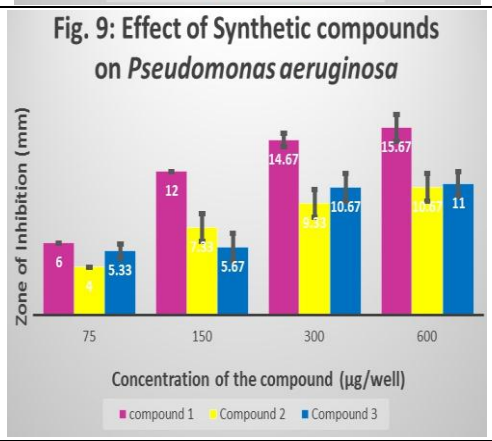


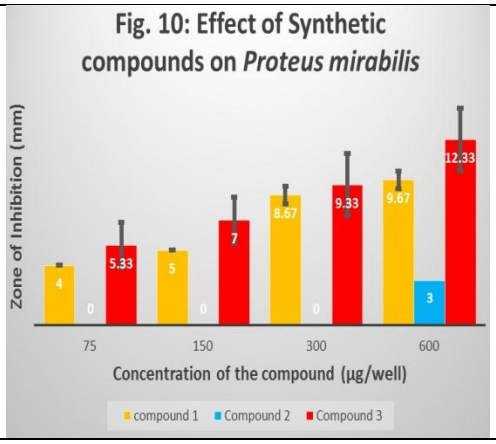












The RPI of compound 3 ranged from 0.04 at a concentration of 75 µg/well to 17.64 at a concentration of 600 µg/well for the Gram positive bacteria MRSA and *Staphylococcus aureus* respectively (Table 6). On the other hand, RPI of the compound showed negative values for Gram negative bacteria at lower concentrations and increased with increase in concentration of the compound. The minimum RPI was found to be 0.01 for *Salmonella paratyphi* A at a concentration of 300 µg/well and a maximum RPI of 25.08 for *Shigella flexneri* at a concentration of 600 µg/well.In general, the RPI for all the 3 compounds increased with increasing concentrations for all the bacteria under examination.

CONCLUSION

2, 3 – dimethyl - 6, 7, 8, 9 - tetrahydro benzocyclohepten-5-one and its derivatives have shown antibacterial activity against both Gram positive and Gram negative bacteria tested, with Compound 1 showing greater activity against *E. coli*, *Citrobacter divergens*, *Shigella flexneri*, *Salmonella paratyphi* A, *Salmonella paratyphi* B and *Pseudomonas aeruginosa* compared to other two compounds. Similarly, Compound 2 has shown more activity on Methicillin Resistant *Staphylococcus aureus* than other two compounds and Compound 3 has shown greater activity on *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Proteus mirabilis* than other

two compounds.

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