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SYNTHESIS AND ANTIBACTERIAL EVALUATION OF 2-SOME SUBSTITUTED BENZIMIDAZOLE-1-CARBODITHIOATE DERIVATIVES

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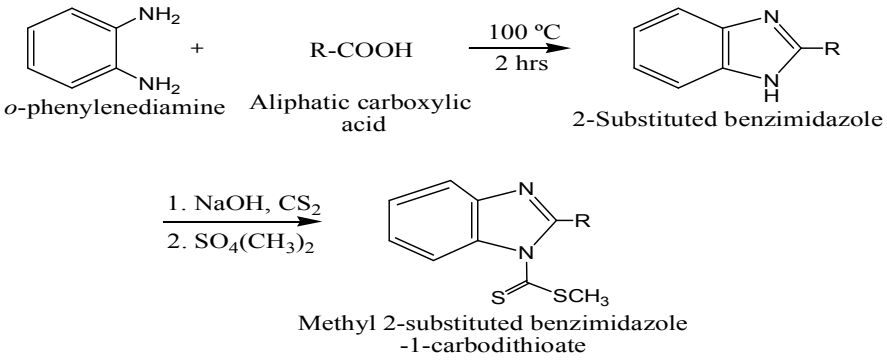
ABSTRACT:A series of methyl 2-substituted benzimidazole-1-carbodithioates were successfully synthesized. Benzimidazoles were prepared by condensation of o-phenylenediamine with substituted Carboxylic acid and by condensation of substituted benzaldehyde, Sodium metabisulphate and o-phenylenediamine. Methyl Carbodithioate derivative of the benzimidazole were prepared by reaction with carbon disulfide. *In vitro* antibacterial activity of the synthesized compounds was analyzed against three gram-positive bacterial species and gram negative microorganism by agar well-diffusion method (Cup plate method).
Key words: Methyl 2-substituted benzimidazole-1-carbodithioates, Benzimidazole, Antibacterial activity, Agar well-diffusion Method.

INTRODUCTION

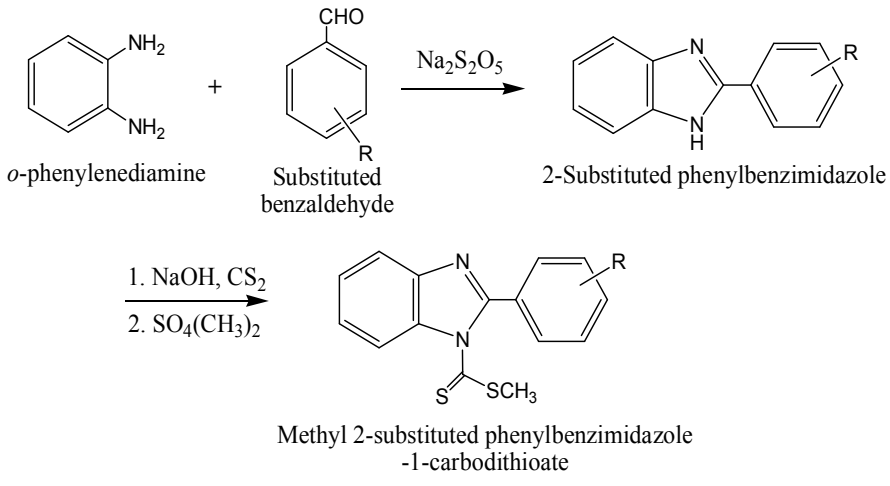
On the basis of exhaustive literature review it is concluded that a little work has been done in field ofantibacterial activity of substituted Methyl 1*H*-benzimidazole-1-carbodithioate.[1-7]

All the reactions were monitored using Thin Layer Chromatography (TLC). The melting points of all compounds were determined using open capillary tube melting point apparatus (EIE Instruments, T-0603105) and are uncorrected. The infrared spectra were recorded using KBr as the medium, using JASCO FT-IR-6100 model within the institute. The proton NMR spectra were measured at CSMCRI, Bhavanagar. The mass spectra were recorded at Panjab University, Chandigarh.

Scheme 1



Scheme 2



o-phenylenediamine

Substituted benzaldehyde

2-Substituted phenylbenzimidazole

Methyl 2-substituted phenylbenzimidazole -1-carbodithioate

EXPERIMENTAL

Synthesis of Benzimidazole

Method 1 (Procedure for compound 1, 2 & 3)

o-phenylenediamine (6.0 g, 0.055 mole) and substituted Carboxylic acid (5.1 g, 0.111 mole) were placed in a round bottom flask The mixture was heated on a water bath at 100 ºC for 2 hours. The reaction mixture was cooled and concentrated ammonia solution was added slowly drop wise, with constant stirring, until the mixture was just alkaline to litmus. Crude benzimidazole was filtered off at vacuum pump, washed with ice-cold water, and recrystallized from 10 % v/v aqueous ethanol. Solvent system for TLC: n-Hexane : Ethyl acetate (7:3)

Method 2(Procedure for compound 4 to 13)

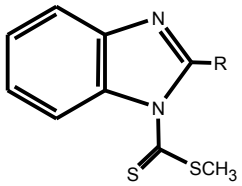
Benzaldehyde (5.0 g, 0.047 mole) was added to methanol (50.0 ml) in a beaker and stirred for few minutes. Saturated solution of Sodium Metabisulfite (10 ml) was added in portion wise into above mixture with constant stirring. The mixture was stirred vigorously and more methanol was added. The mixture was kept in a refrigerator over night. The resulting precipitate was filtered and dried properly (yield more than 90-95%).

o-phenylenediamine (4.1 g, 0.038 mole) was dissolved in DMF (40.0 ml) and benzaldehyde adduct (8.0 g, 0.038 mole) was added into it. The mixture was heated under reflux for 4 hours. The reaction mixture was cooled and poured into cold water. The resulting solid was filtered, dried and recrystallized from ethanol. Solvent system for TLC: n-Hexane : Ethyl acetate (7:3)

Synthesis of methyl carbodithioate derivatives of benzimidazole

Benzimidazole was dissolved in DMSO in 100 ml round bottom flask and this solution was stirred on magnetic stirrer for 5-10 minutes at room temperature. Carbon disulfide and aqueous sodium hydroxide (20 mole solution) was added drop wise simultaneously over 20-30 minutes and further stirred for 1 hour at room temperature. After an hour, dimethyl sulphate was added dropwise to the above reaction mixture with stirring at 5-10 ºC maintained using ice-bath. It was further stirred for 2-3 hours at 5-10 ºC and then poured onto crushed ice with constant stirring. The solid obtained was filtered by vacuum filtration, dried and recrystallized from ethanol.

Table 1. Structure and physical data of the synthesized compounds



Compound	R	Molecular formula	MASS	M.P.	R_f
1	-H	$C_9H_8N_2S_2$	208.29	58 ºC	0.86
2	0	$C_{10}H_{10}N_2S_2$	222.41	266 ºC	0.76
3	-CH_2-Ph	$C_{16}H_{14}N_2S_2$	298.40	159 ºC	0.70
4	-Ph	$C_{15}H_{12}N_2S_2$	284.32	260 ºC	0.59
5	-4'-N(CH_3)$_2$-Ph	$C_{17}H_{17}N_3S_2$	327.44	270 ºC	0.52
6	- 3'-OCH_3-Ph	$C_{16}H_{14}N_2OS_2$	314.4	216 ºC	0.79
7	-3',4'-(OCH_3)$_2$-Ph	$C_{17}H_{16}N_2O_2S_2$	344.42	205 ºC	0.67
8	-2'-Cl-Ph	$C_{15}H_{11}N_2S_2Cl$	318.82	212 ºC	0.4
9	-3'-Cl-Ph	$C_{15}H_{11}N_2S_2Cl$	318.82	220 ºC	0.46
10	-4'-Cl-Ph	$C_{15}H_{11}N_2S_2Cl$	318.82	257 ºC	0.81
11	-2'-NO_2-Ph	$C_{15}H_{11}N_3O_2S_2$	329.37	263 ºC	0.62
12	-3'-NO_2-Ph	$C_{15}H_{11}N_3O_2S_2$	329.37	167 ºC	0.73
13	-4'-NO_2-Ph	$C_{15}H_{11}N_3O_2S_2$	329.37	257 ºC	0.55

The structures of novel synthesized compounds of benzimidazole series were elucidated by IR, ^{1}H NMR, and Mass spectroscopic tools. The summary of physical data and spectral analysis data of the compound 1 to 13 is shown in Table 2.2 and 2.3 respectively

Table 2. Spectroscopic data of the synthesized compounds

Compounds	IR Data
1	IR (KBr, cm^{-1}): 3092 (aromatic C-H stretching), 1603 & 1510 (C=C aromatic stretching), 1365 (C-H bending of methyl carbodithioate group), 1287 (C-N stretching), 1054 (C=S stretching), 766 (C-S stretching)
2	3193 , 1579 & 1489, 1372 , 1231, 1013, 682
3	3079, 3018, 1588 & 1488, 1363, 1223, 1012, 725, 694
4	3047, 1590 & 1495 , 1374, 1227, 1006, 764, 658
5	3075 ,1614 & 1504 , 1398, 1225, 1011, 804, 731
6	3060, 1592 & 1481, 1322, 1288, 1233, 1110, 809, 787
7	3018, 1608 & 1504, 1387, 1256, 1228, 1027, 767 Mass (ESI-MS) (*m/z* [M+1], %): 345.17, 50 % ^{1}H NMR (DMSO-d_6, δ, ppm): 3.84 (s, 3*H*, OCH_3 at C_4), 3.89 (s, 3*H*, OCH_3 at C_3), 7.12-7.78 (m, 7*H*, aro protons), 12.75 (s, 3*H*, SCH_3).
8	3047, 1591 & 1489, 1401, 1232, 1035, 810,742, 732
9	3047,1604 & 1488, 1412,1228, 1114 ,796, 798, 677
10	3052, 1603 & 1449, 1365, 1226 , 1040 , 829, 745,729
11	3025, 1608 & 1504 , 1554 , 1368 1349 1241 1016 , 808 756
12	3059, 1624 & 1501 , 1522, 1387, 1349 1228 1071 791 706
13	2999, 1604 & 1524,1517 1399, 1339, 1227 1011 852 ,709

RESULT AND DISCUSSION

In vitro antibacterial activity of the synthesized compounds was analyzed against three gram-positive bacterial species [*Staphylococcus aureus* (MTCC 737), *Enterococcus faecalis* (MTCC 439), *Bacillus cereus* (MTCC 430)] and three gram-negative bacterial species[*Escherichia coli* (MTCC 1687), *Pseudomonas aeruginosa* (MTCC 2642),*Klebsiella pneumoniae* (MTCC 109)] by agar well-diffusion Method (Cup plate method).[8,9] Four serial dilutions yielded concentrations of 700, 500, 300 and 100 mg per well for the all 13 synthesized compounds were used. Ciprofloxacin was used as a standard reference and DMF as a control which did not exhibit any inhibition. The petridishes were incubated at 37 ± 1 °C for 24 hrs. The diameter of zone of inhibition produced by each compound was measured in millimeter using Antibiotic Zone Reader (Hally Instruments) and the results are presented in Table 3 & 4 and in Figure 1 to 6. The antibacterial activity was determined in triplicate.[10-16]

In the present study, the results revealed that most of the synthesized compounds exhibited comparable inhibitory activity to reference standard drug Ciprofloxacin. Methyl 1*H*-benzimidazole-1-carbo dithioate (1) showed more pronounced antibacterial activity than other compounds of this benzimidazole series, with better inhibitory activity against both gram-positive and gram-negative bacteria. Methyl 2-(4′-nitrophenyl)-1*H*-benzimidazole-1-carbodithioate (13) exhibited remarkable inhibitory activity against all bacteria except *Ps. aeruginosa* and *E. coli*. Other compounds except Methyl 2-methyl-1*H*-benz imidazole-1-carbodithioate (2), Methyl 2-(2′-chlorophenyl)-1*H*-benzimidazole-1-carbodithioate (8) and Methyl 2-(4′-chlorophenyl)-1*H*-benzimidazole-1-carbodithioate (10) exhibited average to moderate activity against all test bacteria.

. **Table 3. Zone of inhibition of the synthesized compounds against selected bacterium species**

Zone of inhibition (mm) of the Synthesized compounds												
	Escherichia coli				***Enterococcus faecalis***				***Pseudomonas aeruginosa***			
CMPND	**700 µg/well**	**500 µg/well**	**300 µg/well**	**100 µg/well**	**700 µg/well**	**500 µg/well**	**300 µg/well**	**100 µg/well**	**700 µg/well**	**500 µg/well**	**300 µg/well**	**100 µg/well**
STD	44.2 ± 0.15*	44.5 ± 0.10	43.0 ± 0.25	42.4 ± 0.15	35.1 ± 0.10*	30.2 ± 0.15	29.8 ± 0.10	28.3 ± 0.21	44.4 ± 0.21*	44.2 ± 0.21	43.9 ± 0.10	43.2 ± 0.15
1	10.8 ± 0.15	10.2 ± 0.15	8.1 ± 0.21	4.1 ± 0.21	22.8 ± 0.10	22.6 ± 0.10	18.8 ± 1.24	14.4 ± 0.32	22.3 ± 0.21	20.0 ± 0.38	10.3 ± 0.15	4.1 ± 0.15
2	3.2 ± 0.15	2.1 ± 0.21	0.0 ± 0.00	0.0 ± 0.00	10.2 ± 0.15	8.4 ± 0.10	8.1 ± 0.15	4.5 ± 0.10	2.7 ± 0.17	2.2 ± 0.15	0.0 ± 0.00	0.0 ± 0.00
3	6.0 ± 0.06	5.7 ± 0.15	5.1 ± 0.10	1.9 ± 0.06	8.4 ± 0.15	6.7 ± 0.17	6.3 ± 0.10	4.1 ± 0.12	1.3 ± 0.10	1.1 ± 0.23	0.0 ± 0.00	0.0 ± 0.00
4	6.4 ± 0.15	6.3 ± 0.10	6.0 ± 0.15	4.2 ± 0.15	6.8 ± 0.06	6.2 ± 0.20	5.7 ± 0.10	4.1 ± 0.12	3.4 ± 0.15	1.2 ± 0.15	0.0 ± 0.00	0.0 ± 0.00
5	6.0 ± 0.25	5.2 ± 0.06	4.8 ± 0.10	4.3 ± 0.31	7.7 ± 0.06	6.5 ± 0.10	6.2 ± 0.06	5.5 ± 0.10	5.8 ± 0.06	4.2 ± 0.21	2.1 ± 0.10	0.0 ± 0.00
6	4.8 ± 0.15	4.0 ± 0.15	3.4 ± 0.20	2.8 ± 0.20	6.5 ± 0.10	6.1 ± 0.10	4.2 ± 0.00	4.0 ± 0.00	4.4 ± 0.15	4.3 ± 0.17	2.2 ± 0.21	0.0 ± 0.00
7	8.8 ± 0.15	8.2 ± 0.15	6.0 ± 0.25	2.1 ± 0.15	8.2 ± 0.20	6.2 ± 0.15	5.6 ± 0.31	4.2 ± 0.15	6.2 ± 0.26	4.8 ± 0.06	3.9 ± 0.15	2.2 ± 0.26
8	7.2 ± 0.10	6.3 ± 0.15	6.1 ± 0.21	0.0 ± 0.00	4.5 ± 0.10	4.2 ± 0.15	0.0 ± 0.00	0.0 ± 0.00	8.2 ± 0.25	4.6 ± 0.25	2.2 ± 0.25	2.2 ± 0.21
9	6.6 ± 0.21	6.1 ± 0.10	6.1 ± 0.10	4.2 ± 0.20	6.2 ± 0.21	4.9 ± 0.15	4.8 ± 0.10	17.3 ± 0.49	4.8 ± 0.10	4.1 ± 0.15	1.1 ± 0.12	0.0 ± 0.00
10	4.7 ± 0.12	4.0 ± 0.15	3.7 ± 0.40	0.0 ± 0.00	1.6 ± 0.15	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	4.3 ± 0.25	1.7 ± 0.10	1.1 ± 0.15	0.0 ± 0.00
11	5.2 ± 0.15	4.5 ± 0.12	2.2 ± 0.15	0.0 ± 0.00	6.5 ± 0.10	6.3 ± 0.15	4.7 ± 0.10	4.2 ± 0.15	6.4 ± 0.15	4.1 ± 0.15	2.2 ± 0.29	0.0 ± 0.00
12	3.0 ± 0.15	2.8 ± 0.15	2.4 ± 0.21	0.0 ± 0.00	8.7 ± 0.10	8.4 ± 0.15	5.6 ± 0.06	5.4 ± 0.15	4.4 ± 0.25	4.2 ± 0.15	2.4 ± 0.15	0.0 ± 0.00
13	4.6 ± 0.15	4.2 ± 0.15	4.0 ± 0.20	2.8 ± 0.15	0.4 ± 0.21	9.9 ± 0.21	9.9 ± 0.06	9.5 ± 0.25	2.9 ± 0.10	1.0 ± 0.10	0.0 ± 0.00	0.0 ± 0.00

Table 3. Continued

Zone of inhibition (mm) of the Synthesized compounds												
	Staphylococcus aureus				***Klebsiella pneumoniae***				***Bacillus cereus***			
CMPND	**700 µg/well**	**500 µg/well**	**300 µg/well**	**100 µg/well**	**700 µg/well**	**500 µg/well**	**300 µg/well**	**100 µg/well**	**700 µg/well**	**500 µg/well**	**300 µg/well**	**100 µg/well**
STD	40.2 ± 0.15*	38.5± 0.12	36.7± 0.15	36.± 0.10	33.2 ± 0.06*	32.6 ± 0.15	32.1 ± 0.10	32.1± 0.15	41.4± 0.15*	40.2± 0.10	39.9± 0.21	38.5± 0.12
1	24.4 ± 0.15	20.3 ± 0.15	18.7± 0.10	18.± 0.00	24.8 ± 0.15	24.3 ± 0.12	24.4 ± 0.15	14.2 ± 0.15	24.7± 0.12	24.3± 0.12	20.2± 0.15	14.2 ± 0.20
2	4.2 ± 0.25	3.8 ± 0.15	2.5 ± 0.20	0.0 ± 0.00	4.6 ± 0.21	4.5 ± 0.17	2.1 ± 0.15	2.1 ± 0.10	4.8 ± 0.20	4.4 ± 0.15	4.1 ± 0.10	0.0 ± 0.00
3	8.3 ± 0.10	6.7 ± 0.10	5.3 ± 0.10	2.7 ± 0.10	2.4 ± 0.15	1.7 ± 0.36	1.0 ± 0.15	0.0 ± 0.00	4.6 ± 0.10	4.1 ± 0.10	2.0 ± 0.15	0.0 ± 0.00
4	6.7± 0.15	6.3 ± 0.12	6.1± 0.10	2.5 ± 0.15	10.2± 0.15	8.7 ±0.15	8.1 ± 0.12	4.1± 0.31	8.1± 0.12	6.4± 0.15	6.1 ± 0.15	2.7 ± 0.10
5	8.3 ± 0.15	6.4 ± 0.25	4.2 ± 0.06	3.8 ± 0.15	4.7 ± 0.21	4.2 ± 0.00	4.1 ± 0.15	3.8 ± 0.10	8.1 ± 0.10	6.0 ± 0.25	5.2 ± 0.06	4.2 ± 0.15
6	8.5 ± 0.10	8.1 ± 0.17	8.0 ± 0.20	4.1 ± 0.06	6.1 ± 0.10	4.5 ± 0.25	4.3 ± 0.10	4.1 ± 0.15	8.6 ± 0.15	8.0 ± 0.15	6.2 ± 0.15	0.0 ± 0.00
7	4.7 ± 0.15	4.2 ± 0.15	3.3 ± 0.10	0.0 ± 0.00	2.0 ± 0.25	1.7 ± 0.10	1.1 ± 0.10	0.0 ± 0.00	8.0 ± 0.25	4.1 ± 0.15	2.3 ± 0.10	0.0 ± 0.00
8	2.5 ± 0.15	2.2 ± 0.20	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	2.2 ± 0.21	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
9	2.3 ± 0.15	1.6 ± 0.21	0.0 ± 0.00	0.0 ± 0.00	4.6 ± 0.15	4.0 ± 0.15	2.9 ± 0.10	2.1 ± 0.10	4.5 ± 0.21	4.5 ± 0.10	2.1 ± 0.10	2.1 ± 0.10
10	4.6 ± 0.06	4.2 ± 0.15	2.2 ± 0.20	2.2 ± 0.15	1.1 ± 0.06	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	2.1 ± 0.10	1.2 ± 0.15	0.0 ± 0.00	0.0 ± 0.00
11	6.4 ± 0.15	6.1 ± 0.06	4.2 ± 0.21	2.1 ± 0.10	8.7 ± 0.15	6.2 ± 0.06	4.1 ± 0.10	2.1 ± 0.06	9.2 ± 0.15	8.3 ± 0.06	4.1 ± 0.15	0.0 ± 0.00
12	4.7 ± 0.17	4.6 ± 0.10	4.2 ± 0.15	0.0 ± 0.00	8.6 ± 0.10	8.1 ± 0.12	7.7 ± 0.21	4.0 ± 0.25	4.7 ± 0.10	4.1 ± 0.10	3.7 ± 0.17	0.0 ± 0.00
13	6.8 ± 0.15	6.2 ± 0.15	4.0 ± 0.06	3.7 ± 0.21	7.2 ± 0.06	6.9 ± 0.10	6.3 ± 0.21	6.2 ± 0.10	8.6 ± 0.21	8.2 ± 0.21	6.1 ± 0.10	6.1 ± 0.17

Figure1. Graphical representation of zone of inhibition of the synthesized compounds against *B. cereus*

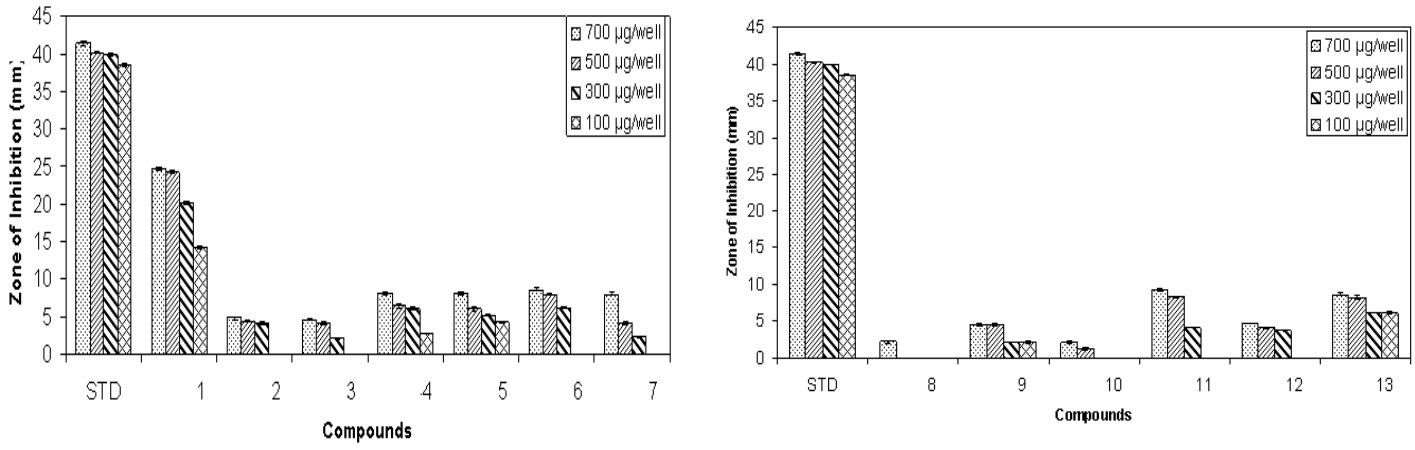


Figure 2. Graphical representation of zone of inhibition of the synthesized compounds against *K.pneumoniae*

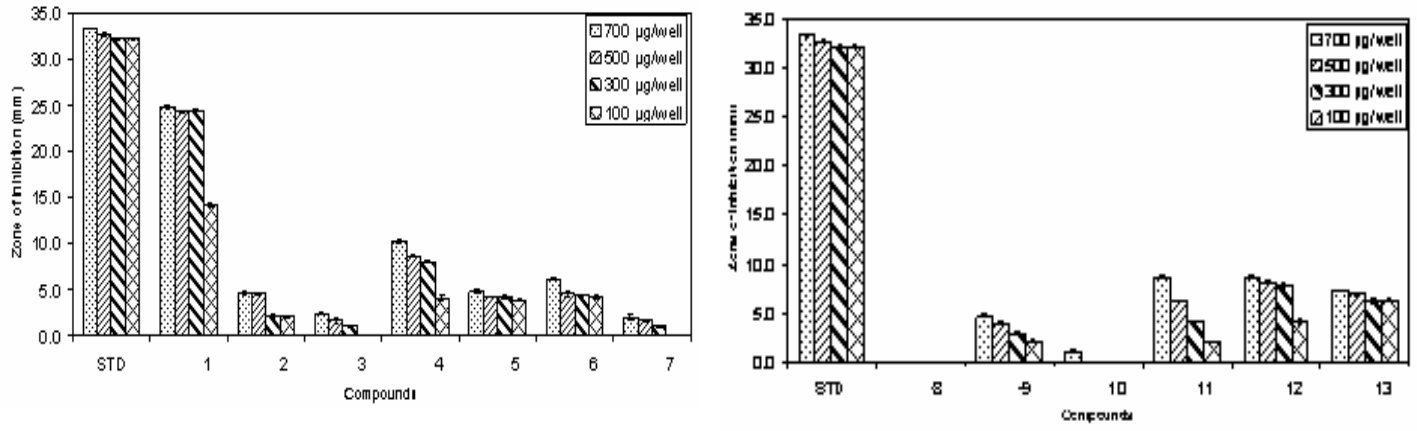


Figure 3. Graphical representation of zone of inhibition of the synthesized compounds against *S. aureus*

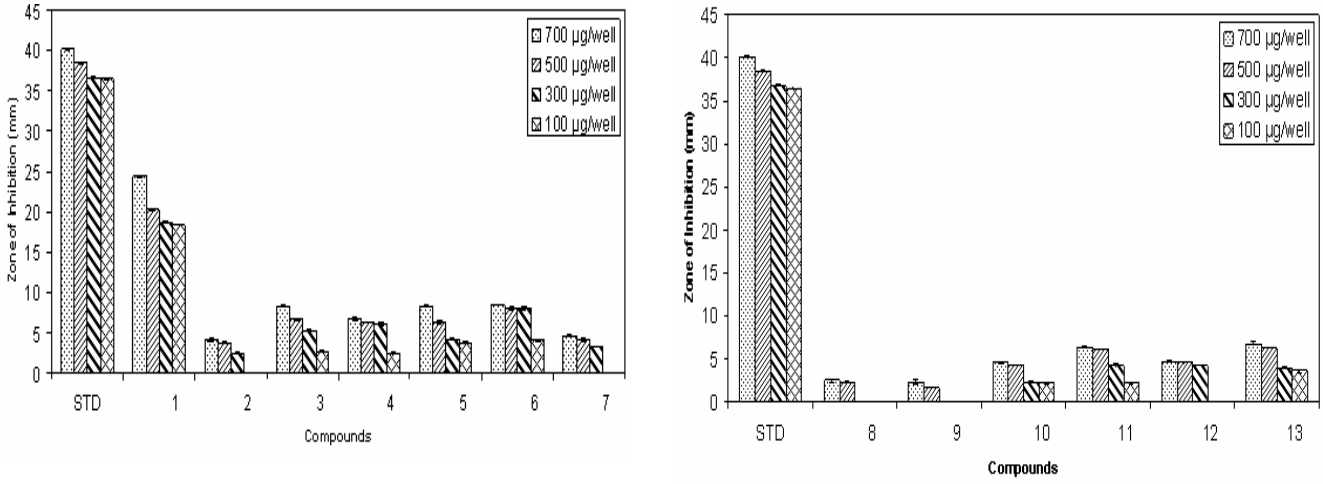


Figure 4. Graphical representation of zone of inhibition of the synthesized compounds against *E. faecalis*

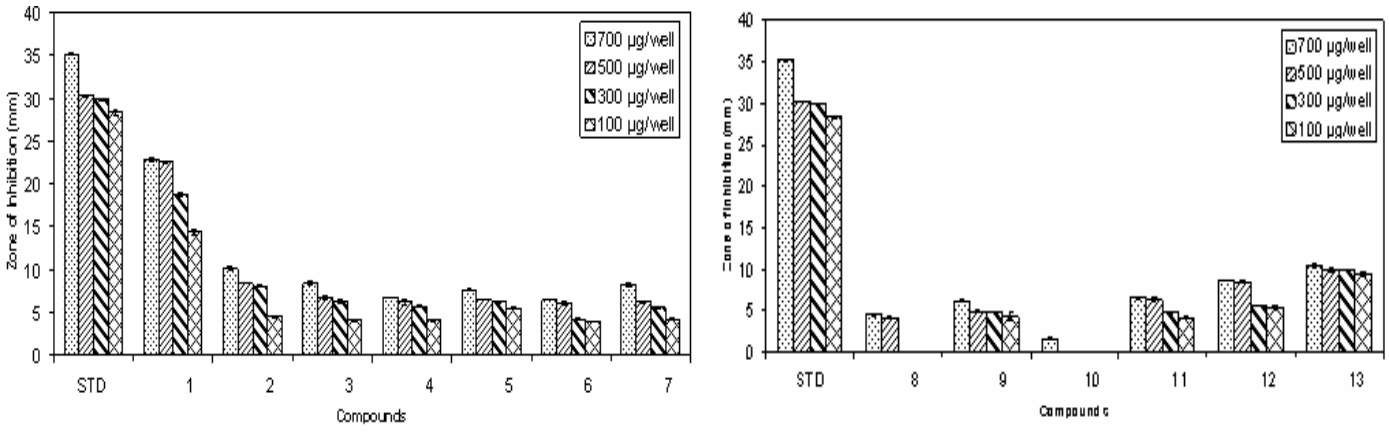


Figure 5. Graphical representation of zone of inhibition of the synthesized compounds against *E. coli*

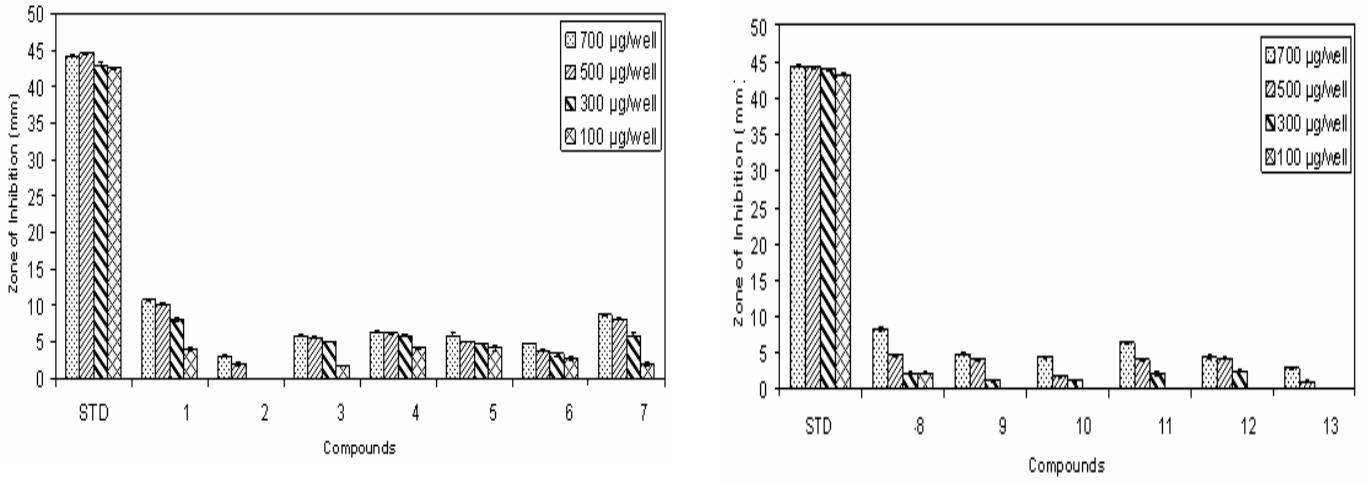
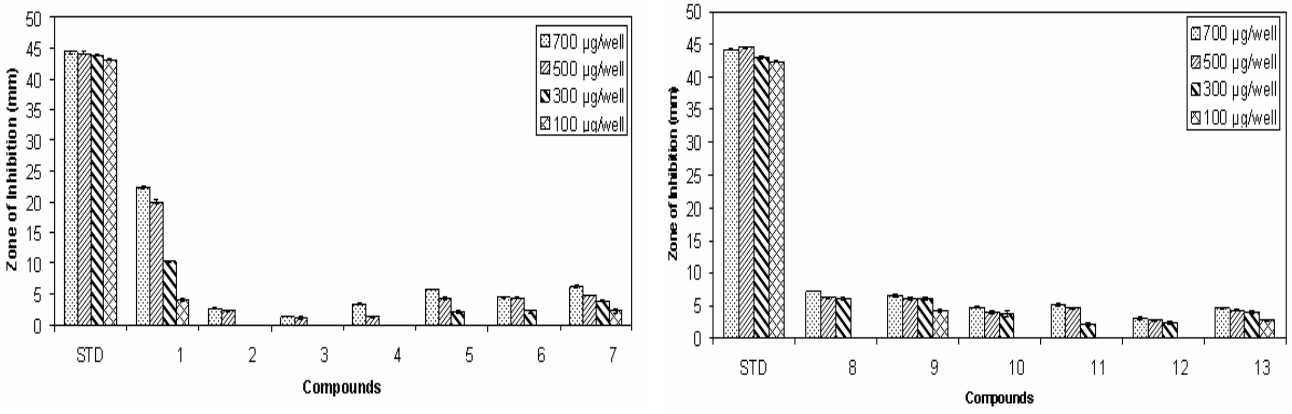


Figure 6. Graphical representation of zone of inhibition of the synthesized compounds against *P. aeruginosa*



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