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ANTIBACTERIAL ACTIVITY OF 26-MEMBER [2+2] MACROCYCLES: A STRUCTURE-REACTIVITY STUDY

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ABSTRACT

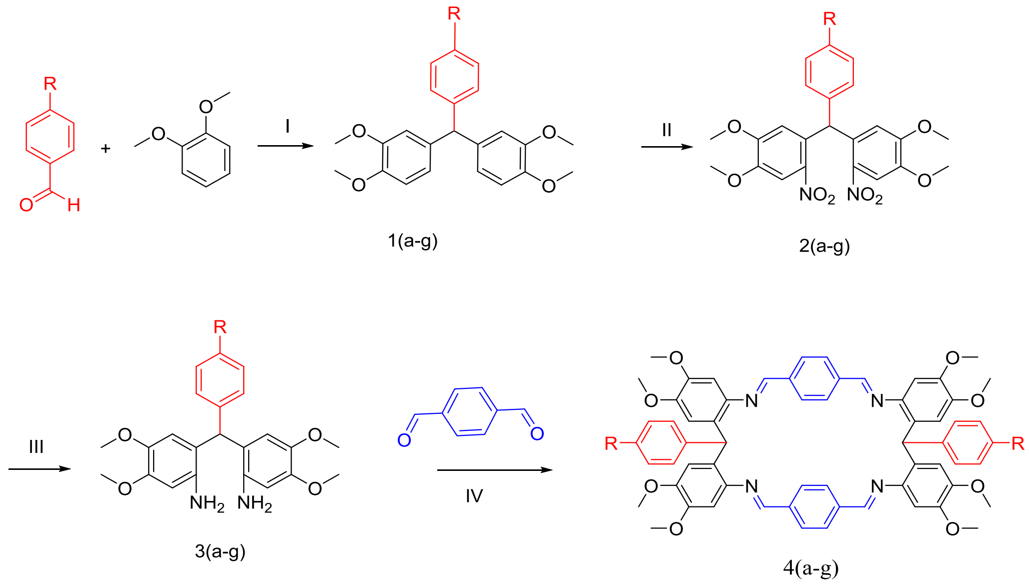
26 member [2+2] macrocyclic Schiff base compounds were investigated for their antibacterial activity against Gram positive and Gram negative bacteria. The recorded data of zone of inhibition showed significant broad activity when compared with standard. The structure reactivity correlation of the compounds has been studied. The antibacterial searching suggests that all the synthesized macrocyclic compounds showed moderate to very good activity against the tested organisms. Among the compounds, -COOH substituted compound showed the most promising antibacterial activity. The inhibition zone diameters of these compounds have been correlated with Hammett substituent constants, F and R parameters. From the results of statistical analysis, the effects of substituent on the antibacterial activity of compounds have been studied.

KEYWORDS: Macrocycle, Schiff base, Cyclic imide, antibacterial activity, correlation studies.

INTRODUCTION

The design and synthesis of macrocycles is one of the captivating areas for pharmacologists because of their biological applications. Schiff-base macrocycles have received considerable attention due to their wide range of pharmacological activity and that can favourably alter the biological and physiochemical properties as well as selectivity.[1,2] Macrocyclic compounds have been studied significantly for their uses in molecular recognition, host–guest chemistry, supramolecular structures, material chemistry and catalysis.[3-7] Latest review articles have discussed the role that macrocycles can play in medicinal chemistry.[8-10] Triarylmethanes are possess a wide range of biological activities such as antioxidant,[11] antitubercular,[12] antitumor,[13] antifungal,[14] anti-inflammatory,[14] antiviral,[15] as well as anti-diabetes.[16] Macrocyclic schiff base with triarylmethane are one opportunity to expand the synthetic toolbox for medicinal chemistry to provide bioactive molecules.

We have synthesized $1^4,1^5,3^4,3^5,9^4,9^5,11^4,11^5$-octamethoxy-2,10-bis(4-methoxyphenyl)-4,8,12,16-tetraaza-1,3,9,11(1,2),6,14(1,4)-hexabenzenacyclohexadecaphane-4,7,12,15-tetraene (4a-4g) derivatives (Fig-1) and evaluated for antibacterial activity. All the macrocyclic compounds were synthesized as per the reported procedure.[17] Compounds (4a-4g) were characterized by UV, IR, NMR and Mass spectrometric techniques**.**



R= $-OCH_3$, $-CH_3$, $-CH_2CH_3$, -H, -Cl, $-COOCH_3$, -COOH.

I) Sulfuric acid at 0-5°C, RT.
II) Nitric acid, Acetic acid at 15-20°C,
III) Raney Nickel, Methanol, Ethyl acetate, 50°C.
IV) Methanol at 60-65°C

Fig. 1: Synthesis of Macrocycles 4a-4g.

Studies of substituent effects on zone of inhibition against the growth of microorganisms in various substituted N-(1-piperidinobenzyl) nicotinamide,[18] 2-benzylidene-1,3-indandiones,[19] and 6-aryl-4-methyl-2-oxo-1, 2, 3, 6 -tetrahydropyrimidine-5-carboxamides[20] have been reported. As a part of our interest in the structure-reactivity study, we have studied the antibacterial activity to find out the substituents effect on macrocycles 4a-4g.

MATERIALS AND METHODS

The reagents were purchased from Aldrich and used without further purification and solvents were purchased from commercial suppliers and used without further purification.

Disc Preparation

The 6 mm (diameter) discs were prepared from Whatmann No. 1 filter paper. The discs were sterilized by autoclave at 121°C. After the sterilization the moisture discs were dried on hot air oven at 50°C. Then discs were mixed with chemical compounds separately and control discs were prepared.

Collection of test microorganisms

The Bacterial strains of *Bacillus subtilis, Escherichia coli, Enterococcus faecalis, Klebsiella pneumonia, Staphylococcus aureus, Streptococcus pneumoniae, and Proteus mirabilis* obtained from Microbial Type culture Collection Centre (MTCC), Chandigarh.

Assay of Antibacterial Activity

Antibacterial activity test was carried out following the modification of the method originally described by Bauer *et al.*[21] Muller Hinton agar was prepared and autoclaved at 15 lbs pressure for 20 minutes and cooled to 45ºC. The cooled media was poured on to sterile petri plates and allowed for solidification. The plates with media were seeded with the respective microbial suspension using sterile swab. The various compounds prepared discs individually were placed on each petri plates and placed control and standard (*nitrofurantoin (300 mcg)*) discs. The plates were incubated at 37ºC for 24 hrs. After incubation period, the diameter of the zone formed around the paper disc were measured. Three inhibition zone diameter measurements were taken for each well and averaged, for each replicates the readings were taken in three different fixed directions and the average values were recorded and expressed in mm. The average inhibition zone diameter for the various bacteria is shown in Table-1

Table 1: Antimicrobial activity (zone of inhibition (mm) values) of macrocycles (4a-4g).

S. No.	Bacteria	Zone of inhibition (mm in diameter)								
		C	S*	$-OCH_3$	$-CH_3$	$-CH_2CH_3$	-H	-Cl	$-COOCH_3$	-COOH
1	*Bacillus subtilis*	-	20	13	14	15	16	19	21	22
2	*Escherichia coli*	-	24	16	17	18	19	21	23	24
3	*Enterococcus faecalis*	-	20	13	14	15	16	18	20	21
4	*Klebsiella pneumonia*	-	25	16	17	18	20	22	25	26
5	*Staphylococcus aureus*	-	27	17	18	19	20	23	25	28
6	*Streptococcus*	-	19	15	16	17	19	21	23	24

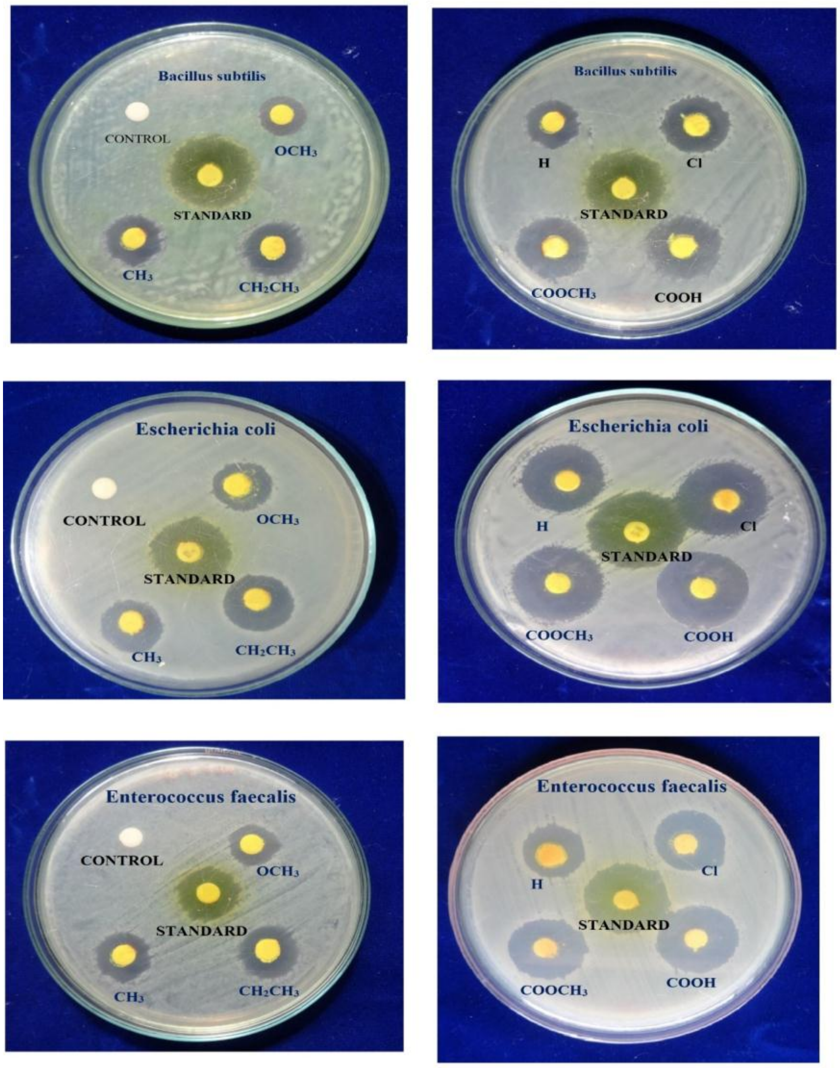
	pneumoniae									
7	*Proteus mirabilis*	-	21	12	13	14	16	18	20	21

RESULTS AND DISCUSSION

In the present investigation, a variety of newly synthesized [2+2] macrocyclic Schiff base compounds were screened for antibacterial activities.

The in vitro antibacterial activities of the compounds were tested against *Bacillus subtilis, Escherichia coli, Enterococcus faecalis, Klebsiella pneumonia, Staphylococcus aureus, Streptococcus pneumoniae and Proteus mirabilis* compared with standard *nitrofurantoin.* Zone of inhibition of the seven compounds against the growth of microorganisms are summarized in Table 1 and Fig. 2. A comparative study of the compounds indicates that compound 4g(-COOH substituted) has higher activity than the other compounds.

$$-OCH_3 < -CH_3 < -CH_2CH_3 < -H < -Cl < -COOCH_3 < -COOH$$



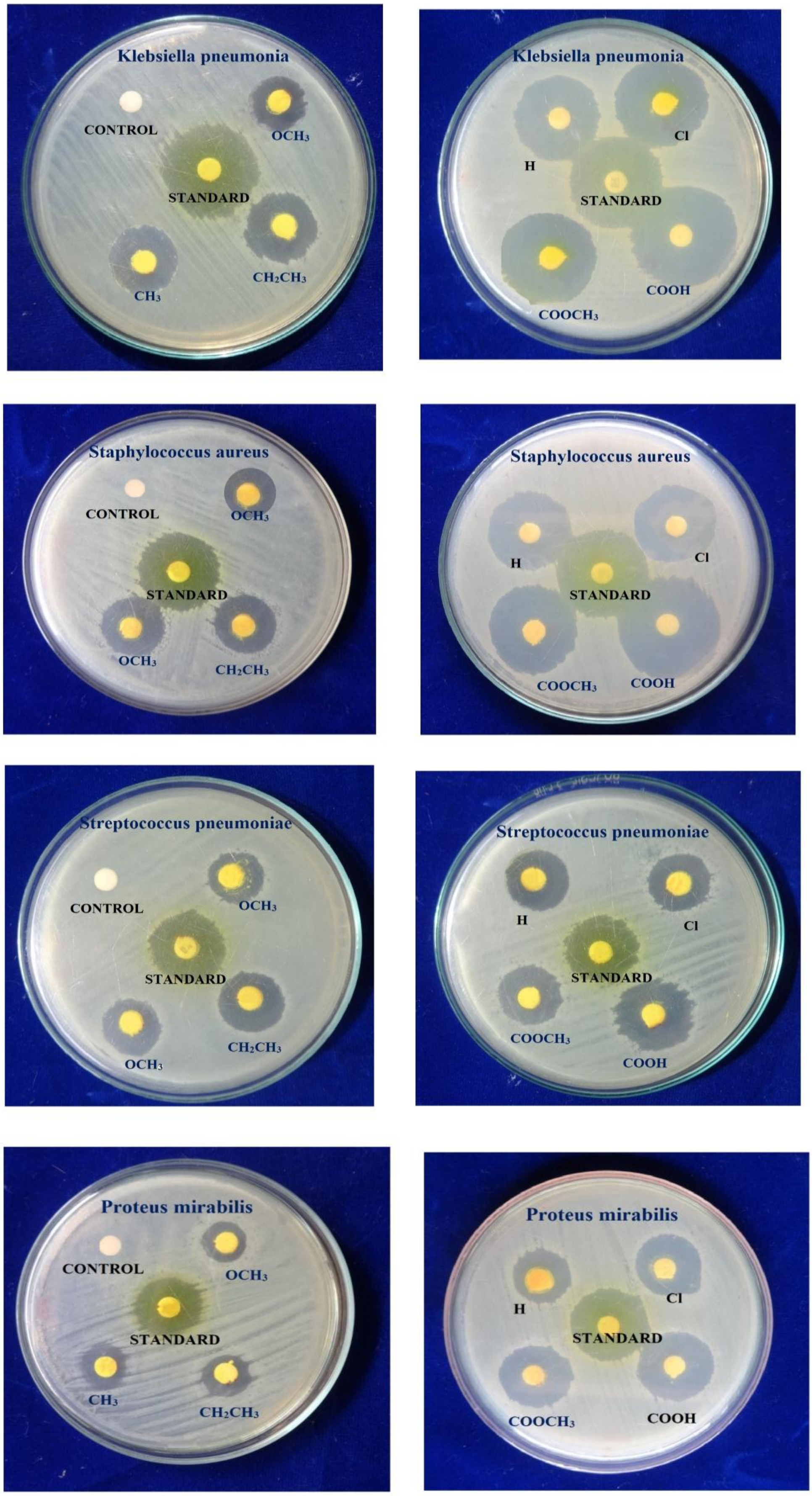


Fig. 2: Antimicrobial activity of macrocycles (4a-g).

In order to express the effect of substituent quantitatively it was considered worthwhile to correlate the logarithm of inhibition zone diameter (IZD) of macrocycles (4a-4g) at the same concentration with the Hammett substituent constants for all the microorganism. The results of statistical SSP analysis are given in Table 2. The corresponding Hammett plot for *Bacillus Subtilis* is shown in Fig. 3.

The positive value of the reaction constant (ρ) equation (1)

$$\log IZD=(0.18\pm0.01)\,\sigma_P + (1.204\pm0.005) \qquad (1)$$

(r=0.992, n=7, F=323.17)

Indicates that electron withdrawing substituents increase the antibacterial activity and electron releasing substituent retard it.

Table 2: Results of statistical treatment of log (IZD) mm with σ_P, σ_P^o, σ_P^+, σ_P^-, σ_P^+/σ_P, σ_P/σ_P^-, σ_P^+/σ_P^- substituent constants using single parameter equation 1.

S. No	Name of the bacteria	Scale	ρ	r	s	F	Log(IZD)^o	n
1	***Bacillus subtilis***	σ_P	0.29±0.02	0.992	0.01	323.17	1.204±0.005	7
		σ_p^o	0.34±0.05	0.974	0.02	54.59	1.182±0.012	5
		σ_P^+	0.19±0.02	0.958	0.03	55.89	1.236±0.011	7
		σ_P^-	0.19±0.03	0.956	0.03	52.58	1.196±0.012	7
		σ_P^+/σ_P	0.19±0.02	0.967	0.02	72.75	1.233±0.009	7
		σ_P/σ_P^-	0.20±0.03	0.959	0.03	57.61	1.195±0.011	7
		σ_P^+/σ_P^-	0.15±0.01	0.977	0.02	103.78	1.219±0.008	7
2	***Escherichia coli***	σ_P	0.22±0.01	0.989	0.01	233.90	1.273±0.004	7
		σ_p^o	0.25±0.04	0.958	0.02	33.73	1.257±0.011	5
		σ_P^+	0.14±0.01	0.965	0.02	67.83	1.298±0.007	7
		σ_P^-	0.15±0.02	0.959	0.02	57.56	1.268±0.008	7
		σ_P^+/σ_P	0.14±0.02	0.970	0.02	79.22	1.296±0.007	7
		σ_P/σ_P^-	0.15±0.02	0.964	0.02	64.87	1.267±0.008	7
		σ_P^+/σ_P^-	0.11±0.01	0.984	0.01	148.31	1.285±0.005	7
3	**Enterococcus faecalis**	σ_P	0.26±0.02	0.989	0.01	219.65	1.197±0.005	7
		σ_p^o	0.30±0.05	0.957	0.03	33.05	1.177±0.014	5
		σ_P^+	0.17±0.02	0.967	0.02	71.10	1.226±0.008	7
		σ_P^-	0.17±0.02	0.957	0.02	54.19	1.190±0.010	7
		σ_P^+/σ_P	0.17±0.02	0.972	0.02	84.54	1.223±0.008	7
		σ_P/σ_P^-	0.17±0.02	0.961	0.02	60.93	1.189±0.010	7
		σ_P^+/σ_P^-	0.13±0.01	0.984	0.02	149.27	1.211±0.006	7
4	***Klebsiella pneumonia***	σ_P	0.27±0.02	0.992	0.01	294.29	1.286±0.005	7
		σ_p^o	0.30±0.06	0.949	0.03	27.34	1.267±0.015	5
		σ_P^+	0.18±0.02	0.967	0.02	72.96	1.316±0.009	7
		σ_P^-	0.18±0.02	0.964	0.02	66.44	1.278±0.010	7
		σ_P^+/σ_P	0.17±0.02	0.969	0.02	78.03	1.313±0.008	7
		σ_P/σ_P^-	0.18±0.02	0.967	0.02	72.21	1.277±0.009	7
		σ_P^+/σ_P^-	0.14±0.01	0.985	0.02	160.36	1.300±0.006	7

5	***Staphylococcus aureus***	σ_P	0.26±0.02	0.981	0.02	126.61	1.304±0.007	7
		σ_P^{o}	0.31±0.05	0.963	0.03	38.36	1.287±0.013	5
		σ_P^{+}	0.17±0.03	0.935	0.03	34.62	1.333±0.012	7
		σ_P^{-}	0.17±0.02	0.960	0.02	59.07	1.297±0.010	7
		σ_P^{+}/σ_P	0.16±0.03	0.944	0.03	40.76	1.331±0.011	7
		σ_P/σ_P^{-}	0.18±0.02	0.963	0.02	64.54	1.296±0.009	7
		$\sigma_P^{+}/\sigma_P^{-}$	0.13±0.02	0.967	0.02	72.61	1.318±0.008	7
6	***Streptococcus pneumoniae***	σ_P	0.26±0.02	0.986	0.02	181.05	1.259±0.006	7
		σ_P^{o}	0.30±0.06	0.949	0.03	27.46	1.241±0.015	5
		σ_P^{+}	0.17±0.02	0.969	0.02	76.79	1.288±0.008	7
		σ_P^{-}	0.17±0.03	0.946	0.03	42.42	1.252±0.011	7
		σ_P^{+}/σ_P	0.17±0.03	0.976	0.02	101.60	1.285±0.007	7
		σ_P/σ_P^{-}	0.17±0.03	0.949	0.03	45.06	1.251±0.011	7
		$\sigma_P^{+}/\sigma_P^{-}$	0.14±0.01	0.979	0.02	115.13	1.273±0.007	7
7	***Proteus mirabilis***	σ_P	0.31±0.02	0.985	0.02	163.78	1.179±0.007	7
		σ_P^{o}	0.35±0.07	0.947	0.04	26.32	1.158±0.018	5
		σ_P^{+}	0.20±0.02	0.970	0.02	80.08	1.214±0.009	7
		σ_P^{-}	0.20±0.03	0.942	0.03	39.79	1.172±0.014	7
		σ_P^{+}/σ_P	0.20±0.02	0.978	0.02	108.77	1.211±0.008	7
		σ_P/σ_P^{-}	0.20±0.03	0.945	0.03	42.27	1.170±0.013	7
		$\sigma_P^{+}/\sigma_P^{-}$	0.16±0.01	0.978	0.02	112.75	1.196±0.008	7

"n=5 means, values calculated without $–CH_2CH_3$ and $-COOCH_3$ groups".

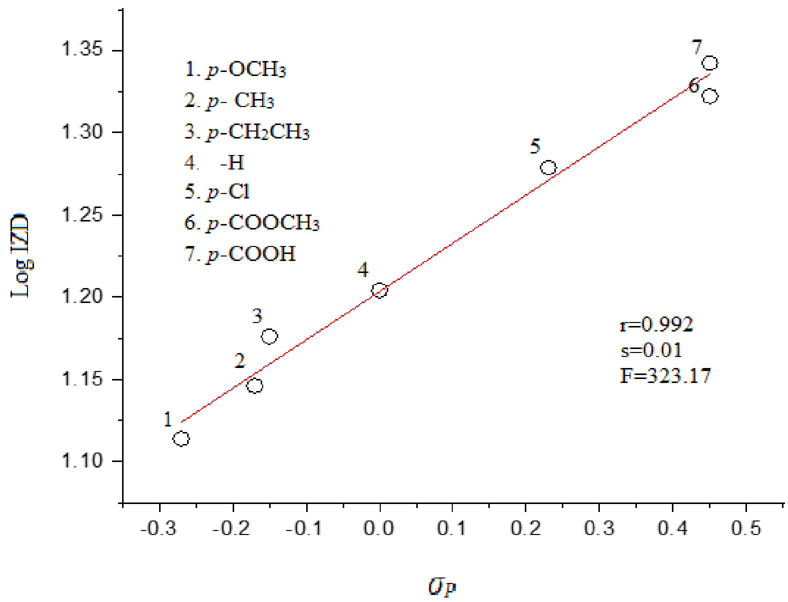


Fig. 3: Hammett plot for *Bacillus Subtilis.*

DSP analysis has been performed for each of the resonance scale (σ_R, σ_R^{+} σ_R^{-}, σ_R^{0}). The best fit of DSP analysis for *Staphylococcus aureus* is taken from good correlation coefficient and least standard error (SE) of the regression equations (2) and (3) and the result obtained given in Table 3.

log IZD=(0.22±0.03) σ_I + (0.28±0.03) σ_R^0 + (1.30±0.01) (2)

(R=0.989, SE=0.01, n=7, F=90.9)

log IZD=(0.25±0.04)F + (0.27±0.03) R + (1.31±0.01) (3)

(R=0.981, SE=0.02, n=7, F=51.1)

Table 3: DSP analysis of log IZR (mm) with dual parameter equations 2 and 3.

S. No	Name of the bacteria	Scale	ρ_I	ρ_R	R	SE	F	Log(IZD)^o	n	λ= ρ_R/ ρ_I
1	*Bacillus subtilis*	σ_I, σ_R	0.35±0.08	0.33±0.08	0.948	0.04	13.2	1.22±0.02	6	0.94
		σ_I, σ_R^o	0.25±0.05	0.30±0.04	0.976	0.02	39.86	1.20±0.01	7	1.20
		σ_I, σ_R^+	0.14±0.09	0.11±0.03	0.917	0.04	10.51	1.24±0.03	7	0.79
		σ_I, σ_R^-	0.35±0.08	0.36±0.09	0.945	0.04	12.51	1.22±0.02	6	1.03
		F, R	0.28±0.03	0.30±0.02	0.993	0.01	137.35	1.21±0.01	7	1.07
2	*Escherichia coli*	σ_I, σ_R	0.25±0.07	0.26±0.07	0.935	0.03	10.41	1.29±0.02	6	1.04
		σ_I, σ_R^o	0.18±0.03	0.23±0.03	0.978	0.02	44.92	1.27±0.01	7	1.28
		σ_I, σ_R^+	0.09±0.07	0.08±0.02	0.918	0.03	10.74	1.30±0.02	7	0.89
		σ_I, σ_R^-	0.25±0.06	0.28±0.06	0.947	0.03	13.16	1.29±0.02	6	1.12
		F, R	0.20±0.02	0.23±0.02	0.993	0.01	133.16	1.28±0.01	7	1.15
3	*Enterococcus faecalis*	σ_I, σ_R	0.30±0.08	0.30±0.08	0.937	0.03	10.88	1.22±0.02	6	1.00
		σ_I, σ_R^o	0.21±0.04	0.28±0.04	0.977	0.02	41.16	1.20±0.01	7	1.33
		σ_I, σ_R^+	0.10±0.08	0.10±0.03	0.918	0.04	10.8	1.23±0.02	7	1.00
		σ_I, σ_R^-	0.30±0.07	0.34±0.08	0.945	0.03	12.62	1.21±0.02	6	1.13
		F, R	0.23±0.03	0.28±0.02	0.992	0.01	128.7	1.20±0.01	7	1.22
4	*Klebsiella pneumonia*	σ_I, σ_R	0.31±0.08	0.31±0.08	0.935	0.04	10.5	1.30±0.02	6	1.00
		σ_I, σ_R^o	0.22±0.04	0.290±0.04	0.980	0.02	48.36	1.28±0.01	7	1.32
		σ_I, σ_R^+	0.11±0.08	0.11±0.03	0.924	0.04	11.65	1.32±0.02	7	1.00
		σ_I, σ_R^-	0.31±0.06	0.35±0.07	0.962	0.03	18.77	1.30±0.02	6	1.13
		F, R	0.24±0.02	0.29±0.02	0.995	0.01	189.93	1.29±0.01	7	1.21
5	*Staphylococcus aureus*	σ_I, σ_R	0.32±0.10	0.30±0.10	0.909	0.04	7.164	1.32±0.03	6	0.94
		σ_I, σ_R^o	0.22±0.03	0.28±0.03	0.989	0.01	90.9	1.30±0.01	7	1.27
		σ_I, σ_R^+	0.12±0.09	0.10±0.03	0.909	0.04	9.54	1.33±0.02	7	0.83
		σ_I, σ_R^-	0.32±0.07	0.35±0.07	0.958	0.03	16.737	1.32±0.02	6	1.09
		F, R	0.25±0.04	0.27±0.03	0.981	0.02	51.5	1.31±0.01	7	1.08
6	*Streptococcus pneumoniae*	σ_I, σ_R	0.31±0.07	0.31±0.07	0.952	0.03	14.55	1.28±0.02	6	1.00
		σ_I, σ_R^o	0.21±0.05	0.27±0.04	0.968	0.02	30.3	1.26±0.01	7	1.29
		σ_I, σ_R^+	0.11±0.07	0.10±0.02	0.930	0.04	12.75	1.29±0.02	7	0.91
		σ_I, σ_R^-	0.30±0.07	0.34±0.07	0.952	0.03	14.49	1.28±0.02	6	1.13
		F, R	0.23±0.03	0.28±0.02	0.99	0.01	98.83	1.27±0.01	7	1.22
7	*Proteus mirabilis*	σ_I, σ_R	0.37±0.08	0.37±0.08	0.954	0.03	15.27	1.20±0.02	6	1.00
		σ_I, σ_R^o	0.25±0.06	0.32±0.05	0.966	0.03	27.75	1.18±0.02	7	1.28
		σ_I, σ_R^+	0.12±0.09	0.12±0.03	0.930	0.04	12.76	1.22±0.03	7	1.00
		σ_I, σ_R^-	0.36±0.08	0.40±0.09	0.949	0.04	13.6	1.20±0.02	6	1.11
		F, R	0.27±0.04	0.33±0.03	0.989	0.02	91.01	1.19±0.01	7	1.22

"n=6 means, values calculated without -COOCH$_3$ group".

The sign of ρ_I and ρ_R are positive, reveals that the normal substituent effects operates on IZD, ie, an electron releasing substituents decrease the IZD and electron withdrawing substituents increase the IZD. The ρ_I values are rather smaller than ρ_R values and this reveals the importance of resonance component.

Multiple regression analysis of log IZR (mm) with σ_P, $(\sigma_P^+ - \sigma_P)$ and σ_P^o, $(\sigma_P^+ - \sigma_P^o)$ constants using Yukava-Tsuno Equation.. The best fit of multiple regression analysis for *Bacillus subtilis* is taken from good correlation coefficient and least standard error (SE) of the regression equation (4) and the result obtained given in Table 4.

$$\log IZD = (0.30\pm0.02)\,\sigma_P^o + (0.09\pm0.02)\,(\sigma_P^+ - \sigma_P^o) + (1.20\pm0.01) \quad (4)$$

(R=0.998, SE=0.01, n=5, F=274.59)

Table 4: Results of multiple regression analysis of log IZR (mm) with σ_P, $(\sigma_P^+ - \sigma_P)$ and σ_P^o, $(\sigma_P^+ - \sigma_P^o)$ constants using Yukava-Tsuno Equation 4.

S. No	Name of the bacteria	Scale	ρ	r	R	SE	F	n
1	*Bacillus subtilis*	σ_P, $(\sigma_P^+ - \sigma_P)$	0.29±0.02	0.02±0.04	0.993	0.01	137.42	7
		σ_P^o, $(\sigma_P^+ - \sigma_P^o)$	0.30±0.02	0.09±0.02	0.998	0.01	274.59	5
2	*Escherichia coli*	σ_P, $(\sigma_P^+ - \sigma_P)$	0.21±0.02	0.03±0.03	0.992	0.01	116.23	7
		σ_P^o, $(\sigma_P^+ - \sigma_P^o)$	0.22±0.02	0.08±0.02	0.994	0.01	85.46	5
3	Enterococcus faecalis	σ_P, $(\sigma_P^+ - \sigma_P)$	0.24±0.02	0.04±0.04	0.991	0.01	113.97	7
		σ_P^o, $(\sigma_P^+ - \sigma_P^o)$	0.26±0.02	0.09±0.02	0.995	0.01	98.93	5
4	Klebsiella pneumonia	σ_P, $(\sigma_P^+ - \sigma_P)$	0.25±0.02	0.04±0.04	0.994	0.01	157.2	7
		σ_P^o, $(\sigma_P^+ - \sigma_P^o)$	0.26±0.03	0.10±0.04	0.990	0.02	50.81	5
5	Staphylococcus aureus	σ_P, $(\sigma_P^+ - \sigma_P)$	0.26±0.04	-0.01±0.06	0.981	0.02	50.85	7
		σ_P^o, $(\sigma_P^+ - \sigma_P^o)$	0.28±0.05	0.07±0.05	0.984	0.02	30.91	5
6	Streptococcus pneumoniae	σ_P, $(\sigma_P^+ - \sigma_P)$	0.24±0.03	0.05±0.04	0.990	0.01	101.22	7
		σ_P^o, $(\sigma_P^+ - \sigma_P^o)$	0.25±0.03	0.10±0.03	0.994	0.01	79.49	5
7	Proteus mirabilis	σ_P, $(\sigma_P^+ - \sigma_P)$	0.28±0.03	0.07±0.05	0.990	0.02	95.41	7
		σ_P^o, $(\sigma_P^+ - \sigma_P^o)$	0.30±0.03	0.13±0.03	0.994	0.02	80.93	5

"n=5 means, values calculated without –CH_2CH_3 and -$COOCH_3$ groups".

The Yukava-Tsuno equation 4 and Table 4 for *Bacillus subtilis* proved the less contribution of polar component.

CONCLUSIONS

In summary, we have synthesized various substituted [2+2] macrocycles from diamine derivatives and terephthaldehyde. The product was confirmed by UV, IR, NMR, Mass spectrometric techniques and single crystal analysis. The antibacterial searching suggests that all the synthesized macrocyclic compounds showed moderate to very good activity against the tested organisms. Among the compounds, -COOH substituted compound showed the most promising antibacterial activity, suggesting further work with similar analogues. The inhibition zone diameters of these compounds have been correlated with Hammett substituent constants, F and R parameters. From the results of statistical analysis, the effects of substituent on the antibacterial activity of compounds have been studied.

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Conflict of interest

The author declare no conflict of interest.

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