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Research Article

ANTIMICROBIAL ACTIVITY OF 6-ARYL-4-METHYL-2-OXO-1, 2, 3, 6-TETRAHYDROPYRIMIDINE-5-(N-ARYL) CARBOXAMIDES: A STRUCTURE-REACTIVITY STUDY

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ABSTRACT
Substituted 6-aryl-4-methyl-2-oxo-1, 2, 3, 6-tetrahydropyrimidine-5-(N-aryl) carboxamides have been prepared and characterized by ^{1}H NMR spectral analysis. The antimicrobial activities and structure reactivity correlation of the compounds have been studied.

Keywords: Biginelli reaction, dihydropyrimidinones, antimicrobial, correlation studies.

1. INTRODUCTION

Synthesis of dihydropyrimidinones (DHP) by Biginelli reactions are gaining importance for various reasons. Biginelli reaction is an acid catalyzed cyclocondensation reaction of a β-ketoester with an aldehyde and urea to yield DHP. The pyrimidine skeleton is available in a wide variety of naturally occurring compounds and also in clinically useful molecules having diverse biological activities and hence, it is of great importance to chemists and biologists. Dihydropyrimidinones have attracted considerable interest because of their pharmacological and therapeutic properties[1-3]. Recently substituent effects on the zone of inhibition against the growth of microorganisms in various substituted 2-benzylidene-1,3-indandiones[4] and substituted 5-benzylidenebarbituric acids[5] have been reported. Recently NH_4Cl[6], ionic liquids[7], heteropolyacids[8], ultrasonic[9] and microwave irradiation[10] have also been used for Biginelli reaction. Although many Lewis acids and transition metal salts have been found to catalyze this reaction, they still have limitations like high cost, limited availability, prolonged reaction duration and the use of strong acids. Keeping these facts in mind, we have been prompted to synthesis some tetrahydropyrimidinones analogous derived from substituted benzaldehyde, urea and aceoacetanilide using the catalyst ($CuCl_2.2H_2O$) and also to study the antimicrobial activity to find the substituent effect on tetrahydropyrimidinones.

2. MATERIALS AND METHODS

All chemicals used were purchased from sigma Aldrich. The purity of the compounds was checked by TLC on silica gel G plates. ^{1}H spectra were obtained on a BRUKER AMX 400MHz spectrometer. The chemical shift of ^{1}Hwas measured with the peak of $CDCl_3$ at δ 7.29 as the internal reference.

2.1 General procedure for the synthesis of 6-aryl-4-methyl-2-oxo-1, 2, 3, 6-tetrahydropyrimidine-5-(N-aryl) carboxamides (1to7).

A mixture of an aromatic aldehyde (10mmol), acetoacetanilide (10mmol), urea (20mmol) and $CuCl_2.2H_2O$ (5mmol) was mixed in an R.B flask and the mixture was magnetically stirred a 70°C for the time needed to complete the reaction (as monitored by TLC). The initial syrupy reaction mixture solidifies within 25-30 minutes. The solid was poured onto crushed ice, filtered and recrystallized by using either ethanol or ethyl acetate and petroleum ether (1:3) (**Scheme I**).

2.2 ^{1}H NMR Spectral analysis of compounds (1 to 7)

Compound 1: 6-(4-methoxyphenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5(N-phenyl) carboxamide

δ: 2.012 (s,3H), 3.625(s,3H), 6.000(s,1H), 6.580(d,2H), 6.893-6.981(m,2H), 7.109-7.186 (m, 3H), 7.328(d, 2H), 9.023((s,1H), 9.685(s,1H) and 9.695(s,1H).

Compound 2: 6-(4-hydroxyphenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5(N-phenyl) carboxamide

δ: 2.060(s,3H), 5.340(s,1H), 6.686(d,2H), 6.922-6.972(m,2H), 7.158-7.209(m,3H), 7.515(d,2H), 8.526(s,1H), 9.179(s,1H), 9.381(s,1H) and 10.680(s,1H).

Compound 3: 6-(4-methylphenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5(N-phenyl) carboxamide

δ: 2.051(s,3H), 2.227(s,3H), 5.405(s,1H), 6.913-6.96 (m,2H), 7.067((d,2H), 7.144-7.203(m,3H), 7.387(s,1H), 7.508(d,2H), 8.542(s,1H) and 9.389(s,1H).

Compound 4: 6-phenyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5(N-phenyl) carboxamide

δ: 2.075(s,3H), 5.450(s,1H), 6.934-6.985 (m,2H), 7.166-7.227(m, 3H), 7.258-7.321(m,3H), 7.505(s, 1H), 7.529(d,2H), 8.626(s,1H) and 9.481(s, 1H).

Compound 5: 6-(4-chlorophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5(N-phenyl) carboxamide

δ: 2.024(s,3H), 4.328(s,1H), 7.27(m,7H), 7.30(d,2H), 7.546(s,1H), 8.768(s,1H) and 9.558(s, 1H).

Compound 6: 6-(4-bromophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5(N-phenyl) carboxamide

δ: 2.055(s,3H), 5.401(s,1H), 6.945-6.990 (m,2H), 7.1792-7.221(m,3H), 7.245(d,2H), 7.46(d,2H),7.525(s,1H), 8.687(s,1H) and 9.507(s,1H).

Compound 7: 6-(4-nitrophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5(N-phenyl) carboxamide

δ: 2.028(s, 3H), 5.514(s,1H), 7.388(m,9H), 7.764(s,1H), 8.894(s,1H) and 9.629(s,1H).

2.3 Antimicrobial activity

Agar well-diffusion method was followed to determine the antimicrobial activity[11]. Nutrient agar (NA) and Potato Dextrose Agar (PDA) plates were swabbed (sterile cotton swabs) with 8 hours old –broth culture of respective bacteria. Wells (6mmdiameter were made in each of these plates using sterile cork borer. Briefly, agar plates were inoculated with bacterial strain under aseptic conditions and wells (diameter=6 mm) were filled with 5 µl of the test samples and incubated at 37°C for 18-24 h for bacterial pathogens and 28°C for 48 hours fungal pathogens. The diameter of the inhibition zone (mm) was measured and the activity index was also calculated. Triplicates were maintained and the experiment was repeated thrice, for each triplicate the readings were taken in three different fixed directions and the average values were recorded. The average inhibition zone diameter for the various bacteria are shown in **Table 1** for the various fungi are shown in **Table 2**.

3. RESULTS AND DISCUSSION

In this study, four bacteria and two fungi were used. The result of the present study showed a broad range of antimicrobial activity (**Figure 1**). Table 1 and 2 show that the antimicrobial activity depends upon substituent only. Compound '7' exhibited excellent antimicrobial activity. The chlorine derivative is characterized by greater antimicrobial activity than that of the methyl and methoxy derivatives. According to Mohamed *et al*.,[12] this may be attributed to the electron-withdrawing character of the chlorine group that decreases the electron density in the pyrimidine group increasing its cationic character. The derivatives with electron withdrawing groups showed strong antimicrobial activity than those of electron donating group. Electron withdrawing substituent increases acidity also. Microbial growth is inhibited by increasing the acidity of the substituent. The order of antimicrobial activity of components (1 to 7) for all the microorganism were in the following sequence.

$-OCH_3 < -OH < -CH_3 < H < -Cl < -Br < -NO_2$

In order to express the effect of substituent quantitatively, it was considered worthwhile to correlate the logarithm of inhibition zone diameter (IZD) of'1' to '7' at the same concentration with the Hammett substituent

constants for all the microorganism. The results of statistical SSP analysis are given in Table 3. The corresponding Hammett plot for *Candida albicano* is shown in F**igure 2.**

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

$$\log IZD=(0.172\pm0.010)\sigma p^{+}/\sigma p + (1.051\pm0.006) \quad (1)$$
$$(r=0.992, n=7, F=290.39)$$

indicates that electron withdrawing substituents increase the antimicrobial activity and electron releasing substituents retard it.

DSP analysis has been performed for each of the resonance scale (σ_R, $\sigma_R^{+}\sigma_R^{-},\sigma_R^{o}$). The best fit of DSP analysis for *Aspergillus Niger* is taken from good correlation coefficient and least standard error (SE) of the regression equations (2) and (3) and the result obtained given in T**able 4**.

$$\log IZD=(0.25\pm 0.06)\sigma_I + (0.44\pm0.06)\sigma_R + (1.01\pm 0.03) \quad (2)$$
$$(R=0.981, SE=0.036, n=6, F=38.298)$$

$$\log IZD=(0.22\pm0.11)F + (0.45\pm0.12) R + (1.00\pm0.05) \quad (3)$$
$$(R=0.943, SE=0.06, n=6, F=12.13)$$

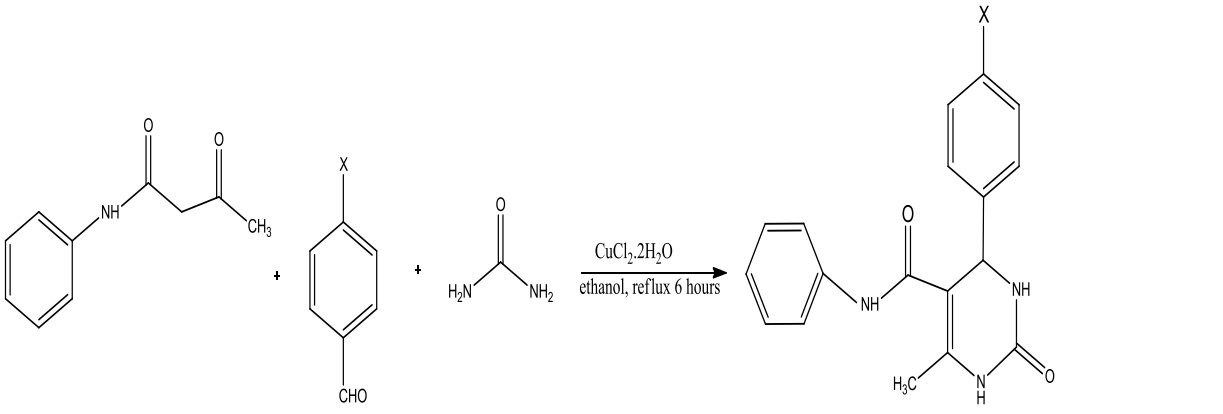
The sign of ρ_I and ρ_R are positive reveals that the normal substituent effects operate on IZD, ie, an electron releasing substituents decrease the IZD and electron withdrawing substituents increase the IZD. The ρ_I values are rather smaller than ρ_R values and this reveals the importance of resonance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

The Yukava-Tsuno equation 4 and **Table 5** for *Aspergillus Niger* proved the less contribution of polar component.

$$\log IZD=(0.24\pm0.03)\sigma_P^{o} + (0.32\pm0.05)(\sigma_P^{+}-\sigma_P^{o})+ (1.03\pm0.02) \quad (4)$$
$$(R=0.992, SE=0.02, n=6, F=89.13)$$

4. CONCLUSION

To summarize, substituted 6-aryl-4-methyl-2-oxo-1, 2, 3, 6-tetrahydropyrimidine-5-(N-aryl) carboxamides have been synthesized and evaluated for their antimicrobial activities. This reaction protocol offers a simple, easier work-up procedure and good yields. The compounds have been characterized by their ^{1}H NMR spectral data. The antimicrobial activities of all synthesized compounds have been studied. 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 the substituent on the antimicrobial activity of compounds have been studied.



Acetoacetanilide | Substituted benzaldehyde (X=-OCH_3,-OH,-CH_3,-H,-Cl,-Br,-NO_2) | Urea | Substituted 6-aryl-4-methyl-2-oxo-1, 2, 3, 6-tetrahydropyrimidine-5-(N-aryl) carboxamides

Scheme-I: Synthesis of 6-aryl-4-methyl-2-oxo-1, 2, 3, 6-tetrahydropyrimidine-5-(N-aryl) carboxamides

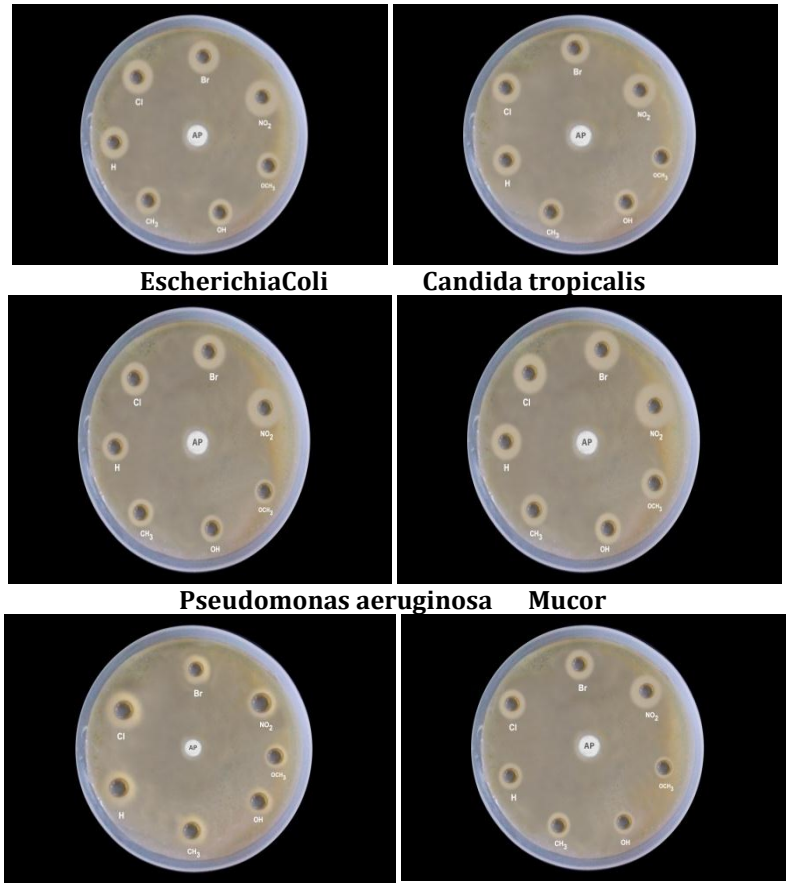


Fig. 1: Antimicrobial activity of 6-aryl-4-methyl-2-oxo-1, 2, 3, 6-tetrahydropyrimidine-5-(N-aryl)carboxamides

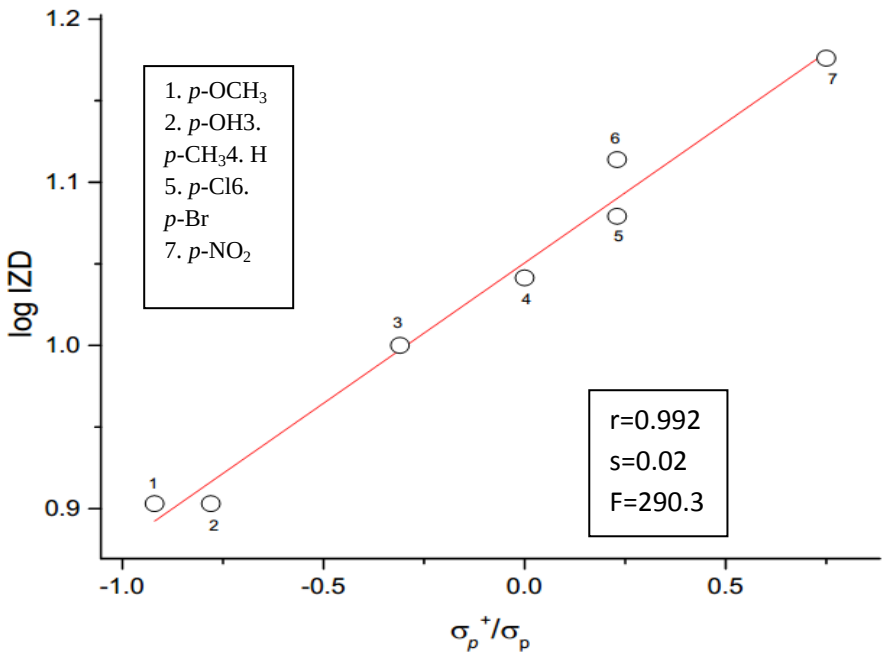


Fig. 2: Hammett plot for Candida albicano

Table 1: Antibacterial activity (zone of inhibition (mm) values) of substituted 6-aryl-4-methyl-2-oxo-1, 2, 3, 6-tetrahydropyrimidine-5-(N-aryl) carboxamides

S. No.	Bacteria	Standard Antibiotic Disk*	Control	Inhibition Zone Diameter(mm)						
				$-OCH_3$	-OH	$-CH_3$	-H	-Cl	-Br	$-NO_2$
1	EscherichiaColi	8	Amphotericin B -	8	9	11	13	15	16	18
2	Candida tropicalis	10	Amphotericin B -	8	9	11	12	14	15	17
3	Pseudomonas aeruginosa	12	Amphotericin B -	7	8	10	11	13	14	16
4	Mucor	14	Amphotericin B -	8	9	10	11	13	14	17

Table 2: Antifungal activity (zone of inhibition (mm) values) of substituted 6-aryl-4-methyl-2-oxo-1,2, 3, 6-tetrahydropyrimidine-5-(N-aryl) carboxamides

S. No.	Fungi	Standard Antibiotic Disk*	Control	Inhibition Zone diameter (mm)						
				$-OCH_3$	-OH	$-CH_3$	-H	-Cl	-Br	$-NO_2$
1	Aspergillus Niger	8	Amphotericin B -	6	8	9	10	11	12	16
2	Candida albicano	10	Amphotericin B -	8	8	10	11	12	13	15

Table 3: Results of statistical treatment of log (IZD) mm with σ_P, σ_P^o, σ_P^+, σ_P^+/σ_P, σ_P^+/σ_P^-, $\sigma_P^+/\sigma_P/\sigma_P^-$substituent constants using single parameter equation 1

S.No	Name of the microorganism	Scale	ρ	R	S	F	Log(IZD)^o	n
1.	Escherichia.Coli	σ_P	0.31±0.06	0.917	0.06	26.25	1.075±0.022	7
		σ_P^o	0.29±0.10	0.821	0.08	8.27	1.062±0.038	6
		σ_P^+	0.21±0.02	0.958	0.04	55.92	1.122±0.016	7
		σ_P^+/σ_P	0.21±0.02	0.973	0.03	89.67	1.117±0.013	7
		σ_P^+/σ_P^-	0.17±0.03	0.912	0.06	24.82	1.104±0.022	7
		$\sigma_P^+/\sigma_P/\sigma_P^-$	0.17±0.03	0.928	0.05	30.95	1.096±0.020	7
2.	Candida tropicalis	σ_P	0.29±0.05	0.923	0.05	28.88	1.059±0.019	7
		σ_P^o	0.27±0.09	0.833	0.07	9.06	1.046±0.034	6
		σ_P^+	0.19±0.03	0.958	0.03	56.50	1.102±0.014	7
		σ_P^+/σ_P	0.19±0.02	0.971	0.03	83.71	1.098±0.012	7
		σ_P^+/σ_P^-	0.15±0.03	0.920	0.05	27.52	1.086±0.019	7
		$\sigma_P^+/\sigma_P/\sigma_P^-$	0.15±0.02	0.937	0.05	36.21	1.079±0.017	7
3.	Pseudomonas aeruginosa	σ_P	0.31±0.06	0.919	0.06	27.47	1.018±0.021	7
		σ_P^o	0.29±0.10	0.827	0.08	8.68	1.004±0.037	6
		σ_P^+	0.21±0.03	0.957	0.04	54.77	1.065±0.016	7
		σ_P^+/σ_P	0.21±0.02	0.970	0.03	80.92	1.060±0.013	7
		σ_P^+/σ_P^-	0.16±0.03	0.917	0.05	26.59	1.047±0.021	7
		$\sigma_P^+/\sigma_P/\sigma_P^-$	0.17±0.03	0.935	0.05	34.98	1.039±0.019	7
4.	Mucor	σ_P	0.29±0.04	0.959	0.03	57.59	1.039±0.013	7
		σ_P^o	0.29±0.07	0.905	0.05	18.11	1.018±0.025	6
		σ_P^+	0.19±0.02	0.956	0.03	53.89	1.081±0.014	7
		σ_P^+/σ_P	0.19±0.02	0.963	0.03	63.88	1.076±0.013	7
		σ_P^+/σ_P^-	0.15±0.02	0.942	0.04	40.05	1.065±0.015	7
		$\sigma_P^+/\sigma_P/\sigma_P^-$	0.15±0.02	0.950	0.03	46.97	1.058±0.014	7
5.	Aspergillus Niger	σ_P	0.36±0.07	0.929	0.06	25.17	0.963±0.026	6
		σ_P^o	0.34±0.10	0.859	0.08	11.28	0.947±0.038	6
		σ_P^+	0.27±0.02	0.987	0.03	156.03	1.011±0.010	6
		σ_P^+/σ_P	0.27±0.02	0.989	0.02	180.18	1.004±0.009	6
		σ_P^+/σ_P^-	0.19±0.03	0.950	0.05	37.36	0.995±0.020	6
		$\sigma_P^+/\sigma_P/\sigma_P^-$	0.20±0.03	0.968	0.04	58.62	0.983±0.017	6
6.	Candida albicano	σ_P	0.26±0.04	0.950	0.04	46.55	1.016±0.013	7
		σ_P^o	0.23±0.07	0.868	0.05	12.20	1.010±0.025	6
		σ_P^+	0.17±0.01	0.985	0.02	164.90	1.055±0.008	7
		σ_P^+/σ_P	0.17±0.01	0.992	0.02	290.3	1.051±0.006	7
		σ_P^+/σ_P^-	0.14±0.02	0.953	0.03	49.37	1.040±0.013	7
		$\sigma_P^+/\sigma_P/\sigma_P^-$	0.14±0.02	0.966	0.03	69.11	1.034±0.011	7

"n=6 means calculated without –OH group"

Table 4: DSP analysis of log IZD (mm) with dual parameter equations 2 and 3

S.No	Name of the microorganism	Scale	ρ_I	ρ_R	R	SE	F	Log(IZD)^o	n	$\lambda = \rho_R / \rho_I$
1.	Escherichia.Coli	σ_I, σ_R	0.24±0.10	0.36±0.10	0.932	0.06	9.92	1.10±0.04	6	1.48
		σ_I, σ_R^+	0.10±0.21	0.16±0.10	0.750	0.11	2.57	1.13±0.10	7	1.51
		σ_I, σ_R^o	0.29±0.20	0.14±0.19	0.682	0.12	1.30	1.06±0.08	6	0.50
		σ_I, σ_R^-	0.23±0.18	0.18±0.15	0.747	0.11	1.90	1.07±0.08	6	0.77
		F, R	0.21±0.10	0.34±0.08	0.935	0.06	13.97	1.10±0.04	7	1.61
2.	Candida tropicalis	σ_I, σ_R	0.22±0.08	0.32±0.09	0.942	0.05	11.80	1.08±0.04	6	1.46
		σ_I, σ_R^+	0.12±0.20	0.13±0.09	0.728	0.10	2.25	1.10±0.09	7	1.11
		σ_I, σ_R^o	0.26±0.17	0.13±0.17	0.695	0.11	1.40	1.04±0.07	6	0.51
		σ_I, σ_R^-	0.21±0.16	0.17±0.13	0.767	0.10	2.14	1.05±0.07	6	0.79
		F, R	0.20±0.09	0.30±0.07	0.934	0.05	13.58	1.08±0.04	7	1.49
3.	Pseudomongs aeruginosa	σ_I, σ_R	0.24±0.09	0.36±0.10	0.940	0.06	11.31	1.05±0.04	6	1.49
		σ_I, σ_R^+	0.12±0.22	0.14±0.10	0.724	0.11	2.21	1.06±0.10	7	1.16
		σ_I, σ_R^o	0.29±0.19	0.15±0.19	0.689	0.12	1.35	1.00±0.08	6	0.51
		σ_I, σ_R^-	0.23±0.18	0.18±0.15	0.760	0.11	2.05	1.01±0.07	6	0.80
		F, R	0.22±0.10	0.33±0.08	0.932	0.06	13.20	1.04±0.04	7	1.53
4.	Mucor	σ_I, σ_R	0.26±0.05	0.30±0.06	0.975	0.03	28.79	1.04±0.02	6	1.14
		σ_I, σ_R^+	0.17±0.17	0.12±0.08	0.797	0.08	3.47	1.06±0.08\	7	0.69
		σ_I, σ_R^o	0.30±0.15	0.14±0.14	0.790	0.09	2.50	1.01±0.06	6	0.46
		σ_I, σ_R^-	0.25±0.13	0.17±0.11	0.856	0.08	4.11	1.02±0.05	6	0.69
		F, R	0.26±0.08	0.27±0.06	0.951	0.04	18.75	1.03±0.03	7	1.03
5.	Aspergillus Niger	σ_I, σ_R	0.25±0.06	0.43±0.06	0.981	0.04	38.30	1.00±0.03	6	1.75
		σ_I, σ_R^+	0.10±0.22	0.16±0.11	0.792	0.11	2.52	1.05±0.11	6	1.52
		σ_I, σ_R^o	0.31±0.20	0.23±0.19	0.739	0.12	1.81	0.96±0.08	6	0.73
		σ_I, σ_R^-	0.22±0.17	0.26±0.14	0.834	0.10	3.43	0.98±0.07	6	1.17
		F, R	0.22±0.11	0.45±0.12	0.943	0.06	12.13	1.00±0.05	6	2.06
6.	Candida albicano	σ_I, σ_R	0.19±0.05	0.27±0.05	0.968	0.03	22.04	1.04±0.02	6	1.42
		σ_I, σ_R^+	0.10±0.18	0.11±0.08	0.710	0.09	2.03	1.05±0.08	7	1.05
		σ_I, σ_R^o	0.22±0.13	0.12±0.13	0.737	0.08	1.78	1.01±0.06	6	0.54
		σ_I, σ_R^-	0.18±0.12	0.15±0.10	0.822	0.07	3.12	1.02±0.05	6	0.86
		F, R	0.17±0.07	0.27±0.05	0.955	0.04	20.93	1.04±0.03	7	1.60

Table 5: Results of multiple regression analysis of log IZD (mm) with σ_P, (σ_P^+-σ_P) and σ_P^o, (σ_P^+-σ_P^o) constants using Yukava-Tsuno equation 4

S.No	Name of the microorganism	Scale	ρ	R	R	SE	F	n
1.	Escherichia Coli	$\sigma_P, (\sigma_P^+ - \sigma_P)$	0.19±0.08	0.25±0.12	0.959	0.05	22.84	7
		$\sigma_P^o, (\sigma_P^+ - \sigma_P^o)$	0.20±0.06	0.30±0.09	0.963	0.04	19.24	6
2.	Candida tropicalis	$\sigma_P, (\sigma_P^+ - \sigma_P)$	0.19±0.07	0.20±0.11	0.958	0.04	22.67	7
		$\sigma_P^o, (\sigma_P^+ - \sigma_P^o)$	0.19±0.05	0.26±0.08	0.965	0.04	20.11	6
3.	Pseudomonas aeruginosa	$\sigma_P, (\sigma_P^+ - \sigma_P)$	0.20±0.08	0.23±0.13	0.958	0.05	22.07	7
		$\sigma_P^o, (\sigma_P^+ - \sigma_P^o)$	0.20±0.06	0.29±0.09	0.964	0.04	19.80	6
4.	Mucor	$\sigma_P, (\sigma_P^+ - \sigma_P)$	0.24±0.06	0.09±0.10	0.966	0.04	27.87	7
		$\sigma_P^o, (\sigma_P^+ - \sigma_P^o)$	0.23±0.04	0.20±0.07	0.977	0.03	31.59	6
5.	Aspergillus Niger	$\sigma_P, (\sigma_P^+ - \sigma_P)$	0.23±0.04	0.34±0.08	0.991	0.02	78.90	6
		$\sigma_P^o, (\sigma_P^+ - \sigma_P^o)$	0.24±0.03	0.32±0.05	0.992	0.02	89.13	6
6.	Candida albicano	$\sigma_P, (\sigma_P^+ - \sigma_P)$	0.17±0.04	0.18±0.06	0.985	0.02	66.19	7
		$\sigma_P^o, (\sigma_P^+ - \sigma_P^o)$	0.17±0.03	0.20±0.05	0.982	0.02	39.42	6

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