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In vitro Antimicrobial activity and QSAR Studies of Some Quinazolinone Substituted Sulphones

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Seven new 2–(3–phenyl–6,8–disubstituted 4–oxo–(3H)–quinazolinyl)– 2'/4'/2', 4'–substituted phenyl sulphones were screened against three bacterial strains *E. coli*, *S. typhi* and *S. aureus* and antifungal against *A. flavus* and *Penicillium* species. Some of them were found to be active.

Key words : Sulphones, Antimicrobial activity.

Dapsone also known as 4,4'–diamine diphenyl sulphone or DDS is the drug of choice in the chemotherapy of leprosy and also for the treatment of nocardiosis, tuberculosis and prophylaxis. A useful chemotherapeutic agent, it exhibits an antibacterial spectrum, the mechanism of action, being similar to sulphanilamide.[1] Substituted sulphones have been reported to possess a broad biocidal spectrum.[2–3]

Quinazolinones also have immense biological potential. Antimicrobial anti-inflammatory, antitubercular are some of the activities reported by this nucleus.[4–7]

MATERIAL AND METHODS

Melting points were taken in a 'Neolab' electrical apparatus. Chemical structures were identified by spectral techniques of IR, PMR, Mass and elemental analysis. 2–mercapto–3–phenyl–6/6,8–disubstituted quinazolin– 4(3H)–ones (1) were synthesized by following the known procedure.[8]

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2–mercapto–(2'/4'/2',4'–aryl substituted)–3–phenyl–6/6,8–disubstituted quinazolin–4(3H)–ones (2)

Equimolar ratio of (1) and an appropriate aryl halide initially dissolved in sodium carbonate solution (1.75 g in 5 ml water) were refluxed in 15 ml of dimethyl formamide for 6–7 hrs. The solution was cooled, diluted with water and filtered. The filtrate was further acidified with conc. HCl. A precipitate was obtained which was filtered, washed with water dried and recrystallised from methanol. Physical data given in Table 1.

2–(3–phenyl–6/6,8–disubstituted–4–oxo–(3H)–quinazolinyl–2'/4'/2',4'–substituted phenyl sulphones (3)

0.01 mole of appropriate quinazolinones (2) were dissolved in 10 ml of glacial acetic acid and hydrogen peroxide (50%), 10 ml was added slowly dropwise with constant stirring. On completion of the addition of the oxidant, the reaction mixture was kept aside for half an hour. The solid which separated was filtered, dried and recrystallised from ethanol. Their physical data is given in Table 1.

Antimicrobial activity

Bacterial and fungal strains were obtained from the Microbial Technology (IMTECH), Chandigarh and subcultured. Nutrient Agar Medium (NAM) was used for bacteria and Potato

Dextrose Agar (PDA) and Yeast Malt Agar (YMA) were used for *Penicillium* species and *A. flavus*.[9] The human pathogenic bacterial strains selected were *E. coli* MTCC 1687, *S. typhi* MTCC 734, *S. aureus* MTCC 737. Disc diffusion technique was used for the antibacterial activity while drug dilution method was followed for the antifungal activity.[10,11]

The petri dishes were thoroughly washed, dried at 35 – 37° C for about 30 minutes. Prepared sterilized medium was then poured into 90 mm diameter sterile petri dishes to a depth of 4 mm (about 25 ml per plate). The plated petri dishes were kept on a plane surface to avoid non–uniform solidification of medium. All these operations were performed in a sterile room fitted with laminar flow. The petri dishes were dried at 35–37° C in an incubator for about 30 minutes.

Sterile loops of about 4 mm diameters were used to apply a loopfull of the test organism and the suspension was placed at the center of the petri dishes. A sterile dry cotton wool swab was used to spread the inoculum evenly on the dishes, which were then incubated for 15 min. Discs of 6.35 mm in diameter were punched from a sheet of Whatman Filter Paper No. 1 and placed in petri dish, allowing a distance of 2 – 4 mm between each disc and sterilized in a hot air oven at 160° C for 1 hrs. Sterilized discs were then impregnated with the prepared stock solution of the test compound. These discs were then dried in an oven at 25° C. Antimicrobic discs were applied to the surface of the plates with sterile forceps. The spatial arrangement of the discs was such that they were not closer than 15 mm from the edges of the dishes to prevent overlapping of the zones of inhibition. The discs were not moved once they came in contact with agar surface. Each test compound was applied in triplicate and the zone of inhibition was determined by taking its average. Simultaneous discs were prepared for the control and the standard drugs. The petri discs were incubated at 37° C for 24 hrs in case of bacteria and at 30° C for 48 hrs for fungi and yeast. Zone of inhibition was measured from the edge of the disc to the edge of the zone by a multimeter scale.

RESULTS AND DISCUSSION

Antibacterial activity

2–(3–phenyl–6,8–disubstituted–4–oxo–(3H)–quinazolinyl)–substituted phenyl sulphones were screened for the antibacterial activity at two concentration levels i.e. 125 µg/mL and 250 µg/

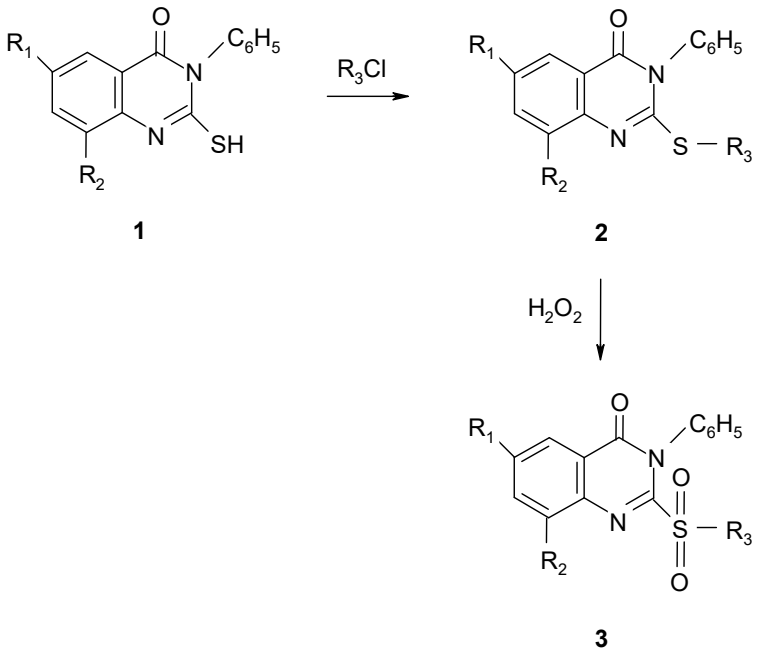

Fig. 1: Synthetic route for the synthesis of sulphones

mL respectively. The compounds have displayed some activity (Table 2).

Maximum inhibition (20-24 mm) was shown by two compounds (3_f and 3_g) against the two gram negative bacteria *E. coli* and *S. typhi*. Compound 3_f was highly active at both the concentrations.

Only two sulphones i.e. 3_b and 3_f were

Table 1.

S.No.	Compound	M.P.	R_1	R_2	R_3
1.	2_a	205	H	H	$C_6H_4NO_2$
2.	2_b	200	H	H	$C_6H_3(NO_2)_2$
3.	2_c	170	H	H	$C_6H_4CH_3$(o)
4.	2_d	185	H	H	$C_6H_4CH_3$(p)
5.	2_e	198	H	H	$C_6H_5CH_2$
6.	2_f	190	Br	Br	$C_6H_4NO_2$
7.	2_g	210	Br	Br	$C_6H_3(NO_2)_2$
8.	3_a	240	H	H	$C_6H_4NO_2$
9.	3_b	240	H	H	$C_6H_3(NO_2)_2$
10.	3_c	227	H	H	$C_6H_4CH_3$(o)
11.	3_d	232	H	H	$C_6H_4CH_3$(p)
12.	3_e	221	H	H	$C_6H_5CH_2$
13.	3_f	210	Br	Br	$C_6H_4NO_2$
14.	3_g	228	Br	Br	$C_6H_3(NO_2)_2$

% yield ranged between 60 – 70%

Table 2. Antimicrobial activity

Compound No.	Concentration	Antibacterial			Antifungal	
		E. coli	*S. typhi*	*S. aureus*	*Penicillium*	*A. flavus*
3_a	125	±	±	±	±	–
	250	±	±	±		
3_b	125	±	±	+	+	–
	250	±	±	+	+	
3_c	125	±	±	±	+	±
	250	±	±	±	+	±
3_d	125	±	±	±	±	±
	250	±	±	±		
3_e	125	±	–	±	±	–
	250	±	±	±		
3_f	125	++	++	+	±	±
	250	++	±	±		
3_g	125	++	±	±	±	±
	250	±	±	±		

Disc size 6.35

Duration : 24–48 hrs.
Control : DMF

– : Inactive
± : Moderately Active (8–12mm)
+ : Active (15–19mm)
++ : Highly Active (20–24mm)
Standard : Ampicillin, Streptomycin (30–35mm)

Duration : 72 hrs.
Control : DMF
– : Inactive (heavy fungal colony)
± : Moderately Active (Two (three fungal colonies)
+ : Active (one fungal colony)
++ : Highly Active (No fungal colony)
Standard : Griseofulvin, Gentamycin 10 µg/disc

Table 3. Structural Parameters

Compound	MIC E 125	LOG (1/MIC) E125	PIE	MR	POLAR	SIGMA
3_a	12	–1.079181246	–0.28	11.48	0.67	0.78
3_b	12	–1.079181246	–0.56	22.96	1.34	1.56
3_c	12	–1.079181246	0.56	5.65	–0.04	–0.17
3_d	12	–1.079181246	0.56	5.56	–0.04	–0.17
3_e	12	–1.079181246	0.05	4.65	0	0
3_f	6	–0.77815125	–0.28	11.48	0.67	0.78
3_g	6	–0.77815125	–0.56	22.96	1.34	1.56
Compound	MIC E 250	LOG (1/MIC) E250	PIE	MR	POLAR	SIGMA
3_a	12	–1.079181246	–0.28	11.48	0.67	0.78
3_b	12	–1.079181246	–0.56	22.96	1.34	1.56
3_c	12	–1.079181246	0.56	5.65	–0.04	–0.17
3_d	12	–1.079181246	0.56	5.56	–0.04	–0.17
3_e	12	–1.079181246	0.05	4.65	0	0
3_f	6	–0.77815125	–0.28	11.48	0.67	0.78
3_g	12	–1.079181246	–0.56	22.96	1.34	1.56
Compound	MIC E 125	LOG (1/MIC) E125	PIE	MR	POLAR	SIGMA
3_a	12	–1.079181246	–0.28	11.48	0.67	0.78
3_b	12	–1.079181246	–0.56	22.96	1.34	1.56
3_c	12	–1.079181246	0.56	5.65	–0.04	–0.17
3_d	12	–1.079181246	0.56	5.56	–0.04	–0.17
3_e	12	–1.079181246	0.05	4.65	0	0
3_f	6	–0.77815125	–0.28	11.48	0.67	0.78
3_g	6	–1.079181246	–0.56	22.96	1.34	1.56
Compound	MIC E 250	LOG (1/MIC) E250	PIE	MR	POLAR	SIGMA
3_a	12	–1.079181246	–0.28	11.48	0.67	0.78
3_b	12	–1.079181246	–0.56	22.96	1.34	1.56
3_c	12	–1.079181246	0.56	5.65	–0.04	–0.17
3_d	12	–1.079181246	0.6	5.56	–0.04	–0.17
3_e	12	–1.079181246	0.05	4.65	0	0
3_f	12	–1.079181246	–0.28	11.48	0.67	0.78
3_g	12	–1.079181246	–0.56	22.96	1.34	1.56
Compound	MIC E 125	LOG (1/MIC) E125	PIE	MR	POLAR	SIGMA
3_a	12	–1.079181246	–0.28	11.48	0.67	0.78
3_b	8	–0.903089987	–0.56	22.96	1.34	1.56
3_c	12	–1.079181246	0.56	5.65	–0.04	–0.17
3_d	12	–1.079181246	0.56	5.56	–0.04	–0.17
3_e	12	–1.079181246	0.05	4.65	0	0
3_f	8	–0.903089987	–0.28	11.48	0.67	0.78
3_g	12	–1.079181246	–0.56	22.96	1.34	1.56
Compound	MIC E 250	LOG (1/MIC) E250	PIE	MR	POLAR	SIGMA
3_a	12	–1.079181246	–0.28	11.48	0.67	0.78
3_b	8	–0.903089987	–0.56	22.96	1.34	1.56
3_c	12	–1.079181246	0.56	5.65	–0.04	–0.17
3_d	12	–1.079181246	0.6	5.56	–0.04	–0.17
3_e	12	–1.079181246	0.05	4.65	0	0
3_f	12	–1.079181246	–0.28	11.48	0.67	0.78
3_g	12	–1.079181246	–0.56	22.96	1.34	1.56

moderately active (15–19 mm) zone of inhibition against *S. aureus*. The other derivatives did inhibit the growth of these strains but with a lesser radii (8–10 mm). However compound 3_e was inactive at 125 µg/disc against *S. typhi*.

A comparative study shows that presence of a nitro substituent (3_b, 3_f and 3_g) have enhanced the activity.

Antifungal Activity

Among the sulphones only one compound 3_b showed maximum activity against Penicillin with development of no fungal colony, followed by compound 3_c, with only one fungal colony. The other derivatives i.e. 3_a, 3_d – 3_g were less active.

Against *A. flavus*, the sulphones 3_a, 3_b and 3_e were inactive. The other derivatives 3_c, 3_d, 3_f and 3_g showed some activity with only 2 – 3 fungal colonies being developed after 72 hrs.

Again the nitro group has been found to be responsible for the antifungal activity.

QSAR Studies

The QSAR studies of the antibacterial activity[12–14] have also been done. The Minimum Inhibitory Concentration MIC for *E. Coli* (MIC_E), *S. Typhi* (MIC_S) and *S. aureus* (MIC_{SA}) were measured and transformed percent zone of inhibition in mm at the fixed concentrations i.e.

Table 4. Correlation Matrix

			LOG (1/MIC)		
	E125	PIE	MR	POLAR	SIGMA
LOG (1/MIC) E125	1.0000	-0.4951	0.4410	0.4906	0.4954
PIE		1.0000	-0.8548	-0.9233	-0.9443
MR			1.0000	0.9831	0.9737
POLAR				1.0000	0.9983
SIGMA					1.0000
		LOG (1/MIC)			
E250	PIE	MR	POLAR	SIGMA	
LOG (1/MIC) E250	1.0000	-0.1907	-0.0348	0.0767	0.0930
PIE		1.0000	-0.8548	-0.9233	-0.9443
MR			1.0000	0.9831	0.9737
POLAR				1.0000	0.9983
SIGMA					1.0000
		LOG (1/MIC)			
	E125	PIE	MR	POLAR	SIGMA
LOG (1/MIC) E125	1.0000	-0.1907	-0.0348	0.0767	0.0930
PIE		1.0000	-0.8548	-0.9233	-0.9443
MR			1.0000	0.9831	0.9737
POLAR				1.0000	0.9983
SIGMA					1.0000
		LOG (1/MIC)			
	E125	PIE	MR	POLAR	SIGMA
LOG (1/MIC) E125	1.0000	-0.4940	0.4410	0.4906	0.4954
PIE		1.0000	-0.8504	-0.9197	-0.9412
MR			1.0000	0.9831	0.9737
POLAR				1.0000	0.9983
SIGMA					1.0000
		LOG (1/MIC)			
	E250	PIE	MR	POLAR	SIGMA
LOG (1/MIC) E250	1.0000	-0.44454	0.4410	0.5566	0.5465
PIE		1.0000	-0.8504	-0.9197	-0.9412
MR			1.0000	0.9831	0.9737
POLAR				1.0000	0.9983
SIGMA					1.0000

Table 5. Multiple Regression Model : LOG (1/MIC) E 125 = (–1.09217) + (0.008178)* MR

Model Summary	
R–Square	19.45%
R–Square Adjusted	3.34%
S (Root Mean Square Error)	0.144413

125 and 250 were correlated. The transformation of zone of inhibition to percentage inhibition was based on weightage value of 24 for one +ve, thus the percentage value of the compounds were fixed between 24 and 96%. The percentage (P) was considered in its logit transformation [log P/100–P)] log P_E or log P_S) of both the activity and the

Parameter Estimates

Predictor Term	Coefficient	SE Coefficient	T	P	VIF	Tolerance
Constant	1.092169687	0.105339504	.10.388	0.0001		
MR	0.008177709	0.007442351	1.099	0.3219	1	1

Analysis of Variance for Model

Source	DF	SS	MS	F	P
Model	1	0.02518004	0.02518004	1.207	0.3219
Error	5	0.104275757	0.020855151		
Lack of Fit	3	0.013656699	0.004552233	0.100469662	0.9526
Pure Error	2	0.090619058	0.045309529		
Total (Model + Error)	6	0.129456	0.021575966		

Durbin–Watson Test for Autocorrelation in Residuals

DW Statistic	0.938208
P – Value Positive Autocorrelation	0.0505
P – Value Negative Autocorrelation	0.9438

Multiple Regression Model : LOG (1/MIC) E 125 = (–1.05905) + (0.117033)* POLAR

Model Summary	
R-Square	24.07%
R-Square Adjusted	8.88%
S (Root Mean Square Error)	0.140216

Parameter Estimates

Predictor Term	Coefficient	SE Coefficient	T	P	VIF	Tolerance
Constant	1.059045524	0.074478289	.14.220	0.0000		
POLAR	0.117033	0.092971357	1.259	0.2837	1	1

Analysis of Variance for Model

Source	DF	SS	MS	F	P
Model	1	0.031153772	0.031153772	1.585	0.2837
Error	5	0.098302025	0.019660405		
Lack of Fit	2	0.007682967	0.003841484	0.127175	0.8851
Pure Error	3	0.090619058	0.030206353		
Total (Model + Error)	6	0.129456	0.021575666		

Durbin–Watson Test for Autocorrelation in Residuals

DW Statistic	0.894810
P - Value Positive Autocorrelation	0.0411
P - Value Negative Autocorrelation	0.9496

Multiple Regression Model : LOG (1/MIC)
E 125 = (-1.05266) + (0.095953)* SIGMA

Model Summary	
R-Square	24.54%
R-Square Adjusted	9.45%
S (Root Mean Square Error)	0.139773

Parameter Estimates

Predictor Term	Coefficient	SE Coefficient	T	P	VIF	Tolerance
Constant	-1.052663391	0.070477436	-14.936	0.0000		
POLAR	0.095952766	0.075240432	1.275	0.2582	1	1

Analysis of Variance for Model

Source	DF	SS	MS	F	P
Model	1	0.031773127	0.031773127	1.626	0.2582
Error	5	0.097682671	0.019536534		
Lack of Fit	2	0.007063612	0.003531806	0.116923	0.8935
Pure Error	3	0.090619058	0.030206353		
Total (Model + Error)	6	0.129456	0.021575966		

Durbin–Watson Test for Autocorrelation in Residuals

DW Statistic	0.923245
P - Value Positive Autocorrelation	0.0443
P - Value Negative Autocorrelation	0.9417

Multiple Regression Model : LOG (1/MIC)
SA 125 = (-1.0674) + (0.06846)* POLAR

Model Summary	
R-Square	24.07%
R-Square Adjusted	8.88%
S (Root Mean Square Error)	0.082020848

Parameter Estimates

Predictor Term	Coefficient	SE Coefficient	T	P	VIF	Tolerance
Constant	1.067402604	0.043587006	-24.500	0.0000		
POLAR	0.068459904	0.054384757	1.259	0.2637	1	1

Analysis of Variance for Model

Source	DF	SS	MS	F	P
Model	1	0.010660233	0.010660233	1.585	0.2637
Error	5	0.033637098	0.00672742		
Lack of Fit	2	0.002628966	0.001314483	0.127175	0.8851
Pure Error	3	0.031008132	0.010336044		
Total (Model + Error)	6	0.044297331	0.007382888		

Durbin-Watson Test for Autocorrelation in Residuals

DW Statistic	2.671
P - Value Positive Autocorrelation	0.7978
P - Value Negative Autocorrelation	0.1223

Multiple Regression Model : LOG (1/MIC)
SA 125 = (-1.06367) + (0.056129)* SIGMA

Model Summary

R-Square	24.54%
R-Square Adjusted	9.45%
S (Root Mean Square Error)	0.081762053

Parameter Estimates

Predictor Term	Coefficient	SE Coefficient	T	P	VIF	Tolerance
Constant	-1.063669295	0.041226657	-25.801	0.0000		
POLAR	0.05612877	0.044012831	1.275	0.2582	1	1

Analysis of Variance for Model

Source	DF	SS	MS	F	P
Model	1	0.010872164	0.010872164	1.626	0.2582
Error	5	0.033425166	0.006685033		
Lack of Fit	2	0.002417035	0.0011208517	0.116923	0.8935
Pure Error	3	0.031008132	0.010336044		
Total (Model + Error)	6	0.044297331	0.007382888		

Durbin-Watson Test for Autocorrelation in Residuals

DW Statistic	2.683
P - Value Positive Autocorrelation	0.8019
P - Value Negative Autocorrelation	0.1176

Multiple Regression Model : LOG (1/MIC)
SA 125 = (-1.115) + (0.005076)* MR

Model Summary

R-Square	36.51%
R-Square Adjusted	23.81%
S (Root Mean Square Error)	0.058096245

Parameter Estimates

Predictor Term	Coefficient	SE Coefficient	T	P	VIF	Tolerance
Constant	-1.115	0.042377239	-26.323	0.0000		
POLAR	0.005076285	0.002993998	1.695	0.1508	1	1

Analysis of Variance for Model

Source	DF	SS	MS	F	P
Model	1	0.00970253	0.00970253	2.875	0.1508
Error	5	0.016875868	0.003375174		
Lack of Fit	3	0.001371802	0.000457267	0.058966784	0.9768
Pure Error	2	0.015504066	0.007752033		
Total (Model + Error)	6	0.0265578368	0.004429733		

Durbin-Watson Test for Autocorrelation in Residuals	
DW Statistic	1.557
P - Value Positive Autocorrelation	0.2173
P - Value Negative Autocorrelation	0.6963

Multiple Regression Model : LOG (1/MIC) SA 125 = (-1.08789) + (0.060165)* POLARR

Model Summary	
R-Square	30.98%
R-Square Adjusted	17.17%
S (Root Mean Square Error)	0.060572144

Parameter Estimates

Predictor Term	Coefficient	SE Coefficient	T	P	VIF	Tolerance
Constant	-1.0878897	0.0321741	-33.813	0.0000		
POLAR	0.060165085	0.040162976	1.498	0.1944	1	1

Analysis of Variance for Model

Source	DF	SS	MS	F	P
Model	1	0.008233475	0.008233475	2.244	0.1944
Error	5	0.018344923	0.003668985		
Lack of Fit	2	0.002840857	0.001420429	0.274850	0.7770
Pure Error	3	0.015504066	0.006168022		
Total (Model + Error)	6	0.026578398	0.004429733		

Durbin-Watson Test for Autocorrelation in Residuals	
DW Statistic	1.655
P - Value Positive Autocorrelation	0.2360
P - Value Negative Autocorrelation	0.6142

Multiple Regression Model : LOG (1/MIC) SA 250 = (-1.08376) + (0.047965)* SIGMA

Model Summary	
R-Square	29.87%
R-Square Adjusted	15.85%
S (Root Mean Square Error)	0.06105575

Parameter Estimates

Predictor Term	Coefficient	SE Coefficient	T	P	VIF	Tolerance
Constant	-1.083763395	0.030785974	-35.203	0.0000		
POLAR	0.047964585	0.032866548	1.459	0.2043	1	1

Analysis of Variance for Model

Source	DF	SS	MS	F	P
Model	1	0.007939376	0.007939376	2.13	0.2043
Error	5	0.018639023	0.003727805		
Lack of Fit	2	0.003134957	0.001567479	0.303303	0.7586
Pure Error	3	0.015504066	0.005168022		
Total (Model + Error)	6	0.026578398	0.004429733		

Durbin-Watson Test for Autocorrelation in Residuals

DW Statistic	1.651
P – Value Positive Autocorrelation	0.2306
P – Value Negative Autocorrelation	0.6161

MIC i.e. (log l/MIC), (log l/MIC_E); log l (MIC_S) and log l/MIC_{SA}. The structure activity analysis in terms of correlation between log l/MIC_E, log l/ MIC_S and log l/MIC_{SA} as dependent parameter while hydrophobic (p), steric (MR) electronic (s and polar) as independent parameters in the derivatives has been given in Table 3 & Table 4.

The statistical significance E 125 (F=1.207; MR); (F=1.585; Polar); (F=1.626; Sigma); against SA 125 (F=1.585; Polar); (F=1.62; Sigma); (F=2.875; MR); while of SA 250 (F=2.130; Sigma) were observed as calculated by the Regression analysis (Table 5). This shows that steric, hydrophobic and Sigma effect of the substituents against *E. coli* while also polarity, against *S. aureus* all had a combined effect on the activity.

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