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SYNTHESIS, SCREENING AND QSAR ANALYSIS OF CHALCONE DERIVATIVES AS POTENTIAL ANTI BACTERIAL AGENTS

Vudumula Kotireddy*[1] and K. Venkata Ramana[1]

[1]*Department of Pharmaceutical Chemistry, A. S. N Pharmacy College, Burripalem Road, Tenali, Andhra Pradesh, India.

ABSTRACT

Chalcones are prepared by claisen Schmidt condensation method they are used to prepare various heterocyclic compounds. Most of them are widely used in pharmaceuticals. Keeping this in mind new chalcones are synthesised and the structures were confirmed by IR, NMR and elemental analysis. Synthesised compounds were screened for their antibacterial activity the molecules were screened for their structural activity relationships by atom based 3D QSAR studies.

KEYWORDS

Chalcones, QSAR and Antibacterial activity.

Author for Correspondence:

Vudumula Kotireddy,

Department of Pharmaceutical Chemistry,

A.S.N Pharmacy College,

Tenali, Andhra Pradesh, India.

Email: vkotireddy9@gmail.com

INTRODUCTION

Chalcones, a group of compounds prepared by claisen Schmidt condensation they contain two aromatic rings joined by a keto-vinyl group, constitute an important class of naturally occurring flavonoids exhibiting a wide spectrum of biological activities. α,β-unsaturated keto vinyl functional group is responsible for the biological activity.

General procedure for the synthesis of chalcones

A mixture of 4-chloroacetophenone (0.0001mole) and the appropriate aryl aldehyde (0.0001mole) was stirred in ethanol (3.5mL) and to it aqueous solution

of KOH (75%, 3.5mL) was added. The mixture was kept for 24 hours and it was acidified with dil. Hydrochloric acid and water, precipitate was obtained and the product was washed with cold water. Characterization of chalcones were given in Table No.1-3.

BIOLOGICAL EVALUATION

Antibacterial activity

The antibacterial activity of the synthesized chalcones was done by determining the MIC, which is defined as the lowest concentration of the compound that completely inhibited the growth of each strain after overnight incubation. MIC was determined using serial tube dilution technique. In this technique the tubes of broth medium containing graded doses of compounds were inoculated with the test organisms. After suitable incubation, growth occurred in those tubes where the concentration of the compound was below the inhibitory level and the culture become turbid. No growth was noticed above the inhibitory level and the tubes remained clear. Results were given in Table No.5.

RESULTS AND DISCUSSION

From the above results it is clear that all the chalcones synthesized, showed antibacterial activity with different MIC values against the tested organisms, but not comparable with that of the standard. Out of 25 compounds tested, compound B_5 which is having difluorophenyl moiety was found to be the most potent against *B.subtilis*, *E.coli* and *P.vulgaris* having a MIC value of 33µg/mL in each case. The chalcones, B_6 having a dichlorophenyl substitution, B_7 having 2-chloro-5-nitrophenyl substitution and B_{15} having bromofuran substitution were also found to be equipotent with a MIC value of 33µg/mL against *E.coli*, *B.subtilis* and *E.coli* respectively.

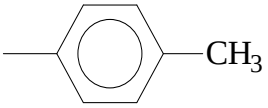
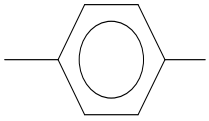
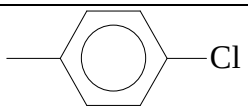
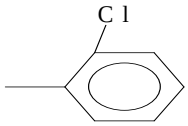
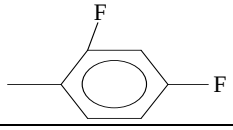
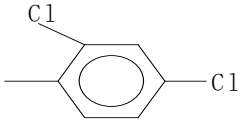
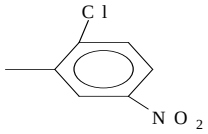
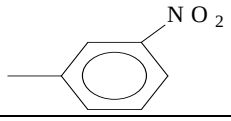
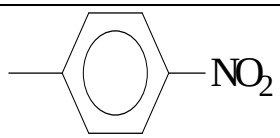
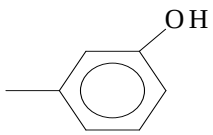
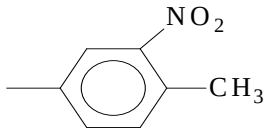
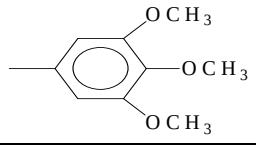
Atom based 3D-QSAR model for antibacterial activity of chalcones against *B.subtilis*

In atom based 3D-QSAR analysis of chalcones, the Correlation Coefficient (R^2) = 0.7922, Cross validation Coefficient (Q^2) = 0.4647 and Standard Deviation (S.D) = 0.1406 were established. From the it was found that the aromatic ring substitution with hydrogen bond donor or electron withdrawing group or hydrophobic group and a conjugated carbonyl system essential for increasing the antibacterial activity, as such regions showed blue cubes characteristic of positive effect on the antibacterial activity. Results of the statistical analysis are shown in the following tables and figures.

Atom based 3D-QSAR model for antibacterial activity of chalcones against *S.aureus*

In atom based 3D-QSAR analysis of chalcones, the Correlation Coefficient (R^2) = 0.9031, Cross validation Coefficient (Q^2) = 0.4858 and Standard Deviation (S.D) = 0.0765 (Table No.3, 5) were established. From the results shown in figures. It was found that the aromatic ring substitution with hydrogen bond donor or electron withdrawing group or hydrophobic group and a conjugated carbonyl system essential for increasing the antibacterial activity, as such regions showed blue cubes characteristic of positive effect on the antibacterial activity. Results of the statistical analysis are shown in the following tables and figures.

Table No.1: Physical characterization data of chalcones (B_1-B_{25})

S.No	Compound	R	Molecular Formula	Relative Molecular Mass (RMM)	Melting Point (°C)	Yield %
1	**B_1**		$C_{16}H_{12}CLO$	256	134-137	85
2	**B_2**		$C_{15}H_9CLFO$	260	87-90	88
3	**B_3**		$C_{15}H_9Cl_2O$	276	121-124	86
4	**B_4**		$C_{15}H_9Cl_2O$	276	130-133	78
5	**B_5**		$C_{15}H_8CLF_2O$	278	110-113	73
6	**B_6**		$C_{15}H_8Cl_3O$	309	93-96	88
7	**B_7**		$C_{15}H_8Cl_2NO_3$	321	131-134	84
8	**B_8**		$C_{15}H_9CLNO_3$	287	114-117	82
9	**B_9**		$C_{15}H_9CLNO_3$	287	122-125	83
10	**B_{10}**		$C_{15}H_{10}CLO_2$	258	132-135	91
11	**B_{11}**		$C_{16}H_{11}CLNO_3$	301	126-129	82
12	**B_{12}**		$C_{18}H_{16}CLO_4$	332	110-111	87

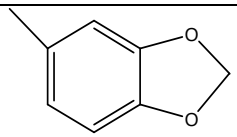
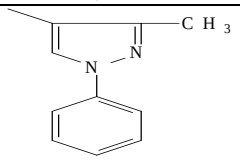
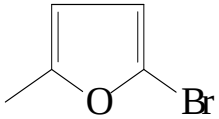
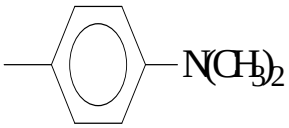
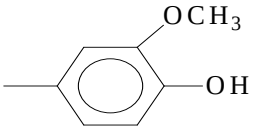
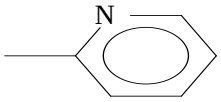
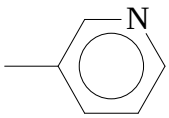
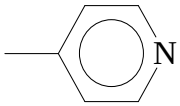
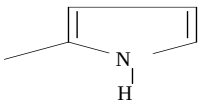
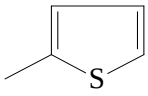
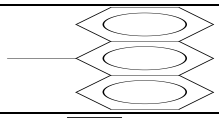
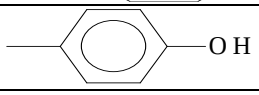
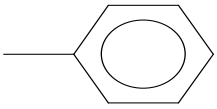
13	**B_{13}**		$C_{16}H_{10}CLO_3$	286	148-151	76
14	**B_{14}**		$C_{19}H_{14}CLN_2O$	322	112-115	70
15	**B_{15}**		$C_{13}H_7CLBrO_2$	311	126-129	76
16	**B_{16}**		$C_{17}H_{15}CLNO$	285	152-155	84
17	**B_{17}**		$C_{16}H_{12}CLO_3$	288	99-102	85
18	**B_{18}**		$C_{14}H_9CLNO$	243	91-94	83
19	**B_{19}**		$C_{14}H_9CLNO$	243	78-81	82
20	**B_{20}**		$C_{14}H_9CLNO$	243	96-99	88
21	**B_{21}**		$C_{13}H_9CLNO$	231	101-104	66
22	**B_{22}**		$C_{13}H_8CLOS$	248	106-109	77
23	**B_{23}**		$C_{23}H_{14}CLO$	342	108-111	85
24	**B_{24}**		$C_{15}H_{10}CLO_2$	258	91-94	84
25	**B_{25}**		$C_{15}H_{10}CLO$	242	66-69	82

Table No.2: IR (KBR disc) spectral data of chalcones

S.No	Compound	Position of absoption band (cm^{-1})
1	B_1	1655 (C=O), 1602 (C=C of Ar), 1505(CH=CH), 925 (C-F)
2	B_2	1664 (C=O), 1580 (C=C of Ar), 1524 (CH=CH), 928 (C-F)
3	B_3	1653 (C=O), 1585 (C=C of Ar), 1505 (CH=CH), 835 (C-Cl), 923 (C-F)
4	B_4	1652 (C=O), 1583 (C=C of Ar), 1502 (CH=CH), 833 (C-Cl), 923 (C-F)
5	B_5	1655 (C=O), 1581 (C=C of Ar), 1510 (CH=CH), 925 (C-F), 926 (C-F)
6	B_6	1663 (C=O), 1578 (C=C of Ar), 1506 (CH=CH), 833 (C-Cl), 921 (C-F)
7	B_7	1658 (C=O), 1603 (C=C of Ar), 1515 (CH=CH), 824 (C-Cl), 1525 (N=O, asymmetric), 1348 (N=O, symmetric), 929 (C-F)
8	B_8	1655 (C=O), 1605 (C=C of Ar), 1508 (CH=CH), 1533 (N=O, asymmetric), 1345 (N=O, symmetric), 925 (C-F)
9	B_9	1652 (C=O), 1610 (C=C of Ar), 1502 (CH=CH), 1541 (N=O, asymmetric), 1346 (N=O, symmetric), 923 (C-F)
10	B_{10}	3520 (O-H), 1648 (C=O), 1612 (C=C of Ar), 1505 (CH=CH), 923 (C-F)
11	B_{11}	1655 (C=O), 1605 (C=C of Ar), 1500 (CH=CH), 1545 (N=O, asymmetric), 1343 (N=O, symmetric), 922 (C-F)
12	B_{12}	1652 (C=O), 1585 (C=C of Ar), 1462 (CH=CH), 1127 (-O-CH_3), 927 (C-F)
13	B_{13}	1643 (C=O), 1574 (C=C of Ar), 1500 (CH=CH), 1240 (O-CH_2-O), 929 (C-F)
14	B_{14}	1663 (C=O), 1610 (C=N), 1588 (C=C of Ar), 1510 (CH=CH), 1391 (C-N), 921 (C-F)
15	B_{15}	1652 (C=O), 1585 (C=C of Ar), 1503 (CH=CH), 929 (C-F)
16	B_{16}	1650 (C=O), 1586 (C=C of Ar), 1505 (CH=CH), 1178 (-N(CH_3)$_2$), 921 (C-F)
17	B_{17}	3450 (O-H), 1648 (C=O), 1606 (C=C of Ar), 1510 (CH=CH), 1225 (-OCH_3), 925 (C-F)
18	B_{18}	1653 (C=O), 1605 (C=C of Ar), 1595 (C=N), 1508 (CH=CH), 1385 (C-N), 922 (C-F)
19	B_{19}	1645 (C=O), 1603 (C=C of Ar), 1590 (C=N), 1502 (CH=CH), 1370 (C-N), 923 (C-F)
20	B_{20}	1650 (C=O), 1605 (C=C of Ar), 1581 (C=N), 1505 (CH=CH), 1373 (C-N), 929 (C-F)
21	B_{21}	1652 (C=O), 1605 (C=C of Ar), 1588 (C=N), 1506 (CH=CH), 1375 (C-N), 921 (C-F)
22	B_{22}	1655 (C=O), 1610 (C=C of Ar), 1505 (CH=CH), 624 (C-S), 923 (C-F)
23	B_{23}	1658 (C=O), 1605 (C=C of Ar), 1503 (CH=CH), 923 (C-F)
24	B_{24}	3460 (O-H), 1648 (C=O), 1606 (C=C of Ar), 1505 (CH=CH), 924 (C-F)
25	B_{25}	1650 (C=O), 1605 (C=C of Ar), 1502 (CH=CH), 929 (C-F)

Table No.3: ^{1}H NMR spectral data of chalcones

S.No	Compound	Chemical shift (δ) in ppm
1	B_1	2.40 (3H, s, Ar-CH_3), 7.23 (1H, d, *J* = 17 Hz, -CO-CH=), 7.73 (1H, d, *J* =17 Hz, =CH-Ar), 7.20-7.78 (7H, Ar-H)
2	B_2	7.15 (1H, d, *J* = 17 Hz, -CO-CH=), 7.62 (1H, d, *J* =17 Hz, =CH-Ar), 7.05-7.71 (7H, Ar-H)
3	B_3	7.45 (1H, d, *J* = 17 Hz, -CO-CH=), 7.82 (1H, d, *J* =17 Hz, =CH-Ar), 7.38-8.20 (7H, Ar-H)
4	B_4	7.43 (1H, d, *J* = 17 Hz, -CO-CH=), 7.80 (1H, d, *J* =17 Hz, =CH-Ar), 7.36-8.21 (7H, Ar-H)
5	B_5	7.40 (1H, d, *J* = 17 Hz, -CO-CH=), 7.73 (1H, d, *J* =17 Hz, =CH-Ar), 7.15-8.10 (6H, Ar-H)
6	B_6	7.68 (1H, d, *J* = 17 Hz, -CO-CH=), 7.85 (1H, d, *J* =17 Hz, =CH-Ar), 7.42-8.20 (6H, Ar-H)
7	B_7	7.49 (1H, d, *J* = 17 Hz, -CO-CH=), 7.65 (1H, d, *J* =17 Hz, =CH-Ar), 7.12-8.60 (6H, Ar-H)
8	B_8	7.40 (1H, d, *J* = 17 Hz, -CO-CH=), 7.62 (1H, d, *J* =17 Hz, =CH-Ar), 7.20-8.55 (7H, Ar-H)
9	B_9	7.43 (1H, d, *J* = 17 Hz, -CO-CH=), 7.68 (1H, d, *J* =17 Hz, =CH-Ar), 7.21-8.59 (7H, Ar-H)
10	B_{10}	7.38 (1H, d, *J* = 17 Hz, -CO-CH=), 7.52 (1H, d, *J* =17 Hz, =CH-Ar), 6.89 (1H, s, Ar-OH), 7.18-7.79 (7H, Ar-H)
11	B_{11}	2.50 (3H. s, Ar-CH_3), 7.40 (1H, d, *J* = 17 Hz, -CO-CH=), 7.65 (1H, d, *J* =17 Hz, =CH-Ar), 7.15-8.53 (6H, Ar-H)
12	B_{12}	7.15 (1H, d, *J* = 17 Hz, -CO-CH=), 7.64 (1H, d, *J* =17 Hz, =CH-Ar), 7.12-7.58 (5H, Ar-H), 3.78 (3H, s, Ar-OCH_3), 3.88 (6H, s, 2x Ar-OCH_3)
13	B_{13}	6.10 (2H,s,-O-CH_2O-), 6.88 (1H, d, *J* = 17 Hz, -CO-CH=), 7.69 (1H, d, *J* =17 Hz, =CH-Ar), 7.10-7.29 (6H, Ar-H)
14	B_{14}	2.45 (3H, s, Ar-CH_3), 6.85 (1H, d, *J* = 17 Hz, -CO-CH=), 7.65 (1H, d, *J* =17 Hz, =CH-Ar), 6.58-7.90 (8H, Ar-H)
15	B_{15}	7.23 (1H, d, *J* = 17 Hz, -CO-CH=), 7.71 (1H, d, *J* =17 Hz, =CH-Ar), 7.18-7.95 (5H, Ar-H)
16	B_{16}	3.10 (6H,s,-$N(CH_3)_2$, 6.88 (1H, d, *J* = 17 Hz, -CO-CH=), 7.75 (1H, d, *J* =17 Hz, =CH-Ar), 6.65-7.90 (7H, Ar-H)
17	B_{17}	7.21 (1H, d, *J* = 17 Hz, -CO-CH=), 7.68 (1H, d, *J* =17 Hz, =CH-Ar), 7.20-7.93 (6H, Ar-H), 6.75 (1H.s, Ar-OH), 3.82 (3H ,s, Ar-OCH_3)
18	B_{18}	7.15 (1H, d, *J* = 17 Hz, -CO-CH=), 7.65 (1H, d, *J* =17 Hz, =CH-Ar), 6.30-8.15 (7H, Ar-H)
19	B_{19}	7.18 (1H, d, *J* = 17 Hz, -CO-CH=), 7.70 (1H, d, *J* =17 Hz, =CH-Ar), 7.12-8.20 (7H, Ar-H)
20	B_{20}	7.15 (1H, d, *J* = 17 Hz, -CO-CH=), 7.75 (1H, d, *J* =17 Hz, =CH-Ar), 7.20-8.15 (7H, Ar-H)
21	B_{21}	7.10 (1H, d, *J* = 17 Hz, -CO-CH=), 7.70 (1H, d, *J* =17 Hz, =CH-Ar), 6.35-7.90 (7H, Ar-H)
22	B_{22}	7.12 (1H, d, *J* = 17 Hz, -CO-CH=), 7.70 (1H, d, *J* =17 Hz, =CH-Ar), 6.62-8.10 (6H, Ar-H)
23	B_{23}	7.35 (1H, d, *J* = 17 Hz, -CO-CH=), 7.60 (1H, d, *J* =17 Hz, =CH-Ar), 7.20-8.90 (12H, Ar-H)
24	B_{24}	7.28 (1H, d, *J* = 17 Hz, -CO-CH=), 7.59 (1H, d, *J* =17 Hz, =CH-Ar), 6.85 (1H, s, Ar-OH), 7.21-7.89 (7H, Ar-H)
25	B_{25}	7.21 (1H, d, *J* = 17 Hz, -CO-CH=), 7.62 (1H, d, *J* =17 Hz, =CH-Ar), 7.11-7.90 (8H, Ar-H)

Table No.4: Experimental and predicted MIC (µg/mL) values of training set and test set molecules based on atom based 3D-QSAR model (Antibacterial activity)

S.No	Compound code	*B.subtilis* MIC(µg/mL)	Experimental -log(MIC)	Predicted-log (MIC) (Training set)	Predicted-log (MIC) (Test set)
1	B_1	128	-2.10721	-1.99786	---
2	B_2	64	-1.80618	---	-1.8522
3	B_3	64	-1.80618	-1.78244	---
4	B_4	64	-1.80618	-1.83539	---
5	B_5	32	-1.50515	-1.77385	---
6	B_6	64	-1.80618	---	-1.61438
7	B_7	32	-1.50515	-1.4236	---
8	B_8	128	-2.10721	-2.13336	---
9	B_9	128	-2.10721	-2.08065	---
10	B_{10}	256	-2.40824	-2.43568	---
11	B_{11}	128	-2.10721	---	-2.11693
12	B_{12}	64	-1.80618	-1.84143	---
13	B_{13}	256	-2.40824	---	-2.24238
14	B_{14}	128	-2.10721	-2.20928	---
15	B_{15}	64	-1.80618	-1.87677	---
16	B_{16}	64	-1.80618	-1.79833	---
17	B_{17}	128	-2.10721	-2.18291	---
18	B_{18}	128	-2.10721	-2.16989	---
19	B_{19}	128	-2.10721	-2.19334	---
20	B_{20}	128	-2.10721	-2.123	---
21	B_{21}	256	-2.40824	-2.33018	---
22	B_{22}	128	-2.10721	-2.0912	---
23	B_{23}	256	-2.40824	-2.34953	---
24	B_{24}	264	-2.4216	---	-2.05839
25	B_{25}	256	-2.40824	-2.01035	---

Table No.5: Antibacterial activity of chalcones (compounds B_1 to B_{12}): (Expressed as MIC in µg/mL)

S.No	z	R	*B.subtilis*	*S.aureus*	*E.coli*	*P.vulgaris*
1	B_1	4"-methyl phenyl	128	128	64	64
2	B_2	4"-fluorophenyl	64	128	64	128
3	B_3	4"-chlorophenyl	64	128	128	64
4	B_4	2"-chlorophenyl	64	128	128	64
5	B_5	2",4"-difluorophenyl	33	64	33	33
6	B_6	2",4-dichlorophenyl	64	64	32	128
7	B_7	2"-chloro-5"-nitro phenyl	33	128	128	128
8	B_8	3"-nitro phenyl	128	256	128	256
9	B_9	4"-nitro phenyl	128	256	128	128
10	B_{10}	3"-hydroxyphenyl	256	256	128	256
11	B_{11}	3"-nitro-4"-methyl phenyl	128	64	128	128
12	B_{12}	3",4",5"-trimethoxyphenyl	64	64	64	32
13	B_{13}	3",4"-methylendioxyphenyl	256	128	256	128
14	B_{14}	1"-phenyl-3"methylpyrazole-4"-yl	128	128	128	256
15	B_{15}	5"-bromofuran-2"-yl	64	64	32	128
16	B_{16}	4"-dimethylaminophenyl	64	128	64	64
17	B_{17}	3"-methoxy-4"-hydroxyphenyl	128	128	128	128
18	B_{18}	2"-pyridinyl	128	256	128	256
19	B_{19}	3"-pyridinyl	128	256	256	256
20	B_{20}	4"-pyridinyl	128	128	128	128
21	B_{21}	2"-pyrrolyl	256	256	64	64
22	B_{22}	2"-thienyl	128	64	128	128
23	B_{23}	9"-anthracenyl	256	128	128	256
24	B_{24}	4"-hydroxyphenyl	264	128	64	64
25	B_{25}	Phenyl	256	256	256	256
26	Standard (Ampicillin)	---	< 1	< 1	< 1	< 1

Table No.5: Summary of atom based 3D QSAR results

S.No	PLS Factors	SD	R^2	F	P	RMSE	Q-squared	Pearson-R
1	4	0.1406	0.7922	14.3	5.28e-05	0.2	0.4647	0.8391

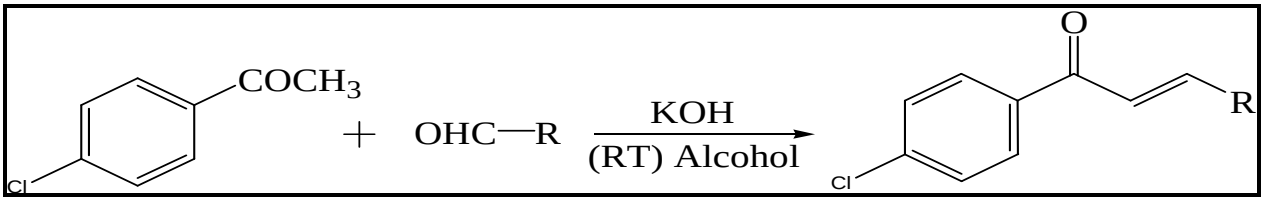
Table No.6: Experimental and predicted MIC (µg/mL) values of training set and test set molecules based on atom based 3D-QSAR model (Antibacterial activity)

S.No	Compound code	*S.aureus* MIC(µg/mL)	Experimental -log(MIC)	Predicted-log(MIC) (Training set)	Predicted-log(MIC) (Test set)
1	B_1	128	-2.10721	-2.03134	---
2	B_2	128	-2.10721	-2.02153	---
3	B_3	128	-2.10721	-2.03373	---
4	B_4	128	-2.10721	-2.03405	---
5	B_5	64	-1.80618	-1.97364	---
6	B_6	64	-1.80618	---	-1.94537
7	B_7	128	-2.10721	---	-2.10334
8	B_8	256	-2.40824	-2.49357	---
9	B_9	256	-2.40824	-2.38831	---
10	B_{10}	256	-2.40824	---	-2.25866
11	B_{11}	64	-1.80618	-1.85607	---
12	B_{12}	64	-1.80618	-1.80874	---
13	B_{13}	128	-2.10721	-2.12386	---
14	B_{14}	128	-2.10721	-2.09377	---
15	B_{15}	64	-1.80618	-1.92587	---
16	B_{16}	128	-2.10721	-2.06055	---
17	B_{17}	128	-2.10721	---	-2.03624
18	B_{18}	256	-2.40824	-2.39162	---
19	B_{19}	256	-2.40824	-2.37156	---
20	B_{20}	128	-2.10721	-2.15377	---
21	B_{21}	256	-2.40824	-2.38607	---
22	B_{22}	64	-1.80618	-1.74819	---
23	B_{23}	128	-2.10721	-2.1409	---
24	B_{24}	128	-2.10721	-2.10705	---
25	B_{25}	256	-2.40824	---	-2.11896

Table No.7: Summary of atom based 3D QSAR results

S.No	PLS Factors	SD	R^2	F	P	RMSE	Q-squared	Pearson-R
1	4	0.0765	0.9031	35	1.94e-07	0.16	0.4858	0.8799

General scheme of reaction



4-chloroacetophenone Aromatic/ Chalcone derivative Heterocyclic aldehyde

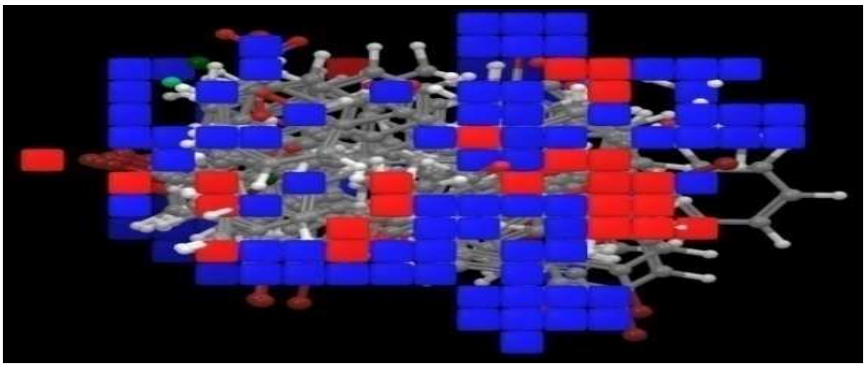


Figure No.1: Atom based 3D-QSAR Model of chalcones along with alignment of structures (Blue cubes indicate favorable regions while red cubes indicate unfavorable region for the activity) against *B.subtilis*

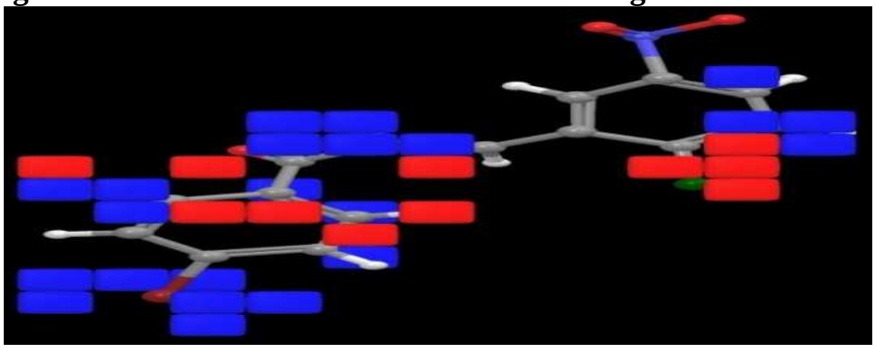


Figure No.2: Atom based 3D QSAR model visualized in the context of highest active compound B_7 against *B.subtilis*

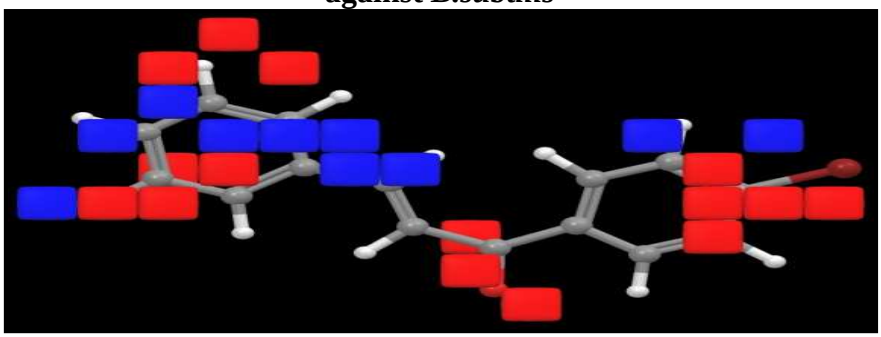


Figure No.3: Atom based 3D QSAR model visualized in the context of lowest active compound B_{25} against *B.subtilis*

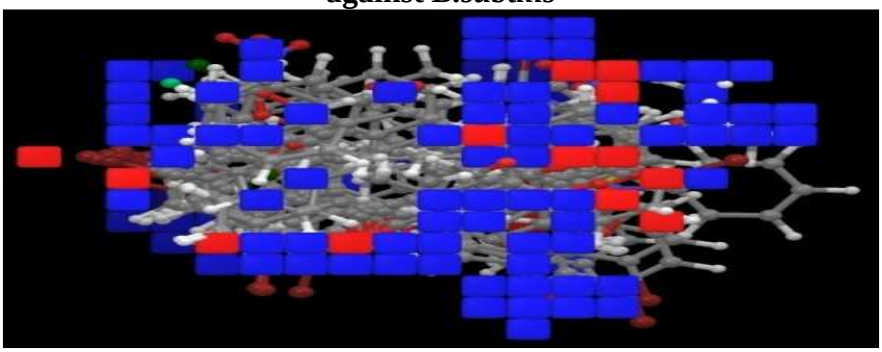


Figure No.4: Atom based 3D-QSAR Model of chalcones along with alignment of structures (Blue cubes indicate favorable regions while red cubes indicate unfavorable region for the activity) against *S.aureus*

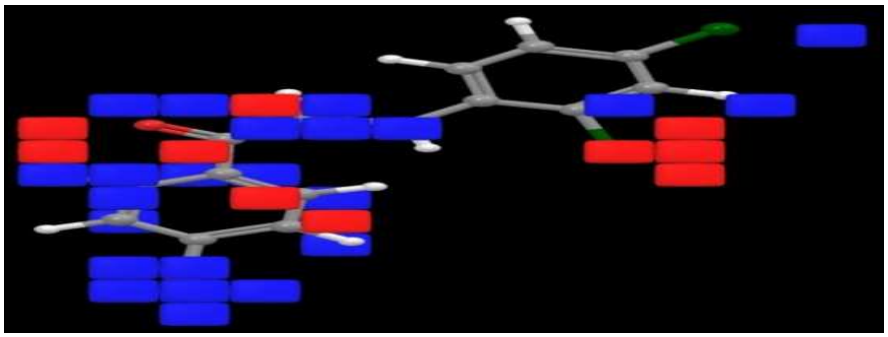


Figure No.5: Atom based 3D QSAR model visualized in the context of highest active compound B_6 against *S.aureus*

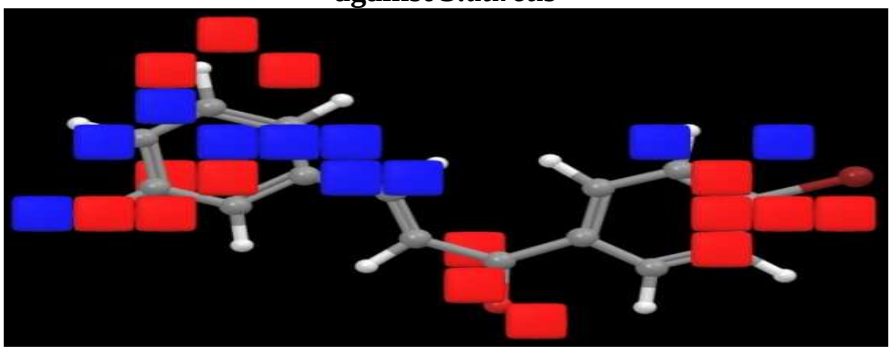


Figure No.6: Atom based 3D QSAR model visualized in the context of lowest active compound B_{25} against *S.aureus*

CONCLUSION

The above results clearly indicated the importance of electron withdrawing groups in increasing the antibacterial activity. When two or more such substituents present on the benzene ring, cumulative effect was observed as seen in the case of B_5 and B_6 having difluoro and dichloro substitution respectively. However, compounds with electron releasing substituents as seen in the case of B_{12} and B_{16} also enhanced the activity. Substitution of electron releasing or electron with drawing groups on the aromatic or heteroaromatic ring at varies positions can be synthesized to concluded with respect to the influence of electronic effects on the antimicrobial activity.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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