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Antifungal activity analysis of α-methylene-γ-butyrolactone derivatives Using physicochemical parameters

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ABSTRACT

A Quantitative-Structure-Activity Relationship (QSAR) study is performed on a set of 36 α-methylene-γ-butyrolactone derivatives using physicochemical parameters, Regression analysis data has indicated that properity can be best modeled in multi-parameteric regression.

Key words: α-methylene-γ-butyrolactone, QSAR, Physicochemical parameters, MLR.

INTRODUCTION

Emerging infectious diseases[1] caused by fungi are increasingly recognized as a presenting a worldwide threat to food security and pathogenic fungi[2] has long been known to constitute a widespread threat to plant species. Plant disease epidemics caused by fungi or the fungal-like oomycetes[3] can infect diverse economically important crops and result in severe yield losses and quality reduction of agricultural production. Chemical fungicides[4] are widely used to protect crops against these losses at present, but the application of chemical fungicides is challenged by the incidence or resistance and residue. To overcome this limitation, an effort to develop environment friendly antifungal agents[5] from natural products, researchers from their laboratory have designed and synthesized.

A series of carabrone derivatives[6] explore the QSAR[7-9] hidden in them and give result that display stronger antifungal activity. The QSAR methods[10-12], with simple molecular indexes, are a promising shortcut to resolve the cost and time issue. The QSAR method enables the

calculation of numerous quantitative descriptors on the basis of molecular structural information and is very useful to optimize important aspects such as fungicidal activity. QSAR is useful in provide further guidance for the design and development of potential new fungicides.

Experimental Details

Antifungal values have been used as reported by Yong-Ling Wo. et al[13].

2.1 Parameters used

We have following physicochemical parameters for modeling of which were calculated by using ACD labs software Chemsketch[14].

(1) Molecular volume (MV)

$$MV = \frac{MW}{d}$$

(2) Molar refractivity (MR)

$$MR = \frac{\mathrm{n2}-1}{\mathrm{n2}-1}.\frac{MW}{d}$$

(3) Parachor (P)

$$\boldsymbol{P_r = \left(\frac{MW}{d}\right)\gamma^{1/4}}$$

(4) Density (d)

$$d = \frac{MW}{MV}$$

(5) Refractive Index(n)

$$\boldsymbol{n = \sqrt{\frac{2MR+MV}{MV-MR}}}$$

(6) Surface tension (γ)

$$\boldsymbol{\gamma = \left(\frac{P_r}{MV}\right)^4}$$

(7) Polarizability (α)

Polarizability=0.3964308.MR

The compounds used in the present study with their values are reported in Table I.

The physicochemical parameters have been calculated using ACD lab software. The values of various parameters obtained are reported in Table II.

Result and Discussion:

3.1 Modeling IC_{50} using physiochemical parameter.

A close look parameter Table III revels that

1) Out of Eight mono-parametric models, D shows the highest regression value for the best model.
2) Out of ten bi-parametric model, MW and PC together shows the highest regression value for the best model.
3) Out of ten tri-parametric model, MW, MV and ST together shows the highest regression value for the best model.
4) Out of ten tetra-parametric model, MR, MV, IR and D together shows the highest regression value for the best model.

Mono-parametric model

IC_{50} = -133.3766(±28.9124 D, B = 224.4267

N = 36, R^2 =0.3850, R^2_A =0.3669, F =21.2810, Se =0.3858.

(1)

When MW and PC were taken together a bi- parametric model has been obtained with improved statistics here R^2 comes out to be 0.4270.

Bi-parametric model

IC_{50} = -0.7979 (±0.1679) MW, -0.3823 (±0.0806) PC, B =57.4933

N = 36, R^2 = 0.4270, R^2_A = 0.3923, F = 12.2950, Se =0.3780.

(2)

A tri- parametric model has been obtained when MR, MV and ST were taken together. In this model the R^2 shows significant improvement.

Tri-parametric model

IC_{50} = -0.8130(±0.1649) MR, – 1.0415 (±0.2102) MV, 0.9977(±0.6368)ST, B= 6.3446

N = 36, R^2 = 0.3402, R^2_A = 0.3002, F =8.5070, Se = 0.4057.

(3)

A tetra- parametric model has been obtained when MR, MV, IR and D was taken together. In this model the R^2 shows significant improved.

Tetra-parametric model

However, very small improvement is observed in a tetra-parametric model when MR, MV, IR and D have been taken as correlating parameter. This model has been found to be excellent for modelling (IC_{50}) activity of the compound of the present study.

IC_{50} = -18.6600(±5.4176) MR, 6.6449 (±1.9302) MV, 1814.232(±507.3076)IR, – 129.8293 (±27.0487) D,

B= -2729.3320

N = 36, R^2 = 0.5687, R^2_A = 0.5131, F =10.2200, Se = 0.3384.

(4)

Validation of model

The model has been validated by plotting a graph between actual and predicted values of IC_{50} activity as in Fig. (i) Based on data which is recorded in table IV obtained from tetra- parametric model. **5 Cross validated parameter**

In this we observed the parameter with high regression value which will obtain the best result.

Conclusions

From the study of α-methylene-γ-butyrolactone, their fungicidal activities against C.lagenarium and B. cinerea was investigated. Compounds containing halogen atom was exhibited excellent fungicidal activity against C.lagenarium as compare to others compounds of α-methylene-γ-butyrolactone. Among the halogen atom, chlorine atom intermediate were more active than other. An important influence of structural characteristics on the fungicidal activity indicated by QSAR and SAR and it also indicated the electron withdrawing substituent on the α-methylene-γ-butyrolactone derivatives has a positive effect on the fungicidal activity. Although the entire compounds were not so effective against B. cinereal and C. lagenarium compared with the positive control.

And It was notable that racemic mixture of present set of compounds; it will be an interesting task for further studies to test the most active compounds in optically pure form. α-methylene-γ-butyrolactone

derivatives level of fungicidal activity and cytotoxic activity observed and provide great impetus for further work on the design of high activity and non- toxic crop-protection agents.

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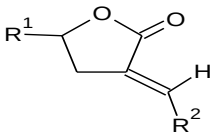
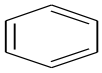
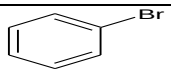
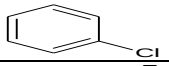
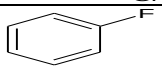
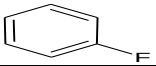
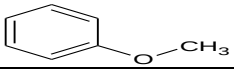
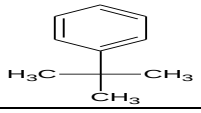
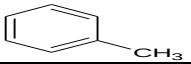
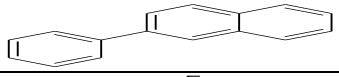
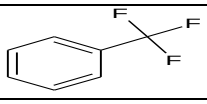
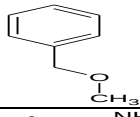
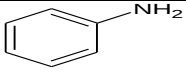
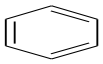
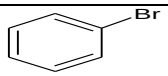
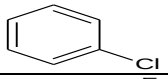
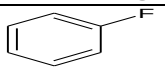
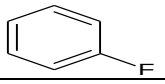
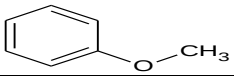
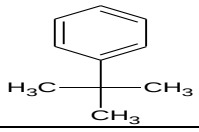
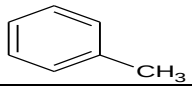
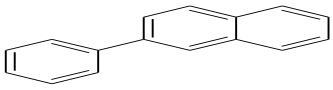
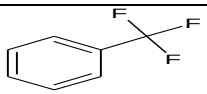
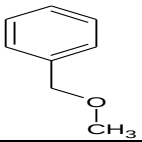
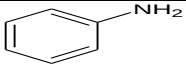
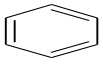
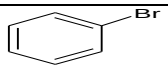
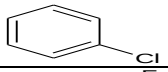
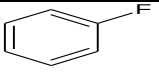
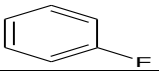
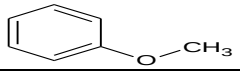
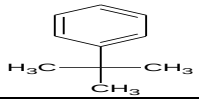
In this study, a series of α-methylene-γ-butyrolactone derivative were studied in order to analysis the role of electron density and steric hindrance influence on the exocyclic carbon-carbon double bond. The promising result obtained from QSAR and cytotoxicity studies based on α-methylene-γ-butyrolactone derivatives will inspiring us to carry on further work to analysis of the high activity and low toxic fungicides agents.

Whole analysis indicated that property can be best modeled in multi-parametric regression.

Table1. Structural details along with their log p Values.



Compound No.	R^1	R^2	Log p
1.	H		1.38
2.	H		2.15
3.	H		1.99
4.	H		1.44
5.	H		1.50
6.	H		1.36
7.	H		3.07
8.	H		1.84
9.	H		4.37
10.	H		2.35
11.	H		1.12
12.	H		0.10

13.	CH3		1.87
14.	CH3		2.64
15.	CH3		2.48
16	CH3		1.93
17.	CH3		2.00
18.	CH3		1.85
19.	CH3		3.56
20.	CH3		2.33
21.	CH3		4.86
22.	CH3		2.84
23.	CH3		1.61
24.	CH3		0.59
25	Cl		1.38
26.	Cl		2.15
27.	Cl		1.99
28.	Cl		1.44
29.	Cl		1.50
30.	Cl		1.36
31.	Cl		3.07

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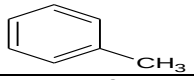
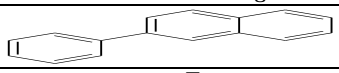
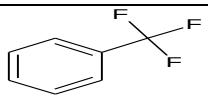
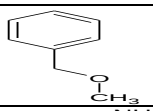
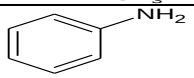
32.	Cl		1.84
33.	Cl		4.37
34.	Cl		2.35
35.	Cl		1.12
36.	Cl		0.10

Table II. Value of the calculated physiochemical parameter used in the present study

Compound No.	MW	MR	MV	PC	IR	ST	D	POL
1	174.196	50.82	144	383.8	1.623	50.4	1.209	20.14
2	253.092	58.51	160.2	434.9	1.651	54.2	1.579	23.19
3	208.641	55.72	155.9	420.9	1.633	53.0	1.337	22.08
4	192.186	50.81	148.2	391.1	1.601	48.4	1.296	20.14
5	192.186	50.81	148.2	391.1	1.601	48.4	1.296	20.14
6	204.222	57.5	168	442.4	1.6	48.0	1.215	22.79
7	230.302	69.21	210.7	538.6	1.57	42.6	1.092	27.43
8	188.222	55.65	160.3	422.1	1.61	48.0	1.174	22.06
9	300.351	93.26	243.4	660.7	1.692	54.2	1.233	36.97
10	242.194	55.8	177.5	445.8	1.541	39.7	1.364	22.12
11	218.248	62.12	183.2	482.5	1.593	48.1	1.191	24.62
12	189.211	55.06	146.3	411.7	1.676	62.7	1.293	21.82
13	190.238	56.99	164.5	431.6	1.609	47.3	1.156	22.59
14	267.119	63.22	180.2	472.9	1.619	47.4	1.482	25.06
15	222.668	60.42	175.9	459	1.602	46.2	1.265	23.95
16	206.213	55.52	168.2	429.2	1.574	42.3	1.225	22.01
17	206.213	55.52	168.2	429.2	1.574	42.3	1.225	22.01
18	218.248	62.21	188	480.4	1.575	42.6	1.16	24.66
19	244.329	73.92	230.7	576.6	1.553	39.0	1.058	29.3
20	202.249	60.35	180.3	460.1	1.584	42.4	1.121	23.92
21	314.377	97.96	263.4	698.8	1.666	49.5	1.193	38.83
22	256.22	60.51	197.5	483.8	1.524	35.9	1.297	23.98
23	232.275	66.82	203.2	520.5	1.571	43.0	1.143	26.49
24	203.237	59.76	166.3	449.8	1.637	53.5	1.222	23.69
25	208.641	54.21	162.2	420.7	1.582	45.2	1.28	21.49
26	287.537	61.93	175.1	471.7	1.624	52.6	1.64	24.55
27	257.113	63.43	189.4	494.2	1.584	46.2	1.35	25.14
28	226.631	54.32	166.9	428	1.564	43.2	1.35	21.53
29	226.631	54.32	166.9	428	1.564	43.2	1.35	21.53
30	238.667	60.57	184.3	479.3	1.57	45.6	1.29	24.01
31	264.747	72.73	227.5	575.4	1.552	40.9	1.16	28.83
32	222.668	58.83	178.1	459	1.574	44.0	1.24	23.32
33	334.796	96.47	254.6	697.6	1.682	56.3	1.31	38.24
34	276.639	59.2	193.8	482.7	1.522	38.4	1.42	23.46
35	252.694	65.2	200.7	519.4	1.563	44.8	1.25	25.85
36	223.656	57.82	165.5	448.6	1.615	53.9	1.35	22.92

Table III. Regression Parameter and quality of correlation when physicochemical parameter for IC_{50}

Model No.	Parameter Used	Ai =(1-6)	B	Se	R^2	R^2A	F
1.	D	-133.3766(±28.9124)	224.4267	0.3858	0.3850	0.3669	21.2810
2.	MV	0.1764(±0.1494)	22.3519	0.4822	0.0394	0.0112	1.3950
3.	MW	-0.1355(±0.1188)	86.2167	0.4828	0.0368	0.0085	1.3010
4.	PC	0.0632(±0.0571)	24.4528	0.4834	0.0347	0.0063	1.2230
5.	POL	0.9728(±0.9747)	30.6105	0.4849	0.0285	0.0000	0.9960
6.	MR	0.3856(±0.3864)	30.6090	0.4849	0.0285	0.0000	0.9960
7.	IR	19.0526(±108.1573)	24.2647	0.4918	0.0009	0.0000	0.0310
8.	ST	0.02817(±0.7975)	53.3653	0.4920	0.0000	0.0000	0.0010
9.	MW PC	-0.7979(±0.1679) 0.3822(±0.0806)	57.4933	0.3780	0.4270	0.3923	12.2950
10.	ST D	0.9704(±0.6430) -146.6940(±29.7245)	196.0006	0.3788	0.4247	0.3898	12.1790
11.	MW MV	0.7457(±0.1627) 0.9419(±0.2048)	55.5907	0.3827	0.432	0.3776	11.617
12.	IR D	87.3901(±86.0479) -138.3860(±29.3169)	91.2812	0.3857	0.4036	0.3657	11.1660
13.	PC D	0.0172(±0.0474) -130.9516(±30.0438)	213.124	0.3909	0.3874	0.3503	10.4340
14.	MR D	0.1139(±0.3175) -131.2909(±29.8607)	214.6558	0.3909	0.3874	0.3502	10.4320
15.	D POL	-131.2908(±29.8609) 0.2875(±0.8009)	214.6579	0.3909	0.3874	0.3502	10.4320
16.	MV D	0.0243(±0.1263) -131.7351(±30.5466)	217.8854	0.3914	0.3856	0.3484	10.3580
17.	MW D	0.0069(±0.1018) -134.0620(±31.0138)	223.6803	0.3916	0.3850	0.3478	10.3310
18.	MW MR	-0.6702(±0.1697) 2.1404(±0.5495)	76.9982	0.4057	0.3402	0.3002	8.5070
19.	MW MV ST	-0.8130(±0.1649) 1.041(±0.2102) 0.9977(±0.6367)	6.3446	0.3744	0.4550	0.4039	8.9050
20.	MW PC POL	-0.8222(±0.1678) 0.7058(±0.27490) -5.4167(±4.4038)	42.4135	0.3751	0.4529	0.4016	8.8290
21.	MW MR PC	-0.8221(±0.1677) -2.1467(±1.7457) 0.7056(±0.2749)	42.4378	0.3751	0.4528	0.4015	8.8280
22.	IR ST D	-201.8904(±218.9584) 2.3868(±1.6659) -154.5613(±30.9899)	462.1010	0.3797	0.4396	0.3870	8.3660
23.	MW MV D	-2.1554(±1.2989) 2.6902(±1.6113) 260.7645(±238.4055)	-268.6299	0.3814	0.4343	0.3813	8.1900

24.	MW MV PC	-0.7964(±0.1697) 0.3345(±0.6225) 0.2563(±0.2481)	56.0789	0.3822	0.4321	0.3789	8.1160
25.	MW PC IR	-0.8043(±0.1703) 0.3909(±0.0834) -43.4600(±87.3667)	124.2283	0.3824	0.4314	0.3781	8.0920
26.	MW MV IR	-0.7777(±0.1657) 0.9649(±0.2060) 86.4069(±86.0023)	-79.1272	0.3825	0.4311	0.3778	8.0840
27.	MW PC D	-0.7581(±0.509) 0.3637(±0.2373) -7.3188(±88.0936)	66.3883	0.3838	0.4271	0.3734	7.5920
28.	MW PC ST	-0.7979(±0.1705) 0.3823(±0.0819) -0.01752(0.6225)	58.2977	0.3839	0.4270	0.3733	7.9490
29.	MR MV IR D	-18.6600(±5.4175) 6.6449(±1.9302) 1814.2320(±507.3076) -129.8293(±27.0487)	-2729.3320	0.3384	0.5687	0.5131	10.2200
30.	MV IR D POL	6.5973(±1.9256) 1801.7230(±506.1078) -129.949(±27.0824) -46.7317(±13.6331)	-2709.0130	0.3388	0.5676	0.5118	10.1720
31.	MW MR MV IR	-0.7083(±0.1488) -16.9707(±5.4798) 6.9221(±1.9323) 1654.7390(±512.1375)	-2631.397	0.3396	0.5655	0.5095	10.0880
32.	MW MV IR POL	-0.7090(±0.1489) 6.8776(±1.9273) 1642.8180(510.7979) -42.4858(13.7863)	-2612.1590	0.3400	0.5645	0.5083	10.047
33.	MV PC ST D	8.5367(±2.9098) -3.2006(±1095) 9.2280(±2.8806) -135.1460(±28.1431)	-238.1308	0.3455	0.5504	0.4924	9.4870
34.	MW MV PC ST	-0.7425(±0.1546) 8.48899(±2.9111) -2.8364(±1.1063) 8.2743(±2.8982)	-358.2128	0.3455	0.5503	0.4943	9.4850
35.	MW MR MV ST	-0.8364(±0.1566) -4.4918(±2.0875) 2.7971(±0.8399) 3.8956(±1.4758)	-165.0270	0.3548	0.5258	0.4646	8.5940
36.	MW MV ST POL	-0.8365(±0.1566) 2.7945(±0.8395) 3.8907(±1.4749) -11.3127(±5.2627)	-164.7832	0.3549	0.5257	0.4645	8.5900
37.	MR MV ST D	-4.6761(±2.1402) 1.8364(±0.8305) 4.0123(±1.5162) -149.9241(±29.5213)	13.2683	0.3632	0.5030	0.4389	7.840
38.	MV	1.8338(±0.8300)	13.5041	0.3633	0.5029	0.4388	7.8420

	ST D POL	4.0076(±1.5153) -149.9291(±29.5249) -11.7787(±5395)					

Table IV. Experimental and observed value of IC_{50}

Sr. No	Actual IC_{50}	Predicted IC_{50}	Residual
1	61.660	66.762	-5.102
2	38.020	33.675	4.345
3	27.540	55.926	-28.386
4	34.670	43.649	-8.979
5	26.300	43.649	-17.349
6	63.100	59.084	4.016
7	83.180	85.853	-2.673
8	66.070	65.904	0.166
9	51.290	57.397	-6.107
10	38.90	27.548	11.352
11	97.720	64.293	33.427
12	85.110	88.175	-3.065
13	72.440	69.331	3.109
14	44.670	33.222	11.448
15	30.900	54.228	-23.328
16	41.690	48.891	-7.201
17	28.840	48.891	-20.051
18	95.500	65.877	29.623
19	97.720	104.434	-6.714
20	77.620	70.811	6.809
21	61.660	60.616	1.045
22	54.950	50.413	4.537
23	125.890	75.807	50.083
24	102.330	71.833	30.497
25	35.480	40.839	-5.359
26	29.510	11.962	17.548
27	22.910	44.075	-21.165
28	27.540	28.274	-0.734
29	18.890	28.274	-9.384
30	44.670	45.945	-1.275
31	52.980	90.319	-37.339
32	42.690	50.963	-8.273
33	37.150	43.782	-6.632
34	33.880	30.674	3.206
35	58.880	61.018	-2.138
36	56.230	46.187	10.043

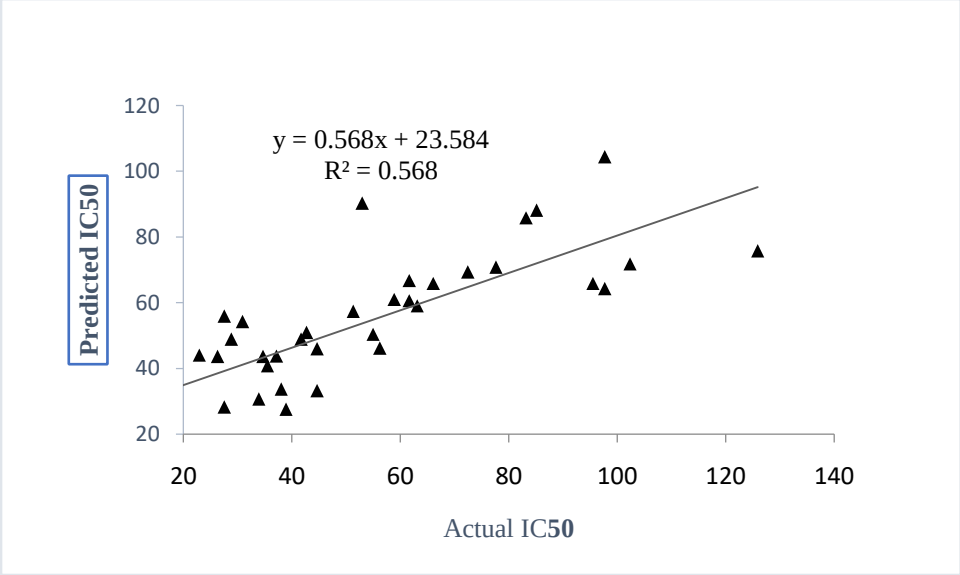


Fig. (i) Correlation between actual and predicted IC_{50} values

Table V. Cross-validated parameter for the best obtained model

Model No	Parameter Used	PRESS/SSY	R^2cv	SPRESS	PSE
1.	D	1.5977	-0.5977	3.6184	3.4174
9.	MW PC	1.3419	-0.3419	3.5984	3.2986
19.	MW MV ST	1.1978	-0.1978	3.6191	3.2169
29.	MR MV IR D	0.7583	0.2416	3.3233	2.8617

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