ISSN NO. 2320–7418 DOI: 10.22270/jmpas.V10I4.1420

International open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com

Research article

QSAR studies of some Substituted Imidazole Derivatives as Potent Antifungal Agents

Sumeet Prachand[1]*, Sanjay Jain[1], Hemant Khambete[1], Arun K Gupta[2]

1. Faculty of Pharmacy, Medi-Caps University, Indore, Madhya Pradesh, India
2. Chameli Devi Institute of Pharmacy, Indore, Madhya Pradesh, India

ABSTRACT

Fracture of distal radius is the commonest fracture present in the upper limb. In fact, it is most commonly treated by the doctor. An outstretched hand is the most common cause of distal radius or wrist fractures. The fracture of distal radius can also lead to nerve injury mostly median nerve. Physical Therapy plays important role which provides positive effect in treating post fracture cases. A case of 45 years female is presented in this report who had a fall over right wrist joint and diagnosed with distal radius fracture and operated conservatively results into pain over wrist joint, decrease in physical activities. Rehabilitation protocol is explained below in the report. We report that there were improvement in patient outcomes level increases in muscles strength, provide pain relief and improvement in patient functional Independence.

Keywords: QSAR, Drug Design, Imidazole

Received - 23/06/2021, Reviewed - 17/07/2021, Revised/ Accepted- 28/08/2021

Correspondence: Sumeet Prachand* ✉ sumeet6882@gmail.com

Assistant Professor, Faculty of Pharmacy, Medi-Caps University, Indore, Madhya Pradesh, India

INTRODUCTION

QSAR is the prefect suggestive method which can be employed to check the extent of possibilities for understanding and designing various selective controls of bio chemical processes. Thus, looking into this domain some imidazole analogs which are very known, as they offer the ray of hope to get relief from fungal infections. Looking into current scenario of COVID-19 pandemic these imidazole moieties were considered for screening by conventional methods.

QSAR analysis in the present work. For the duration of the earlier decades the intensity and frequency of invasive as well as systemic fungal has increased exponentially specially in those peoples who have altered immunity. Current available therapy for curing fungal infection has various problems which are associated with toxicity, drug-drug interactions, non-optimized pharmacokinetics parameters and drug resistance1. Azoles are currently the most widely studied class of antifungal agents. In current scenario the classical QSAR methods plays a vital role in designing of new drugs irrespective of availability of molecular modeling and protein crystallography. These classical methods are cheap and it has easy tools to operate and to prove the hypothesis on structure-activity relationships in a quantitative manner. Arrangement of the molecular descriptors/substituent in a quantitative information technique relating to the effects led to improved antifungal activity in the series of compounds. Exploring diverse structures and diverge mode of interactions of such compounds through molecular modelling studies gave probable insight of key interaction with macromolecules and their responsible physicochemical properties[2]. Therefore, it is worthwhile to study substituted imidazole derivatives for their quantitative structure activity relationship (QSAR) and subsequently designing synthesis and evaluation.

MATERIAL AND METHOD [4, 5, 6]

The in vitro activity data of reported compounds (substituted imidazole derivatives) for antifungal activity were taken from Sharma *et.al*. The MIC values were used for QSAR analysis by taking negative logarithm

$$pMIC = - \log (MIC)$$

The series was divided into a training set and a test set on the basis of structural diversity and activity. Training set contains 17 compounds (compound no: 3,5,6,10,11,12,14,15,16,17,19,
20, 22, 23, 24, 25 and 26) while test set contains 9 compounds (Compound no: 1,2,4,7,8,9,13,18 and 20)

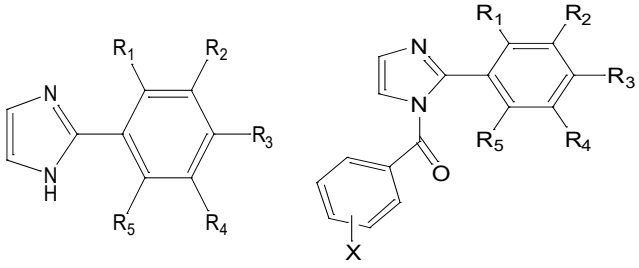


Table-1 Structure and Activities of Substituted Imidazole Derivatives Used in Training and Test Sets

Compo-und	R_1	R_2	R_3	R_4	R_5	X	[a]MIC	[b]pMIC
1	Cl	H	H	H	H	-	702	2.41
2	H	H	Cl	H	H	-	35	3.71
3	H	Cl	H	H	H	-	35	3.73
4	H	NO_2	H	H	H	-	33	3.76
5	NO_2	H	H	H	H	-	33	3.73
6	H	H	NO_2	H	H	-	33	3.64
7	H	H	H	H	H	-	43	3.64
8	COOH	H	H	H	H	-	66	3.46
9	H	H	OCH_3	H	H	-	65	3.47
10	CH_3	CH_3	H	H	H	-	72	3.38
11	CH_3	H	H	CH_3	CH_3	-	36	3.68
12	H	H	Br	H	H	-	28	3.64
13	H	NO_2	H	H	H	4-NO_2	18	4.27
14	NO_2	H	H	H	H	4-NO_2	36	3.97
15	Cl	H	H	H	H	4-NO_2	38	3.94
16	H	H	Cl	H	H	4-NO_2	19	4.24
17	COOH	H	H	H	H	4-NO_2	18	4.27
18	H	Cl	H	H	H	4-NO_2	38	3.94
19	H	H	NO_2	H	H	4-NO_2	18	4.27
20	H	H	OCH_3	H	H	4-NO_2	18	4.25
21	NO_2	H	H	H	H	2-Br	33	4.05
22	H	NO_2	H	H	H	2-Br	16	4.37
23	Cl	H	H	H	H	2-Br	17	4.33
24	H	H	Cl	H	H	2-Br	17	4.33
25	H	H	OCH_3	H	H	2-Br	16	4.35
26	H	H	NO_2	H	H	2-Br	16	4.37

A) Minimum inhibitory concentration (in µg/mL) aganists Candida Albicans

B) Negative logarithm of MIC values aganists Candida albicans

The substituted imidazole analogs were subjected to QSAR studies using CS Chem Bio Office Software (Cambridge soft) running on a core 2 duo processor. Compounds structures were drawn using program builder module of the program. Electronic descriptors such as electronic energy (ElcE), Highest occupied molecular orbital energy (HOMO), Lowest unoccupied molecular orbital energy (LUMO), Dipole moment of X-component (DPL1), Dipole moment of Y-component (DPL2), Dipole moment of Z-component (DPL3), Resultant dipole (DPL4), Repulsion energy (NRE), VDW-1,4- energy (E14), Non-1, 4-VDW energy (Ev) and Total energy (Et) were also calculated. The minimized molecules were saved as "MOL" file format. The "MOL" file was further used for calculation of various molecular descriptors using DRAGON software.

The data was transferred to the statistical program in order to establish a correlation between physicochemical parameters as independent variables and anti-fungal activity (pMIC) as dependent variable. The sequential multiple linear regression analysis method was employed using VALSTAT program. In sequential multiple regression the program searches for all permutations and combinations sequentially for the data set. The equations were selected on the basis of various statistical parameters such as correlation coefficient (r), standard error of estimation (SEE), sequential Fischer test (F). The robustness and applicability of QSAR equation as best model, on the structural analogs was further confirmed, using various QSAR validation technique like leave one out cross validated square correlation coefficient (Q2) using cross validation method, boot-strapping square correlation coefficient (r2bs), randomized biological activity data test (chance), test for outliers (Z-score value) and predictivity of test set (r2pred).

QSAR Analysis of Antifungal Activity

A correlation was established between physicochemical parameters and antifungal activity using the sequential multiple linear regression technique considering adjusted square correlation coefficient (r2adj). Initially uni-variant expressions were explored and X4A showed significant correlation coefficient value (Eqn. 1) with 71.3% explained variance in the activity. The ± data within the parentheses is the standard deviation, associated with the coefficient of descriptors in regression equations.

pMIC = 25.752(±15.656) X4A + 0.788
n =17, r = 0.318, r2adj = 0.064, SEE = 0.429, F = 2.7 (Eqn.1)
SEQ-MLR revealed that the r2adj value is increasing significantly from the uni to the bi-variant expressions i.e. 0.064, and 0.413 respectively. Boosting of r2adj value from uni- to bi-variant revealed that incorporation of second physicochemical descriptor improve the quality of mathematical expression in a comprehensible manner.

pMIC =119.029(±26.893) X4A + 75.771(±19.386) PW5 - 17.109
n = 17, r = 0.678, r2adj = 0.413, SEE = 0.340, F = 9.796 (Eqn.2)
SEQ-MLR revealed that the r2adj value is increasing significantly from the bi to the tri-variant expressions i.e. 0.413 and 0.785 respectively. Several statistically significant equations with a coefficient of correlation (r) ≥ 0.900 were obtained, which accounts for more than 80% of the explain variance in the activity (Table 4). Eqns. 3-7 were considered for further study.

pMIC = 190.957(±24.948) X4A + 115.974(±16.677) PW5 + 5.8409(±1.045) ATS7e - 35.318
n = 17, r = 0.909, r2adj = 0.785, SEE = 0.151, F = 20.509 (Eqn.3)

pMIC = -0.394(±0.111) GATS7p - 0.324(±0.090) GATS5e - 0.053(±0.009) RDF090u + 5.680
n = 17, r = 0.898, r2adj = 0.762, SEE = 0.159, F =18.096 (Eqn.4)

pMIC = -0.236(±0.035) DP08 + 0.042(±0.010) G(O..Br) - 6.876 (±1.616) HATS5v + 6.769
n =17, r = 0.882, r2adj = 0.727, SEE = 0.170, F =15.197 (Eqn.5)

pMIC = 35.725(± 8.628) PW5 - 18.308(±4.631) G3s - 4.264(±0.681) BEHp4 + 16.798
n =17, r = 0.880, r2adj = 0.723, SEE = 0.172, F =14.929 (Eqn.6)

pMIC = -0.003(0.0004) DDI - 1.178(±0.301) E2m - 20.219(±4.802) G3s + 9.409
n = 17, r = 0.876, r2adj = 0.714, SEE = 0.174, F = 14.309 (Eqn.7)

Table-2 Regression Parameters and Quality of Correlation of Tri-parametric Equations

Eqn. No.	n	r^2	r^2_{adj}	F	QF	PE	Outlier
3	17	0.83	0.79	20.51	6.01	0.03	NIL
4	17	0.81	0.76	18.09	5.65	0.03	NIL
5	17	0.78	0.73	15.19	5.18	0.04	NIL
6	17	0.78	0.72	14.93	5.13	0.04	NIL
7	17	0.77	0.71	14.31	5.02	0.04	NIL

A high correlation coefficient alone is not enough to select the equation as a model and hence various statistical approaches were employed to confirm the robustness and the practical applicability of the equations. Equations were screened though various internal and

external statistical validation techniques. Internal statistical significance level of the equations was confirmed using sequential Fischer test. All the equations have significance level more than 99.9% as it exceeded the tabulated F (3, 13 □0.001) = 11.899. Sequential Fischer test recommended that equations are applicable for more than 999 times out of 1000. The inter dependency of physicochemical properties for each equation was checked in order to confirm inimitable contribution of the properties to the expression (Table 5).

All the regression expressions were checked for the presence of outliers using Z-score method. This test confirmed the applicability of equation on structurally diverse analogs. Bootstrapping technique was employed to confirm the contribution of physicochemical properties of the molecules to the activity whether equip-intense or of different rank. The value of the bootstrapping squared correlation coefficient and the bootstrapping standard deviation implies that the equations were proper representatives of the group of analogs. The chance of fortuitous correlation was checked with the help of randomized biological activity test. The value of chance statistics (Chance) is less than 0.001. Data of chance statistics revealed that the results were not based on chance correlation. The internal consistency of the training set was confirmed though leave-n-out method of cross-validation. Although equations showed good internal consistency (1Q2 = 0.625-0.706 & 3Q2 = 0.503-0.669), they may not be applicable for the analogs, which were never used in the generation of the correlation (Table 3, 5). Therefore, predictive power of Eqns. (3-7) was further confirmed by a test set of nine compounds (Table 4, 6). On the basis of statistical studies, Eqns. 3 is considered as best model for further study

Table-3: Pair Wise Correlation and VIF Values of the Descriptors used in QSAR Model

Eqn.	*Descriptors*	*VIF*	*Pair wise correlation*		
3			**X4A**	**PW5**	**ATS7e**
	X4A	14.32	1		
	PW5	12.98	0.89	1	
	ATS7e	2.9	0.31	0.06	1
4			**GATS7p**	**GATS5e**	**RDF090u**
	GATS7p	1.18	1		
	GATS5e	1.18	0.39	1	
	RDF090u	1	0.05	0.02	1
5			**DP08**	**G(O...Br)**	**HATS5v**
	DP08	2.47	1		
	G(O...Br)	1.48	0.37	1	
	HATS5v	2.16	0.64	0.1	1
6			**PW5**	**G3s**	**BEHp4**
	PW5	2.69	1		
	G3s	5.07	0.63	1	
	BEHp4	7.79	0.78	0.89	1
7			**DDI**	**E2m**	**G3s**
	DDI	4.87	1		
	E2m	1.19	0.27	1	
	G3s	5.28	0.89	0.38	1

Table 4: Internal and External Statistics of Tri-parametric Equations

Eqn.	n	Boots Trapping			Randomized			Leave One Out			Test Set (n=9)	
		r^2_{b2}	SE_{b2}	Chance	R^2_{max}	R^2_{mean}	R^2_{red}	IQ^2	S_{1F22}	S_{IHT}	R^2_{pred}	SEP
3	17	0.8	0.1	0.001	0.68	0.18	0.1	0.6	0.21	0.1	0.56	0.5
4	17	0.8	0.103	0.001	0.628	0.182	0.125	0.706	0.196	0.171	0.263	0.551
5	17	FPE	FPE	0.001	0.644	0.183	0.123	0.648	0.215	0.188	0.816	0.692
6	17	0.892	0.079	0.001	0.687	0.185	0.125	0.649	0.214	0.187	0.866	0.477
7	17	0.792	0.173	0.001	0.676	0.192	0.127	0.649	0.222	0.194	0.946	0.584

RESULT AND DISCUSSION

QSAR Analysis of Substituted Imidazole Analogues

2D QSAR analysis was performed on substituted imidazole analogues having antifungal activity. Several equations were obtained using sequential multiple linear regression analysis. The best model was selected on the basis of various statistical parameters such as correlation coefficient (r), adjusted square correlation coefficient (r2adj) standard error of estimation (SEE) and sequential Fischer test (F). The model was further validated using cross validated method. Although equations showed good internal consistency (1Q2 = 0.625-0.706 & 3Q2 = 0.503-0.669), they may not be applicable for the analogues, which were never used in the generation of the correlation. Therefore, predictive power of Eqns. (3-7) was further confirmed by a test set of nine compounds. On the basis of statistical studies, Eqn. 3 is considered as best model for further study.

pMIC = 190.957(±24.948) X4A + 115.974(±16.677) PW5 +5.841(±1.045)ATS7e -35.318

n = 17, r = 0.909, r2adj = 0.785, SEE = 0.151, F = 20.509 (Eqn.3)

The best QSAR model having coefficient of correlation (r=0.909) which explain 78.5% variance in the activity. The model showed overall internal statistical significance level more than 99.9% as it exceeded the tabulated F (3,13 α 0.001) = 11.899. The model was validated through leave out method. Calculated and calculated (loo) pMIC values are shown in table 20, while predicted pMIC of test set are shown in table 5

Table-5: Calculated, Calculated (loo), Residual and Z-score of Imidazole Derivatives Obtained from Model

Compound	pMIC					
	[a]obs	[b]cal	[c]cal_{res}	[d]Z-value	[e]loo	[f]loo_{res}
3	3.733	3.988	-0.255	-1.873	4.030	-0.297
5	3.734	3.858	-0.125	-0.917	3.889	-0.156
6	3.640	3.641	-0.001	-0.007	3.641	-0.001
10	3.379	3.416	-0.037	-0.272	3.437	-0.058
11	3.679	3.556	0.124	0.911	3.380	0.299
12	3.643	3.716	-0.073	-0.537	3.727	-0.084
14	3.973	3.966	-0.007	0.052	3.965	0.008
15	3.936	4.074	-0.139	-1.017	4.108	-0.172
16	4.237	4.190	0.047	0.342	4.179	0.058
17	4.273	4.063	0.210	1.544	4.035	0.238
19	4.274	4.169	0.105	0.771	4.156	0.118
21	4.052	4.174	-0.121	-0.891	4.200	-0.148
22	4.367	4.299	0.068	0.496	4.287	0.079
23	4.328	4.128	0.199	1.466	3.893	0.435
24	4.328	4.395	-0.067	-0.490	4.439	-0.111
25	4.349	4.159	0.189	1.395	4.135	0.213
26	4.367	4.499	-0.133	-0.973	4.551	-0.184

Table-6 Predicted and Residual Value of Test Set of Imidazole Derivatives Obtained from Model

Compound	pMIC		
	[a]Obs	[b]Pred	[c]$Pred_{res}$
1	2.406	2.613	-0.207
2	3.708	2.834	0.874
4	3.758	3.602	0.156
7	3.644	3.751	-0.108
8	3.455	3.771	-0.316
9	3.466	3.792	-0.326

13	4.274	4.344	-0.070
18	3.936	3.768	0.168
20	4.254	4.254	0.001

A Observed pMIC value of compound, b Predicted pMIC value of test compounds using model; c Residual pMIC value of predicted data.

Figure 1. A Plot of Observed pMIC vs Predicted LOO pMIC of Training Set of Imidazole Derivatives Obtained from Model

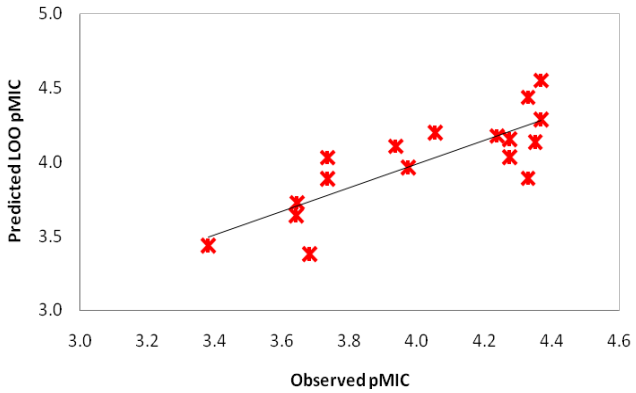
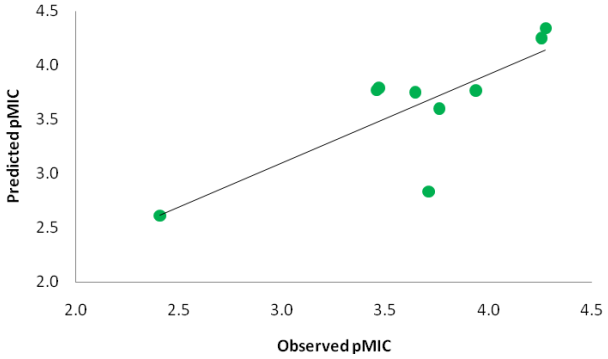


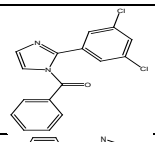
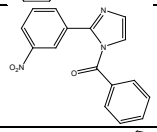
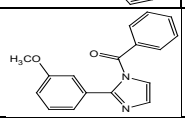
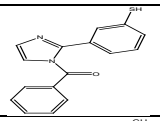
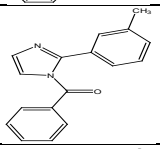
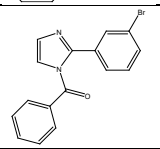
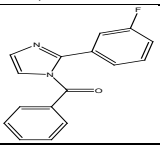
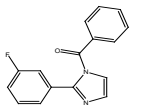
Figure 2. A Plot of Observed pMIC versus Predicted LOO pMIC of Test Set of Imidazole Derivatives Obtained from Model



Design, Biological activity Prediction of Imidazole's

On the basis of contributing molecular descriptors a set of imidazole analogs were designed and activity was predicted through selected QSAR model. The structure and predicted activity of designed imidazole analogs are shown in table 7

Table 7 Structure and Predicted Activity of Designed Compounds

Compd Code	Structure	IUPAC Name	[a]pMIC
C-1		2-(3,5-dichlorophenyl)-1*H* imidazol-1-yl(phenyl) methanone	4.29
C-2		(2-(5-nitrophenyl)-1*H* imidazol-1-yl(phenyl) methanone	4.30
C-3		(2-(3-methoxyphenyl)-1*H* imidazol-1-yl(phenyl) methanone	4.26
C-4		2-(3-mercaptophenyl)-1*H* imidazol-1-yl(phenyl) methanone	4.29
C-5		2-(3-methylphenyl)-1*H* imidazol-1-yl(phenyl) methanone	4.33
C-6		2-(3-bromophenyl)-1*H* imidazol-1-yl(phenyl) methanone	4.3
C-7		2-(3-fluorophenyl)-1*H* imidazol-1-yl(phenyl) methanone	4.27
C-8		(2-(3-fluorophenyl)-1*H* imidazol-1-yl(phenyl) methanone	4.25

SUMMARY AND CONCLUSION

The incorporation of the imidazole nuclei is an important synthetic strategy in drug discovery. The high therapeutic properties of the related drugs have encouraged the medicinal chemists to synthesize the large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicine.

QSAR study was performed on the selected series. Structures of all the compounds were sketched using builder module of the program. The sketched structures were subjected to energy minimization using molecular mechanics (MM2) until the RMS gradient value became smaller than 0.1kcal/mol Å. The energy minimized molecules were subjected to optimization via PM3 method until the RMS gradient attains a value smaller than 0.0001 kcal/mol Å using MOPAC. The geometry optimization of the lowest energy structure was carried out using EF routine. The minimized molecules were saved as MOL file format. The MOL file was further used for calculation of molecular descriptors using DRAGON software. The activity of the compounds was predicted through QSAR model (Eqn. 3) using VALSTAT program. In QSAR analysis all the values of dependent and independent parameters were correlated using multiple linear regression technique. The best QSAR model was selected on the basis of statistical significance criteria i.e., internal and external validation, which is shown as Eqn 3.

pMIC =190.957(±24.948) X4A +115.974(±16.677) PW5 +5.841(±1.045) ATS7e -35.318
n=17, r = 0.909, r2adj = 0.785, SEE = 0.151, F = 20.509 (Eqn 3)

The best QSAR model having coefficient of correlation (r=0.909) which explain 78.5% variance in the activity. The model showed overall internal statistical significance level more than 99.9% as it exceeded the tabulated F (3, 13 α 0.001) = 11.899. The model was

validated through leave out method. Calculated and calculated (loo) pMIC values are shown in table 5 and 6

Acknowledgements

The authors are highly thankful to Vice Chancellor Medic-Caps University & Dean, Faculty of Pharmacy for providing Necessary facilities to carry out this research.

Conflict of Interest: NIL

Author's contribution

All authors made best contribution to the concept, assessment and evaluation, data acquisition, and analysis and interpretation of the data.

REFERENCES

1. Sharma P, Virmani T, 2020. Synthesis, Antimicrobial Evaluation and QSAR Studies of Some Newly Synthesized Imidazole Derivatives, Synthesis. 29(3):6513-6520.
2. Chintakunta R, Meka G, 2020. Synthesis, in silico studies and antibacterial activity of some novel 2-substituted benzimidazole derivatives. Future J Pharm Sci. 6:128.
3. Asif, 2019. Green synthesis of Benzimidazole derivatives: an overview on green chemistry and its applications, Chemical Methodologies. 3:620-631.
4. CS Chem Office, Version 8.0, 2003.Cambridge Soft Corporation, Software Publishers Association. USA: 1730 M Street, Suite 700, Washington D C, 6 (202) :452-1600.
5. Gupta AK, Babu MA, Kaskhedikar SG. 2004. VALSTAT: Validation program for quantitative structure activity relationship studies Indian. J. Pharm. Sci., 66, 396-402.
6. Todeschini R, Consonni V, (2001). DRAGON-Software for the Calculation of Molecular Descriptors. rel. 1.12 for Windows
7. Hassan Y Aboul-Enein, Ahmed A El Rashedy, 2004. Benzimidazole Derivatives as Antidiabetic Agents, Med Chem, Volume 5(7):318-325.
8. Kardile D, Arora P, 2018. Review on: Benzimidazole derivatives as potent biological agent, Journal of Current Pharma Research. 9(1):2676-2694.
9. Mudhafar AM, Redayan MA, Baqir Ali M, 2019. Synthesis, characterization and antibacterial evaluation of some novel bis benzimidazole derivatives. Journal of Physics: Conf. Series 1294:052012.
10. Kumar A, Kumar Y, Sahu J, Kumar S, 2018. Synthesis, characterization and antimicrobial evaluation of some N-substituted benzimidazole derivatives. Curr Drug Discov Technol 15:87–91.
11. Majed H, Askar F 2018. Synthesis and biological evaluation of new benzimidazole derivatives. AL-Mustansiriyah J Sci 29(1):107.
12. Mohammadi R, Sajjadi A, 2019. J. Med. Chem. Sci. 2:55

How to cite this article

Sumeet Prachand, Sanjay Jain, Hemant Khambete, Arun K Gupta, 2021. QSAR studies of some Substituted Imidazole Derivatives as Potent Antifungal Agents". Jour. of Med. P'ceutical & Allied. Sci. V 10 - I 4, 1420, P- 3346-3350. doi: 10.22270/jmpas.V10I4.1420.