International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 15, Issue 3, 2023

Original Article

2D-QSAR STUDY ON SOME NOVEL DIHYDROPYRIMIDINE-4-CARBONITRILE ANALOGS AS AN ANTIFUNGAL ACTIVITY

RIDDHI PATEL[1*], T. Y. PASHA[2], SANDIP PATEL[1]

[1]N. R. Vekaria institute of Pharmacy, Junagadh, Gujarat, India, [2]Sri Adichunchanagiri College of Pharmacy, B G Nagara, Nagamangala Taluk Mandya, Karnataka, 571448, India
Email: riddhi.mdh@gmail.com

Received: 07 Dec 2022, Revised and Accepted: 24 Jan 2023

ABSTRACT

Objective: The present study was designed to study the antifungal activity of Dihydropyrimidine-4-Carbonitrile analogs against the fungi *Candida albicans* by a 2D quantitative structure-activity relationship (QSAR) model.

Methods: The pyrimidine derivatives were produced using lipophilic, electronic, and steric parameters by Quantitative Structure Activity-Relationships (QSAR). A relationship between dependent and independent variables (biological activities and physicochemical descriptors, respectively) was resolved statistically using regression analysis. The F value shows the level of statistical significance of the regression (r^2) was used to report the fitness of data. The newly synthesized derivatives were evaluated for *in vitro* antifungal activity against *Candida albicans*by Nutrient agar and Seaboard dextrose agar media.

Results: Multiple linear regression is a method of crucial importance, it allowed us to obtain a relation between the calculated parameters and the antifungal activity; this we can interpret the variance of the activity by contribution to the calculated descriptors. Quantitative structure-activity relationship (QSAR) model showing a significant activity-descriptors relationship accuracy of 90% ($R^2 \geq 0.90$) and activity prediction accuracy of 81% ($R^2cv = 0.81$). These values prove that the model obtained is reliable. Out of the three descriptors studied; log P has minimum potency, molar refractivity has more potency and heat of formation has moderate potency.

Conclusion: Important structural understanding in the pattern of potent antifungal agents by Quantitative Structure Activity-Relationships (QSAR) study. The acquired physicochemical properties (electronic, topological, and steric) show the important structural features required for antifungal activity against *Candida albicans*.

Keywords: 2D-QSAR, Antifungal agents, Dihydropyrimidine

DOI: https://dx.doi.org/10.22159/ijpps.2023v15i3.47008. Journal homepage: https://innovareacademics.in/journals/index.php/ijpps.

INTRODUCTION

Some novel antifungal agents have been evaluated as a very important step for investigators. In general, the research programmed attempts are handled toward the design of new drugs because of the acquisition of resistance by the infecting organisms to present drugs and the unsatisfactory status of the present drug's side effects. Standard antibiotic resistance of common microorganisms is rapidly becoming a major health problem throughout the world [1, 2]. There is a real viewed need for the discovery of new derivatives provided with antifungal activity. The importance of organisms and treatment and methods of prevention differ with each group. Over a decade, the ubiquity of systemic fungal infections has increased significantly [3].

In the past 10 y, the use of broad-spectrum antibiotics used is increased, so the development of antifungal drugs has expanded, but there is still a deficiency in the range and scope of current antifungal properties. The modifications of existing drug molecules have been developed to improve activity and eliminate toxicity [4-6]. In short, antifungal activity has developed rapidly in the past few years analyzed to previous years, and the direction for the treatment of fungal infections is modified shortly soon as our knowledge of fungal infections enhance and new antifungal therapies are invented [7]. The quantitative structure-activity/property relationships (QSAR/QSPR) of substances are investigated by drug discovery, medicinal chemistry, biochemistry, and an important aspect of modern chemistry.

The information acquired is made by mathematical equations relating the chemical structure of the derivatives to a huge variety of their physical, biological, chemical, and technological properties. Those not synthesized, yet those derivatives can readily be screened *in silico* for selection of structures with desired properties. Once a correlation between structure and activity/property is established, any number of derivatives. Hence, it is possible to select the most favorable derivatives for synthesis and testing in the laboratory [8, 9]. Theoretical drug designs have been most widely and effectively used in the analysis of quantitative structure-activity relationships (QSAR). This method has also been called the Hansch approach method and it supposes that the strength of a certain biological activity applied by a series of corresponding derivatives can be shown in terms of a function of various physical and chemical (electronic, hydrophobic, and steric) properties [10-12].

These purposes could be produced in a quantitative structure-activity relationships(QSAR)equation appearing certain effects approving for the antifungal activity, structural modifications that enhance various physical and chemical (electronic, hydrophobic, and steric) properties would be awaited to generate good active derivatives.

MATERIALS AND METHODS

Antifungal activity

The newly synthesized derivatives were evaluated for in vitro antifungal activity against Candida albicans ATCC 10231(HIMEDIA). Nutrient agar and Seaboard dextrose agar were worked for fungal growth. The means of the standard twofold serial dilution method determined Minimal Inhibitory Concentrations (MIC) by using agar media. Stock solutions of tested derivatives were developed in Dimethyl sulfoxide (DMSO) at a concentration of 1 mg/ml. A Suspension containing around 106 CFUs/ml of fungi was arranged from broth cultures. Fungal plates were prepared in triplicate and incubated at 37 °C within 48–72 h for fungi. Clotrimazole was also shown under the same conditions as an antifungal drug. MIC is explained as the minimum concentration of derivatives that inhibited visible growth [13].

Simulation calculation of physicochemical parameters

The physicochemical parameters molar refractivity for steric, logP for lipophilic and index of reflection for electronic parameters were calculated using the software ChemBioDraw Ultra 12.0.

QSAR analysis

Data set

Some novel synthesized Dihydropyrimidine derivatives were studied in this. The candidate set of variables was analyzed by lipophilic, electronic, steric, and structural parameters. The physicochemical parameters in this QSAR study were molar refractivity for steric, logP for lipophilic it, and index of reflection for electronic parameters. The data set was around divided into two subsets: the training set containing 16 derivatives and the test set containing 4 derivatives. The training set was shown to make a regression model, and the test set was shown to estimate the predictive ability of the model acquired**.** The properties data for the complete set of derivatives are presented in table 2. To obtain QSAR models, a proper representation of the chemical structure is necessary. For this reason, descriptors of the structure are commonly used. The physicochemical parameters used in this work were calculated using ACD Labs software and chem. Draw ultra.

Multiple linear regression method

A relationship between dependent and independent variables (biological activities and physicochemical descriptors, respectively) was resolved statistically using regression analysis [14]. Linear regression is reached by fitting a best-fit straight line to the data using the least squares method. Descriptors that are incorporated in a feasible QSAR equation should show low inter-correlation and, thus, behave as independent variables. The inter-correlation between descriptors was used for selecting descriptors for the equation and the quality of fit for a regression equation was evaluated relative to its standard deviation and correlation coefficient. The F value shows the level of statistical significance of the regression. For a regression model, r^2 was used to report the fitness of data.

RESULTS AND DISCUSSION

Twenty derivatives were synthesized and biologically screened for antifungal activity. The biological activity data of MIC (Minimum Inhibitory Concentration) was converted to negative log dose in mol (pMIC) for the QSAR study [15]. The data file was applied to stepwise Multiple Linear Regression analysis to achieve QSAR analysis between antifungal activity as a dependent variable and substituent constants as independent variables, and some equations were acquired [16]. Physicochemical descriptors and the regression analysis of antifungal activity data, a statistically significant equation with a coefficient of correlation (r^2) were shown as a model for antifungal activity [17].

A quantitative structure-activity relationship (QSAR) studies were performed to explore the antifungal compound from the Dihydropyrimidine derivatives. Theoretical results are in accord with the *in vitro* experimental data with reported growth inhibitory activity towards *Candida albicans*. Antifungal activity was predicted through the quantitative structure-activity relationship (QSAR) model, developed by forward feed multiple linear regression method with a leave-one-out approach. Quantitative structure-activity relationship (QSAR) model showing a significant activity-descriptors relationship accuracy of 90% (R^2 0. 90) and activity prediction accuracy of 81% (R^2 cv = 0.81). Initially, a total of 20 derivatives were used for Quantitative structure-activity relationship (QSAR) modeling against physicochemical descriptors [18]. According to the quantitative structure-activity relationship (QSAR) equation 1 (table 3) is dependent on logP, the heat of formation, and molar refractivity for the antifungal activity against *Candida albicans*. Out of the three descriptors studied; log P has minimum potency, molar refractivity has more potency, and heat of formation has moderate potency. The logP value has lipophilic properties. The property suggested the lipid solubility and affinity of derivatives toward lipids. The lopP value has a positive interaction with the activity; this shows that the substituent, which increased activity, will give decrease solubility in water. The decrease in water solubility or increase in the lipophilic nature of derivatives will lead to increased penetration of the derivatives across the cell wall [19].

The steric parameter of molar refractivity is dependent on the spatial selection of the aromatic ring in the synthesized derivatives. The spatial position also is required to work the interaction of the ligand with the receptor. The molar refractivity is positively correlated with the antifungal activity against *Candida albicans*. This shows that the aromatic ring arrangement exit on the pyrimidine ring should be far for maximum activity.

The heat of the formation of derivatives negatively correlated with the antifungal activity and decreases in the heat of the formation of molecules might be managed for the kinetics or dynamics of the derivatives inside the fungal cell. Thus, a molecule having less heat of formation will need less energy of activation for relation with the receptor target. Substitutions favoring high lipophilic values and high molar refraction may achieve an increase in activity [20].

We showed for a simpler descriptor for the prediction of biological *in vitro* activity for the studied class of derivatives. Quantitative structure-activity relationship (QSAR) studies indicate that logP, the heat of formation, and molar refractivity correlate well with biological activity (table 1). The quantitative structure-activity relationship (QSAR) mathematical model equation derived through the multiple linear regression method is given below, showing the relationship between *in vitro* experimental activity (MIC) and dependent descriptors: The best 2DQSAR and the statistics obtained are listed in the quantitative structure-activity relationship (QSAR) equation 1 (table 3).

These results could offer useful references for understanding mechanisms and directing the molecular design of new lead compounds with improved antifungal activity.

Calculated physico-chemical properties

Table 1: Physicochemical properties done for the training set derivatives

S. No.	Derivatives	Log P	Heat of formation	Molar refraction [cm3/mol]	Zone of inhibition (µg/ml)
1	PMD1	4.43	182.81	145.22	8.52
2	PMD2	4.55	336.14	132.67	8.68
3	PMD4	4.16	173.83	136.19	8.22
4	PMD5	5.16	265.87	150.76	9.39
5	PMD7	5.38	354	143.17	10.20
6	PMD8	4.04	155	141.54	7.51
7	PMD9	4.17	143.75	153.32	8.23
8	PMD10	5.04	316	136.47	9.34
9	PMDI	6.02	427.75	168.67	10.51
10	PMDII	6.15	592.48	154.92	11.23
11	PMDIII	6.71	564.77	162.42	11.87
12	PMDIV	5.76	412.57	161.63	10.33
13	PMDV	6.75	515.92	175.70	14.28
14	PMDVII	6.98	602.07	164.45	13.21
15	PMDVIII	5.63	254.52	167.76	10.67
16	PMDX	6.63	559.00	164.60	10.49

Table 2: Physicochemical properties done for the test set derivatives

S. No.	Derivatives	Log P	Heat of formation	Molar refraction [cm3/mol]	Zone of inhibition (µg/ml)
1	PMD3	5.12	319.837	138.28	10.29
2	PMD6	4.86	365.42	147.65	9.85
3	PMDVI	6.54	610.76	172.95	13.53
4	PMDIX	5.97	403.7	181.44	12.17

2D-QSAR models development

Table 3: 2D-QSAR models developed

Model No.	Equation	Observations	R^2	Standard error	F
1	Zone of Inhibition=-1.06+(1.77*log p)+(0.013* Molar refraction)-(0.0014*Heat of formation)	16	0.924	0.799	23.56
2	Zone of Inhibition=-1.06+(1.48*log p)+(0.02*Molar refraction)	16	0.913	0.772	37.78
3	Zone of Inhibition=-2.06+(0.064* Molar refraction)-(0.006*Heat of formation)	16	0.901	0.871	28.22
4	Zone of Inhibition=-0.324+(2.08*log p)-(0.0025*Heat of formation)	16	0.900	0.773	37.61

Training set

Table 4: Comparison of predicted value and the observed value for the training set

S. No.	Derivatives	pMIC	Predicted value
1	PMD1	8.52	8.42
2	PMD2	8.68	8.25
3	PMD4	8.22	7.86
4	PMD5	9.39	9.77
5	PMD7	10.20	9.85
6	PMD8	7.51	7.77
7	PMD9	8.23	8.21
8	PMD10	9.34	9.25
9	PMDI	10.51	11.23
10	PMDII	11.23	11.10
11	PMDIII	11.87	12.32
12	PMDIV	10.33	10.72
13	PMDVI	14.28	12.45
14	PMDVII	13.21	12.87
15	PMDVIII	10.67	10.50
16	PMDX	10.49	12.19

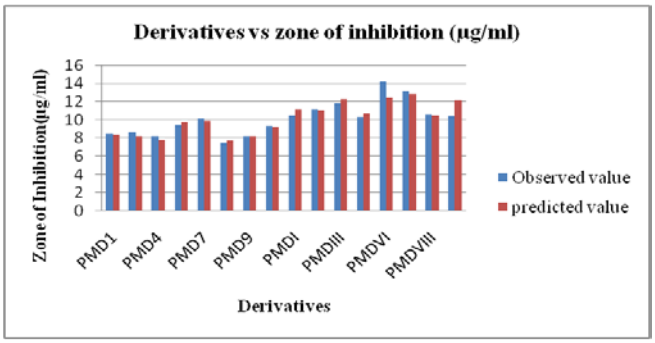

Fig. 1: Chart of comparison between the observed and predicted zone of inhibition for the training set

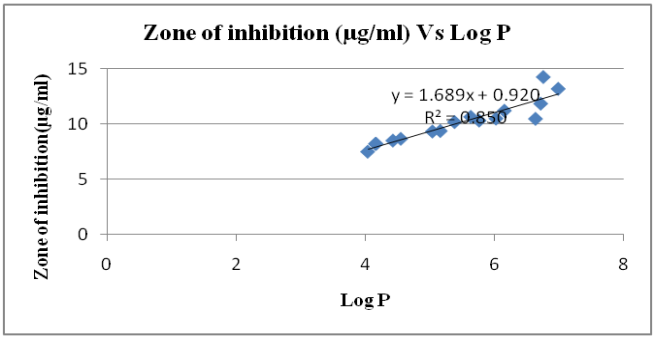

Fig. 2: Chart of comparison between a zone of inhibition values and parameter (Log P) for the training set

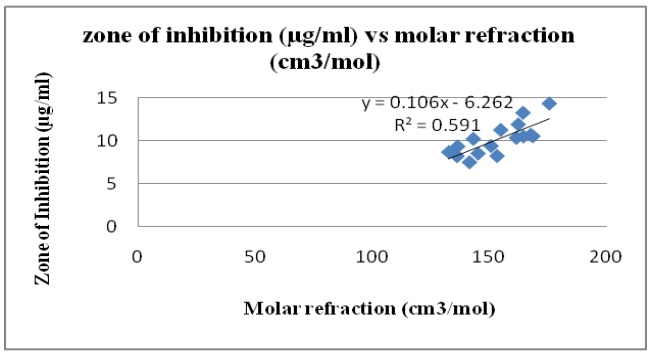

Fig. 3: Chart of comparison between molar refraction anda zone of inhibition values for the training set

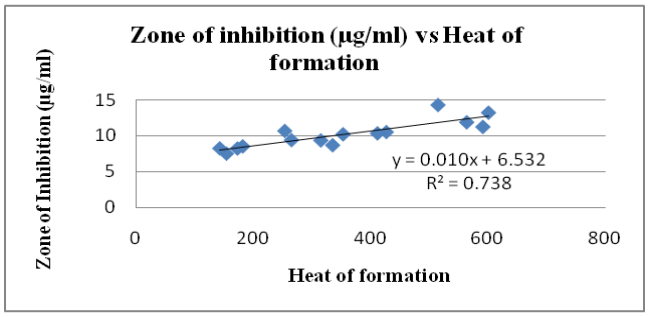

Fig. 4: Chart of comparison between the heat of formation and zone of inhibition values for the training set

Test set

Table 5: Comparison of the observed and predicted values for the test set.

S. No.	Derivatives	Observed value	Predicted value
1	PMD3	10.43	10.29
2	PMD6	8.39	9.85
3	PMDVI	14.87	13.53
4	PMDIX	12.54	12.17

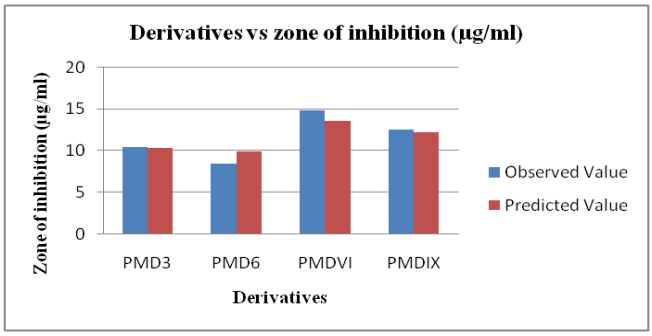

Fig. 5: Chart of comparison between the observed value and predicted value for the test set

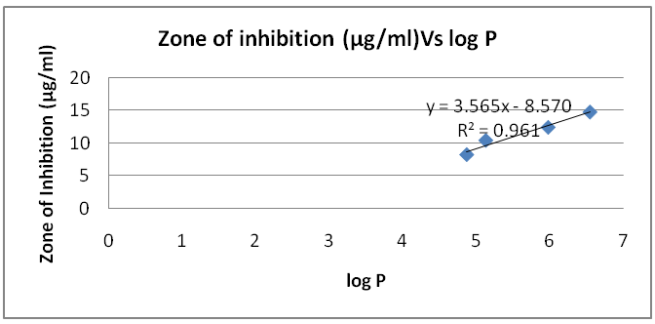

Fig. 6: Chart of comparison between Log P and a zone of inhibition values for test set

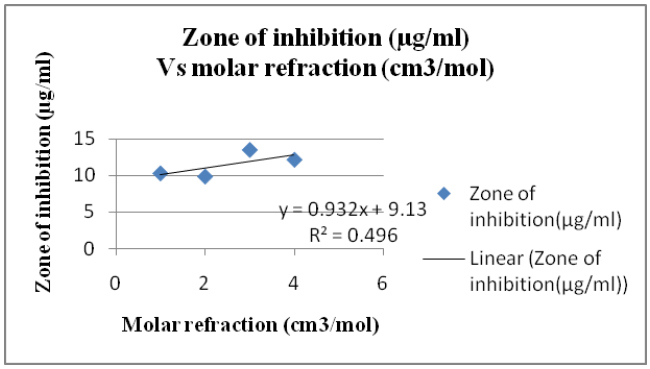

Fig. 7: Chart of comparison between parameter molar refraction and zone of inhibition values for test set

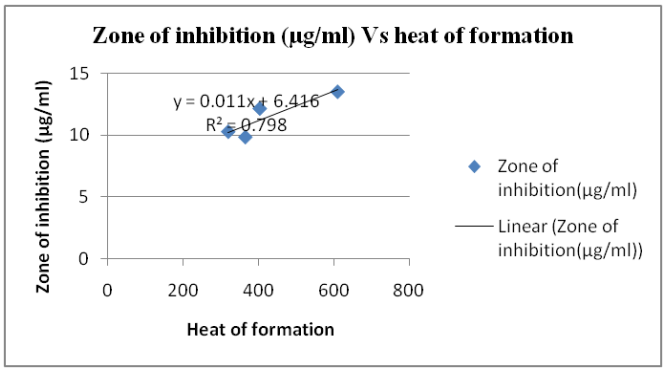

Fig. 8: Chart of comparison between parameter Heat of formation and zone of inhibition values for test set

CONCLUSION

Series of Dihydropyrimidine-4-Carbonitrilederivatives were approached by classical with well-expressed antifungal activity. It has good correlation between biological activity and parameters as R^2cv=0.81 and $R^2 \geq 0.90$variance in inhibitory activity. The low standard error demonstrates the accuracy of the model. Descriptors used in the important Quantitative structure–activity relationship (QSAR) Model-1 with value is shown in table 3. Quantitativestructure–activity relationship studies proposed that the antifungal activities of these synthesized derivatives against the test microorganisms are mainly controlled by polarizability, the molar refractivity parameter. Thus, high polarized substitution on the aromatic ring probably betters the potency of these derivatives as antifungal agents.

ACKNOWLEDGMENT

The authors are thankful to the Principal Dr. Sai Shivam and the Management of N. R. Vekaria institute of pharmacy, Junagadh, Gujarat, India, for providing facilities.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

The experiment was conducted under the guidance of Dr. T Y Pasha. Sandip Patel contribution to the conduct of experiments, literature collection, and analysis. Management provided facilities for the experiments

CONFLICT OF INTERESTS

The authors declare no conflict of interest

REFERENCES

1. Munita JM, Arias CA. Mechanisms of antibiotic resistance. Microbiol Spectr. 2016;4(2):VMBF-0016. doi: 10.1128/ microbiolspec.VMBF-0016-2015, PMID 27227291.
2. Vallabhaneni S, Kallen A, Tsay S, Chow N, Welsh R, Kerins J. Investigation of the first seven reported cases of candida auris, a globally emerging invasive, multidrug-resistant Fungus-United States, May 2013-August 2016. Am J Transplant. 2017;17(1):296-9. doi: 10.1111/ajt.14121, PMID 28029734.
3. Miller CD, Lomaestro BW, Park S, Perlin DS. Progressive esophagitis caused by candida albicans with reduced susceptibility to caspofungin. Pharmacotherapy. 2006;26(6):877-80. doi: 10.1592/phco.26.6.877, PMID 16716141.
4. Kontoyiannis DP, Lewis RE. Antifungal drug resistance of pathogenic fungi. Lancet. 2002;359(9312):1135-44. doi: 10.1016/S0140-6736(02)08162-X.
5. Ryder NS. Activity of terbinafine against serious fungal pathogens. Mycoses. 1999;42Suppl 2:115-9. doi: 10.1111/j.1439-0507.1999.tb00026.x, PMID 10865917.
6. Perlin DS. Resistance to echinocandin-class antifungal drugs. Drug Resist Updat. 2007;10(3):121-30. doi: 10.1016/j.drup.2007.04.002. PMID 17569573.
7. Padmaja A, Payani T, Reddy GD, Padmavathi V. Synthesis, antimicrobial and antioxidant activities of substituted pyrazoles, isoxazoles, pyrimidine and thioxopyrimidine derivatives. Eur J Med Chem. 2009 Nov;44(11):4557-66. doi: 10.1016/j.ejmech.2009.06.024, PMID 19631423.ejmech.2009.06.024.
8. Smee DF, Mckernan PA, Nord LD, Willis RC, Petrie CR, Riley TM. Novel pyrazolo[3,4-d]pyrimidine nucleoside analog with broad-spectrum antiviral activity. Antimicrob Agents Chemother. 1987;31(10):1535-41. doi: 10.1128/AAC.31.10.1535, PMID 3435102.
9. Smee DF, Alaghamandan HA, Cottam HB, Sharma BS, Jolley WB, Robins RK. Broad-spectrum *in vivo* antiviral activity of 7-Thia-8-Oxoguanosine, a novel immunopotentiating agent. Antimicrob Agents Chemother. 1989;33(9):1487-92. doi: 10.1128/AAC.33.9.1487, PMID 2817849.
10. Soni HM, Patel PK, Chhabria MT, Rana DN, Mahajan BM, Brahmkshatriya PS. 2D-QSAR study of a series of pyrazoline-

based anti-tubercular agents using genetic function approximation. Comp Chem. 2015;03(4):45-53. doi: 10.4236/cc.2015.34006.

11. Singh P, Kumar R, Sharma BK. Quantitative structure-activity relationship study of 5-iodo- and diaryl-analogs of tubercidin: inhibitors of adenosine kinase. J Enzyme Inhib Med Chem. 2003;18(5):395-402. doi: 10.1080/1475636031000121910, PMID 14692505.
12. Hansch C, Rockwell SD, Jow PY, Leo A, Steller EE. Substituent constants for correlation analysis. J Med Chem. 1977;20(2):304-6. doi: 10.1021/jm00212a024. PMID 836503.
13. Fernandes CJ, Stevens DA, Groot obbink DJ, Ackerman VP. A replicator method for the combined determination of minimum inhibitory concentration and minimum bactericidal concentration. J Antimicrob Chemother. 1985 Jan;15(1):53-60. doi: 10.1093/jac/15.1.53, PMID 3972758.
14. Bamnela R, Shrivastava SP. Synthesis and *in vitro* antimicrobial, anthelmintic and insecticidal activities study of 4(4′-bromophenyl)-6-substituted-aryl-1-acetyl pyrimidine-2-thiols. E-Journal of Chemistry. 2010;7(3):935-41. doi: 10.1155/2010/927601.
15. Sharma MC, Sahu NK, Kohali DV, Chaturvedi SC, Sharma S. QSAR, synthesis and biological activity studies of some thiazolidinones derivatives. Dig J Nanomater Biostructures. 2009 Mar;4(1):223-32.
16. Cai Z, Zafferani M, Akande OM, Hargrove AE. Quantitativestructure–activity relationship (QSAR) study predicts small-molecule binding to RNA structure. J Med Chem. 2022;65(10):7262-77. doi: 10.1021/acs.jmedchem.2c00254. PMID 35522972.
17. Podunavac Kuzmanovic SO, Cvetkovic DD, Barna DJ. QSAR analysis of 2-amino or 2-methyl-1-substituted benzimidazoles against pseudomonas aeruginosa. Int J Mol Sci. 2009;10(4):1670-82. doi: 10.3390/ijms10041670, PMID 19468332.
18. Dwivedi N, Mishra BN, Katoch VM. 2D-QSAR model development and analysis on variant groups of anti-tuberculosis drugs. Bioinformation. 2011;7(2):82-90. doi: 10.6026/97320630007082, PMID 21938210.
19. Le T, Epa VC, Burden FR, Winkler DA. Quantitative structure-property relationship modeling of diverse materials properties. Chem Rev. 2012;112(5):2889-919. doi: 10.1021/cr200066h, PMID 22251444.
20. Echeverria J, Opazo J, Mendoza L, Urzua A, Wilkens M.Structure–activity and lipophilicity relationships of selected antibacterial natural flavones and flavanones of Chilean flora. Molecules. 2017 Apr;22(4):608. doi: 10.3390/molecules22040608, PMID 28394271.
21. Kesar S, Paliwal SK, Mishra P, Chauhan M. Quantitative structure-activity relationship analysis of selective rho kinase inhibitors as neuro-regenerator agents. Turk J Pharm Sci. 2019 Jun;16(2):141-54. doi: 10.4274/tjps.galenos.2018.70288. PMID 32454707.
22. Shahlaei M. Descriptor selection methods in quantitative structure–activity relationship studies: a review study. Chem Rev. 2013;113(10):8093-103. doi: 10.1021/cr3004339, PMID 23822589.
23. Sharma P, Rane N, Gurram VK. Synthesis and QSAR studies of pyrimido[4,5-d]pyrimidine-2,5-dione derivatives as potential antimicrobial agents. Bioorg Med Chem Lett. 2004;14(16):4185-90. doi: 10.1016/j.bmcl.2004.06.014, PMID 15261267.
24. Bhaskar PV, Ramachandraiah A. Synthesis, spectral and molecular modeling studies of coumarin derivatives. Int J Curr Pharm Sci 2017;9(3). doi: 10.22159/ijcpr.2017.v9i3.19984.