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TWO DIMENSIONAL QSAR OF NOVEL PYRAZOLE-BENZIMIDAZOLE DERIVATIVES FOR ANTI-TUMOR ACTIVITY AGAINST HCT116 CELL LINE

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ABSTRACT

The present study aimed to develop and validate two-dimensional Quantitative Structure–Activity Relationship (2D-QSAR) models for novel pyrazole-benzimidazole derivatives to predict their anti-tumor activity against the HCT116 cancer cell line. A dataset of 37 derivatives reported in previous studies was selected, and IC50 values were converted into pIC50 for correlation analysis. Molecular structures were drawn using ChemDraw, energy-minimized with Chem3D MM2, and further optimized using MOPAC. Physicochemical descriptors, including molar refractivity, molecular mass, partition coefficient (LogP), LogS, and polar surface area, were calculated. Statistical analysis and model generation were performed using VALSTAT through multiple linear regression (MLR) with stepwise variable selection. Several QSAR models were generated, among which Model 1 showed the best statistical performance with r^2 = 0.1078 and standard deviation = 0.1464. The study revealed that molar refractivity, lipophilicity, and polar surface area significantly influenced cytotoxic activity. Increased molar refractivity and lipophilicity were associated with enhanced anti-tumor activity, indicating that bulky and less polar substituents favored enzyme inhibition. In contrast, higher polar surface area negatively affected activity. Validation using cross-validation and external test set prediction confirmed the predictive reliability of the developed models, with predicted pIC50 values closely matching experimental observations except for a few outliers. Overall, the findings demonstrate that steric and electronic properties play a crucial role in determining the anti-tumor potential of pyrazole-benzimidazole derivatives and may assist in designing improved chemotherapeutic candidates.

Keywords: *QSAR, Anti-Tumor, Pyrazole, Benzimidazole, ChemDraw.*

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INTRODUCTION

As the most common and feared disease in the late period, cancer poses a major threat to one's health and well-being. Cancer killed 8.8 million people in 2015, making it the second most common cause of death worldwide behind cardiovascular disease, according to a World Health Organization data. Cancer is the cause of about one in six deaths worldwide. Approximately 70% of cancer fatalities take place in nations with poor and moderate incomes [1]. According to WHO estimates, 15 million people will die from cancer globally by 2030 [2]. Cancer is a disease that arises when aberrant cells grow excessively and develop into a mass known as a malignant tumor. One type of cancer is unchecked tumor cell proliferation, and cancer is now the mostdeadly illness due to the rapid growth of tumor cells. Despite the long history of using chemotherapeutic drugs to treat cancer, there is still a

pressing need to create novel chemotherapy compounds based on the limited anticancer medicines and resistance mechanisms [3]. This is the reason why, during the past fifteen years, new anti-cancer medicines have been developed on a daily basis [4]. Cancer is one of the most significant health issues of our time. It is defined as the unchecked growth and dissemination of aberrant cells [5]. Chemotherapy medications are frequently utilised in clinical cancer treatment. However, chemotherapy medications such paclitaxel, thiotepa, cisplatin, and chlorambucil were unable to fully stop the proliferation of cancer cells. The problem with conventional chemotherapy is that it is not selective for tumour cells.[6]Thus, there has been an increasing focus on the discovery of novel antitumor agents [7]. In the context of drug design and research, the benzimidazole ring is a fundamental moiety among heterocyclic pharmacophores and has demonstrated an impressive presence in a variety of medications. This unique shape is linked to a variety of biological processes, such as bactericidal [8], fungicidal [9], analgesic [10], anti-viral [11] etc. Furthermore, the strength of medications such as carbendazim [12,13], nocodazole [14], dovitinib [15,16], etc. have been shown to be effective against a variety of cancer cell lines by having benzimidazole structures [17]. The sulfo rhodamine B (SRB) growth inhibition assay was used to screen all of the synthesised benzimidazole-pyrazole derivatives for their antiproliferative activity against human tumour cell line: HCT116cell line [18]. Therefore, it is crucial to discover new anti-cancer medications with pharmacological activity that is greater than that of the ones that are currently on the market. QSAR analysis is crucial in this case to reduce trial and error when creating novel antimalarial medications.[19] In terms of descriptors, the QSAR technique aids in the correlation between the measured or calculated molecular properties of a group of substances and their particular biological activities or physical characteristics.[20]The development of new molecular pharmaceuticals is accelerated and resources are saved by using QSAR approaches. Finding a regression function that accurately predicts the molecule's activity is the main goal of a systematic QSAR study that has not yet been conducted for a number of novel pyrazole-benzimidazole derivative compounds, despite the fact that there have been numerous QSAR studies pertaining to the design of anti-malarial medications [21].

MATERIAL AND METHODS

The materials used in this study were pyrazole-benzimidazole derivative compounds synthesized by [22]. The Inhibition Concentration (IC50) was the dependent variable in Table 1.

Instrumentation

In this research, an Asus Laptop equipped with Intel®Core i5; RAM 8Gb, and SDD 500GBwas used. All the compounds physiochemical properties (Table 1) were calculated using package Chemoffice Program Version 16.0 for Windows and complete geometry optimization with the semi-empirical Chem3Dand there were analyzed using the statistical program Valstat version 16 for windows.

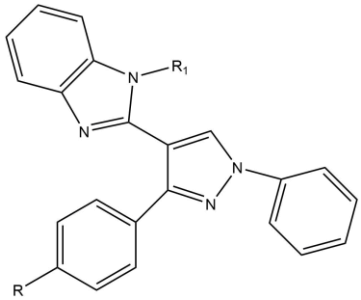

Table 1: Structure, IC50 and biological activity of pyrazole-benzimidazole analogues.

S.No.	Compounds	Substitution		IC50 (µM)	Biological Activity
		R	R_1		
1.*	1.	Br	Benzyl	19.1	4.718966633
2.	2.	Br	2-Fluorobenzyl	6.53	5.187086643
3.	3.	Br	3-Fluorobenzyl	5.43	5.26760624
4.	4.	Br	4-Fluorobenzyl	8.01	5.096910013
5	5	Br	2-Chlorobenzyl	9.65	5.017728767
6.	6.	Br	4-Chlorobenzyl	7.26	5.142667504
7.	7.	Br	2-Bromobenzyl	7.49	5.13076828
8.	8.	Br	3-Bromobenzyl	6.67	5.180456064
9.	9.	Br	2-Iodobenzyl	6.63	5.26760624
10.	10.	Br	3-Iodobenzyl	5.40	5.055517328
11.	11.	Br	2-(Trifluoromethyl)benzyl	8.80	5.366531544
12.	12.	Br	4-(Trifluoromethyl)benzyl	4.33	5.013228266
13.	13.	Br	3,5-Difluorobenzyl	9.79	5.200659451
14.	14.	Br	2-Chloro-4-fluorobenzyl	6.35	5.050609993
15.	15.	Br	2-Bromo-5-fluorobenzyl	8.97	5.107905397

16.	16.	Br	2-Bromo-5-chlorobenzyl	7.83	5.017728767
17.	17.	Br	2-Bromo-4-methoxybenzyl	9.67	5.096910013
18.	18.	Br	4-Bromo-2- Fluorobenzyl	8.07	5.229147988
19.	19.	Br	3,5-Dimethylbenzyl	5.96	5.008773924
20.	20.	Br	2,3,4,5,6-Pentafluorobenzyl	9.83	5.292429824
21.	21.	Br	Propyl	5.15	5.292429824
22.	22.	Br	Allyl	5.19	5.283996656
23.	23.	Br	Propargyl	5.22	5.13076828
24.	24.	Br	Ethoxycarbonylmethyl	7.49	5.142667504
25.	25.	Br	1-Methylallyl	7.26	5.214670165
26.	26.	Br	4-Fluorobenzyl	6.17	5.173925197
27.	27.	Br	4-Chlorobenzyl	6.72	5.148741651
28.	28.	Br	2-Bromobenzyl	7.19	5.244125144
29.	29.	Br	3-Bromobenzyl	5.78	5.318758763
30.	30.	Br	3-Iodobenzyl	4.84	5.259637311
31.	31.	Br	4-Cyanobenzyl	5.58	5.229147988
32.*	32.	Br	3,5-Difluorobenzyl	5.99	4.782516056
33.	33.	Br	2-Bromo-5-Chlorobenzyl	16.5	5
34.	34.	Br	2-Bromo-5-methoxybenzyl	10.0	5.207608311
35.	35.	Br	3,5-Dimethylbenzyl	6.27	5.22184875
36.	36.	Br	Cinnamyl	6.03	5.102372909
37.*	37.	Br	1-Methyallyl	7.98	4.806875402

* test set compounds

Data Set

QSAR analysis was used to link the physicochemical characteristics of pyrazole-benzimidazole derivatives to their inhibitory activity. The data series were extracted from Ren B et al.'s published study from 2021.[22] The chosen series has total 37. For the purpose of developing QSAR models, the structure and diversity of activities in both sets are thereby preserved. The inhibitory concentration (IC50) in micromolar concentrations was used to express the biological activities. The stated IC50 values were first translated to their molar units and then to the free energy-related negative logarithmic state, or Log (1/IC50) or pIC50, for correlational purposes.

Molecular structure generation

The QSAR model is developed in five steps. Identifying the series of pyrazole-benzimidazole compounds to be examined and the IC50 value obtained from the laboratory experiment constitute the first phase. In order to optimize for the most stable skeleton structure of the series of pyrazole-benzimidazole compounds, the second step is to choose a set of descriptors that are probably connected to the biological activity of interest. The next step involves using the optimised structure to compute descriptors. The fourth stage is to use statistical analysis with VALSTAT Software for Windows to create a mathematical equation model that represents the link between the biological activity and the selected descriptors. The last step is to validate the QSAR models.

Using Chem Draw 16.0, all of the pyrazole-benzimidazole derivative structures were shown. Each molecule was searched for lower energy conformations using the molecular mechanics (MM2) approach. The compounds with the lowest energy were re-optimized utilising molecular orbital property accompany name (MOPAC). Each molecule's geometry was optimised using a variety of starting points in order to avoid the local stable conformations of the compounds. The conformation with the lowest energy was taken into account when calculating the molecular descriptors [23]. ChemOffice 2001 was used to calculate the thermodynamic, electronic, steric, and molecular descriptors of the QSAR study. Shown in table 2.

Table 02: Descriptors for training and test set compounds of series

S.No.	Molar Refractivity	Mass	Partition Coefficient	LogP	LogS	Polar Surface Area	Sum of Degree	Sum of Val. Degree	Wiener Index
1.	140.92	505.41	7.69	8.01	-9.56	31.2	78	116	3221
2.	141.14	523.4	7.83	8.17	-9.76	31.2	80	124	3461
3.	141.14	523.4	7.83	8.17	-9.76	31.2	80	124	3489
4.	141.14	523.4	7.83	8.17	-9.77	31.2	80	124	3517
5	145.73	539.86	8.4	8.63	-10.26	31.2	80	117.77	3461
6.	145.73	539.86	8.4	8.63	-10.26	31.2	80	117.77	3517
7.	148.55	584.31	8.55	8.8	-10.38	31.2	80	118	3461
8.	148.55	584.31	8.55	8.8	-10.38	31.2	80	118	3489
9.	153.33	631.31	8.51	9.07	-10.66	31.2	80	117.48	3461
10.	153.33	631.31	8.81	9.07	-10.66	31.2	80	117.48	3489
11.	146.9	573.41	8.57	8.93	-10.51	31.2	86	142	4292
12.	146.9	573.41	8.57	8.93	-10.51	31.2	86	142	4516

13.	141.36	541.39	7.98	8.33	-10.04	31.2	82	132	3761
14.	145.95	557.81	8.55	8.79	-10.46	31.2	82	125.77	3761
15.	148.76	602.3	8.7	8.96	-10.58	31.2	82	126	3734
16.	153.35	618.75	9.27	9.42	-11.08	31.2	82	119.77	3734
17.	155	614.34	8.61	8.71	-10.41	40.43	84	126	4097
18.	148.76	602.3	8.7	8.96	-10.58	31.2	82	126	3761
19.	151.01	533.47	8.69	8.88	-10.29	31.2	82	120	3761
20.	142.01	595.37	8.2	8.81	-10.74	31.2	88	156	4571
21.	125.58	457.37	7.23	7.05	-8.29	31.2	68	100	2295
22.	125.47	455.35	6.95	6.9	-8.23	31.2	68	102	2295
23.	123.89	453.34	6.27	6.56	-7.95	31.2	68	104	2295
24.	129.89	469.38	7.26	7.42	-8.63	31.2	70	104	2469
25.	131.91	501.38	6.47	6.42	-8.01	57.5	74	116	2989
26.	141.14	523.4	7.83	8.17	-9.77	31.2	80	124	3517
27.	144.57	490.99	7.49	7.74	-9.47	40.43	82	123.77	3830
28.	147.39	535.44	7.64	7.91	-9.59	40.43	82	124	3772
29.	147.39	535.44	7.64	7.91	-9.59	40.43	82	124	3801
30.	152.17	582.44	7.9	8.18	-9.87	40.43	82	123.48	3801
31.	145.507	481.55	6.21	6.85	-8.88	64.22	84	132	4177
32.	140.2	492.52	7.07	7.44	-9.29	40.43	84	138	4087
33.	152.19	569.88	8.36	8.53	-10.29	40.43	84	125.77	4059
34.	153.85	565.47	7.7	7.81	-9.66	49.66	86	132	4439
35.	149.85	484.6	7.78	7.99	-9.5	40.43	84	126	4087
36.	150.08	482.58	7.64	7.71	-9.34	40.43	84	128	4293
37.	128.73	420.51	6.35	6.53	-7.85	40.43	72	110	2726

Statistical analysis

A data matrix (D) with a dimension of (n × m) was used to collect the estimated descriptors for each enzyme inhibitory activity. The numbers n and m represent the number of molecules in each data set and the number of calculated descriptors for each molecule, respectively. The descriptors were first examined for values that were constant or nearly constant, and those that were found were eliminated from the original data matrix. The correlation between the descriptors and the activity data was then ascertained. The statistical program VALSTAT was used to conduct the correlation analysis and choose the main characteristics influencing the activity.

Model development and validation

Multiple linear regression (MLR) analysis obtained by QSAR models. To choose the most pertinent subset of descriptors, the stepwise selection of variables-a combination of forward selection and backward elimination procedures—\-was applied. VALSTAT program conducted regression analysis. The QSAR model was validated by external validation. The activity of every compound in the test set is calculated using this method. The cross-validation coefficient q2 was computed using the observed and calculated activity. The cross-validation coefficient q2 can be regarded as a measure of a model's stability and predictive capacity. A dependable model should have a square of the cross-validation coefficient (q2) of at least 0.5.

RESULT AND DISCUSSION

The descriptors used in this study include Molar Refractivity, Mass, Partition Coefficient, LogP, LogS, Polar Surface Area, Sum of Degree, Sum of Val. Degree, Wiener Index. Following the process of geometry optimisation, the descriptors were derived from each compound's structural attributes. They used the semi-empirical PM3 approach to derive the descriptors of the series of pyrazole-benzimidazole derivatives. A number of pyrazole-benzimidazole derivatives may be analysed using this approach as they are organic molecules made up of the atoms C, H, N. The QSAR models and their statistical characteristics were discovered through the statistical analysis using a regression approach.

All of the training set's chemicals were subjected to multiple linear regressions and other statistical analyses. Based on their correlation coefficient, descriptors were chosen for the model, and those with an interred correlation coefficient less than 0.6 were taken into consideration. Multiple linear regression (MLR) analysis produced a variety of models. A number of statistical metrics, including the correlation coefficient, regression coefficient (r2), Fischer statistical value (F), and standard error, were used to assess the predictive power of the model. According to the VALSTAT, all of these statistical characteristics were calculated.

Allof the training molecules underwent the initial regression analysis, producing a regression model. Large F, low p-value, r2 and q2 values around 1, and P<0.001 are characteristics of the best QSAR model. The following equation represents the optimal QSAR model developed with the multiple linear regression (MLR) method:

Model no. 1 results are...

BA = [5.03802(± 0.313039)] +Refractivity [0.00198458(± 0.00104741)] +Partition [0.128241(± 0.22902)] +Coeficient [0.251799(± 0.253375)] +Polar [0.00359031(± 0.00376229)]

n=37, r=0.328461, r^2=0.107887, r^2adj=-0.00362768, variance=0.0214444, std=0.146439, QF=2.24298, PE=0.097775, F=0.967469, FIT=0.0730165, LOF=1.19826, AIC=0.0281458

Molar Refractivity, Partition Coefficient, and Polar Surface Area descriptors with r^2 = 0.107887 and std = 0.146439 were used for developing Model 1. Std was higher and r^2 was lower. Thus, we created Model 2 by substituting the Mass descriptor for the logP descriptor, and we discovered a r2 value of 0.106341 and a standard deviation of 0.146566.

Model no. 2 results are.....

BA = [5.16362(± 0.422667)] +Refractivity [0.00176621(± 0.00102085)] +Coeficient [0.0966148(± 0.0783062)] +LogS [-0.00705007(± 0.0138886)] +Polar [0.00430948(± 0.00511652)]

n=37, r=0.3261, r^2=0.106341, r^2adj=-0.00536582, variance=0.0214816, std=0.146566, QF=2.22494, PE=0.0979444, F=0.951965, FIT=0.0718464, LOF=1.20034, AIC=0.0281946

We explored to develop other models using various descriptors, and we discovered that Models 1 and 2 have the descriptors Molar Refractivity together with Partition Coefficient and Polar Surface Area. With a r2 value of 0.107887 and a standard deviation of 0.146439, along with one outlier, we discovered that model 1 is superior to the other two models. There is a favourable correlation between MR and Anti-tumor activity. Higher molecular weight or bulky group chemicals are crucial for improved Anti-tumor activity, according to the positive correlation of MR. The Molar Refractivity negative correlation suggested that an electrophilic group would boost activity. Additionally, the Partition Coefficient showed a correlation, suggesting that less polar groups are more active.Using model-1, the Predicted pIC50 & biological activity values of the training and test sets of series are displayed in table 3, Figure–1 and Figure – 2represent the Residual Value and Compounds (RV= pIC50 – Biological Activity).

Table 3: The Actual BA and predicted pIC50 values of the training set of series by using model-1

S.No	Predicted pIC50	Biological Activity (BA)	Residual Value
1.*	5.104	4.718966633	0.385033
2.	5.109	5.187086643	-0.07809
3.	5.106	5.26760624	-0.16161
4.	5.110	5.096910013	0.01309
5	5.061	5.017728767	0.043271
6.	5.041	5.142667504	-0.10167
7.	5.136	5.13076828	0.005232
8.	5.132	5.180456064	-0.04846
9.	5.176	5.26760624	-0.09161
10.	5.218	5.055517328	0.162483
11.	5.121	5.366531544	-0.24553
12.	5.243	5.013228266	0.229772
13.	5.122	5.200659451	-0.07866
14.	5.093	5.050609993	0.04239
15.	5.175	5.107905397	0.067095
16.	5.131	5.017728767	0.113271
17.	5.219	5.096910013	0.12209
18.	5.166	5.229147988	-0.06315
19.	5.087	5.008773924	0.078226
20.	5.168	5.292429824	-0.12443
21.	5.083	5.292429824	-0.20943
22.	5.091	5.283996656	-0.193
23.	5.154	5.13076828	0.023232
24.	5.116	5.142667504	-0.02667
25.	5.278	5.214670165	0.06333
26.	5.107	5.173925197	-0.06693
27.	5.052	5.148741651	-0.09674
28.	5.141	5.244125144	-0.10313
29.	5.138	5.318758763	-0.18076
30.	5.194	5.259637311	-0.06564

31.	5.035	5.229147988	-0.19415
32.*	50.193	4.782516056	45.41048
33.	5.132	5	0.132
34.	5.202	5.207608311	-0.00561
35.	5.065	5.22184875	-0.15685
36.	5.091	5.102372909	-0.01137
37.*	5.209	4.806875402	0.402125

Compound 1, 32 & 37 was outlier.

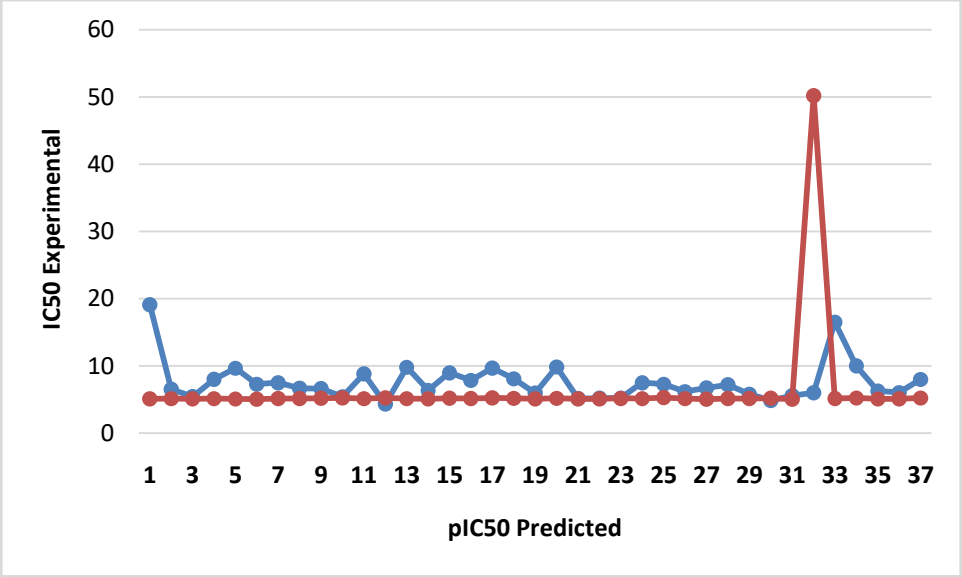

Figure 01: Corelation between Experimental IC50 value and Predicted pIC50 value

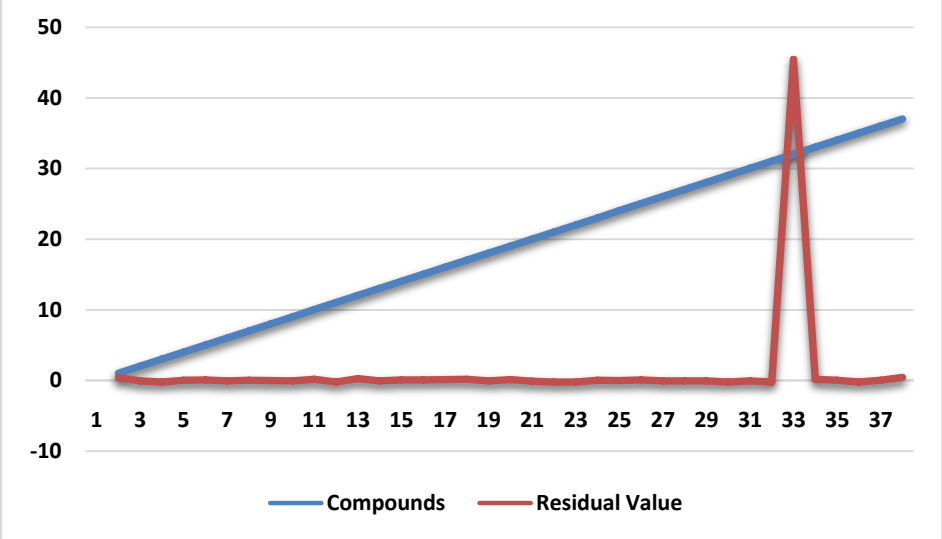

Figure 02: Graph between Residual Value and Compounds

CONCLUSION

We developed a QSAR model for the HCT116 inhibitory activity of pyrazole-benzimidazole compounds. The thermodynamic and electrical nature of the substituents has a significant impact on the Anti-Tumor activity of pyrazole-benzimidazole derivatives, it may be determined. When developing novel compounds for their potential HCT116 inhibitory action, the maximum Molar Refractivity, Partition coefficient, Polar Surface Area, and molecular weight should be taken into consideration, according to the developed QSAR model. Using this QSAR model, novel compounds with strong Anti-tumor inhibitory activity can be developed further.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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ETHICAL APPROVAL
This study has not required any ethical approval.

AUTHOR CONTRIBUTION
All authors are contributed equally.

INFORM CONSENT
Not Applicable.

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