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Molecular Modeling Studies of Some Substituted 2-Phenyl-benzimidazole Derivatives as Inhibitors of IgE Response

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Abstract

We perform the two-dimensional (2D) QSAR studies of a series of substituted 2-phenyl-benzimidazole analogues to elucidate the structural properties required inhibitors of IgE response. The 2D-QSAR studies were performed using three statistical methods: the multiple linear regressions, giving square of correlation coefficient r^2=0.8386, cross validated squared correlation coefficient q^2=0.7218 and predictable ability pred_r^2=0.7525; Multiple linear regression (MLR). The results show that the proposed 2D-QSAR models are valid and that they can be applied to predict the activities of substituted 2-phenyl-benzimidazole inhibitors of IgE response.

Keywords: 2D QSAR; Multiple linear regression; Benzimidazole analogues; IgE responses; Asthma

Introduction

Asthma is a chronic respiratory disease that affects 300 million adults and children worldwide, including 15.7 million adults and 6.5 million children in the United States [1]. The prevalence has increased by 50% in the past few decades, particularly in Westernized countries. Although corticosteroids and β2-agonists are effective in managing asthma symptoms, there is no curative therapy. There are also concerns regarding the side effects from chronic use of current drugs, particularly by children. The chronic nature of asthma and the lack of preventive and curative therapy are leading patients with asthma in Western societies to seek complementary and alternative medicine (CAM) treatment [2,3]. Human allergic disorders (type I hypersensitivity responses) ranging from hay fever, excema, and food allergies to potentially life threatening asthma and anaphylactic shock are increasing worldwide [4]. Central to the cascade of events that lead to these clinical allergic manifestations are protein-protein binding events between human immunoglobulin E (hIgE) and its class specific Fc receptors on effector cells [5-7]. Allergic asthma is a multifactorial disease, influenced by genetic and environmental factors, and is characterized by bronchial hyperresponsiveness, the presence of IgE antibodies to inhalant allergens and often also by enhanced total serum IgE levels. A switch recombination of antibodies to IgE requires two signals from activated T cells: the expression of the ligand for CD40 and the secretion of IL-4 or IL-13. Both IL-4 and IL-13, independently of each other, are able to induce IgE antibody [8-10]. The allergen-IgE interactions on the mast cell surface initiate a complex series of downstream signaling cascades, including phosphorylation of the immunoreceptor tyrosine-based activation motifs (ITAMs) in the β- and γ-chains of FcεRI, resulting in mast cell degranulation [11,12]. While there are a number of pharmacological agents available for the treatment of asthma and allergic rhinitis, a major shortcoming of many of these therapeutic alternatives is that they impact the disease state by targeting a single mediator that modifies a response at the target organ. By acting on effecter molecules, these drugs provide some symptomatic relief but do not modulate the course of the disease. Anti-histamines, for example, continue to be the drugs of choice for allergic rhinitis because they are somewhat effective and are linked to few side effects [13].

QSAR refers to a discipline in computational chemistry that addresses the modeling of biological activities or chemical reactivity based on the quantitative description for the chemical structure of molecules. QSAR relies on the basic assumption that molecules with similar physicochemical properties or structures will have similar activities [14].

Quantitative structure activity relationship (QSAR) is one of the most important areas in chemometrics, and is a valuable tool that is used extensively in drug design and medicinal chemistry. Once a reliable QSAR model is established, we can predict the activities of molecules, and know which structural features play an important role in biological processes [15]. Since the QSAR model and properties of molecules can be obtained based on descriptors, choosing the most relevant descriptors is necessary. Therefore, using a technique as variable selection for extent number of descriptors is the most essential step in QSAR study [16]. The present paper deals with the novel development of drugs for the category, substituted 2-phenyl-benzimidazole derivatives inhibitors of IgE response.

The main purpose of quantitative structure–activity relationship (QSAR) analyses is to make activity predictions for unknown compounds to guide the structure-based design of new analogues. Multiple linear regression (MLR) models have been developed as a mathematical equation which can relate chemical structure to the activity. The results obtained will be helpful to pharmacologists, chemists and medicinal chemists to come up with improved IgE responses drugs.

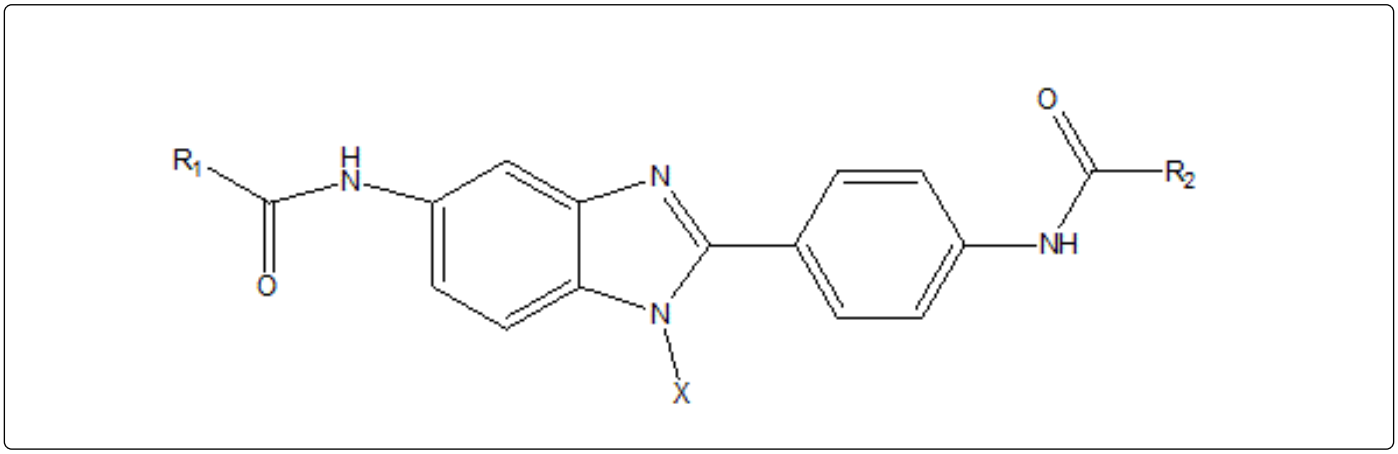
Materials and Method

A dataset of ninety four 2-phenyl-benzimidazole derivatives [17] (Richards et al.) for their IgE response have been taken for present QSAR work given in Table 1. Total of ninety four molecules were

considered for this study out of which twenty four molecules were used as test set.

The test set was chosen so as to accommodate compounds with activities in a different range. QSAR models were developed for both the training and the test set molecules, and the test set was used to validate the developed models.

In logIC_{50} values were converted to -logIC_{50} in order to bring out better linear correlations and reduce clustering of compounds while generating QSAR regression lines. The experimental information associated with biological activity, which is used as dependent variables in building a QSAR model. In this study, computational work (2D-QSAR) was performed using Vlife MDS QSAR plus software [18] on a HP computer with Core2 Duo processor and a window XP operating system.



S.No	R1	R2	X	Y	IC_{50}	pIC_{50}
1	Phenyl	Phenyl	H	H	20	7.698
2	4-Bromopheny	4-Bromophenyl	H	H	200	6.698
3	3-Chlorophenyl	3-Chloropheny	H	H	25	7.602
4	2-Chlorophenyl	2-Chloropheny	H	H	45	7.346
5	3,4-Dichlorophenyl	3,4-Dichlorophenyl	H	H	40	7.397
6*	2,3-Dichlorophenyl	2,3-Dichlorophenyl	H	H	10	8.000
7	3,5-Dichlorophenyl	3,5-Dichlorophenyl	H	H	70	7.154
8	2,4-Dichlorophenyl	2,4-Dichlorophenyl	H	H	30	7.522
9	2,6-Dichlorophenyl	2,6-Dichlorophenyl	H	H	400	6.397
10*	Penta-fluoro-phenyl	Penta-fluoro-phenyl	H	H	4	8.397
11	Phenyl	4-Chlorophenyl	H	H	90	7.045
12	4-Nitrophenyl	4-Nitrophenyl	H	H	150	6.823
13*	4-Cyanophenyl	4-Cyanophenyl	H	H	100	7
14	4-Methoxyphenyl	4-Methoxyphenyl	H	H	30	7.522
15	3,4-Dimethoxyphenyl	3,4-Dimethoxyphenyl	H	H	700	6.154
16	4-S-methyl-phenyl	4-S-methyl-phenyl	H	H	150	6.823
17*	4-Methylphenyl	4-Methylphenyl	H	H	20	7.698
18	1-Naphthalene	1-Naphthalene	H	H	80	7.096
19	CH2-2-thiophene	CH2-2-thiophene	H	H	500	6.301
20	Cyclohex-3-ene	Cyclohex-3-ene	H	H	400	6.397

21*	Phenyl-	Cyclohexyl	H	H	10	8
22	CH3	Cyclohexyl	H	H	100	7
23	3,4-Dichlorophenyl	Cyclohexyl	H	H	0.8	9.096
24	4-Chlorophenyl	Cyclohexyl	H	H	6	8.221
25*	Cyclohexyl	3,4-Dichlorophenyl	H	H	0.4	9.397
26	Cyclohexyl	4-Chlorophenyl	H	H	8.0	8.096
27	1-Adamanty	2-Fluorophenyl	H	H	10	8
28	1-Adamanty	4-Fluorophenyl	H	H	10	8
29	2-Pyridyl	1-Adamanty	H	H	6	8.221
30*	3-Pyridyl	1-Adamanty	H	H	20	7.698
31	Cyclohexyl	Cyclohexyl	H	H	4	8.397
32	1-Adamantyl	1-Adamantyl	H	H	4	8.397
33	Cycloheptyl	Cycloheptyl	H	H	1.5	8.823
34*	Cyclobutyl	Cyclobutyl	H	H	400	6.397
35	Cyclopropyl	Cyclopropyl	H	H	1000	6
36	4-Methyl-cyclohexyl	4-Methyl-cyclohexyl	H	H	4	8.397
37	Cinnamyl	Cinnamyl	H	H	70	7.154
38*	Phenyl	Phenyl	CH_3	H	800	6.096
39	Cyclohexyl	Cyclohexyl	$COOCH_2CH_3$	H	7	8.154
40	Cyclohexyl	Cyclohexyl	$COCH_3$	H	1.5	8.823
41	Cyclohexyl	Cyclohexyl	H	H	2	8.698
42*	4-Methyl-phenyl	4-Methyl-phenyl	H	H	40	7.397
43	4-Fluorophenyl	4-Fluorophenyl	H	H	150	6.823
44	4-Methoxyphenyl	4-Methoxyphenyl	H	H	100	7
45	Phenyl	3,4-Dichlorophenyl	H	H	100	7
46*	Phenyl	5-Methyl-2-pyridyl	H	H	300	6.522
47	Cyclohexyl	Phenyl	H	H	9	8.045
48	1-Adamantyl	Phenyl	H	H	25	7.602
49	Phenyl	1-Adamantyl	H	H	8	8.096
50*	1-Adamantyl	4-Chlorophenyl	H	H	9	8.045
51	1-Adamantyl	3,4-Dichlorophenyl	H	H	1.5	8.823
52	2-Adamantyl	3,4-Dichlorophenyl	H	H	16	7.795
53	Cyclohexyl	4-Fluorophenyl	H	H	5	8.301
54	Cyclohexyl	4-Chlorophenyl	H	H	3	8.522
55*	2-Adamantyl	4-Methoxyphenyl	H	H	7	8.154
56	4-Methoxyphenyl	1-Adamantyl	H	H	40	7.397

57	4-Fluorophenyl	2-Adamantyl	H	H	40	7.397
58*	1-Adamantyl	2-Pyridyl	H	H	10	8
59	2-Adamantyl	2-Pyridyl	H	H	10	8
60	2-Adamantyl	3-Pyridyl	H	H	20	7.698
61*	2-Adamantyl	4-Pyridyl	H	H	40	7.397
62	2-Pyridyl	2-Adamantyl	H	H	40	7.397
63	2-Pyridyl	1-Adamantyl	H	H	40	7.397
64	2-Adamantyl	5-Methyl-2-pyridyl	H	H	20	7.698
65*	Cyclohexyl	Cyclohexyl	H	H	80	7.096
66	1-Adamantyl	1-Adamantyl	H	H	16	7.795
67	4-Methyl-cyclohexyl	4-Methyl-cyclohexyl	H	H	35	7.455
68	1-Adamantyl	Cyclohexyl	H	H	8	8.096
69*	2-Adamantyl	2-Methyl-cyclohexyl	H	H	4	8.397
70	2-Methyl-cyclohexyl	1-Adamantyl	H	H	4	8.397
72	Phenyl	Phenyl	H	H	400	6.397
72	3,4-Dichlorophenyl	Phenyl	H	H	50	7.301
73*	Phenyl	Cyclohexyl	H	H	70	7.154
74	Cyclohexyl	Phenyl	H	H	130	6.886
75	1-Adamantyl	Phenyl	H	H	150	6.823
76*	Phenyl	1-Adamantyl	H	H	4	8.397
77	3,4-Dichlorophenyl	1-Adamantyl	H	H	0.7	9.154
78	3,4-Dichlorophenyl	Bicycloheptyl	H	H	40	7.397
79*	3,4-Dichlorophenyl	Cyclohexyl	H	H	15	7.823
80	Cyclohexyl	Cyclohexyl	H	H	50	7.301
81	1-Adamantyl	1-Adamantyl	H	H	6	8.221
82	Cycloheptyl	Cycloheptyl	H	H	3	8.522
83	Cycloheptyl	Cycloheptyl	H	H	500	6.301
84*	Bicycloheptyl	Bicycloheptyl	H	H	30	7.522
85	2-Methyl-cyclohexyl	2-Methyl-cyclohexyl	H	H	60	7.221
86	4-Methyl-cyclohexyl	4-Methyl-cyclohexyl	H	H	3	8.522
87	1-Adamantyl	Cyclohexyl	H	H	60	7.221
88*	Cyclohexyl	1-Adamantyl	H	H	4	8.397
89	4-Methyl-cyclohexyl	1-Adamantyl	H	H	3	8.5228
90	Cyclohexyl	Bicycloheptyl	H	H	30	7.522
91*	1-Adamantyl	Bicycloheptyl	H	H	20	7.698
92	1-Adamantyl	Cycloheptyl	H	H	3	8.522

93	1-Adamantyl	Cycloheptyl	H	H	70	7.154
94	2-Pyridyl	1-Adamantyl	H	H	40	7.397
*Test compound						

Table 1: Structures and activities of benzimidazole derivatives as inhibitors of IgE response.

All the 2D descriptors were calculated for QSAR analysis using Vlife MDS 3.5 software. Energy minimization and geometry optimization were conducted using Merck molecular force field as force field and charge, maximum number of cycles were 1,000, convergence criterion (RMS gradient) was 0.01 and medium's dielectric constant of 1 by batch energy minimization method. The dataset of 94 molecules was divided into training set (71 compounds) and test set (23 compounds) by Sphere Exclusion (SE) method [19] for multiple linear regression (MLR) model with dissimilarity value of 11.2 using pEC50 activity field as dependent variable and various 2D descriptors as independent variables.

Energy-minimized geometry was used for calculation of descriptors, a total of 208 2D descriptors were calculated which encoded different aspects of molecular structure and consists of electronic, thermodynamic, spatial, and structural descriptors, e.g., retention index (chi), atomic valence connectivity index (chiV), path count, chain path count, cluster, path cluster, element count, estate number, semi-empirical, molecular weight, molecular refractivity, logP, and topological index.

Multiple linear regression (MLR)

MLR is a method used for modeling linear relationship between a dependent variable Y (pIC_{50}) and independent variable X (2D descriptors). MLR is based on least squares: the model is fit such that sum-of-squares of differences of observed and a predicted value is minimized. MLR estimates values of regression coefficients (r^2) by applying least squares curve fitting method. The model creates a relationship in the form of a straight line (linear) that best approximates all the individual data points. In regression analysis, conditional mean of dependant variable (pEC50) Y depends on (descriptors) X. MLR analysis extends this idea to include more than one independent variable. Regression equation takes the form

$$Y=b1 * x1+b2 * x2+b3 * x3+c$$

Where Y is dependent variable, 'b's are regression coefficients for corresponding 'x's (independent variable), 'c' is a regression constant or intercept [20,21].

Results and Discussion

For QSAR analysis regression was performed using pIC_{50} values as dependent variables and calculated parameters as independent variables. In any thorough investigation of the effects of molecular properties, it is essential to prove that the results are both statistically valid. 2D-QSAR equations were selected by optimizing the statistical results generated along with variation of the descriptors in this model.

pIC_{50}=0.3821(±0.0259) SsOHE-index+0.1694(±0.0117) ChiV3Cluster +0.4181(±0.0356) SssCH2E-index -0.2025(±0.0011) T_C_F_2+ 0.3689(±0.0770) SsClE-index

Ntraining=71, Ntest=23, r^2=0.8386, q^2=0.7218, F test=43.3584, r^2_se=0.1236, q^2_ se=0.1733, pred_r^2=0.7525, pred_r^2se=0.4268.

In above QSAR models, r^2 is a correlation coefficient that has been multiplied by 100 gives explained variance in biological activity. Predictive ability of generated QSAR models was evaluated by q^2 employing LOO method. F value reflects ratio of variance explained by models and variance due to error in regression. High F value indicates that model is statistically significant. Eq. (1) shows 84 % variance in the observed activity values. The low standard error of r^2_se=0.1236 demonstrates accuracy of the model.

Cross validated q^2 of this model 0.7218, indicates good internal prediction power of the model. Another parameter for predictivity of test set compounds is high pred_r^2=0.7525, which shows good external predictive power of the model. The electro-topological parameter SsClcount define the total number of chlorine atoms connected with one single bond. The positive coefficient of the descriptor suggests that IgE responses of Substituted 2-phenyl-benzimidazole may be increased by increasing the number of chlorine atoms present in the nucleus.

The positive coefficient of the molecular connectivity index descriptor in the model suggests that the decrease in branching in the molecule and the presence of heteroatoms increases the IgE responses. An estate contribution electro-topological state descriptor SssCH2E-index, which represents the indices for number of -CH_2 group connected with two single bonds, is inversely proportional to the activity. The positive coefficient of T_C_F_2 in the QSAR model reveal that the presence of [fluoro-phenyl at the end terminal of benzimidazole increases activity. The contribution charts of selected descriptors are represented in Figure 1a. The Observed activity and Predicted activity pIC_{50} along with residual values are shown in Table 2 and plots of observed vs. predicted values of pIC_{50} are shown in Figure 1b.

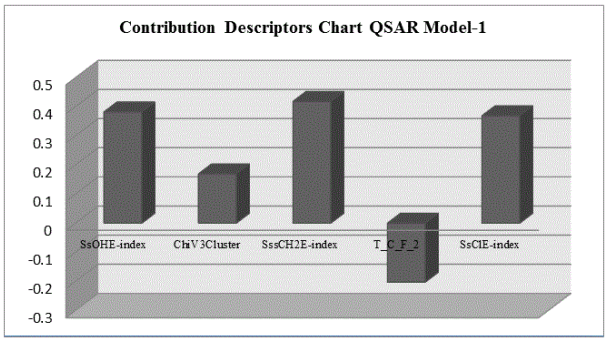


Figure 1a: Plot of contribution chart of 2D QSAR Model.

Com	pIC_{50}	2D-QSAR Model-1	
		Pred.	Res.
1	7.698	7.5014	0.1966
2	6.698	6.1844	0.5136
3	7.602	7.1742	0.4278
4	7.346	7.1565	0.1895
5	7.397	7.2394	0.1576
6*	8	8.1913	-0.1913
7	7.154	7.1385	0.0155
8	7.522	7.3699	0.1521
9	6.397	6.317	0.08
10*	8.397	8.3898	0.0072
11	7.045	7.3238	-0.2788
12	6.823	6.38	0.443
13*	7	6.9905	0.0095
14	7.522	7.3895	0.1325
15	6.154	6.3705	-0.2165
16	6.823	6.3512	0.4718
17*	7.698	7.349	0.349
18	7.096	7.4522	-0.3562
19	6.301	6.308	-0.007
20	6.397	6.2796	0.1174
21*	8	8.2619	-0.2619
22	7	7.3976	-0.3976
23	9.096	9.3444	-0.2484
24	8.221	8.4161	-0.1951
25*	9.397	9.3997	-0.0027
26	8.096	8.445	-0.349
27	8	8.378	-0.378
28	8	8.3608	-0.3608
29	8.221	8.395	-0.174
30*	7.698	7.3062	0.3918
31	8.397	8.3479	0.0491
32	8.397	8.2606	0.1364
33	8.823	8.3629	0.4601
34*	6.397	6.3113	0.0857

35	6	6.2892	-0.2892
36	8.397	8.2849	0.1121
37	7.154	7.1138	0.0402
38*	6.096	6.1735	-0.0775
39	8.154	8.1753	-0.0213
40	8.823	8.1666	0.6564
41	8.698	8.2351	0.4629
42*	7.397	7.1904	0.2066
43	6.823	6.1705	0.6525
44	7	7.3229	-0.3229
45	7	7.3268	-0.3268
46*	6.522	6.3362	0.1858
47	8.045	8.2932	-0.2482
48	7.602	7.3312	0.2708
49	8.096	8.3279	-0.2319
50*	8.045	8.3315	-0.2865
51	8.823	8.3254	0.4976
52	7.795	7.2976	0.4974
53	8.301	8.3018	-0.0008
54	8.522	8.364	0.158
55*	8.154	8.2889	-0.1349
56	7.397	7.2641	0.1329
57	7.397	7.2266	0.1704
58*	8	8.3328	-0.3328
59	8	8.3162	-0.3162
60	7.698	7.3431	0.3549
61*	7.397	7.3523	0.0447
62	7.397	7.3951	0.0019
63	7.397	7.3285	0.0685
64	7.698	7.3244	0.3736
65*	7.096	7.336	-0.24
66	7.795	7.2644	0.5306
67	7.455	7.2963	0.1587
68	8.096	8.2371	-0.1411
69*	8.397	8.278	0.119
70	8.397	8.2609	0.1361

72	6.397	6.242	0.155
72	7.301	7.238	0.063
73*	7.154	7.093	0.061
74	6.886	6.9321	-0.0461
75	6.823	6.4323	0.3907
76*	8.397	8.3511	0.0459
77	9.154	9.3763	-0.2223
78	7.397	7.4799	-0.0829
79*	7.823	7.4276	0.3954
80	7.301	7.4261	-0.1251
81	8.221	8.4405	-0.2195
82	8.522	8.4509	0.0711
83	6.301	6.4649	-0.1639
84*	7.522	7.4487	0.0733
85	7.221	7.4676	-0.2466
86	8.522	8.5002	0.0218
87	7.221	7.4985	-0.2775
88*	8.397	8.4923	-0.0953
89	8.522	8.4921	0.0299
90	7.522	7.5365	-0.0145
91*	7.698	7.571	0.127
92	8.522	8.3909	0.1311
93	7.154	7.4208	-0.2668
94	7.397	7.4738	-0.0768
*Test compound			

Table 2: Predicted activities according to 2D QSAR models results of benzimidazole with bacterial strains.

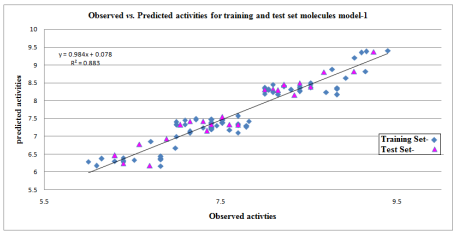


Figure 1b: Graphs of observed vs. predicted activity of 2D QSAR model-1.

Conclusion

A multiple linear regression (MLR) procedure was used to model the relationships between molecular descriptors and the inhibitors of IgE response of the benzimidazole derivatives. The quantitative structure-activity relationship (QSAR) analysis of some synthesized substituted 2-phenyl-benzimidazole derivatives inhibitors of IgE response were performed to find out the structural requirements of their IgE responses activities. Various 2D descriptors were calculated and used in the present analysis. The knowledge of Structure-Activity Relationship (SAR), together with the generation of QSAR, constitutes a large body of evidence that may assist in the development of new molecules with excellent biological activity and low toxicity. The results obtained from present investigation of IgE responses studies indicate that the presence of a chlorophenyl, fluoro-phenyl substituent leads to increase in the activity in comparison to the presence of a methyl group. QSAR analysis has been used to study the quantitative

effects of the molecular structure of the benzimidazoles on their inhibitory activity. In this model special emphasis was given to the contribution of electrotopological in predicting biological activity of 2-phenyl-benzimidazole derivatives and they were found to improve the QSAR model and make it more precisely predictive.

Acknowledgments

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